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OPTIC COHERENCE TOMOGRAPHY RESULTS IN PATIENTS WITH BEHÇET'S DISEASE

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ABSTRACT

Significance: Retina is considered to be an easily traceable part of the brain. Even though the retina does not contain myelin, it is an ideal model of neuronal tissue where degeneration of the ganglion cell neurons and their associated axons may occur. **Purpose:** We aimed at examining ganglion cell complex structures such as the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and inner plexiform layer (IPL) by Optical Coherence Tomography (OCT), determining whether inflammatory factors caused damage to the retinal neuronal network in patients with Behçet's disease (BD) who did not show optic atrophy, i.e., did not develop chronic retinal vascular ischemia. **Methods:** Forty-two patients with BD and 42 healthy volunteers were included in the study, and their eye RNFL, GCL, and IPL thicknesses were measured using OCT. **Results**: It was determined that there was a significant decrease in both GCL and IPL thicknesses in patients with BD when compared with those in control patients. There was a statistically significant negative correlation between C-reactive protein levels and GCL and IPL thicknesses. There was a negative correlation between C-reactive protein (CRP), GCL, and IPL, which was statistically significant ($r = -0.36$ and $P = .001$ between GCL and CRP and $r = -0.22$ and $P = .039$ between IPL and CRP). **Conclusion:** In patients with BD without optic nerve involvement who did not develop optic atrophy, degeneration was detected in some layers of the retinal nerve network (GCL and IPL), suggesting that this degeneration develops before the possible vascular endothelial damage in the optic nerve. Therefore, performing a retinal nerve follow-up using OCT in the early stages of BD may be an important aspect in monitoring the progression of the disease.

KEYWORDS: Behçet's disease; Optical Coherence Tomography; Retinal nerve degeneration.

INTRODUCTION

Behçet's disease (BD) is a chronic recurrent vasculitis that can affect many organs and systems in the body. It is an autoimmune and multisystemic disease characterized by recurrent aphthous ulcers, genital ulcers, skin lesions, and anterior and posterior uveitis.

Ocular involvement is observed in 28.9%–80% of patients with BD.[1] Bilateral pan-uveitis is the most common form of ocular involvement and can lead to blindness.[2] Common ocular symptoms are anterior uveitis, with retinal vasculitis and hypopyon, which was initially observed as periphlebitis and vascular occlusion.[3] The course of the disease involves chronic and recurrent inflammation, and the disease may affect the anterior and posterior segments of the eye. Anterior segment complications include iris neovascularization, glaucoma, and cataract. Posterior segment complications include retinal vasculitis and occlusion, which progress to edema, exudation, and hemorrhage.[4] Several methods such as fundus fluorescein angiography, indocyanine green angiography, ultrasonic biomicroscopy, multifocal electroretinogram, and optical coherence tomography (OCT) can be used in addition to clinical examinations in evaluating the posterior segment complications associated with BD.[5,9] OCT is a non-invasive technique that measures the retinal nerve fiber layer (RNFL) thickness, macular thickness (MT), macular volume (MV), choroid layer thickness (CLT), and ganglion cell layer (GCL) thickness and has been widely used in recent years for demonstrating retinal and choroidal pathological changes.[10,13] To the best of our knowledge, there are very few studies on the use of OCT in BD and no studies on the GCL and inner plexiform layer (IPL).

Optical Coherence Tomography

OCT allows images of tissues and pathologies to be taken in a way that is similar to that of B-scan ultrasonography but at a much higher resolution [1–15 microns (μ)] by measuring the reflection delay time and intensity of an approximately 800 nm wavelength infrared light that is incident on the tissues and reflects back from their different layers.[14]

