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Optical coherence tomography findings due to structural changes of the choroid and retina in Behçet's uveitis

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ABSTRACT

Aims: To evaluate the change in central macular and retinal nerve fiber layer (RNFL) thickness by using optical coherence tomography (OCT) and choroidal thickness by using enhanced depth imaging optical coherence tomography (EDI-OCT) in posterior uveitis of Behcet's disease, to compare these results with the healthy population and to investigate the relationship between these parameters and Behcet's disease duration, the number of ocular attacks and visual acuity.

Methods: Sixteen patients with the active phase and 33 patients with the inactive phase of Behcet's disease, were followed up at Uvea Clinic in Ulucanlar Eye Training and Research Hospital, and 35 healthy cases were enrolled in this prospective study. All the individuals underwent visual acuity testing, intraocular pressure measurement, biomicroscopy, and fundus examinations. By using OCT and EDI-OCT central macular, RNFL thicknesses and subfoveal, at nasal 500 µm, nasal 1000 µm, temporal 500 µm, and temporal 1000 µm choroidal thicknesses were measured in all cases. The results of Behcet's patients and healthy subjects were compared and the relationship between these parameters and Behcet's disease duration, the number of ocular attacks, and visual acuity were assessed.

Results: Five patients (31.3%) were female, 11 (68.8%) were male in the active group and 8 patients (24.2%) were female and 25 (75.8%) were male in the inactive group. In active patients central macular and RNFL thicknesses were significantly thicker than inactive patients and the control group (p=0.000). In inactive patients with Behcet's disease duration and the number of ocular attacks RNFL thickness was getting thinner than in active patients (p=0.023, p=0.007). In active, inactive patients and healthy subjects subfoveal choroidal thicknesses were 449.31±111.36, 318.21±94.81 and 364.34±82.88 µm respectively; at nasal 500 µm choroidal thicknesses were 437.44±105.51, 308.33±95.36 and 355.97±83.81 µm respectively; at nasal 1000 µm choroidal thickness were 418.25±112.71, 286.33±96.06 and 337.26±87.11 µm respectively; at temporal 500 µm choroidal thickness were 429.44±102.98, 305.67±88.56 and 360.51±83.78 µm respectively; at temporal 1000 µm, choroidal thickness were 407.44±102.64, 299.73±76.30 and 360.71±86.67 µm respectively. In active patients subfoveal, at nasal 500 and 1000 µm choroidal thickness was significantly thicker than inactive patients and control group (p<0.01), in inactive patients at temporal 500 and 1000 µm choroidal thickness were significantly thinner than control subjects (p<0.05).

Conclusion: By using OCT and EDI-OCT, in patients with active phase of Behcet's disease central macular, RNFL, and choroidal thicknesses were found significantly thicker than inactive and control subjects. In inactive patients, choroidal thicknesses were significantly thinner than in healthy cases. In this study, the results showed that OCT and EDI-OCT findings were found to be beneficial in ocular Behcet's disease diagnosis and follow-up period.

Keywords: Behcet's disease, choroid thickness, EDI-OCT, macular thickness, RNFL

INTRODUCTION

Behçet's disease (BD) is a relapsing multisystemic vasculitic disorder characterized by recurrent and episodic uveitis, oral ulcers, genital ulcerations, and skin lesions. The disease is characterized by an immune-mediated occlusive vascular involvement.[1] Its ocular involvement occurs in approximately 70% to 75% of patients with BD. The most common ocular findings with BD include recurrent iridocyclitis, vitritis, retinitis, retinal vasculitis, and retinal vascular occlusion.[2-4] Posterior segment involvement determines the prognosis of ocular BD. This unique form of ocular BD is seen in up to 82.9% of patients with eye involvement.[4] Choroidal involvement in Behcet's uveitis has been shown in indocyanine green angiography and also has been previously implicated in histopathologic studies, which reported a diffuse and focal infiltration of the choroid with inflammatory cells.[5-8]

Optical coherence tomography (OCT) is a non-contact noninvasive technique that allows invivo imaging of the retina, choroid, optic nerve head, retinal nerve fiber layer, and the anterior structures of the eye. It is the standard diagnostic technique in the detection, monitoring of treatment, and determination of prognosis in uveitic macular edema as well as other inflammatory macular pathologies, including epiretinal membrane formation, vitreomacular traction, foveal atrophy, and lamellar/full-thickness macular holes. With the introduction of

