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ORIGINAL PAPER

Quantitative analysis of retinal microcirculation in optical coherence tomography angiography in cases with Behçet's disease without ocular involvement

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Abstract
Purpose To evaluate the retinal vascular plexus and choriocapillaris structures in patients with non-ocular Behçet's disease (BD) using optical coherence tomography angiography (OCTA).
Methods The study included 42 eyes of non-ocular BD patients (study group) and 40 eyes of 20 healthy subjects (control group). Flow area (mm^2), mean vascular density (VD) (%) and foveal avascular zone (FAZ) (mm^2) were measured using OCTA (Optovue Inc., Fremont, CA, USA). Subfoveal choroidal thickness (CT) (μm) and central macular thickness (CMT) (μm) measurements were also performed.
Results The mean superficial capillary plexus, deep capillary plexus and choriocapillaris flow area values were found to be significantly lower in the study group than in the control group ($p < 0.001$, $p < 0.001$, $p = 0.008$, respectively). In respect of mean VD, a statistically significant difference was determined between the study and control groups in both superficial and deep VD ($p < 0.001$). No statistically significant difference was found out between the groups in respect of superficial FAZ, deep FAZ and CMT ($p = 0.165$, $p = 0.477$, $p = 0.457$, respectively). The subfoveal CT was also measured to be significantly thicker in the study group than in the control group ($p < 0.001$).
Conclusion The results obtained with OCTA revealed that there could be both retinal and choroidal involvement in non-ocular BD patients before the emergence of evident clinical findings.

Keywords Vascular density · Flow area · Non-flow area · Non-ocular Behçet's disease · Optical coherence tomography angiography (OCTA)

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Introduction

Behçet's disease (BD) is a chronic vasculitis, which is seen in the form of attacks, and several areas of the body can be affected including the eyes, skin, mucosa, genital system, joints, gastrointestinal and central nervous system [1]. It was first defined in 1937 by the Turkish dermatologist, Hulusi Behçet, as a multisystem disorder characterised by recurrent oral aphthous ulcers, genital ulcers, thrombophlebitis and hypopyon iridocyclitis [2].

Although seen worldwide, it has been noticed that the prevalence of the disease is currently increasing from the Mediterranean and Central Asia to Japan [3]. There is ocular involvement in approximately half of

all cases. Ocular findings generally emerge in the first 5 years after the onset of the disease, and those cases comprise 70–80% young males and the remainder are females and elderly [4, 5]. Although initially there are usually limited inflammation findings in the anterior segment of the eye, arteries and veins in the posterior segment can also be affected. Typical ocular involvement is panuveitis and retinal vasculitis seen in the form of attacks and remissions [1]. Histopathological examinations and clinical data have shown the basic pathology to be obstructive vasculitis originating from the circulation of abnormal immune complexes [6].

The involvement of the posterior segment, especially the vascular structures, is prominent in Behçet's uveitis, and fluorescein angiography (FA) is the gold standard in the diagnosis of this disease. FA is a useful diagnostic tool in the determination of vascular blockages, peripheral ischaemic areas, neovascularisation and, especially, the inflammatory activity [7]. However, the use of FA may be limited because of the use of intravenous dye due to the fact that it is invasive, and may lead to allergic reactions ranging from nausea to anaphylaxis [8].

OCTA provides non-invasive and rapid evaluation of the retina and choroidal vascular structures. It is based on the principle of decorrelation, in which the signals of red blood cells on B-scan images are seen to fluctuate in each specific area of the retina. OCTA has the advantage of demonstrating the retinal vascular structure layer by layer, thereby facilitating the separate differentiation of the superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris (CC) [9]. A further advantage of OCTA is that allergic reactions do not develop as contrast dye is not used [8].

The diagnostic efficacy of OCTA has been shown in several retinal vascular diseases such as diabetic retinopathy, age-related macular degeneration, retinal artery and vein obstruction, and sickle cell anaemia [10]. Khairallah et al. [11] reported that OCTA was superior to FA in the visualisation and characterisation of perivascular and microvascular changes in eyes with active Behçet's uveitis.

