ORIGINAL ARTICLE

Ocular Blood Flow Changes in Behçet Disease Patients with/without Thrombotic Disease

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ABSTRACT

In this study, the authors aimed to evaluate ocular blood flow changes in Behçet disease (BD) with and without thrombotic disease. Ninety eyes of 90 patients with a diagnosis of BD (30 eyes with active uveitis, 23 eyes with inactive uveitis, 25 eyes without ocular involvement, and 12 eyes without ocular involvement and with a history of thrombosis) and 30 eyes of 30 age- and sex-matched control patients without any systemic disease with a total of 120 eyes were evaluated. In all cases, ophthalmic, central retinal, and ciliary artery flow parameters were measured with colour Doppler ultrasonography (CDU). The ocular blood flow parameters of all vessels in patients with active uveitis were found to be affected. All the flow parameters in the CRAs of the study groups were significantly different from the control group ($p < 0.001$). Additionally, in non-ocular BD patients with thrombosis, blood flow parameters were affected more than the parameters in non-ocular BD patients without thrombosis and control patients. In conclusion, major haemodynamic changes were observed using CDU in the ophthalmic vessels of ocular Behçet patients. Also, CDU may detect ocular blood flow alterations before initial ocular clinical manifestations appear in BD patients

Keywords: Behçet, Doppler, thrombosis, uveitis

INTRODUCTION

Behçet disease was (BD) first described in 1937 by Turkish dermatologist, Dr. Hulusi Behçet. BD is a multisystemic disorder characterised by recurrent oral aphthous ulcers, genital ulcers, thrombophlebitis, and iridocyclitis with hypopyon.¹ The basic pathology of the disease is chronic, recurrent vasculitis. The histopathological examinations and clinical data showed that the primary pathology is occlusive vasculitis caused by the circulation of abnormal immune complexes.²

In BD, eye involvement is often bilateral and within 3 to 4 years of ocular findings, patients lost their vision.^{3,4} Despite anti-inflammatory and conventional immunomodulatory treatments, recurrent episodes of intraocular inflammation may eventually lead to the

loss of useful vision in 15.6% of patients with Behçet uveitis.⁵ Retinal vasculitis is the most vital complication of BD, and it affects the arteries and veins of the posterior segment. Vascular pathologies, such as vascular occlusive lesions and necrotizing arteriolitis, have been reported in histopathological studies.⁶ The prevalence of vascular involvement varies from 7.7% to 43% in BD patients, depending to the ethnicity.^{7–11} Vein thrombosis constitutes the most frequent vascular manifestations and occurs in 6.2% to 33% of BD cases.¹²

Colour Doppler ultrasonography (CDU) is sensitive enough to show the vessels in the eye even if they are 0.1 to 1.0 mm in diameter. In addition, CDU, which is a non-invasive, inexpensive, and practical radiological method, does not require the use of pharmacological agents and does not cause discomfort.

CDU provides quantitative information about blood flow separate from the state of ocular media and transparency, and it is easy to use for testing.^{13,14}

Our aim in this study was to evaluate ocular blood flow changes in both ocular BD and non-ocular BD patients with or without thrombotic disease and compare the blood flow changes with a healthy control group. To our knowledge, this is the first study that compares the blood flow changes in ocular BD patients and non-ocular BD patients with or without thrombotic disease.

MATERIALS AND METHODS

Patients and Methods

The study protocol was approved by the ethics committee, and informed consent was obtained from the study participants prior to their participation in the study. Ninety Behçet's patients with and without ocular involvement, diagnosed according to the International Study Group Criteria, were evaluated in this study.¹⁵

The study subjects were classified in five groups: group 1 included BD patients with active uveitis, group 2 included BD patients with inactive uveitis, group 3 included BD patients without uveitis, group 4 included BD patients without uveitis but with systemic thrombotic disease (thrombophlebitis or deep vein thrombosis), and group 5 was the healthy control group. Ocular blood flow measurements were performed on the involved eyes of the ocular BD patients (the right eye was selected in case of bilateral uveitis) and the right eyes of the groups without ocular involvement.

