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Original research

Choroidal thickness in non-ocular Behçet's disease – A spectral-domain OCT study

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Abstract

Purpose: To evaluate choroidal thickness in patients with non-ocular Behçet's disease (BD) using spectral domain optical coherence tomography (SD-OCT) and to compare the results to normal eyes.

Methods: In this retrospective observational comparative study, we collected OCT and clinical data from the charts of 4 patients (7 eyes) with BD who had been referred for a screening eye exam and had a normal ocular examination. Data from 9 healthy volunteers (17 eyes) were collected as age-matched controls. The choroid was manually segmented from volume OCT scans using custom Doheny Image Reading Center OCT grading software (3D-OCTOR). Main outcome measures were choroidal thickness and intensity were compared between eyes of patients with BD and those of healthy controls.

Results: Eyes of patients with non-ocular BD had significantly thinner mean central subfield choroidal thickness (227.5 ± 56.93 versus 306.85 ± 17.85, $P = 0.04$) and central subfield choroidal volume (0.18 ± 0.04 vs 0.24 ± 0.02, $P = 0.005$). There was no significant difference in mean choroidal thickness in the whole ETDRS grid or in mean choroidal intensity in the central subfield and the whole ETDRS grid between eyes of patients with non-ocular BD and those of controls.

Conclusion: This study demonstrates that BD may have subclinical manifestations in the choroid, resulting in thinning of the choroid relative to normal eyes, even without overt signs of ocular involvement.

Keywords: Choroidal thickness; Behçet's disease; Spectral domain optical coherence tomography; Choroidal intensity; Choroidal reflectivity

Introduction

Behçet's disease (BD) is a chronic, systemic, autoimmune inflammatory vasculitis affecting multiple organs; the most common sites of involvement are ocular, oral, genital, and central nervous system.[1] Ocular involvement is found in 70–90% of patients with BD and usually presents with recurrent attacks of bilateral panuveitis.[2] Both the anterior and posterior segments of the eye can be involved, frequently resulting in iridocyclitis with hypopyon and retinal vasculitis.[3] Uveitis associated with BD has also been found to affect the choroid in histopathological studies, with diffuse infiltration of

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inflammatory cells into the choroid.[4] Recurrent inflammation of the posterior segment results in decreased visual acuity that does not generally improve when the inflammation resolves.[5] Ocular involvement and the ensuing loss of visual acuity can be the most troubling symptom perceived by patients with BD.

Fluorescein angiography (FA) and indocyanine green angiography (ICGA) are traditional methods used to evaluate the fundus abnormalities in BD.[6] Spectral-domain optical coherence tomography (SD-OCT) is a newer imaging modality that allows accurate visualization and quantitative measurement of the retina and choroid.[7–11]

Several studies have shown FA, ICGA and SD-OCT changes in patients with active or treated BD.[8,12–18] Although the primary site of ocular involvement is the retina, a few studies have reported choroidal abnormalities as well.[12–15] In addition, abnormal FA findings have been reported in patients with non-ocular BD.[19] The aim of the current study was to evaluate choroidal changes in patients who have clinically diagnosed BD without clinical ocular involvement.

Methods

For this retrospective comparative case series, we reviewed the charts of all patients with a confirmed diagnosis of BD who visited in the Doheny Eye Clinic from June 2009 to June 2012 and for this study, selected those individuals who had a normal ocular examination by slit-lamp biomicroscopy and ophthalmoscopy. Since all our study subjects were clinically normal on exam, angiography was not performed. The diagnosis of Behçet's was made using the Behçet's Syndrome International Study Group (ISG) criteria, and all cases were deemed by the uveitis specialist to have definite Behçet's. An age-matched group of healthy individuals with normal ocular examinations served as controls. The Medical Institutional Review Board of the University of California Los Angeles approved the study. All procedures conformed to the tenets of the Declaration of Helsinki and complied with the requirements of the Health Insurance Portability and Accountability Act.