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enhanced depth imaging (EDI-OCT), visualization of the choroid and choriocapillaris has become possible.[9]

In this prospective study, by using OCT we evaluated the changes in central macular thickness, retinal nerve fiber layer thickness (RNFL), and choroidal thickness of patients with posterior uveitis of BD and compared the results with the sex-matched, age-matched healthy population. Furthermore, we assessed the correlation between these parameters and Behçet's disease duration, the frequency of the relapses of uveitis, and visual acuity.

METHODS

The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (Date: 21.04.2014, Decision No: 15/12). All of the study procedures were conducted following the Declaration of Helsinki and informed consent was taken from all of the participants after approval from the Institutional Review Board.

We prospectively evaluated 16 patients with active periods and 33 patients with an inactive period of posterior uveitis of BD and 35 healthy individuals between April 2013 and August 2014. In this study, the diagnosis of BD was reached according to the criteria of the International Study Group for BD.[10]

On clinical examination, BD patients who had cells in the vitreous, periarteritis, periphlebitis, edema of the disc, edema of the macula, edema of the retina, papillitis, and active peripheral lesions were encountered in the active period, and the patients without those findings but with residual damage at least within the last 3 months were encountered in the inactive period of BD. Patients were separated into three groups based on the findings of the clinical ocular examination. The first group included 16 ocular BD patients with posterior segment involvement in the active period; the second group included 33 patients with posterior segment involvement in ocular BD in the inactive period; the third group included 35 healthy adult subjects.

Exclusion criteria of the study were: eyes with spherical equivalent refractive error of more than ±3.0 diopters, visually significant cataract, media opacity or anterior uveitis obscuring the precise visualization of choroidal layers, end-stage uveitis which is characterized by optic atrophy, vascular occlusion, and gliotic sheathing, eyes with diabetic retinopathy, glaucoma or another concurrent ocular disease, or history of posterior segment surgery. To eliminate the potential influence of previous treatment with intravitreal injections with triamcinolone or antivascular endothelial growth factor agents on the measurement of choroidal thickness, eyes that had received intravitreal injections within the past year were excluded.

For the control group, age-matched, sex-matched, spherical equivalent–matched healthy individuals were enrolled in the study. Eyes with no ocular disease and intraocular surgery, no medication, and no systemic disease, such as diabetes and hypertension, were recruited as control subjects. Subjects were required to have a best-corrected visual acuity of 20/25 or better and a spherical equivalent refractive error of fewer than ±2.0 diopters.

Demographic features and clinical information included duration of Behcet's uveitis, number of uveitic attacks through the last 2 years, and medications of the individuals were recorded. In addition, all the individuals underwent refraction, intraocular pressure, axial length measurement, best spectacle-corrected visual acuity (BSCVA), slit-lamp biomicroscopy, and fundus examinations. All patients were examined by the same uveitis specialist (NB). BSCVA was measured according to the decimal Snellen scale and converted to the logarithm of the minimal angle of resolution (logMAR) scale for statistical analysis. All patients underwent spectral domain OCT (SD-OCT) examination (Spectralis OCT, Heidelberg Engineering, Germany). By using SD-OCT central macular thickness and RNFL thickness were measured and recorded. SD-OCT was placed close enough to the eye and the EDI option allowed the chorioretinal interface to be placed adjacent to the zero delays, and an upright image of the retina and choroid was obtained. Choroidal thickness was defined as the distance from the outer border of the hyperreflective line corresponding to the RPE perpendicular to the chorioscleral interface. Using digital calipers provided by the Heidelberg Spectralis OCT software, choroidal thickness was measured at the subfoveal region, at 500 μm, 1000 μm nasal to the fovea and 500 μ, 1000 μm temporal to the fovea. A magnification of at least 100% to 200% was used to place the measurement line precisely at the outermost RPE layer and the chorioscleral interface. Both eyes of individuals underwent examinations, but in bilateral involvement of ocular BD, one eye was randomly selected, and in unilateral involvement of ocular BD affected eye was selected for analyses of the study. In the control group, the left eyes of healthy subjects were selected for the study.