The use of OCT has become increasingly widespread in recent years because it is a non-invasive and rapid

imaging method that measures RNFL, MT, MV, and ganglion cell complex (GCC) thickness.[15] In particular, nowadays, using OCT, it has become possible to separate GCC from the normal retinal layer with an increased resolution as well as to measure the GCC thickness.[14] The retinal ganglion cells comprise three layers: RNFL, which comprises ganglion cell axons, GCL, which comprises ganglion cell bodies and IPL, which comprises ganglion cell dendrites. All three layers comprise GCC. The spectral-domain OCT developed in recent years has improved image resolution, imaging speed, and sensitivity, resulting in three-dimensional images of high quality that demonstrate all retinal layers in detail.[16] Thus, it has become an important tool in the follow-up requiring eye involvement in patients with BD. In our study, we wanted to examine the retinal nerve network using OCT to show a possible degeneration of the retinal nerves in patients with BD without any neurological involvement. Because the retina with its receptors, ganglion cells, glial support cells, and axons is considered to be an extension of the brain by many anatomists. From this perspective, the retina is considered to be an easily traceable part of the brain. Even though the retina does not contain myelin, it is an ideal model of neuronal tissue where degeneration of the ganglion cell neurons and their associated axons may occur.

In our study, we performed segmentation of the GCC structure and compared the GCL that makes up the nerve cell body, axonal extension RNFL and IPL, which comprise the dendritic layer. We aimed to investigate GCC such as RNFL, GCL and IPL to investigate possible neuronal damage in the retinas during the follow-up of patients who were diagnosed with BD at our clinic.

MATERIALS AND METHODS

Forty-two patients (16 males, 26 females) who were diagnosed with BD according to the criteria of the International BD Study Group[17] received regular follow-ups in the Internal Medicine Polyclinic and who agreed to participate in the study were included. The study was approved by the Ethics Committee and the study protocol adhered to the tenets of the Declaration of Helsinki. A signed confirmation form was filled in for the participation of both groups in the study. RNFL, GCL, and IPL thickness measurements were evaluated in these 42 patients with BD who provided consent for their OCT images to be included in the study. Forty-two patients (22 males, 20 females) who do not have BD and whose sociodemographic data were similar to those of our patient group were selected as the control group. In the control group, RNFL, GCL and IPL thicknesses were measured and recorded. In addition, ophthalmologic examinations were performed at the Eye Diseases Policlinic for both the case and control groups, and their best corrected visual activity, intraocular pressure, slit-lamp biomicroscopy and fundus examination through eye dilatation were completed. Control patients with normal eye findings were included in the study.

In the 85,000 Hz OCT2 Next Generation Spectralis OCT Module device (Spectralis OCT, Version 6.0; Heidelberg Engineering, Germany), the RNFL thickness in the right and left eyes, measurements obtained from three areas of the choroid structure and their average and GCL and IPL thicknesses were measured and recorded. The main segments of RNFL are temporal (T) and Nasal (N). These segments are evaluated as belonging to the superior (TS, NS) and inferior (TI, NI) quadrants. Analyses were made by measuring the thicknesses of the layers separately for both eyes. Consequently, a total of six regions (N, NS, NI, T, TS, and TI) in each eye was analyzed, and the mean values of RNFL thickness for both eyes were compared.

Patients with primary eye disease (glaucoma, retinal diseases, refraction defects, and so on) and additional rheumatological and systemic disease were excluded from the study.

Statistical Methods

To evaluate the assumption of normality in the data, the Kolmogorov–Smirnov test was used; and to describe the data, frequency (percent), mean ± SD, median and range were used. For evaluation of the differences between the two groups, we utilized t-test, Mann–Whitney and chi-square tests; and to compare groups while considering the correlation of eyes in one subject, generalized estimating equation (GEE) analysis was used. The *P*-value less than 0.05 was considered as statistically significant. All statistical analysis was performed by SPSS software (version 21.0, Microsoft Co., Chicago, IL, USA). Spearman's correlation test was used for to correlate the variables, and $P < .05$ indicated statistical significance.

RESULTS

The study group comprised 42 patients with BD and 42 control patients. The patient group comprised 16 males (38.1%) and 26 females (61.9%) with a mean age of 37.38 ± 10.73 years, whereas the control group comprised 22 males (52.4%) and 20 females (47.6%) with a mean age of 40.88 ± 15.66 years. Sex and age characteristics of the patient and control groups are given in **Table 1**. There was no significant difference between the two groups in terms of the socio-demographic data. In the patient group, mean RNFL, GCL and IPL thicknesses were found to be significantly decreased compared with those in the control group ($P < .05$) (**Table 2**).