Ocular involvement is one of the most disabling complications of BD. When left untreated, it can cause visual loss progressing to blindness. Therefore, early diagnosis and treatment are important in respect of visual prognosis [1]. Data about the evaluation of non-ocular BD patients with OCTA are limited [12]. Therefore, the aim of the current study was to evaluate the early microvascular changes in the retinal vascular plexus and choriocapillaris in patients with non-ocular BD, using OCTA.

Methods

Study design and participants

The study was approved by the Ethics Committee of Sutcu Imam University, Kahramanmaras, Turkey, and all procedures were applied in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant.

The study included 42 eyes of 21 patients, diagnosed with non-ocular BD according to the Behçet's Syndrome International Study Group Criteria [13], who were followed up in the Ophthalmology Department of Sutcu Imam University Medical Faculty. A control group was formed from 40 eyes of 20 healthy individuals.

The patients included in the study were those with BD and no active or previous uveitis findings and, therefore, accepted as non-ocular BD. Following physical examination, measurements were taken with OCTA from participants with full vision and no pathological findings determined in the examination. Patients were excluded if they had any active or previous findings of uveitis (ciliary injection, anterior chamber inflammatory cells, keratic precipitations, papillitis, inflammatory cells in the vitreous or retinal vasculitis), any additional ocular or systemic disease (glaucoma, diabetic retinopathy, etc.), a history of topical or systemic medication, ocular surgery and treatment for uveitis, or if good-quality images could not be obtained with OCTA.

Study measurements

Each subject underwent a comprehensive ophthalmic assessment including best-corrected visual acuity (BCVA), pupillary reaction, slit-lamp biomicroscopy, air-puff tonometer. After dilatation with 0.5% tropicamide and 2.5% phenylephrine hydrochloride, fundus examination was made and the OCTA images were taken. Both eyes of each participant were used in the study.

Optical coherence tomography angiography techniques

High-quality images of the retinal structure and vessel network were obtained using spectral domain OCTA, RTVue-XR AngioVue (software version: 2015.1.0.90; Optovue Inc., Fremont, CA, USA). The XR Avanti AngioVue spectral domain OCTA (software version 2015.1.1.98, Optovue Inc., Fremont, CA) is a device which obtains volumetric scans of 304 × 304 A-scans at 70,000 A-scans per second, using a light source of 840 nm and an axial resolution of 5 mm. The Optovue AngioVue system technology provides quantitative analysis and numerical data about VD and flow area. The OCTA system, which uses blood flow as intrinsic contrast, is based on the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm. Using 5 repeated B-scans at 216 raster positions, three-dimensional (3D) OCTA scans were obtained over regions 6 × 6 mm in size. Each B-scan was formed of 216 A-scans, with 304 pixels × 304 pixels in the transverse dimension. The B-scan frame rate was 270 frames per second, and thus each scan was obtained in approximately 3.0 s [14].

The OCTA images were obtained using an RTVue-XR Avanti machine (AngioVue; Optovue Inc., Fremont, CA). The integral SSADA algorithm and motion correlation technology of the AngioVue system were both used. Discrimination of the SCP, DCP, outer retina and choroidal capillary layers was provided by the automatic segmentation of the intraretinal layers. The segmentation of the SCP on the OCTA image was applied with the placement of an inner boundary 3 mm below the internal limiting membrane and an outer boundary 16 mm below the inner plexiform layer and the DCP 16 mm to 70 mm below the inner plexiform layer. The outer retina is defined as 70 mm below the inner plexiform layer and 30 mm below the retinal pigment epithelium [15, 16].

All OCTA scans and measurements were performed by 2 experienced operators (A.Ç and A.B) using the RTVue-XR Avanti with AngioVue (Optovue Inc., Fremont, CA, USA). Angiographic analysis was made using a 6 × 6 mm frame which allowed the evaluation of the perifoveal region, the FAZ and the parafoveal region. The evaluation was made according to the integrity of the perifoveal capillary arcade, areas of capillary non-perfusion and changes in perifoveal capillary vessel rarefaction at the level of both plexuses. These terms have been defined and used in previous studies [12].

