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Research Article

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Quantitative Measurement of Vascular Density and Flow Using Optical Coherence Tomography Angiography in Patients with Vasculitis; Can OCTA detect the vasculitis?

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Abstract

Purpose: To evaluate the quantitative parameters of optical coherence tomography angiography (OCTA) in patients with vasculitis.

Methods: Patients with uveitis and vasculitis in at least one eye were included and compared with 50 eyes from healthy individuals. The OCTA was done for each patient and control subject. The images were analysed at three capillary plexuses layers (superficial and deep retinal capillary layers and choriocapillaris layer). contact lens was placed on the corneal surface. Corneal edema decreased gradually in one month post-operatively.

Results: Fifty-five eyes from 28 patients were enrolled in the study. Studied eyes were categorized into 4 groups: 1-eyes with posterior vasculitis (38 eyes), 2-eyes with peripheral vasculitis without posterior vasculitis (7 eyes), 3-fellow uninvolved eyes of patients with unilateral vasculitis (10 eyes), and 4-eyes of healthy controls (50 eyes). The whole vascular density and parafoveal vascular density in both superficial and deep retinal capillary plexuses were reduced significantly from group 4 to group1. A decreasing trend in macular blood flow was also observed from group 4 followed by group 3, group 2 and group 1 in all three capillary layers including superficial retinal capillary plexus, deep retinal capillary plexus and choriocapillaris. By choosing the threshold of 26.2, the formula (-0.447×F1ch+75.82×VDdp) was the best model to differentiate the vasculitis group from the control group with an area under the curve (AUC) of 0.979, the sensitivity of 98% and specificity of 92.3%. (F1ch: flow in the central 1mm-radius-circle of the choriocapillaris, and VDdp: vascular density of parafoveal in the deep capillary network).

Conclusion: In patients with vasculitis, especially in the cases with posterior pole involvement, OCTA showed reduced vascular density and flow in all three capillary layers. OCTA might be a helpful tool to give us additional information about the macular microvasculature changes under inflammatory conditions.

Keywords

Optical Coherence Tomography-Angiography; Uveitis; Vasculitis

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Introduction

Retinal vasculitis is a sign of inflammation of the posterior segment of the eye and affects approximately 14.9% of patients with uveitis [1-4]. Retinal vasculitis is a sight-threatening condition and manifests as vascular sheathing and/or occluded vessels on examination and vascular leakage and staining in Fluorescein Angiography (FA) [4]. Additional clinical findings accompanying retinal vasculitis include vitritis, intraretinal haemorrhage, retinal neovascularization and capillary no perfusion in FA [3-6].

Fluorescein angiography is the most indispensable diagnostic tool for establishing the diagnosis of retinal vasculitis. However, the invasive nature of this modality and the fact that patients with retinal vasculitis usually need frequent FA imaging for monitoring the progression of disease and response to treatment, make finding a non-invasive alternative method desirable. Moreover, FA cannot illustrate deep retinal capillary and choriocapillaris plexuses [7-10]. The new non-invasive technique of Optical Coherence Tomography Angiography (OCTA) provides high-resolution images of retinal and choroidal capillary plexuses [11]. In contrary to FA, OCTA cannot demonstrate vascular leakage and stain directly. In this study, we assessed different levels of posterior pole vasculature in patients with retinal vasculitis with OCTA to find alterations that might help to detect retinal vasculitis and to evaluate the OCTA parameters as an alternative for FA.

Materials and Methods

This observational case-control study was performed at Farabi Eye Hospital after obtaining approval from the Institutional Review Board (IRB) of Tehran University of Medical Sciences from December 2018 until March 2019. The tenets of the Declaration of Helsinki were followed. Complete ocular examination, fundus fluorescein angiography (Heidelberg Retinal Angiography 2; Heidelberg, Germany) and OCTA (Optovue, Inc., Fremont CA, USA) were done for each patient. Systemic evaluation and laboratory tests were performed for the suspected diagnosis and typically consisted of complete blood count (CBC), Erythrocyte Sedimentation Rate (ESR), C Reactive Protein (CPR), Antinuclear Antibody (ANA), Angiotensin-Converting Enzyme (ACE), Purified Protein Derivative (PPD) test and Venereal Disease Research Laboratory (VDRL) test. Healthy subjects matched for the age and gender of our cases were recruited as the control group. Data on complete ocular examination and OCTA were collected for the control group. Visual acuity was measured by the Snellen chart and converted to LogMAR for analysis.

