Optical Coherence Tomography Angiography Findings in Noninfectious Posterior Uveitis: A Controlled Study

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ABSTRACT

Purpose: To analyze the microvascular parameters using optical coherence tomography angiography (OCTA) in noninfectious posterior uveitis (PU) patients.

Material and Methods: In this cross-sectional study, OCTA images of patients with noninfectious 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 the eyes with PU. 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 PU were not significant. In the PU 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 noninfectious PU.

Keywords: posterior uveitis; optical coherence tomography angiography; retinal microvasculature; capillary plexus; vessel density; foveal avascular zone.

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 nonperfusion 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 pole but not 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, and 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] Optic coherence tomography angiography seems to be a promising technique, and is likely to give precise data on the inflammation induced microvascular changes, in particular in 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 when providing quantitative and qualitative data. Moreover, the vascular network can only be evaluated in the early frames

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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 the superficial capillary plexus (SCP) and DCP, as well as the foveal avascular zone (FAZ), in noninfectious 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 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 the Declaration of Helsinki were followed.

Participants

Patients who were diagnosed with noninfectious 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 a full ophthalmological examination. The diagnosis of PU was based on 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 over 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, a history of trauma, glaucoma, and concomitant retinal vascular diseases not associated with uveitis were excluded. Eyes with macular edema (ME) were excluded to avoid the 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 a criterion for exclusion. In cases 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) and brought into alignment following a thorough discussion.

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, and perifoveal zones and the whole grid were measured. The FAZ was delineated automatically and measured with the non-flow function of the software. [13]

The software calculated the foveal density, VD, in a 300-wide zone around the FAZ, combining both the SCP and the DCP (FD-300).[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, and 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 the Student's t test for normally distributed data and the Mann Whitney U test for the data that was 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 consisted of 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 compared to 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.

The average FA severity score was 23.8±3.6 in eyes with uveitis. The fluorescein angiography severity score was positively correlated with the 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 noninfectious 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-into 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. In addition FAZ area was found to be significantly enlarged in uveitic eyes.

In uveitis, ocular inflammation has been associated with parafoveal capillary loss in the SCP and consequent capillary remodeling, and dysregulation and/or enlargement of the FAZ. [15, 16]

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 the 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.[17]

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, 18-23] 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, the VD was significantly decreased in all ETDRS sectors.[18] 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 was decreased and the FAZ was enlarged; the capillary disruptions were found to be more frequent in the SCP.[19] Accorinti and co-workers found a significant VD decrease in both plexuses, being more severe in the DCP

