Optical Coherence Tomography Angiography Findings in Non-Infectious Posterior Uveitis: A Controlled Study

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Research Article

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Abstract

Background: To analyze the microvascular parameters using optical coherence tomography angiography (OCTA) in non-infectious posterior uveitis (PU) patients.

Methods: In this cross-sectional study, OCTA images of patients with non-infectious PU were evaluated. The vessel densities (VD) in the superficial and deep capillary plexuses (SCP & DCP), foveal avascular zone (FAZ) area were measured and compared to healthy controls.

Results: The study cohort comprised 64 patients with age and gender-matched groups. The VD in the SCP was 43.9±3.9% in the whole image; 18.4±4.8% in the fovea, 43.9±4.6% in the parafoveal area, and 43.4±9.7% in the perifoveal zone, in eyes with uveitis. These were respectively 48.8±2.9%, 22.9±6.9%, 50.9±3.0%, and 49.2±3.1% in the control group (p=0.0001, 0.043, 0.0001, 0.01, respectively). The changes in the DCP in eyes with uveitis were not significant. In the uveitis group, the FAZ was significantly enlarged compared to controls (0.37±0.1 microns vs. 0.24±0.2 microns, p=0.046).

Conclusion: OCTA depicted significant changes including decreased VD in the SCP and enlarged FAZ in non-infectious PU.

Introduction

Uveitis, particularly involving the posterior segment of the eye, is known to be associated with inflammation induced alterations in the retinal structure and microvasculature [1]. Until recently, fluorescein angiography (FA) and optical coherence tomography (OCT) were the techniques to evaluate the posterior retinal changes in uveitis [2]. Fluorescein angiography successfully demonstrates capillary non-perfusion or leakage; however, the technique fails to reveal the microvascular structure of the capillary network and being an invasive procedure, it has several limitations including adverse drug reactions. Optical coherence tomography can monitor the whole structural anatomy of the posterior fundus but the vasculature.

Optical coherence tomography angiography (OCTA) is a non-invasive technique, recently developed to demonstrate the morphology of the retinal and choroidal microvasculature and provide volumetric data [3,4]. Optical coherence tomography angiography not only provides high resolution images of the foveal microvasculature, but also allows quantitative analysis. It is gaining popularity in various retinal vascular disorders like diabetic retinopathy, retinal vein occlusion, sickle cell retinopathy [5].

The technique is also becoming popular in the diagnosis of uveitis. The retinal microvasculature was reported to be affected in all retinal layers due to the associated inflammation, as recently demonstrated by OCTA [6-9]. Seeming to be a promising technique, OCTA is likely to give precise data on the inflammation induced microvascular changes in particularly, the posterior pole. Optical coherence tomography angiography was reported to be superior to FA to depict these microvascular changes clearly, as FA fails to demonstrate the deep capillary plexus (DCP); even providing quantitative and qualitative

data. Moreover, the vascular network can only be evaluated in the early frames of the FA, as fluorescein leakage from the inflamed vessel wall causes obscurations and window defects can prevent accurate analysis of the retinal detail [8,10]. In this current study, we aimed to analyze the changes in superficial capillary plexus (SCP) and DCP, as well as the foveal avascular zone (FAZ) in non-infectious posterior uveitis (PU) and compare them to healthy controls. We further aimed to correlate these changes with FA-based disease severity as well.

Materials And Methods

This single-center, cross-sectional, case-control, prospective study was approved by the Cukurova University Board of Clinical Research and Ethics (76/18, 13 April 2018) and a signed informed consent was obtained from each participant. The tenets of Declaration of Helsinki were followed.

Participants

Patients who were diagnosed with non-infectious PU between May 2018 and December 2019 were enrolled. For all patients, the presentation was the first attack of uveitis and the patients were treatment-naive. The participants underwent full ophthalmological examination. The diagnosis of PU was based upon the Standardization of Uveitis Nomenclature criteria [11]. At presentation patients were evaluated with multimodal imaging including FA (together with OCT) and OCTA.