SD-OCT acquisition, development of choroidal thickness maps, and analysis

All SD-OCT images were obtained with a scan field of 20° horizontally and 20° vertically and 37 horizontal sections using a Spectralis HRA + OCT instrument (Heidelberg Engineering, Heidelberg, Germany). SD-OCT raw data were imported into and segmented using the Doheny Image Reading Center OCT grading software (3D-OCTOR).[20] The inner and outer boundaries of the choroid were manually delineated for all 37 B scans by a certified reading center grader (MGN). The inner boundary was defined as the outer portion of the retinal pigment epithelium-Bruch's membrane complex; the outer boundary was defined as the innermost portion of hyper reflective sclera, as previously described elsewhere.[11] The 3D-OCTOR program automatically generated the thickness, volume and intensity of the delineated area in the whole image area and in each 9 ETDRS field centered on the fovea. Scans with image quality insufficient to reliably delineate the choroidal borders were excluded.

The central retinal subfield thickness automatically generated by the software was recorded. Also, the choroidal thickness, volume, and intensity measurements for the central subfield and all fields of the ETDRS grid were recorded. Data were entered using SPSS software (version 16, SPSS Inc., Chicago, Illinois). Mann-Whitney Test was used for analysis. A P-value of <0.05 was considered statistically significant. Inter eye correlation between choroidal thickness was adjusted using a generalized estimating equation.

Results

Seven eyes of 4 patients with non-ocular BD (3 females, 1 male; mean age, 47 ± 6.4 years) were evaluated. One eye from the case cohort was excluded from the analysis due to poor visibility of the choroid outer border. The control group consisted of 17 eyes of 9 healthy subjects (5 females, 4 males; mean age, 41.7 ± 3.8 years). There was no statistically significant difference in age and sex between the two groups ($P = 0.1$ and $P = 1$, respectively).

Table 1 shows the retinal and choroidal measurements from the two groups. Mean choroidal volume (whole grid), central subfield choroidal thickness and volume and central subfield retinal thickness were significantly less in the case group ($P = 0.02$, $P = 0.04$, $P = 0.005$ and $P = 0.004$, respectively). Choroidal thickness in the whole grid and choroidal intensities in central subfield and whole grid were not significantly different between the two groups.

Table 1
Retinal and choroidal thickness measurements non-ocular Behçet's disease (BD) eyes (baseline) and normal control eyes.

		Non-ocular Behçet's disease (BD) (mean ± SD) (range)	Normal controls (mean ± SD) (range)	P value
In the whole grid area	Choroidal thickness (μm)	221.5 ± 50.3 (172–294)	286.5 ± 18.06 (263–314)	0.05
	Choroidal volume (mm^3)	6.2 ± 1.4 (4.9–8.1)	8.07 ± 0.56 (7.38–8.92)	**0.02**
	Choroidal intensity (log units)	0.35 ± 0.12 (0.16–0.49)	0.34 ± 0.06 (0.28–0.46)	0.9
In the central subfield area	Choroidal thickness (μm)	227.5 ± 56.93 (175.8–301.7)	306.85 ± 17.85 (295–348)	**0.04**
	Choroidal volume (mm^3)	0.18 ± 0.04 (0.14–0.23)	0.24 ± 0.02 (0.23–0.28)	**0.005**
	Choroidal intensity (log units)	0.31 ± 0.13 (0.13–0.47)	0.32 ± 0.07 (0.25–0.46)	0.8
	Retinal thickness (μm)	228.2 ± 12.3 (211–243)	249.3 ± 11.7 (229–264)	**0.004**

SD: Standard deviation; P – Significance levels; Statistically significant values highlighted.

Discussion

In this study, choroidal thickness and volume were significantly lower in eyes of patients with non-ocular BD compared to those of normal controls. In addition, retinal thickness was significantly lower in the eyes of those with non-ocular BD. To our knowledge, this is the first study to examine in vivo changes of the choroidal thickness and intensity as measured by SD-OCT in patients with BD before identification of ocular manifestations of the disease.