Statistically Analysis

SPSS software version 16.0 (SPSS for Windows software; SPSS, Inc., Chicago, IL) was used for statistical analysis. Data were recorded as the mean±standard deviation (SD). Categorical variables were compared with the chi-square test and Fisher's Exact Test. Differences among groups were tested for significance by using the one-way ANOVA. Tukey's multiple comparison post

hoc test was used to compare pairs of groups when a significant difference occurred. Mann-Whitney U test and Kruskal Wallis test were used to compare the eyes with the active, and inactive periods of BD and healthy subjects. Pearson's and Spearman correlation coefficient was used to evaluate the correlation between the study parameters. For all comparisons, p<0.05 was considered statistically significant.

RESULTS

The active ocular BD group consisted of 16 patients (16 eyes),of which 11 were male (68.8%) and 5 were female (31.3%) with a mean age of 29.6±9.1 (range,18-50 years). The inactive ocular BD group consisted of 33 patients (33 eyes), of which 25 were male (75.8%) and 8 were female (24.2%) with a mean age of 41.3±11.3 (range, 20-59 years). The control group consisted of 35 healthy subjects (35 eyes), of which 24 were male (68.6%) and 11 were female (31.4%) with a mean age of 35.5±5.7 (range, 24-49 years). The mean age of the inactive ocular BD group was significantly higher than the active ocular BD group and the control group (p=0.026 and p<0.001 respectively). There was no difference regarding the gender of the three studied groups (p>0.50). The mean duration of ocular BD, defined as the time passed from the diagnosis of ocular BD to the initiation of the study, was 4.56 (±4.5) years in the active ocular BD group and 11.58 (±7.9) years in the inactive ocular BD group. The mean frequency of uveitic attacks through the last 2 years in the active and the inactive ocular BD group were 1.75 and 1.45 respectively. The mean visual acuity of the active ocular BD group was 0.49 (±0.43) logMAR, inactive ocular BD group was 0.19 (±0.30) logMAR and both of them were significantly lower than the mean visual acuity of the control group (p=0.001). There was no significant difference in the axial lengths of the three study groups (p=0.771). In the active ocular BD group, vitritis was found in 8 patients (50%), vasculitis was found in 4 patients (25%), macular edema was found in 2 patients (12.5%) and retinitis was found in 2 patients (12.5%).

Table 1. Demographic findings of active and inactive Behçet disease groups and control group

	Active BD group n=16	Inactive BD group n=33	Control group n=35	p value
Age				<0.001*
Mean	29.63±9.13	41.33±11.35	35.57±5.73	
St. Deviation	18-50	20-59	24-49	
Gender				0.779
Female	5 (31.3%)	8 (24.2%)	11 (31.4%)	
Male	11 (68.8%)	25 (75.8%)	24 (68.6%)	

The mean of central macular thickness in the active, inactive ocular BD group and control group were 335.75±96.79, 269.39±23.08 and 270.74±19.42 μm respectively and RNFL thickness in the active, inactive ocular BD group and control group were 136.44±41.90, 102.03±15.85 and 104.11±7.71 μm respectively. In the active ocular BD group central macular and RNFL thicknesses were significantly thicker than the other two groups (p<0.001). In the active, inactive ocular BD group and control group subfoveal choroidal thicknesses were 449.31±111.36, 318.21±94.81 and 364.34±82.88 μm respectively; at nasal 500 μm choroidal thicknesses were 437.44±105.51, 308.33±95.36 and 355.97±83.81 μm respectively; at nasal 1000 μm choroidal thickness were 418.25±112.71, 286.33±96.06 and 337.26±87.11 μm respectively; at temporal 500 μm choroidal thickness were 429.44±102.98, 305.67±88.56 and 360.51±83.78 μm respectively; at temporal 1000 μm, choroidal thickness were 407.44±102.64, 299.73±76.30 and 360.71±86.67 μm respectively. The mean of subfoveal, at nasal 500 and 1000 μm choroidal thickness of active ocular BD group was significantly thicker than inactive patients and control group (p<0.01), the mean of at temporal 500 and 1000 μm choroidal thickness of inactive ocular BD group were significantly thinner than the control group (p<0.05).