Posterior uveitis patients above 18 years-old were included in the study. All patients had a negative serologic panel regarding infections associated with uveitis. Eyes with media opacities that would interfere with image quality, vitreomacular interface abnormalities detected on B-scan OCT images, history of trauma, glaucoma, and concomitant retinal vascular diseases not associated with uveitis were excluded. Eyes with macular edema (ME) were excluded to avoid a potential interference of ME induced changes in OCTA images. Having systemic diseases likely to affect the circulatory system, such as diabetes mellitus and hypertension, was also criterion for exclusion. In case of bilateral involvement, the right eye was taken for analysis. Age and gender matched healthy subjects formed the control group and underwent OCTA only for analysis.

Image Acquisition

Spectral domain OCTA (RTVue XR Avanti with AngioVue, Optovue Inc, Fremont, CA, USA) FA (Spectralis HRA, Heidelberg Engineering, Heidelberg, Germany) were performed consecutively for each patient, by experienced technicians. The images were examined by two retina specialists (SS & EE) independently. The OCTA scans were checked for the accuracy of automated segmentation and FAZ borders. In case of a discordance, the images were evaluated by a third retina specialist (ND) after a manual correction.

Optical coherence tomography angiography scans were taken in 6 mm x 6 mm scans with the built-in “AngioAnalytics” software of the device (version name: 2018.1.0.33). This updated version of the software was enhanced with Projection Artifact Removal algorithm. Only high-quality scans (Quality Index > 7) were accepted for analysis [12]. The SCP and DCP were automatically segmented by the software of the device. The vessel densities (VD), defined as the percentage area occupied by vessels in the given zone of the SCP and the DCP were analyzed based on the Early Treatment Diabetic Retinopathy Study grid sectors; VDs of the foveal, parafoveal, perifoveal zones and the whole grid were measured. The FAZ was delineated automatically and measured with the non-flow function of the software [13]. Foveal density, VD in a 300 µ wide zone around the FAZ combining both the SCP and the DCP (FD-300) was calculated by the software [12].

The severity of the inflammation was scored on FA images based on optic disc hyperfluorescence, retinal vascular staining and/or leakage, capillary leakage, retinal capillary non-perfusion, neovascularization (at the optic disc and elsewhere), pinpoint leaks, retinal staining and/or subretinal pooling, ME as described by Tugal-Tutkun et al [14].

Statistical Analysis

Statistical analysis was performed using the statistical package SPSS (Version 17.0, SPSS Inc., Chicago, IL, USA). Continuous variables were described as the mean ± standard deviation (p>0.05 in Shapiro-Wilk (n<30)). Comparisons between groups were applied using Student’s t test for normally distributed data and Mann Whitney U test were used for the data not normally distributed. Correlations were tested by Spearman’s correlation test. Spearman’s correlation coefficients were interpreted as either excellent relationship r ³ 0.91; good 0.90 £ r ³ 0.71; fair 0.70 £ r ³ 0.51; weak 0.50 £ r ³ 0.31; little or none r £ 0.3. A p value of 0.05 was taken as the level of significance.

Results

In a cohort of 64 subjects, each group comprised 18 males and 14 females. The mean age of the patients was 36.9±12.1 and the mean age of the controls was 35.4±9.2 (p=0.636). In SCP, the VDs were significantly diminished in the whole image; fovea, parafovea and perifovea in eyes with uveitis compared to the control group (p=0.0001, 0.043, 0.0001, 0.01, respectively). The VDs in DCP were also decreased in eyes with uveitis regarding the healthy controls; however, this did not reach significance. The FAZ was significantly enlarged in uveitic eyes (p=0.046). Also, uveitis caused a decrease in VD in a 300 µ wide zone around the FAZ (FD-300) (p=0.002). The comparison of OCTA parameters between the patients and the control group is given in Table 1.

Table 1
Comparison of OCTA parameters between groups.