The following findings were accepted as active ocular involvement: ciliary injection, inflammatory cells in the anterior chamber, keratic precipitates, papillitis, retinal vasculitis, and perivenous cuffing in ophthalmoscopic examination. Patients with none of the above findings but with lesions for at least the last 2 months were considered to be inactive BD uveitis.

Thirty normal control subjects with no history of systemic (systemic hypertension and glaucoma) or ocular disease were included in the study. Patients with other forms of ocular pathology, such as systemic hypertension, diabetes mellitus, or a history of any systemic disease, were excluded.

Examinations

Following each subject's ocular examination, a haemodynamic evaluation of the orbital vessels was conducted using CDU. All CDU examinations were performed by the same radiologist (C.H.), who was unaware of subjects' clinical status, and with the same

scanner, a Toshiba SSH 140-A (Toshiba, Tokyo, Japan) with a 7.5-MHz linear array transducer of 14-mm aperture size.

The blood flow in the central retinal artery (CRA), ophthalmic artery (OA), and the temporal posterior ciliary artery (TPCA) was measured using CDU to determine the peak systolic velocity (PSV), end-diastolic velocity (EDV), resistivity index (RI), and the pulsatility index (PI). In each patient, three measurements were obtained, and the mean values were calculated for each of the above parameters. These results were then compared among the five subject groups.

Statistical Analysis

Statistical evaluation was conducted using SPSS 15.0 (Statistical Packages for Social Sciences; SPSS Inc., Chicago, IL, USA). The Kruskal-Wallis test was used for variance analysis and a p value less than 0.05 was considered statistically significant. The data obtained from the study groups were compared using the non-parametric Mann-Whitney U test with the Bonferroni correction; a p value less than 0.005 was considered statistically significant.

RESULTS

The general characteristics of the subjects are summarised in Table 1.

There was a statistically significant difference in the flow parameters (PSV, EDV, RI, and PI) of the OA, CRA, and TPCA among the groups ($p < 0.001$). The OA, CRA, and TPCA flow parameters of the patients are given in Table 2. With the exception of group 1, the OA flow parameters of the study groups were not different from the control group. In the OA parameters of group 1, EDV and PSV were lower and PI and RI were higher than the control and other study groups ($p < 0.001$).

All the flow parameters in the CRAs of the study groups were significantly different from the control group ($p < 0.001$). The PSV values were significantly different in the comparisons among study groups ($p < 0.001$), except for the comparison between groups 3 and 4 ($p = 0.039$). The EDV values were significantly different among all the study groups, except for the comparison between groups 2 and 4 ($p = 0.327$). The RI and PI values were significantly different in all comparisons between the study groups, except the comparisons of groups 4 and 2 (for RI $p = 0.694$ and for PI $p = 0.073$) also groups 3 and 4 (for RI $p = 0.007$ and for PI $p = 0.215$).

All the TPCA flow parameters in groups 1 and 2 showed statistically significant differences when compared with the control group ($p < 0.001$).

TABLE 1 Group demographics.

Characteristic	Ocular BD		Non-ocular BD		Healthy control	<i>p</i> Value
	Active	Inactive	Without thrombosis	With thrombosis		
Age (years)	33.0 ± 6.3 (22–52)	32.0 ± 6.9 (21–44)	32.3 ± 7.5 (15–49)	31.5 ± 5.4 (25–44)	29.1 ± 6.6 (18–48)	0.151
Gender (female/male)	13/17	16/7	9/16	5/7	12/18	0.149

BD = Behçet's disease.

TABLE 2 OA, CRA, and TPCA flow parameters in groups.