There is no correlation in central macular thickness and choroidal thickness with visual acuity, Behçet's Disease duration, number of attacks (p>0.05).

Table 2. Oct findings, visual acuity and axial lengths of active, inactive Behçet Disease groups and control group. RNFLT (retinal nevre fiber layer thickness)

	Active BD group n: 16	Inactive BD group n: 33	Control group n: 35	p value
Visual Acuity	0.44±0.39	0.73±0.31	0	<0.001*
Axial Length (mm)	23.60±0.78	23.64±0.71	23.50±0.92	0.771
Central macular thickness (μm)	335.75±96.79	269.39±23.08	270.74±19.42	<0.001*
RNFLT (μm)	136.44±41.90	102.03±15.85	104.11±7.71	<0.001*
Subfoveal choroidal thickness (μm)	449.31±111.36	318.21±94.81	364.34±82.88	<0.001*
Choroidal thickness at nasal 500 μm (μm)	437.44±105.51	308.33±95.36	355.97±83.81	<0.001*
Choroidal thickness at nasal 1000 μm (μm)	418.25±112.71	286.33±96.06	337.26±87.11	<0.001*
Choroidal thickness at temporal 500 μm (μm)	429.44±102.98	305.67±88.56	360.51±83.78	<0.001*
Choroidal thickness at temporal 1000 μm (μm)	407.44±102.64	299.73±76.30	360.71±86.67	<0.001*

DISCUSSION

OCT has become an indispensable ancillary test in the diagnosis and management of inflammatory diseases. The macular thickness analysis function helps diagnose complications of posterior uveitis such as macular edema or macular atrophy.RNFL analysis is used to evaluate early-stage damage related to retinal nerve fiber loss and optic disc damage by providing quantitative measurements of RNFL in different quadrants. EDI-OCT, on the other hand, evaluates the microarchitecture of the posterior choroid and facilitates the understanding of choroidal abnormalities underlying various chorioretinal diseases.[9,11-15]

In the present study, we found that central macular thickness in the active ocular BD group was significantly thicker than inactive ocular BD and control groups. But there was no significant difference between the inactive ocular BD group and the control group. In ocular BD macular edema which is the most common complication reported in 11 to 62 % of patients can be the result of an inflammatory process or the consequence of branch retinal vein occlusion.[2,4,16,17.] The rate of macular edema in the active ocular BD group was 12.5% in our study. Takeuchi and his colleagues found in inactive ocular BD retinal thickness was remarkably reduced: the thickness at the fovea was almost 130–140 μm and that at the inner and outer macula was 200–220 μm.[19] Consistent with the literature, we found that macular thickness was reduced in the inactive BD group as compared to the active ocular BD group. The main pathology in BD is occlusive vasculitis. As a result of recurrent vasculitis, ischemia followed by atrophies occurs in areas fed by the occluded vessels. Also in BD, it has been found that ocular blood flow decreases. By the effect of these factors, it was thought that the retina and its layers are becoming thinner.[20]

Tekeli and Ozdemir[20] evaluated optic disc topography using Heidelberg Retinal Tomography in BD patients with and without ocular involvement and in healthy controls and revealed that the average disk area, cup area, cup volume, and cup depth in BD patients with and without ocular involvement were significantly smaller than the control group. Unlikely, in the present study, according to the patients with macular edema in the active ocular BD group, we found that RNFL thickness was significantly thicker in the active ocular BD group compared with the inactive ocular BD group and control group ($p<0.001$). In the inactive ocular BD group with increasing Behcet's disease duration time and the number of ocular attacks RNFL was getting thinner ($p=0.023$, $p=0.007$) and we thought this negative correlation was an effect of recurrent vasculitis resulted in atrophies of retinal layers. Berker and his colleagues analyzed optic disc topography in BD patients with mild and severe uveitis. They found that the mean cup volume, rim volume, cup area, and cup depth were significantly smaller in BD patients with severe uveitis compared with BD patients with mild uveitis.[21] Ataş and his colleagues found that there was no statistically significant difference in RNFL thickness between patients with BD and the control subjects. However, BD patients with ocular involvement had statistically significant thinning in superonasal, nasal, and inferotemporal quadrants and average values compared with BD patients without ocular involvement.[22]