		Patients	Controls	p
VD – SCP (%)	**WI**	43.9±3.9	48.8±2.9	*0.0001*
	Fovea	18.4±4.8	22.9±6.9	*0.043*
	Parafovea	43.9±4.6	50.9±3.0	*0.0001*
	Perifovea	43.4±9.7	49.2±3.1	*0.010*
VD – DCP (%)	**WI**	46.6±6.1	44.7±4.8	0.256
	Fovea	35.5±7.4	37.4±7.7	0.404
	Parafovea	52.5±6.1	51.3±3.4	0.440
	Perifovea	47.9±6.7	45.6±5.2	0.210
FAZ (mm^2)		0.37±0,1	0.24±0,2	*0.046*
FD-300 (%)		49.1±5.2	53.4±3.3	*0.002*

VD: vessel density; SCP: superficial capillary plexus; DCP: deep capillary plexus; WI: whole image; FAZ: foveal avascular zone area; FD-300: foveal VD in a 300 µ wide zone around the FAZ

The average FA severity score was 23.8±3.6 in eyes with uveitis. Fluorescein angiography severity score was positively correlated with FAZ area (r=0.58, p=0.005). There was a negative correlation between FA score and FD-300 (r=-0.56, p=0.036).

Figure 1 shows the FAZ and FD-300 measurements and en face OCTA angiogram with color-coded VD of the SCP in a patient and a healthy control.

Discussion

In this current study, we found a decreased VD at the posterior pole in eyes with active non-infectious PU without ME, compared to healthy controls. The VD decreased significantly in the SCP and slightly but insignificantly in the DCP. All the changes were quantitative, obtained with the algorithms built-up in the software of the device. The VD analysis was based on the ETDRS grid; thus, the decrease was evident in the whole image; foveal, parafoveal, and perifoveal regions for both plexuses. These changes represent an inflammation-induced disturbance in the foveal microvasculature. A literature search reveals similar findings with some discrepancies.

Waizel M and co-workers in their patients with PU of various etiologies, reported a significant enlargement of FAZ – regardless of ME - in the DCP compared to healthy controls; whereas, this enlargement was insignificant in SCP. They reported a significant effect of disease activity on FAZ enlargement only in the

DCP; however, in contrast to the current study, their group consisted mostly of inactive eyes (3 vs. 23) and eyes with ME were included as well [15].

As a specific uveitis entity, mainly involving retinal vessels, Behcet's disease was the most common in which OCTA features were evaluated in a number of reports [7,16-21]. In their report, Khairallah and co-workers found that the microvascular changes were more prominent in the DCP than the SCP. The authors used a manual measurement for quantitative analysis and eyes with ME were not excluded [7]. In another study, which also did not exclude ME, the VD was significantly lower in the DCP of Behcet patients compared to healthy controls; in the SCP, VD was significantly decreased in all ETDRS sectors [16]. Optical coherence tomography angiography depicted significant changes in Behcet's patients compared to healthy controls in the report by Pei and co-workers: the VD in both plexuses were decreased and the FAZ was enlarged; the capillary disruptions were found to be more frequent in the SCP [17]. Accorinti and co-workers found significant VD decrease in both plexuses, being more severe in the DCP which was prominently correlated with duration of the disease. They also reported enlarged FAZ areas [18]. A report correlating microvascular damage and outer retinal disruption reported VD decrease was prominent in DCP and limited – albeit significantly – in SCP of eyes with Behcet's disease; however, the enlargement in FAZ did not reach significance [19].

In one study analyzing the OCTA features of intermediate uveitis, in patients which retinal vasculitis accompanied, the VD decreased significantly in the SCP and insignificantly in the DCP, compared to controls, in accordance with our findings. The decrease was not resolved after removal of the projection artifacts in DCP [22]. Projection Artifact Removal algorithm could have helped better evaluation of the DCP in our group, as DCP was reported to be more prone to projection artifacts, resulting in an artificial increase in flow [23,24]. Moreover, Fenner and co-workers reported a higher repeatability of VD measurements for the SCP, than the DCP. The authors suggested that, this was likely the result of higher resolution of the SCP compared with the DCP [25].

The decreased VD is the sign of the perfusion deficit and the enlargement in FAZ shows macular ischemia; thus, OCTA which depicts the microvasculature of the posterior fundus successfully is rapidly becoming an important diagnostic tool. Optical coherence tomography angiography has been reported to be superior to FA to demonstrate the inflammation-induced microvascular changes in uveitis [7]. The changes in the SCP were concerned to be more strictly related to the active stage of the disease, and the change in DCP was correlated with the duration of the disease. [18]. Our results reporting a decreased VD in both SCP and DCP – though the latter is insignificant - are in accordance with the findings of the aforementioned studies. Our patients presented with a short duration of the disease as it was the first attack they experienced. It could be interpreted that, the VD change in the SCP was significant due to disease activity, whereas it did not reach significance in the DCP due to a relatively short disease duration.