When we assessed the patient group, there was no correlation between disease duration, joint involvement, smoking, and GCL ($P > .05$). There was a negative correlation between C-reactive protein (CRP), GCL, and IPL, which was statistically significant ($r = -0.36$ and $P = .001$ between GCL and CRP and $r = -0.22$ and $P =$

.039 between IPL and CRP). As the CRP value increased, thinning increased in GCL and IPL (**Table 3) (Figure 1, 2**).

There were no significant differences between the subgroups of RNFL in the patient and control groups (*P* > .05) (**Table 4**).

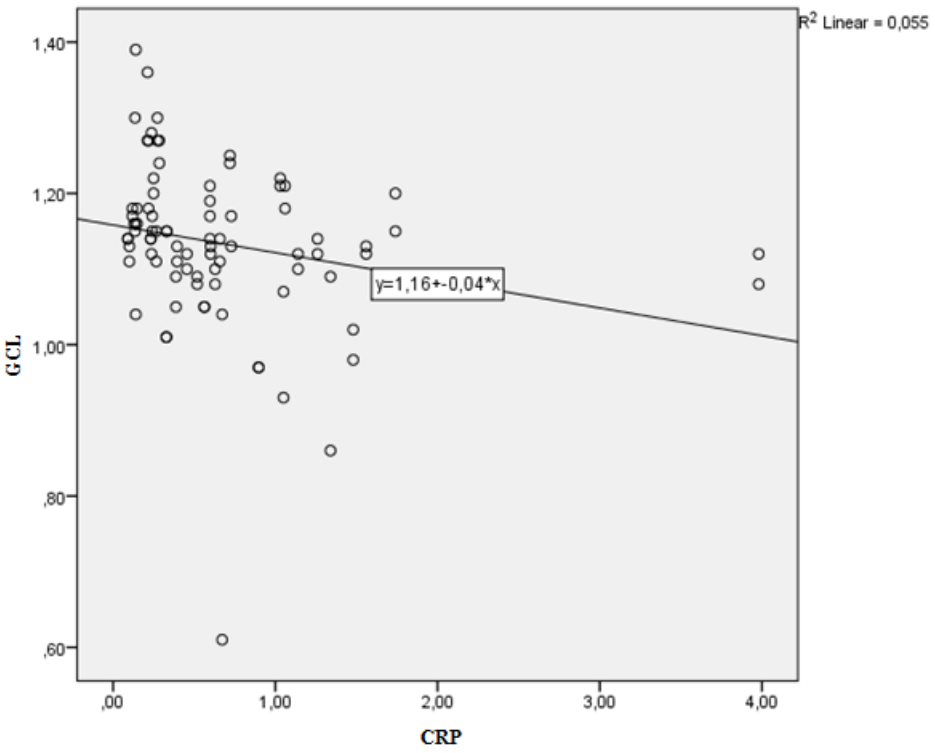

Figure 1: Scatter Plot of C-reactive protein (CRP) and ganglion cell layer (GCL).