Patients with posterior uveitis or panuveitis who showed evidence of retinal vasculitis in fluorescein angiography at least in one eye were included. Patients with hazy media or poor fixation interfering with obtaining good quality OCTA images were excluded. Also patients with any other retinal vascular or degenerative disorders, uncontrolled glaucoma, eyes with visual acuity less than 20/200, refractive error > +3 and <-3 and having an OCTA signal strength of 5/10 or lower were excluded.

Two ophthalmologists reviewed OCTA and fluorescein angiography images. OCTA images were obtained from the superficial

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retinal capillary network, deep retinal capillary network, outer retina, and choriocapillaris at 30 μm below the retinal pigment epithelium (RPE). Blood flow at these levels and vascular density in retinal capillary networks were calculated for the central 1mm-radius circle of the 3×3 mm image and for the central 3 mm-radius circle of the 8×8 mm image (Figure 1 and Figure 2). Vascular density was calculated in 2 circles (1 and 3 mm circles of ETDRS) consisted of 3 parameters: whole vascular density (total vascular density inside 3 mm circle), foveal vascular density (total vascular density inside 1 mm circle) and parafoveal vascular density (vascular density inside the 3 mm circle with removing vascular density inside 1 mm circle). Automated segmentation with Angio-Vue present module was utilized for each measurement. The retinal slab for Superficial Capillary Plexus (SCP) end face image was defined at an inner boundary at 3 μm beneath the Internal Limiting Membrane (ILM) and an outer boundary set at 15 μm below the inner plexiform layer (IPL), whereas the Deep Capillary Plexus (DCP) end face image started at 15 μm beneath the IPL and ended at 70 μm beneath the IPL. A manual correction was executed in case of erroneous determination by the built-in software.

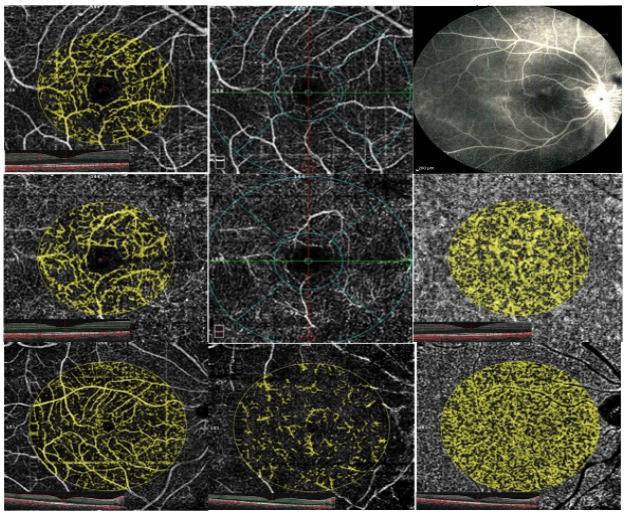

Figure 1: Illustration of optical coherence tomography angiography and fluorescein angiography (C) of patient with uveitis and vasculitis without macular edema; Measurement of flow (within a circle with 1 mm and 3 mm radius in image scan 3×3 mm^2 [A: superficial capillary network, D: deep capillary network, F: choriocapillary] and 8×8 mm^2 [G,H and I: superficial, deep and choriocapillary level] respectively) and vascular density (B: superficial and E: deep level in fovea [red arrow] and parafoveal area [green arrow]).

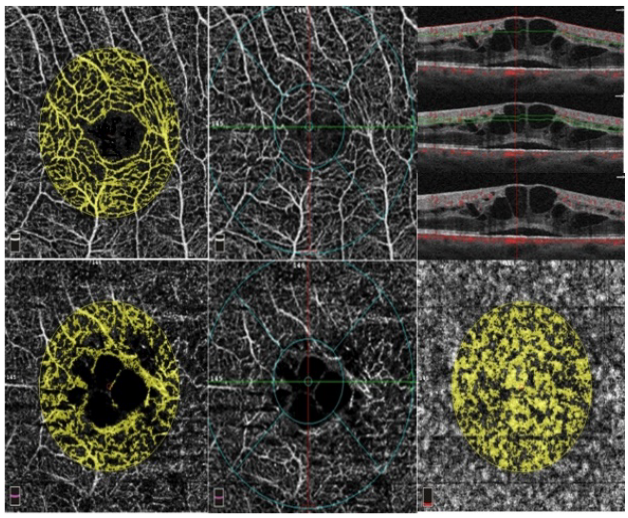

Figure 2: Optical coherence tomography angiography of patient with uveitis, vasculitis and cystoids macular edema in image 3×3 mm^2; measurement of flow (A: superficial, D: deep and F: choriocapillary) and vascular density (B: superficial and E: deep capillary level). C shows the B scan level of superficial (top: between red and green lines), deep (middle: between green lines) and choriocapillary level (bottom: between red lines)