Perhaps, exclusion of eyes with ME helped us to obtain accurate measurements of the DCP, as the cystoid spaces were depicted to be devoid of flow, localized in the DCP, causing peripheral displacement

of retinal capillaries [7,16]. Foveal avascular zone in the DCP could not even be determined in all of the eyes with ME and as ME resolved with treatment, the VD in DCP was reported to increase significantly [23]. Being apart from the SCP, the DCP is not directly connected to the retinal arterioles; thus, it was concerned that this structural diversity makes it prone to ischemic attack in uveitis as well as retinal vascular disorders [7,18,26]. On the other hand, it was reported that, in hypoxic conditions oxygen was supplied to the DCP from the choroid in a rat model. They asserted that this could possibly be the underlying mechanism why the DCP was less affected [27]. Considering our results, this hypothesis is more likely to be admissible. Perhaps, further studies would help to elucidate these concerns.

We found that, FD-300 which was recently reported to demonstrate the VD in a 300 μ width zone around the FAZ, was significantly decreased indicating reduced perfusion. This parameter combines the SCP and the DCP and has been introduced to detect early signs of diabetic retinopathy [12,28]. We believe, this is a promising parameter which OCTA offers. Depending on a thorough literature search ours is the first report to depict FD-300 in uveitis patients.

We made a correlation analysis of severity score based on FA findings as previously reported [14]. Covering FA findings regarding the whole retina, we believe this system is a favorable indicator of severity of inflammation. Our results revealed a positive correlation with FAZ area and negative correlation with FD-300. We consider that these findings which could be interpreted as the severity of inflammation were associated with enlarged FAZ, reduced VD in a 300 μ width zone around the FAZ. More severe the inflammation was the more decreased perfusion in the retinal microvasculature.

As we excluded any concomitant diseases like retinal vascular diseases or glaucoma, we believe these microvascular changes could be attributed to a particular consequence of inflammation. All patients included were treatment-naïve with recent-onset active inflammation; thus, this eliminated a potential effect of therapy on the results. We conducted an automated, quantitative analysis which could eliminate possible interobserver variability of semi-automated or manual measurements. Automated algorithms, taking the mean brightness of the central FAZ area as threshold, were reported to decrease a confounding effect of tissue reflectance on quantification of VD [19].

Our study has several limitations. The sample size was relatively small and the study group comprises a variety of patients with different etiologies. It is considerable that, the investigation in a set of patients with a particular diagnosis could give more consistent results. However, in PU, all entities cause an inflammation in the posterior eye and it is not always possible to delineate these entities strictly. The lack of search for a potential correlation between the microvascular changes and visual outcome is another limitation.

In conclusion, OCTA depicted a decreased VD in the capillary plexuses and enlarged FAZ in eyes with non-infectious PU. With the non-invasive nature and repeatability, OCTA seems to be a promising method for the diagnosis, management, and follow-up of PU. Perhaps, further studies focusing on various uveitis entities would provide more precise data.

Declarations

- ## Ethics approval and consent to participate:

This study was approved by the Board of Clinical Research and Ethics of Cukurova University (76/18, 13 April 2018). The tenets of the Declaration of Helsinki were followed. A signed informed consent was obtained from all patients prior to surgery.

- ## Consent for publication:

Not applicable

- ## Availability of data and materials:

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

- ## Conflicts of interest:

The authors declare that they have no competing interests.

- ## Funding:

Not applicable.

- ## Author contributions:

SS, EE, and PIE wrote the main manuscript text and SS prepared figure 1 and table 1. All authors reviewed the manuscript.