The flow area was defined as the percentage of the area covered by vessels in a 6 × 6 mm square in the centre of the FAZ. With AngioVue software, the flow area in the related area was automatically calculated in the SCP and DCP (Fig. 1a, b). For measurements of the CC flow area, the analysis was made using Optovue software with flow function of a 6 × 6 mm macular angiogram of the CC layer (Fig. 1c) [15, 16].

VD was calculated as the percentage of the selected region covered by vessels and microvessels. The mean VD was automatically calculated by the software in both the SCP and DCP (Fig. 2a, b). Avascular region (larger than the normal gap between capillaries) is a significant area displaying lack of flow signal on en face angiogram. The FAZ was used as an anatomical landmark to locate the retinal point of fixation and was measured on SCP and DCP (Fig. 1d, e).

Subfoveal CT measurements were taken manually using enhanced HD line scans. The CT measurement was taken using a built-in calliper tool adjusted perpendicularly from the outer edge of the retinal pigment epithelium to the choroid–sclera boundary at the fovea. The average of two measurements was used in the analysis. All measurements of the patients were compared with those of the 40 eyes of the 20 healthy control subjects.

The primary outcome measure of this study was the difference of the OCTA parameters between the two groups.

Statistical analysis

The statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, version 15, for Windows; SPSS Inc.). The conformity of the data to normal distribution was evaluated with the Kolmogorov–Smirnov and Shapiro–Wilk tests. In the group comparisons, the independent Student's *t* test was applied to numerical data that met parametric assumptions and the Mann–Whitney *U* test was applied to numerical data that did not meet parametric assumptions. The categorical variables between the groups were analysed using the Chi-square test. Pearson analysis was applied to determine the relationships between parameters with normal distribution, and the Pearson's correlation coefficient was used for those that did not conform to normal