Statistical Analysis

All statistical analyses performed by R (R Core Team (2014). R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). A p-value of less than 0.05 was considered statistically significant. Kolmogorov Smirnov test as well as Q-Q plot were used to check for the normal distribution of data. We used Generalized Estimating Equation (GEE) method to compare the flow and vascular density parameters between patients with retinal vasculitis and controls when there was the probability of correlation of measurements in the eyes within a subject. Furthermore, Receiver-Operator Characteristic (ROC) curve analysis was undertaken for each parameter. Also, the areas under the ROC curve (AUC) were calculated and the optimal threshold was chosen based on Youden's J statistics, then sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) as well as diagnostic accuracy levels for detecting patients with vasculitis, and corresponding thresholds were calculated for each parameter. To achieve the best combination of parameters that can improve the diagnostic ability, we used logistic regression. Therefore, we obtained all 4095 possible models of the combination of 12 parameters (212-1=4095) and the model with the smallest AIC (Akaike information criterion) and smallest BIC (Bayesian information criterion) was considered as the best model (fortunately all these criteria led to a single model). To obtain the most damaged parameter among the studied parameters, we calculated the ratio of each parameter in vasculitis patients to their control average. Then the selected parameter was chosen based on repeated measure analysis of variance (Repeated measure ANOVA). The Bonferroni correction method was used to adjust the type I error in comparing all the possible pairs.

Results

OCTA was done for 35 patients who had FA-proven vasculitis in at least one eye and 25 healthy individuals as a control group. Images from seven patients were excluded due to low quality. The remaining 28 patients consisted of 17 cases with bilateral uveitis, 10 cases with unilateral uveitis and one monocular patient with uveitis. With reference to FA imaging, 55 eyes (from 28 patients) showed the presence of posterior vasculitis in 38 eyes, peripheral vasculitis without posterior vasculitis in 7 eyes, and no vasculitis in 10 eyes.

We further categorized the eyes into 4 groups: 1- eyes with posterior vasculitis (38 eyes), 2- eyes with peripheral vasculitis without posterior vasculitis (7 eyes), 3- fellow uninvolved eyes of patients with unilateral vasculitis (10 eyes), and 4- eyes of healthy controls (50 eyes).

The mean age of these 28 patients was 34.21 ± 14.85 (range: 9-65) years and for the 50 controls was 35.24 ± 9.86 (range: 20-63) years (p: 0.74). The proportion of male to female was 19/9 in patients and 29/21 in the control group (Chi-square test and p: 0.39).

From 28 patients, 21 patients were treatment naïve and the

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remaining 7 patients were receiving treatment. The etiologic diagnoses of uveitis were Behcet's disease (9 patients) and idiopathic (19 patients). The duration of uveitis was 87 ± 100 days (median: 30, range: 1-360 days). The mean visual acuity of these patients was 0.42 ± 0.53 LogMAR.

Optical coherence tomography revealed cystoid macular edema affected 10 eyes. Central macular thickness was measured as 344 ± 147 µm (median: 300 µm, range of 232-908 µm).

Vascular Density and flow index

In group1 as compared to group 4, with the exception of vascular density in superficial and deep foveal capillary networks, all other parameters were significantly reduced (Table 1). Excluding the eyes with cystoid macular edema, did not significantly change the results (Table 2).

Results similar to the comparison of group 1 with group 4,

Table 1: Vascular density and blood flow of the retinal capillary networks and choriocapillaris in eyes with posterior vasculitis (case) compared to healthy eyes (control).