Parameter	Ocular BD		Non-ocular BD		Healthy control V
	Active I	Inactive II	Without thrombosis III	With Thrombosis IV	
Ophthalmic artery					
PSV	25.0±3.4	31.4±2.3	33.1±3.0	33.4±2.3	33.3±3.9
EDV	8.4±1.7	10.2±1.1	10.8±1.2	10.9±1.4	11.0±1.0
RI	0.71±0.29	0.64±0.27	0.63±0.27	0.64±0.17	0.63±0.25
PI	1.56±0.16	1.29±0.08	1.25±0.13	1.30±0.11	1.23±0.13
Central retinal artery					
PSV	8.1±1.1	8.9±0.8	10.9±0.8	10.3±0.8	11.6±1.1
EDV	2.6±0.4	2.9±0.3	3.5±0.3	3.0±0.3	4.5±0.5
RI	0.69±0.34	0.63±0.27	0.59±0.51	0.63±0.03	0.5±0.06
PI	1.38±0.2	1.18±0.1	1.05±0.12	1.10±0.12	0.78±0.15
Temporal posterior ciliary artery					
PSV	10.0±1.1	12.0±1.0	13.0±0.7	12.7±1.0	14.1±1.8
EDV	3.2±0.5	3.9±0.4	4.6±0.3	4.5±0.3	4.9±0.5
RI	0.71±0.03	0.65±0.02	0.58±0.03	0.6±0.02	0.56±0.04
PI	1.43±0.12	1.19±0.11	0.91±0.09	0.94±0.1	0.89±0.09

OA = ophthalmic artery; CRA = central retinal artery; TPCA = temporal posterior ciliary artery; PSV = peak systolic velocity; EDV = end-diastolic velocity; RI = resistivity index; PI = pulsatility index.

When the study groups were compared with each other, the statistics were as follows: In group 1, EDV and PSV were lower whereas RI and PI were higher than the other groups ($p < 0.001$). In group 2, EDV and PSV were lower and PI and RI were higher than the other groups ($p < 0.001$), except for the PSV comparison between groups 2 and 4 ($p = 0.073$). There was no statistically significant difference among the other groups ($p > 0.05$).

DISCUSSION

Behçet's disease is a chronic, inflammatory, and systemic disease characterised by vasculopathy.^{2,6} The ocular manifestations of BD are panuveitis and vasculitis, which develop in 70% to 85% of patients, and the outcome of the inflammation is usually sight-threatening.^{3,4} Posterior ocular involvement affects the retinal pigment epithelium (RPE), choriocapillaris, and more specifically, the inner retinal layers and retinal vessels.^{2,16,17}

Both arteries and veins are affected by BD, leading to periphlebitis and/or arteritis obliterans. Histologically, there is a perivascular infiltration of lymphocytes and mononuclear cells involving the large and small arteries, veins, arterioles, venules, and

capillaries. Vascular endothelial cell damage, smooth muscle cell proliferation, and thrombus in the lumen have been found in BD patients.^{8,17,18} The pathogenesis of BD is explained by obliterative vasculitis, probably caused by circulating abnormal immune complexes.⁶

There are several studies conducted to examine the orbital haemodynamic changes in BD.^{19–27} In these studies, reduction in orbital blood flow and increase in RI were reported in BD patients and the most common finding was the reduction in the CRA blood flow compared with the normal subjects.^{20,23,28} Reduction in OA and TPCA blood flows have also been found in BD patients.²⁰

BD mainly affects inner retinal layers. Therefore, involvement of the CRA plays an important role in the pathogenesis of BD.²⁰ Celebi *et al.* and Ozdemir *et al.* showed that the PSV and EDV in the CRA of ocular BD patients were lower than that of non-ocular BD patients and the control group.^{20,21} Duranoglu *et al.* and Caca *et al.* report that non-ocular BD patients' PSV and EDV in the CRA were lower and their RI was higher than control group.^{23,27} In our study, when active ocular BD was compared with non-ocular BD with and without thrombosis, the CRA's PSV and EDV values were lower and the RI and PI were higher in active ocular BD patients. Also, flow changes were

apparent in the comparison between active and inactive uveitis patients.