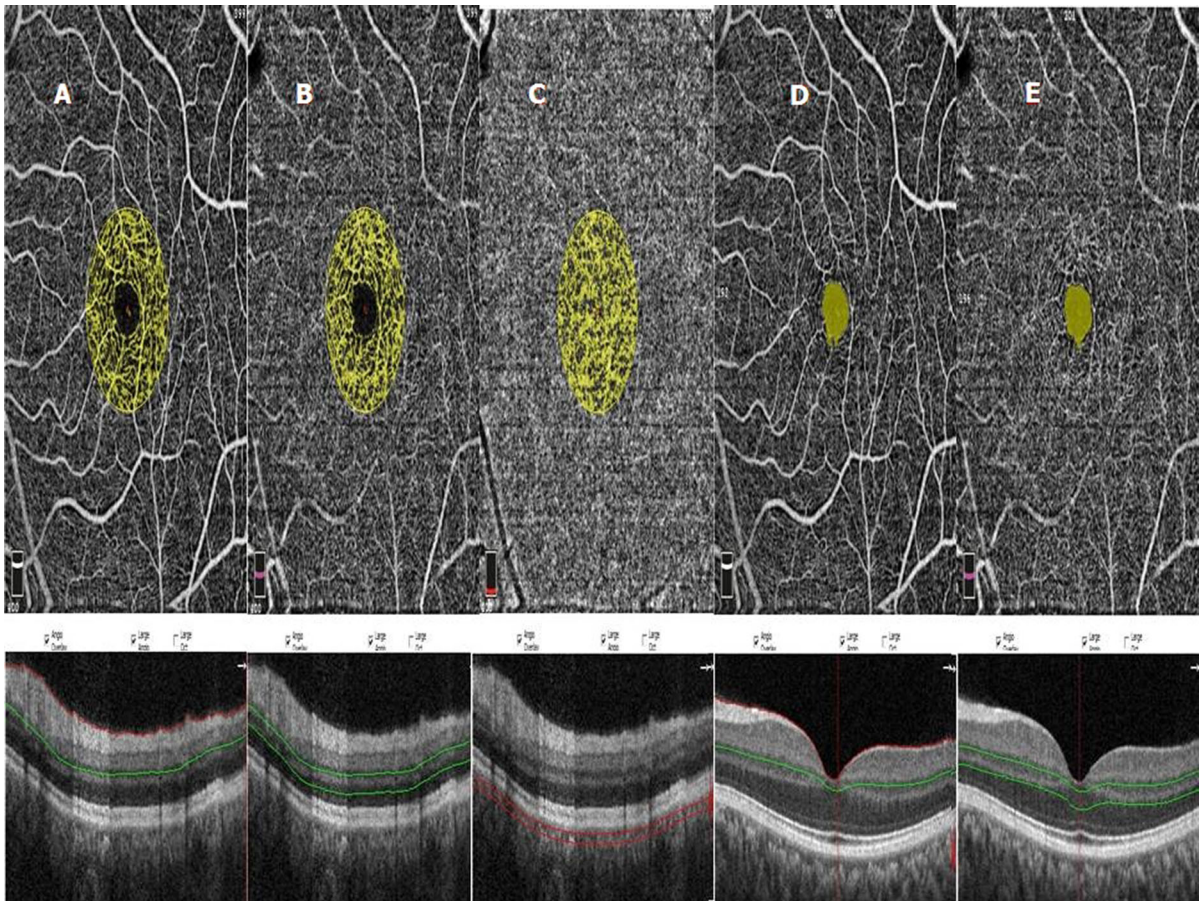

Fig. 1 Macular perfusion parameters of a healthy eye on 6 × 6 mm OCT angiogram. **a** SCP flow area indicated in yellow within a 3 mm diameter. **b** DCP flow area indicated in yellow within a 3 mm diameter. **c** CC flow area indicated in yellow within a 3 mm diameter. **d** Superficial FAZ automatically defined using integral software and indicated in yellow. **e** Deep FAZ automatically defined using integral software and indicated in yellow

distribution. Continuous data were expressed as mean ± standard deviation (SD) and categorical data as number (*n*) and percentage (%). A value of $p < 0.05$ was accepted as statistically significant.

Results

The evaluation was made among 42 eyes of 21 patients with non-ocular BD, comprising 11 (52.4%) males and 10 (47.46%) females with a mean age of 39.81 ± 8.93 years. The control group included 40 eyes of 20 healthy individuals comprising 10 (50%) males and 10 (50%) females with a mean age of 41.21 ± 9.87 years. No statistically significant difference was determined between the groups in respect of age and gender ($p = 0.764$, $p = 0.829$, respectively). The mean duration of the disease in the BD patients was 6.04 ± 5.07 years (range 1–18 years). In both groups, BCVA was 20/20 Snellen equivalent, the anterior chamber was formal, the lens was clear, and fundus examination was normal in all eyes. The mean intraocular pressure (IOP) was 14.75 ± 3.46 mmHg in the non-ocular BD group and 15.19 ± 3.93 mmHg in the control group, with no statistically significant difference determined between the groups ($p = 0.640$).

The retinal and choroidal measurements made with OCTA of the non-ocular BD patients and the control subjects are shown in Table 1. The mean SCP, DCP and CC flow area values were found to be significantly lower in the BD group than in the control group