In our study, we found that choroidal thickness at subfoveal, nasal 500, and 1000 μm in the active ocular BD group were thicker than inactive ocular BD and control groups. We also found that in the inactive ocular BD group choroidal thickness at temporal 500 and 1000 μm were significantly thinner than active ocular BD and control groups. Kim et al.[23] found an increase in subfoveal choroidal thickness in both active and inactive phases of BD patients with posterior uveitis. They also showed that there was a correlation between the thickening in the choroid and retinal vascular leakage revealed by fluorescein angiography (FA). Ataş et al.[22] researched the subfoveal choroidal thickness in patients with and without ocular involvement and compared it with the control group. They found the subfoveal choroidal thickness respectively, 325.13±64.63, 325.41±60.24 and 336.50±10.08 μm in Behçet's patients with and without ocular involvement and control group. They found that subfoveal choroidal thickness in patients with ocular involvement of BD was thicker than in the control group and BD patients without ocular involvement, but the differences were not significant. Coşkun et al.[24] found the subfoveal choroidal thickness in Behçet's patients with active posterior uveitis and remission phase respectively 291±64 μm and 284±103 μm, but there was no significant difference between the two groups. In the same study BD patients without ocular involvement and control group were 289±74, 337±88 and 329±64 μm respectively, the subfoveal choroidal thickness was significantly thinner in patients with ocular involvement than without ocular involvement in Behçet's patients and the control group ($p=0.026$). Ishikawa et al.[25] researched the difference in subfoveal choroidal thickness in 5 active phases of BD patients with infliximab treatment and found that subfoveal choroidal thickness was significantly thicker in the active phase than in the remission phase of BD patients. In the same study, it was found that there was a correlation between subfoveal choroidal thickness and the scores of inflammation in the anterior chamber and posterior segment but there was no correlation between subfoveal choroidal thickness and visual acuity.

The subfoveal choroidal thickness in an inactive period of Behçet's patients is found both thicker and thinner in recent studies. The cause of getting thinner in subfoveal choroidal tissue in the inactive period was related to choroidal atrophy and fibrosis secondary to impaired choroidal circulation which was affected by recurrent uveitis attacks.[23,24] The studies with indocyanine green angiography (ICG) in Behçet's patients showed choroidal involvement with hyperfluorescent and hypofluoroscent choroidal lesions, vascular leakage, and irregular filling defects.[7,26] By ICG the choroidal circulation can be detected but the architecture of choroid and choroidal quantitive data cannot be determined. With the technology of EDI-OCT, those problems have been overcome. In this study, we showed that the choroidal thickness has been changing in Behçet's patients. In inactive Behçet's patients, the choroidal thickness was found thinner and it was thought to be secondary to choroidal atrophy and fibrosis as a result of capillary hypoperfusion and ischemia, on the other hand in active Behçet's patients it was found thicker as supporting to choroidal inflammation.

The studies which found the choroidal thickness got thicker in inactive patients claimed that it was caused by subclinical involvement. In these studies researchers also claimed that the choroidal thickness was related to the inflammation of the choroid, even clinically they were inactive period they would come out with obvious involvement in the future and before obvious involvement, it could be easily treated.[22,23] But the limitations of those studies were not applying ICG and not evaluating the correlation between ICG findings and OCT data. Also, to prove all of these claims the inactive Behçet's patients with thicker choroidal thickness were need to be followed whether they would show obvious involvement and compare the progression data.

In our study limitations were a minority of several patients in the active BD group and not evaluating data with FFA and ICG.

CONCLUSION

In this study, we evaluated the demographic data of Behçet's patients, the changes in retinal and choroidal thickness, and the relationship between visual acuity and BD duration with these changes. We found significant changes in retinal and choroidal thickness of the active and inactive periods of BD. Retinal involvement in BD was always taken into account and analyzed but choroidal alterations were neglected because of choroidal imaging limitations and achieving quantitive data. With clinical studies with a large number of BD patients and comparing the data of imaging techniques such as OCT and EDI-OCT with BD progression and the response of treatment, we thought OCT and EDI-OCT would be a precious examination in diagnosis and follow-up of BD attacks.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (Date: 21.04.2014, Decision No: 15/12).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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