	Groups		Diff	95% CI		P§
	Control	Case		Lower	Upper	
Flow in superficial capillary network in 3×3 mm image	1.513 ± 0.064	1.139 ± 0.318	0.396	0.274	0.519	<0.001
	1.521 (1.273 to 1.683)	1.22 (0.273 to 1.662)				
Flow in deep capillary network in 3×3 mm image	1.592 ± 0.083	0.993 ± 0.498	0.627	0.444	0.81	<0.001
	1.607 (1.258 to 1.752)	1.127 (0 to 1.61)				
Flow in choriocapillaris in 3×3 mm image	1.971 ± 0.036	1.585 ± 0.474	0.383	0.245	0.52	<0.001
	1.975 (1.861 to 2.06)	1.779 (0.171 to 1.989)				
Whole vascular density of superficial capillary network	54.93 ± 1.91	46.35 ± 5.5	8.557	6.617	10.497	<0.001
	54.78 (49.89 to 58.28)	47.54 (35.37 to 55.22)				
Foveal vascular density of superficial capillary network	32.93 ± 5.18	31.41 ± 8.2	1.652	-1.776	5.081	0.345
	33.02 (19.3 to 47.73)	29.46 (12.65 to 59.23)				
Parafoveal vascular density of superficial capillary network	57.15 ± 2.06	47.32 ± 6.18	9.79	7.689	11.892	<0.001
	57.28 (51.8 to 60.86)	47.82 (30.99 to 56.72)				
Whole vascular density of deep capillary network	60.08 ± 1.77	49.87 ± 5.74	10.424	8.296	12.552	<0.001
	60.42 (54.58 to 63.33)	50.34 (37.87 to 59.97)				
Foveal vascular density of deep capillary network	30.68 ± 7.16	30 ± 9.88	0.955	-3.313	5.223	0.661
	30.46 (13.6 to 49.65)	28.44 (12.5 to 58.85)				
Parafoveal vascular density of deep capillary network	62.88 ± 1.93	52.11 ± 6.22	11.032	8.688	13.376	<0.001
	62.97 (57.74 to 66.45)	52.68 (38.78 to 62.76)				
Flow in superficial capillary network in 8×8 mm image	12.958 ± 0.745	10.348 ± 2.765	2.7	1.713	3.686	<0.001
	12.987 (10.721 to 14.925)	10.439 (1.49 to 14)				
Flow in deep capillary network in 8×8 mm image	12.775 ± 1.506	6.627 ± 4.34	6.309	4.748	7.871	<0.001
	13.014 (7.753 to 15.31)	6.814 (0 to 13.524)				
Flow in choriocapillaris in 8×8 mm image	17.738 ± 0.447	14.978 ± 3.319	2.773	1.722	3.825	<0.001
	17.721 (16.42 to 19.003)	16.315 (3.296 to 18.277)				

Table 2: Vascular density and blood flow of the retinal capillary networks and choriocapillaris in eyes with posterior vasculitis without macular edema (case) compared to healthy eyes (control).

	Groups		Diff	95% CI		P§
	Control	Case		Lower	Upper	
Flow in superficial capillary network in 3×3 mm image	1.513 ± 0.064	1.172 ± 0.28	0.339	0.222	0.457	<0.001
	1.521 (1.273 to 1.683)	1.22 (0.5 to 1.501)				
Flow in deep capillary network in 3×3 mm image	1.592 ± 0.083	1.045 ± 0.509	0.548	0.34	0.756	<0.001
	1.607 (1.258 to 1.752)	1.168 (0 to 1.61)				
Flow in choriocapillaris in 3×3mm image	1.971 ± 0.036	1.757 ± 0.18	0.207	0.131	0.283	<0.001
Flow in choriocapillaris in 3×3 mm image	1.975 (1.861 to 2.06)	1.838 (1.362 to 1.989)				
Whole vascular density of superficial capillary network	54.93 ± 1.91	47.46 ± 5.45	7.318	4.986	9.65	<0.001
	54.78 (49.89 to 58.28)	48.76 (35.37 to 55.22)				
Foveal vascular density of superficial capillary network	32.93 ± 5.18	31.49 ± 9.22	1.578	-2.463	5.62	0.444
	33.02 (19.3 to 47.73)	29.02 (12.65 to 59.23)				
Parafoveal vascular density of superficial capillary network	57.15 ± 2.06	48.66 ± 5.82	8.261	5.785	10.736	<0.001
	57.28 (51.8 to 60.86)	49.24 (36.5 to 56.72)				
Whole vascular density of deep capillary network	60.08 ± 1.77	51 ± 5.76	8.984	6.548	11.419	<0.001
	60.42 (54.58 to 63.33)	51.81 (37.87 to 59.97)				
Foveal vascular density of deep capillary network	30.68 ± 7.16	31.02 ± 9.7	-0.239	-4.831	4.353	0.919
	30.46 (13.6 to 49.65)	28.63 (18.42 to 58.85)				
Parafoveal vascular density of deep capillary network	62.88 ± 1.93	53.08 ± 6.28	9.761	7.095	12.427	<0.001
	62.97 (57.74 to 66.45)	53.23 (38.78 to 62.76)				
Flow in superficial capillary network in 8×8 mm image	12.958 ± 0.745	10.648 ± 2.66	2.294	1.249	3.34	<0.001
	12.987 (10.721 to 14.925)	10.721 (1.589 to 14)				
Flow in deep capillary network in 8×8 mm image	12.775 ± 1.506	7.156 ± 4.554	5.636	3.727	7.544	<0.001
	13.014 (7.753 to 15.31)	8.135 (0 to 13.524)				
Flow in choriocapillaris in 8×8mm image	17.738 ± 0.447	15.615 ± 2.888	2.091	1.016	3.166	<0.001
	17.721 (16.42 to 19.003)	16.812 (3.296 to 18.277)				