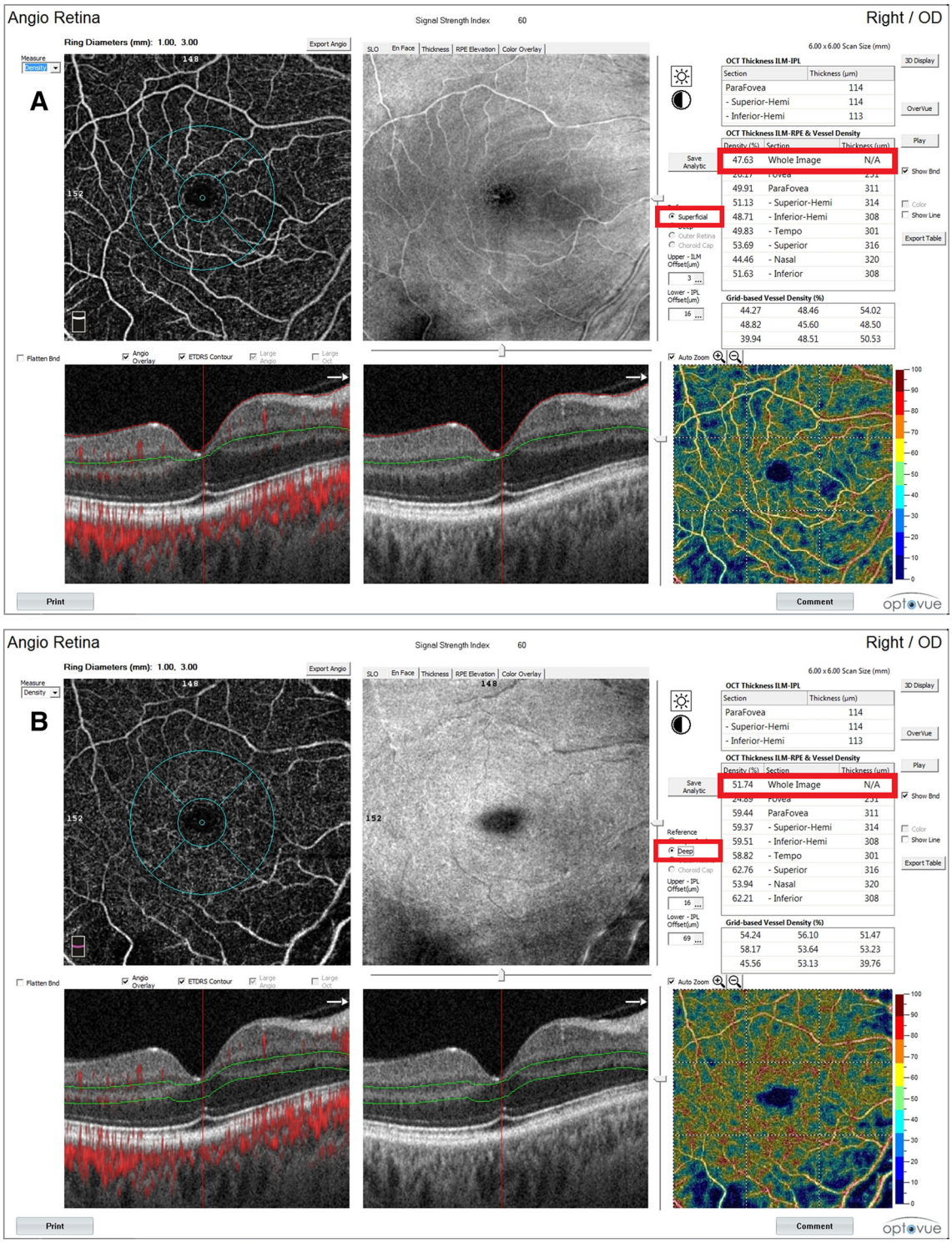

Fig. 2 Images of the vessel intensity in a non-ocular BD case (**a** SCP; **b** DCP). Vessel intensity in the SCP and DCP was calculated automatically. In this case, mean vascular density was 47.63% in the SCP and 51.74% in the DCP

Table 1 Retinal and choroidal measurements of the non-ocular BD patients and the control group using OCTA

	Non-ocular BD (n = 42)	Control group (n = 40)	p value
Superficial retinal flow area (mm^2)	14.00 ± 1.2	15.28 ± 3.9	< 0.001*
Deep retinal flow area (mm^2)	14.74 ± 1.6	16.17 ± 5.5	< 0.001*
CC flow area (mm^2)	19.06 ± 6.5	19.38 ± 4.1	0.008*
Superficial FAZ area (mm^2)	0.31 ± 0.11	0.28 ± 0.05	0.165
Deep FAZ area (mm^2)	0.35 ± 0.12	0.33 ± 0.04	0.477
Superficial VD (%)	50.48 ± 3.24	55.17 ± 2.57	< 0.001*
Deep VD (%)	56.91 ± 4.15	61.59 ± 2.54	< 0.001*
Subfoveal CT (μm)	348.59 ± 38.10	302.97 ± 36.03	< 0.001*
CMT (μm)	182.40 ± 24.84	179.25 ± 11.06	0.457