Prior histologic and imaging studies using FA, ICGA, and OCT have demonstrated increased thickness and volume of the choroid in patients with BD, but these findings were obtained during periods of inflammation affecting the retinal vasculature and choroid or subsequent to previous inflammation.[10–18] Although the pathophysiology of BD is unknown, studies have shown increased diffuse and focal infiltration of proinflammatory cells such as CD4+ T cells and macrophages in the choroid, as well as antibody and complement deposition.[3] These changes are believed to result in increased permeability of the choroidal vessels, leading to increased leakage that would be apparent on ICGA imaging.[15] We hypothesize that the thinning of the choroid identified here may be related to a number of factors. Subclinical involvement of the choroid over time may lead to the aforementioned changes in the choroid and subsequent thinning. BD is a systemic inflammatory condition, and it is unknown what precipitates acute manifestation of the disease. Therefore, it is reasonable to assume the components of the immune system involved may be ever-present in an altered state, allowing for both relapses of the disease and this subclinical manifestation of choroidal thinning, even without apparent ocular involvement. Interestingly, in subjects with BD, center subfield retinal thickness was also significantly thinned when compared to normal cohort; this may be due to subclinical apoptosis of outer retinal layers. Further longitudinal studies are needed to evaluate this.

In previous studies, we have validated choroidal intensity as another tool to track the progress of disease. Choroidal intensity (or reflectivity) refers to the brightness of the reflected light from the choroidal layer and may provide additional information regarding the effects of retinal disease, which may not be conveyed by layer thickness alone.[21] For example infiltration of the choroidal stroma or a reduction in choroidal vascularity may increase overall reflectivity. SD-OCT allows direct visualization of retinal morphology and architecture. It is an optical signal acquisition and processing method that captures the reflected signal from the optical scattering media (i.e., the retinal and choroidal tissues), and thus can be used for the quantitative analysis of the tissue optical properties. Because of the interferometric technique, the SD-OCT image is essentially the intensity profiles of the reflected light of retinal layers.[21,22] The various layers of the retina may exhibit different optical properties affected differentially by various diseases. Quantification of the optical properties of these layers may facilitate the understanding of retinal disease. The importance of tissue intensity has been reported in neovascular age-related macular degeneration[23] but has not been well studied in BD. As BD is an inflammatory disease, one might expect that significant infiltration of inflammatory cells, if present, could alter the brightness of the choroid. Choroidal intensity has been shown to follow disease progress, choroidal thickness, and choroidal volume in both Vogt-Koyanagi-Harada disease[24] and age-related macular degeneration.[23] In this study, no significant difference in choroidal intensity was noted; however, given the small sample size, our study was likely under-powered to identify small differences in intensity. Given a larger number of patients or a greater number of longitudinal visits, intensity may be further validated in BD as another tool to non-invasively and quantitatively assess choroidal health.

This study has several significant limitations. The most important is small sample size, with only 4 unique patients and 7 eyes which satisfied the inclusion criteria. In addition, the laborious and time-intensive nature of manually segmenting the data contributed to the limited nature of the study. The data was collected retrospectively, allowing for possible ascertainment bias. Lack of information in regards to systemic medication, hence we didn't study the influence of these medications on study parameters. Although the same OCT acquisition protocol was followed for each patient, it was performed by different operators, resulting in another possible source of variability. Finally, while standard SD-OCT is powerful and superior to ordinary OCT for examining deep structures of the eye, it is inferior to enhanced depth imaging OCT or swept source OCT for evaluating the choroid. Although we were able to measure the full extent of the choroid in this particular small study, the reflectivity analysis may have been affected by the sensitive loss with depth inherent to SD-OCT. Future studies may correlate choroidal thickness with dynamic angiography. These additional studies may be able to follow the same cohort as its members develop ocular manifestations of the disease, identifying the subclinical to clinical transition on OCT and its effect on the choroid.

In conclusion, our results demonstrate that choroidal changes on SD-OCT may exist in patients with BD without clinical ocular involvement. Further studies with a larger sample size and longitudinal data are needed to confirm our findings.

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