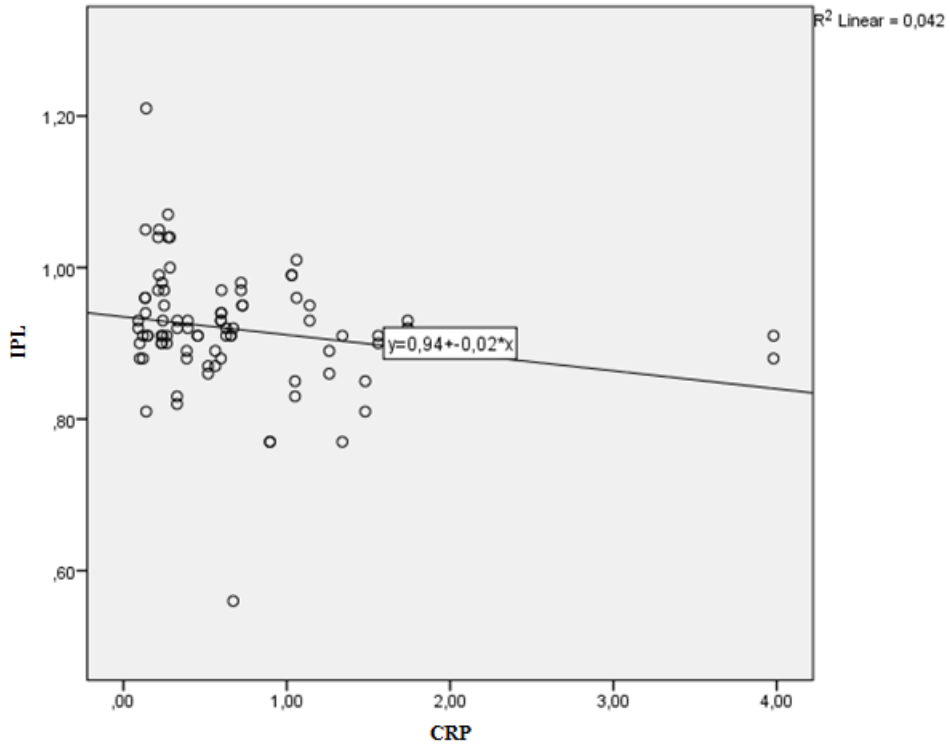

Figure 2: Scatter Plot of C-reactive protein (CRP) and inner plexiform layer (IPL).

Table 1: Sex and age characteristics of the patient and control groups.

	Patient (N = 42) N %	Control (N = 42) N %	*P* value
Sex			
Male	16 38.1	22 52.4	
Female	26 61.9	20 47.6	***P* = .273**
	Mean ± SD	**Mean ± SD**	
Age			
Male	39.62 ± 9.31	39.59 ± 12.97	
Female	36.00 ± 11.47	42.30 ± 18.43	
Overall avarage	37.38 ± 10.73	40.88 ± 15.66	***p* = .236**

Table 2: Ganglion cell layer (GCL) and inner plexiform layer (IPL) thicknesses.

	Diagnosis	Mean ± SD(mm3)	*P* value
GCL	Patient Control	1.13 ± 0.10 1,20 ± 0.49	***P* = .000**
IPL	Patient Control	0.91 ± 0.07 0.96 ± 0.05	***P* = .000**

Table 3: Correlation between C-reactive protein (CRP), ganglion cell layer (GCL) and inner plexiform layer (IPL).

	CRP
GCL	**R = -0.36** ***P* = .001**
IPL	**r = -0.22** ***P* = .039**

Table 4: Subgroups of Retinal nerve fiber layer (RNFL).

	Diagnosis	Mean ± SD (micrometer)	*P*-value
Nasal Superior	Patient Control	113.89 ± 21.63 119.28 ± 21.39	***P* = .**106
Nasal	Patient Control	77.92 ± 12.77 80.79 ± 14.76	***P* = .**180
Nasal Inferior	Patient Control	114.84 ± 27.49 126.88 ± 26.47	***P* = .004**
Temporal	Patient Control	77.32 ± 116.13 73.95 ± 8.54	***P*=** .093
Temporal Inferior	Patient Control	148.64 ± 229.87 153.35 ± 17.32	***P* =** .213
Temporal Superior	Patient Control	142.84 ± 25.48 146.48 ± 14.79	***P* =** .259
MEAN	Patient Control	103.71 ± 13.16 107.52 ± 9.04	***P* = .030**

DISCUSSION

Even though eye involvement develops in 20% of the patients with BD at the initial stage, 50%–90% of them usually show eye involvement 2 years after developing oral involvement; eye involvement may also develop much later, such as 14 years after developing oral involvement. BD may involve the anterior and posterior segment of the eye separately or together.[18] Obstructive vasculitis is the main pathology in BD, wherein the most common ocular involvement comprises uveitis and retinal vasculitis.[19,20]

The main etiopathogenesis of eye involvement in patients with BD is the emergence of retinal ischemia and atrophy in the area fed by the vein that is occluded after recurrent vasculitis. Because of the progressive and relapsing nature of the disease, severe atrophy occurs in the retina and eventually, end-stage disease accompanied by optic atrophy develops. Chronic ischemic vaso-occlusive attacks lead to demyelination in the optic nerve and retina and axonal necrosis. Kansu et al. associated progressive optic atrophy of the optic disc in patients with neuro-BD in their study with the secondary axonal damage and ischemic demyelination caused by small vessel occlusions in severe cases.[21] Optic neuropathy was shown to be caused by the spread of inflammation from the uveal tract, occlusion of the small veins of the optic nerve, or demyelination induced by ischemia.[21,23] In conclusion, mainly retinal nerve injury and optic

atrophy caused by chronic ischemia consequent to vasculitic reactions are observed in patients with BD.