* means statistically significant

CC choriocapillaris, *FAZ* foveal avascular zone, *VD* vascular density, *CT* choroidal thickness, *CMT* central macular thickness

($p < 0.001$, $p < 0.001$, $p = 0.008$, respectively). The mean VD in the non-ocular BD group was significantly lower than in the control group at both the SCP and DCP levels ($p < 0.01$). No statistically significant difference was observed between the two groups in respect of the superficial and deep FAZ areas ($p = 0.165$, $p = 0.477$). No significant difference was determined between the groups in respect of CMT ($p = 0.457$). The subfoveal CT was determined to be significantly thicker in the non-ocular BD patients ($p < 0.001$).

In the morphological examination of OCTA images, HD quality images were obtained. A clear and organised microvascular network was observed in the control group (Fig. 3a1, a2). In 81% (34/42 eyes) of the non-ocular BD group, the disorganisation of the microvascular network, reduced perifoveal capillary VD and widespread capillary non-perfusion areas were determined in both SCP and DCP (Fig. 3b1, b2).

No significant correlation was observed between the duration of the disease and superficial VD ($r = 0.80$, $p = 0.613$), deep VD ($r = 0.091$, $p = 0.564$), CC flow area ($r = 0.076$, $p = 0.277$) and subfoveal CT ($r = 0.177$, $p = 0.262$).

Discussion

BD is an inflammatory disease that affects retinal vessels [1]. Although the cause of the disease is not fully known, histopathological studies have shown characteristic findings of necrotising and obliterative vasculitis in eyes with BD uveitis [6]. As vascular involvement in the posterior segment is prominent in the disease, FA is the gold standard in diagnosis [7]. However, one of the major advantages of OCTA over FA is that it provides the possibility of separate and more detailed evaluation of the internal and external retinal circulation and the CC. In other words, OCTA provides high-resolution images of the structure and blood flow information of the retina and choroid microvasculature, and it allows quantitative measurement of the capillary perfusion of the macula and optic nerve [17, 18].

In an OCTA study including patients with active BD uveitis, Khairallah et al. [11] exhibited widespread microvascular changes which were more evident in the DCP than in the SCP and the disorganisation of the normal structure of the capillary network and suggested that OCTA was more advantageous than FA in the determination of these microvascular changes. In another study of BD cases with uveitis, it was reported that OCTA was a non-invasive alternative method in the determination of macular ischaemia in particular [19].

Studies investigating the non-ocular BD patients were limited in the literature. Therefore, this study was conducted to comprehensively evaluate the retinal and choroidal changes in this group of patients by using OCTA.

In a study of non-ocular BD cases by Raafat et al. [12], widespread non-flow areas and microvascular changes such as disruption of the perifoveal arcade, vessel rarefaction or perifoveal capillary dilatation with or without telangiectasia were determined with OCTA in both the SCP and the DCP. In the same