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

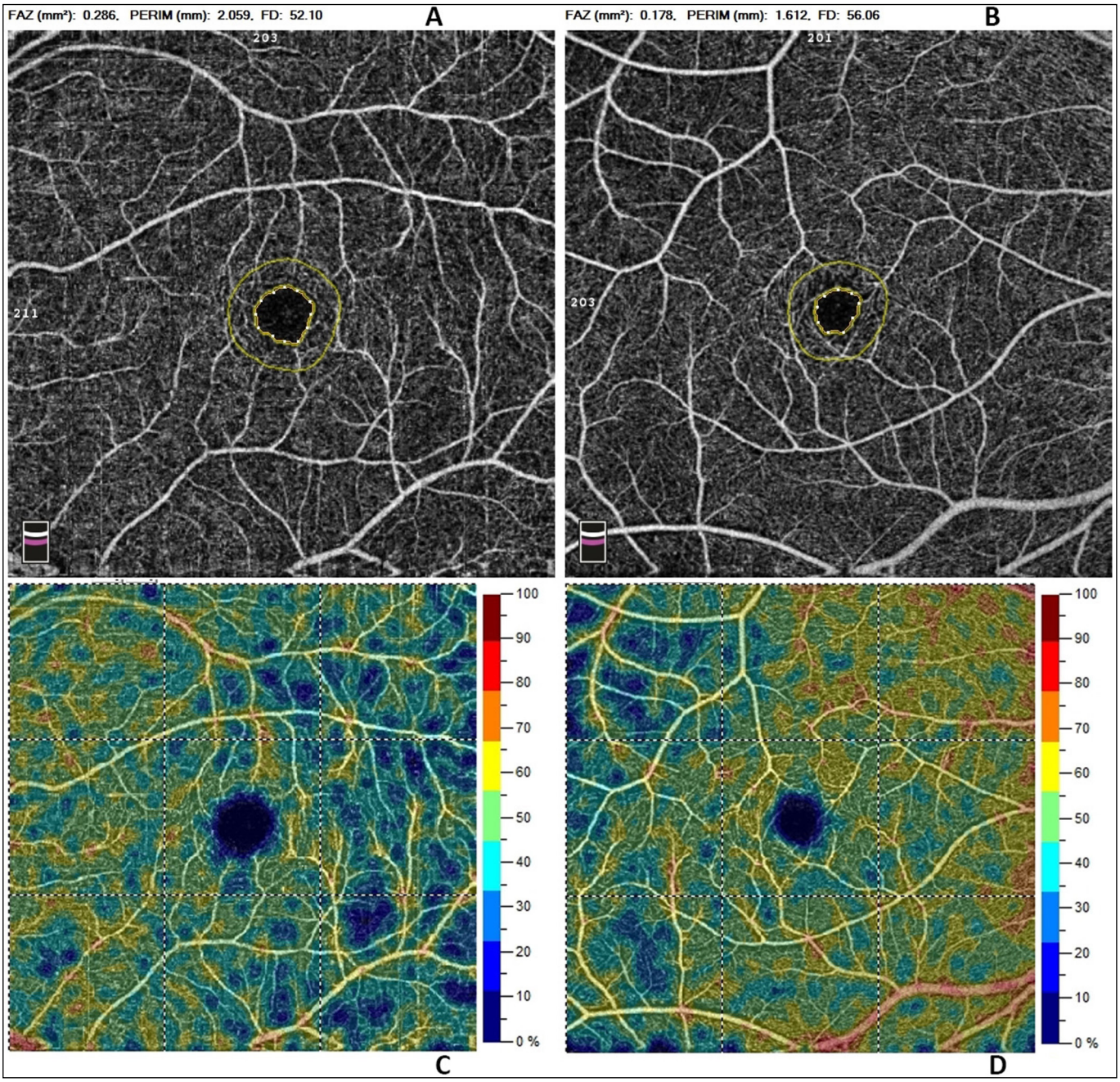

Figure 1: *Optical coherence tomography angiography maps.*
Optical coherence tomography angiography map showing ***(A)*** *the borders of the FAZ (inner yellow ring) and FD-300 (outer yellow ring) of a patient;* ***(B)*** *FAZ and FD-300 in a healthy individual;* ***(C)*** *en face OCTA angiogram with color coded vessel density in the SCP of a patient;* ***(D)*** *a healthy individual.*

which was prominently correlated with the duration of the disease. They also reported enlarged FAZ areas.[20]

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.[21]

In one study analyzing the OCTA features of intermediate uveitis, in patients with retinal vasculitis, 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 the removal of the projection artifacts in DCP.[24] A projection Artifact Removal algorithm could have helped with a 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.[25, 26] 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 the higher resolution of the SCP compared with the DCP.[27]

The decreased VD is the sign of the perfusion deficit, and the enlargement in FAZ shows macular ischemia; thus, OCTA, which successfully depicts the microvasculature of the posterior fundus, 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 considered to be more strictly related to the active stage of the disease, and the change in the DCP was correlated with the duration of the disease.[20] Our results, which report a decreased VD in both SCP and DCP - though the latter is insignificant - are in accordance with the findings of the aforementioned studies.

Because it was their first attack, our patients had a short duration of the disease. It could be said that the VD change in the SCP was important because the disease was active, but it wasn't important in the DCP because the disease had only been around for a short time.

Perhaps, the exclusion of eyes with ME helped us 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, 18] The 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 the DCP was reported to increase significantly.[25] 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, 20, 28] 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 explaining why the DCP was less affected.[29] 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, 30] We believe, this is a promising parameter that 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 the severity of inflammation. Our results revealed a positive correlation with the FAZ area and a negative correlation with the FD-300 area. We consider that these findings, which could be interpreted as the severity of inflammation, were associated with an enlarged FAZ, reduced VD in a 300 µ width zone around the FAZ. The more severe the inflammation, the lower the perfusion in the retinal microvasculature.

In a recent report, Chu and co-workers demonstrated a flow deficit in the choriocapillaris in patients with uveitis, and with an automated algorithm, this was significantly different in PU patients compared to other forms of uveitis.[31] Apart from theirs, our findings were limited to the retinal layers. According to the authors, swept-source OCTA has deeper penetrance, which means that the deeper retinal layers and even the choriocapillaris can be evaluated.

Nevertheless, we believe that, this finding somehow supports our data. A choriocapillaris flow deficit was reported in posterior uveitis entities.[32, 33]

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 the potential effect of therapy on the results. We conducted an automated, quantitative analysis that could eliminate possible interobserver variability of semi-automated or manual measurements.

Automated algorithms based on the mean brightness of the central FAZ area were found to reduce the confounding effect of tissue reflectance on VD quantification.[21]

Our study has several limitations. The sample size was relatively small, and the study group comprises a variety of patients with different etiologies. For this reason, subgroup analysis could not be performed among posterior uveitis types. It is considered that, the investigation of a set of patients with a particular diagnosis could give more consistent results. However, in PU, all entities cause inflammation in the posterior eye, and it is not always possible to delineate these entities strictly.

Another limitation is the lack of investigation into a possible relationship between microvascular changes and visual outcome.

In conclusion, OCTA depicted a decreased VD in the capillary plexuses and enlarged FAZ in eyes with

non-infectious PU. With its 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.

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