- ## Acknowledgement:

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Figures

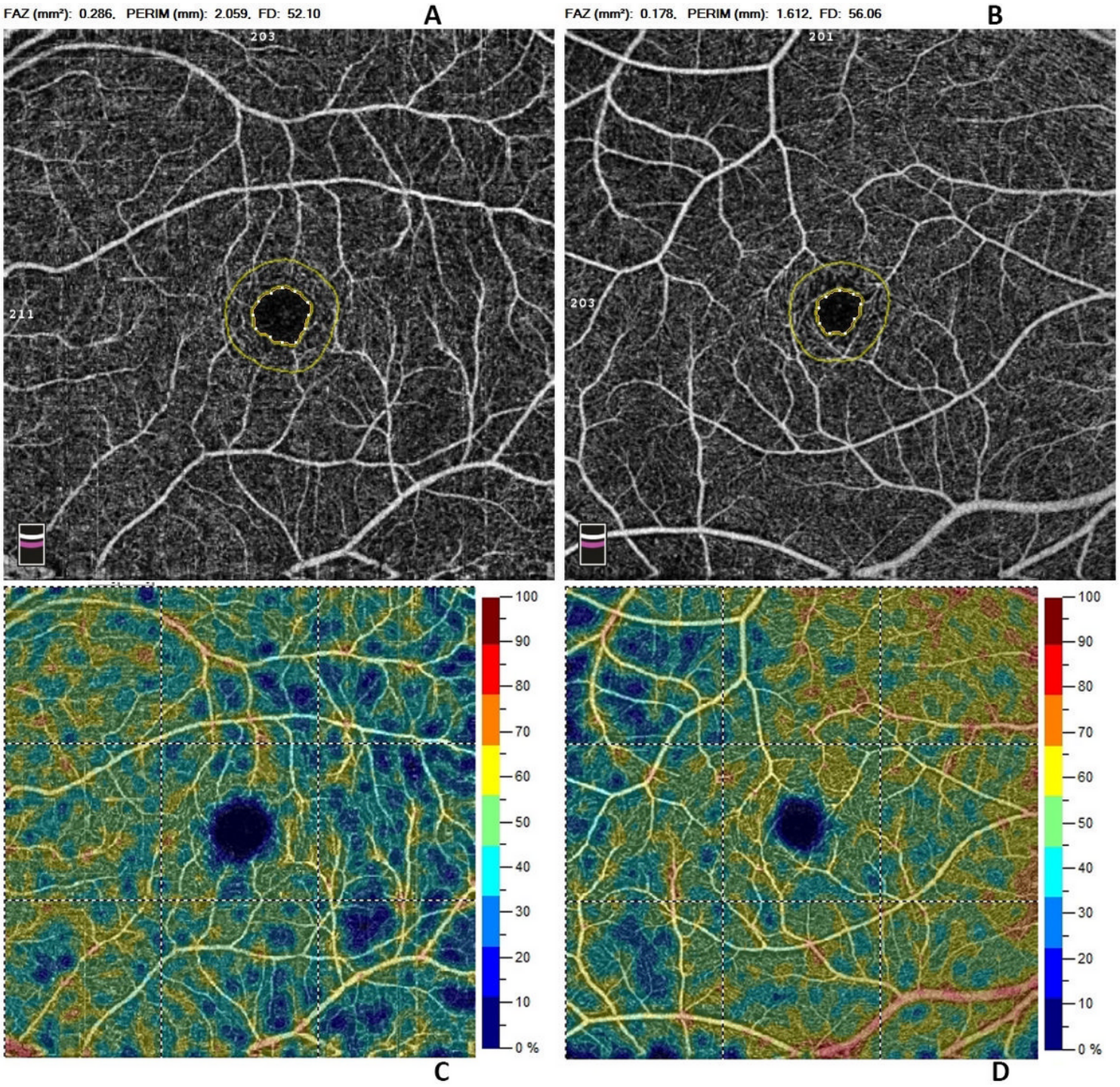

Figure 1

Optical coherence tomography angiography maps. Optical coherence tomography angiography map showing (A) the borders of the FAZ (inner yellow ring) and FD-300 (outer yellow ring) of a patient; (B) FAZ and FD-300 in a healthy individual; (C) en face OCTA angiogram with color coded vessel density in the SCP of a patient; (D) a healthy individual.