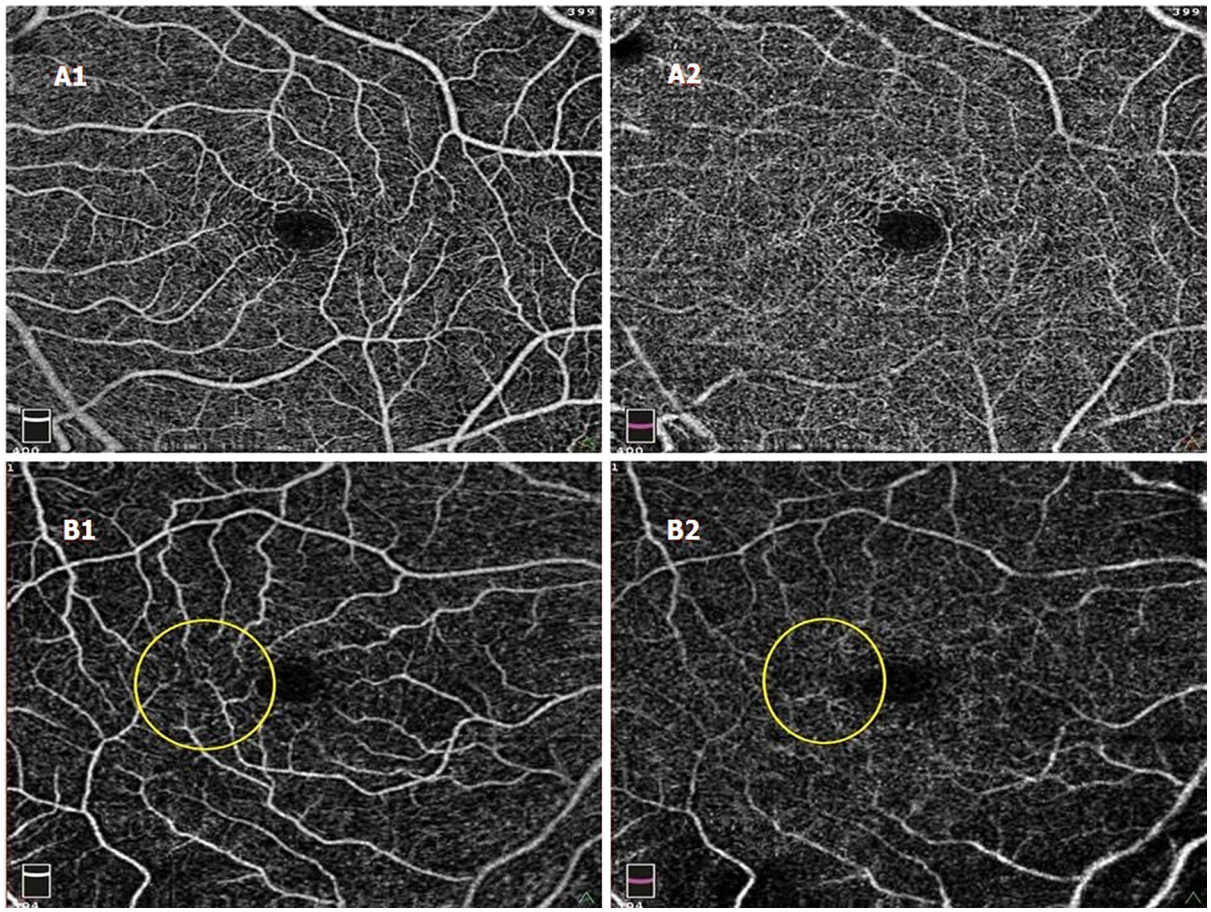

Fig. 3 6 × 6 mm OCT angiogram of a healthy, control eye (**a1** superficial capillary plexus, **a2** deep capillary plexus) and an eye with non-ocular BD (**b1** superficial capillary plexus, **b2** deep capillary plexus). Clear and organised microcapillary network seen in the control eye (**a1**, **a2**). Non-ocular BD eye showing capillary non-perfusion area (within the yellow ring) and capillary network disorganisation and reduced perifoveal capillary vessel intensity in the SCP and DCP (**b1**, **b2**)

study, the mean VD in the SCP was found to be significantly lower in the non-ocular BD patients compared to the control group ($p < 0.001$). There was reported to be no significant difference between the two groups in respect of FAZ area measurements in the SCP ($p = 0.68$). In the current study, widespread non-flow areas and the disruption of the normal structure of the capillary network were seen morphologically in the non-ocular BD group in both the SCP and DCP.

In the current study, the mean VD and superficial FAZ measurement results in the SCP were consistent with the results of Raafat et al. We also determined a reduction in mean VD in the DCP and in CC flow area and an increase in subfoveal CT of the non-ocular BD patients compared to the control group. These OCTA findings in the non-ocular BD group are important in respect of showing that both choroidal and retinal microvascular structures are affected before the emergence of clear clinical signs of BD.