Many studies show that the PSV and EDV of TPCA were found to be lower in ocular BD patients than in the normal control group and non-ocular BD patients.^{21,22} In addition, increased TPCA PI values have been reported in ocular BD patients compared with the control group.^{23,26} These findings (EDV and PSV reduction and PI increase in TPCA) indicate that choroidal circulation is also involved by vasculitis, which is difficult to detect clinically. Previous studies showed no differences in the TPCA flow parameters between non-ocular BD patients and the normal control subjects.^{21,22} In our study, the TPCA's PSV and EDV values were lower and PI and RI values were higher in patients with ocular BD particularly in who had active uveitis.

In our study, the OA flow parameters only changed in group 1. There was a decreased OA PSV and EDV and an increased PI value were found in this group. There were no changes in the OA flow parameters of the other groups. Other studies show different OA flow parameter results, however. Ozdemir et al. and Atilla et al. show no significant difference in the OA flow parameters.^{21,22} Celebi et al. report a decreased OA PSV,²⁰ and Duranoglu et al. report a decreased OA EDV²³ in BD. Uçakhan et al. report an increased OA PSV and EDV in BD patients.²⁴

The CRA, TPCA, and OA flow parameters in BD patients with ocular involvement are explained by increased vascular resistance caused by the narrowing or closure of the small blood vessels due to vasculitis, according to clinical and histopathological findings.²⁰ The CRA's EDV and PSV decreased in BD patients without ocular involvement; however, there were no changes in the TPCA, so it is suggested that the TPCA parameters were affected during the later stages of the disease. TPCA flow parameter changes appear when ocular involvement begins in the later stages of the disease.

Increases in the RI and PI signify increased vascular resistance caused by vasculitis in BD patients. In previous studies, PI and RI values of the CRA and TPCA increased significantly in ocular BD patients compared with the control group.^{20,29}

In our study, blood flow changes were detected in all of the active uveitis patients' vessels. There was a significant decrease in the blood flow of active uveitis patients compared with the other groups. Active uveitis patients had lower blood flow and higher vascular resistance than patients with inactive uveitis. Seckin et al. and Soyulu et al. did not report any differences in all three vessels of the eyes for active and inactive uveitis patients.^{25,26}

BD, which is systemic vasculitis, may involve both arteries and veins. However in more than 90% of cases it involves veins.^{8,17} Thrombophlebitis particularly in the superficial and deep veins of the lower extremities

is the most common venous finding in BD patients.^{1,8,11,30}

Unlike the other studies, we also evaluated the effect of having accompanying thrombotic disease in the blood flow parameters of BD patients and found that CRA EDV value of non-ocular BD with thrombosis was significantly lower than that of non-ocular BD without thrombosis. According to this information, one may suggest that BD as a systemic occlusive vasculitis may affect orbital blood flow even in the patients without any clinical finding for ocular involvement. The cause of thrombosis in BD is unknown. Although obliterative vasculopathy due to circulating immune complexes was thought to be the main factor, many other factors were found in the pathogenesis of thrombosis, such as endothelial dysfunction and disturbances in some haematological parameters.

In conclusion, in this study major haemodynamic changes were observed using CDU in the ophthalmic vessels of ocular Behçet patients. Ocular blood flow of ocular BD patients is found to be reduced more than the non-ocular BD patients and in non-ocular BD patients with thrombosis, and blood flow parameters were affected more than those in non-ocular BD patients without thrombosis. New studies may investigate the role of orbital CDU findings in the development of the ocular BD in the same patient population. Also, in patients with active ocular BD, ocular blood flow was found to be more reduced than inactive ocular BD patients, so CDU might be used in the follow-up of the treated patients.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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