In this study, we aimed at determining whether inflammatory factors caused damage to the retinal neuronal network in patients with BD who did not show optic atrophy, i.e., did not develop chronic retinal vascular ischemia. For this purpose, we examined whether there was a significant decrease in RNFL, GCL and IPL thicknesses of the retinal neuronal network using OCT. Consequent to our work, when patients with BD and control patients were compared, we determined that there was a significant reduction in GCL and IPL thicknesses, whereas there was no significant difference in the RNFL thickness. Therefore, it was shown that there was a decrease in the thickness of GCL that constitutes the soma of the retinal nerve structure and in the thickness of IPL that constitutes the dendritic structure; however, there was no difference in the thickness of RNFL that constitutes the axonal component of the retinal nerve. These results may be an indication that retinal neuron damage may occur in patients with BD without optic nerve involvement. It is also thought that neuronal damage may be initiated primarily in GCL and IPL. Conversely, the absence of a reduction in RNFL thickness may indicate that there is no axonal degeneration, i.e., optic atrophy has not yet developed. This suggests that the inflammatory process has a direct toxic effect on the neuronal layer of the retina before the occurrence of ischemia associated with vascular endothelial insufficiency in patients with BD. In some studies, the results showing a decrease in RNFL thickness in patients with BD and central nervous system involvement but no ocular involvement may be due to direct toxic effects of inflammatory factors on neurons.[24,25] Pro-inflammatory cytokines are said to cause neuronal apoptosis by a degenerative effect on neurons.[26] Considering the fact that the retina is an extension of the central nervous system, similar factors may play a role in the neurodegeneration of the retinal nerves. Indeed, it was shown in animal experiments that optic neuritis may occur before the onset of inflammatory infiltration in the optic nerve.[27]

Conversely, RNFL damage detection with ophthalmoscopy and photographs in various studies showed that the damage is possible only after 50% ganglion cell damage.[28] Indeed, in studies showing that inflammation may cause degeneration in the retinal nerve by having a toxic effect on retinal neurons, it is suggested that primarily GCL and IPL losses occur, but RNFL damage may be observed at the later stages of the disease.[29] There are several studies on RNFL in patients with BD. Consistent with our study, Sakalar et al. and Atas et al. reported that there was no significant decrease in RNFL thickness in the BD group compared with that in the control group.[30] In light of these results, when we assume that degeneration occurs in GCL and IPL at an earlier stage than that in RNFL (axonal degeneration) in BD without optic involvement, it can be thought that GCL and IPL may be an early follow-up tool in BD. In addition, longitudinal OCT follow-ups are required for axonal degeneration (RNFL).

Another result of our study is that there is a significant negative correlation between C-reactive protein (CRP) level and GCL and IPL thicknesses in BD, i.e., when the CRP level as an inflammatory marker increased, thinning in GCL and IPL increased. This may ultimately be an indication of the direct effect of inflammatory factors on GCL and IPL. Conversely, there is no laboratory marker that correlates well with the clinical activity of BD. However, Melikoglu et al. determined that there was a correlation between the activity of BD and CRP and IL-6 levels and that CRP and IL-6 were indicators of disease activity in patients with BD.[31] Muftuoglu et al. found that there was a relationship between newly developed erythema nodosum, acute thrombophlebitis, and arthritis and high erythrocyte sedimentation rates (ESR) and CRP positivity; therefore, ESR and CRP may be indicators of general disease activity.[32] Cho et al. found that CRP levels were significantly higher in patients with BD and rheumatoid arthritis than it was in those in the control group.[33] Consequent to these studies, despite being nonspecific, inflammatory markers play a role in showing inflammation and its severity in many rheumatic diseases.

Therefore, in our study, degeneration was detected in some layers of the retinal nerve network (GCL and IPL) in patients with BD without optic nerve involvement and optic atrophy, suggesting that this degeneration developed before the possible vascular endothelial damage in the optic nerve. Therefore, we believe that performing a retinal nerve follow-up using OCT in the early stages of BD may be an important aspect in monitoring the progression of the disease.

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