No significant difference was observed between the groups in respect of both the superficial FAZ area and the deep FAZ area. Khairallah et al. [11] reported that the FAZ areas in both SCP and DCP were not found to be wider in the eyes of BD uveitis patients than in the control group ($p = 0.23$). The changes in FAZ size and shape in different diseases have been recently investigated with OCTA. In an OCTA study in which eyes with type 1 diabetes mellitus non-proliferative diabetic retinopathy were compared with a healthy control group, no difference was determined between the groups in respect of the FAZ area in both the SCP

and DCP [20]. In a study by DeCarlo et al. [21], a significant difference was determined in the FAZ area measurements between diabetic patients with no apparent clinical symptoms and a healthy control group. It has been suggested that this inconsistency could be due to the great variations of the FAZ region in healthy individuals. Since no significant difference has been seen in the measurements of the size of the FAZ area between control groups and both ocular and non-ocular BD patients [11, 12], it can be speculated that FAZ area measurements with OCTA may not be a sensitive method to determine early retinal involvement in non-ocular BD cases.

Choroidal involvement in BD uveitis has been previously reported in histopathological studies showing focal and diffuse infiltration of the choroid [22, 23]. Furthermore, several in vivo studies using FA and indocyanine green angiography (ICGA) demonstrated the choroidal involvement in BD uveitis [24, 25]. Kim et al. [26] determined that subfoveal CT was significantly higher in both the active and dormant phases of BD uveitis compared to the control group in a study using enhanced depth imaging optical coherence tomography (OCT). A significant correlation was found between these changes in CT and leakage with the use of FA. It has been stated that the increase in exudate which is accumulated as a result of altered ocular blood flow associated with choroidal vascular inflammation could contribute to choroidal thickening. In the same study, the subfoveal CT in patients with unilateral BD uveitis was not observed to be significantly different compared to the fellow unaffected eye. This showed that even if no inflammation is seen, the choroid of the other eye could be equally affected. In the current study, the subfoveal CT of the BD patients was determined to be significantly higher and choroidal flow was significantly lower compared to the control group. When it is considered that BD is a chronic, systemic, inflammatory disease that affects both arteries and veins, it can be assumed that there could be subclinical choroidal involvement in patients known to have BD with no evident ocular involvement.

In a study by Ataş et al. [27], macular thickness which was measured by using spectral domain OCT was determined to be thinner in the BD group compared to the control group ($p = 0.05$). In another study made with OCTA of eyes with active BD uveitis, foveal retinal thickness was found to be significantly thinner compared to the control group and a correlation was determined between the reduction in visual acuity and this thinning is associated with permanent retina structural loss in the foveal area [19]. In the current study, no difference was observed between the groups in respect of CMT measurements. This could be attributed to the absence of patients with findings of a previous uveitis attack (it can be considered that recurrent uveitis attacks could cause macular thinning), or it could be due to the recruitment of cases with visual acuity of 20/20 Snellen equivalent.

In a previous study using wide-angle FA on 100 eyes of 50 BD patients with no previous ocular involvement, fluorescein leakage was observed in the peripheral retina of 44% of the cases [28]. Since HD 6 × 6 mm OCTA, in the current study, only allowed the evaluation of a small area in the posterior pole, microvascular changes in the peripheral retina of the non-ocular BD cases may not have been able to be determined. A significant limitation of the current study was that the findings could not be correlated with FA.

The main limitation of the study was the relatively small sample size. However, we compared a special subgroup of BD with normal population and obtained some positive outcomes.

In conclusion, retinal vasculitis and its progression make the greatest contribution to BD resulting in blindness. The sooner the condition can be diagnosed, the better it can be treated and better outcomes can be obtained in the visual prognosis of the patients. The results of this study with OCTA showed that there could be subclinical retinal and choroidal vascular involvement in non-ocular BD patients. Although OCTA is a new technique, it has some advantages such as being simple, non-invasive and repeatable. Therefore, it can be extrapolated that this new imaging modality may provide further insights into the understanding of disease processes with additional technological improvements in the future.

Compliance with ethical standards

Conflict of interest No potential conflict of interest was reported by the authors.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from each participant included in the study.

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