obtained in comparison group 1 with group 3 and group 2 with group 4. As it is shown in Figure 3 (2 top images), a decreasing trend in macular blood flow was observed from group 4 followed by group 3, group 2 and group 1. The highest and lowest macular blood flow was observed in groups 4 and 1 respectively. The flow between group 1 and group 2 was not significantly different (p>0.05).

The whole vascular density and parafoveal vascular density were significantly reduced in posterior vasculitis (group 1) versus peripheral vasculitis (group 2) in both superficial (46.47± 5.52 versus 51.27± 5.92 with p: 0.033 in whole vascular density and 47.45± 6.20 versus 53.23 ± 6.29 with p: 0.021 in parafoveal vascular density, respectively) and deep capillary plexuses (50.07± 5.67 versus 55.17± 5.81 with p: 0.037 in whole vascular density and 52.33± 6.14 versus 57.48 ± 6.17 with p: 0.026 in parafoveal vascular density, respectively).

By comparing group 3 with group 4, the significant difference was observed in all parameters (flow in 3×3 mm image (superficial capillary network 1.40±0.16 vs. 1.51±0.06 with p<0.001, deep capillary network 1.42±0.18 vs. 1.59±0.08 with p<0.001 and choriocapillaris 1.91±0.17 vs. 1.97±0.03 with p:0.015,) and vascular density (whole superficial network 52.54±4.47 vs. 54.92±1.91 with p:0.002, superficial network in fovea 29.02±5.04 vs. 32.93±5.18 with p=0.032, superficial network in parafoveal 54.84±5.31 vs. 57.15±2.05 with p:0.008, whole deep network 56.21±5.68 vs. 60.08±1.77 with p<0.001, deep network in fovea 24.93±6.82 vs. 30.68±7.16 with p:0.023 and deep network in parafoveal 59.23±6.33 vs. 62.88±1.93 with p<0.001) with the exception of flow in 3 measured layers in 8×8 mm image (flow in superficial capillary network 12.56±0.74 vs. 12.95±0.74 with p:0.128, deep capillary network 12.09±2.59 vs. 12.77±1.50 with p:0.226 and choriocapillaris 17.69±0.63 vs. 17.73±0.44 with p:0.877) (Figure 3).

There was a significant direct correlation between visual acuity and parameters of OCTA including vascular density (with exception of vascular density in the fovea in both superficial and deep capillary plexuses) and flow in eyes with posterior vasculitis (Table 3).

Mean Ratio

To achieve the most involved parameter among the studied parameter, we calculated the mean ratio which is the ratio of each parameter in group 1 to their control average of group 4 (Table 4). The most damaged parameter found to be the flow in a 3mm radius circle in deep capillary network followed by flow inside the 1mm radius circle in the same network

The mean ratio of flow inside the 3mm radius circle was statistically lower than any other parameter (all P-values < 0.001, based on Bonferroni correction method) with an exception for flow inside the 1mm radius circle in the macula in the deep network which did not reach to a statistically significant difference (P=0.089).

Roc curve: ROC curve analysis was performed for each parameter. The area under the ROC curve (AUROCs) was calculated for all parameters (Table 5). The best combination of parameters (Figure 4) that may improve the diagnostic ability of vasculitis was:

-0.447×F1ch+75.82×VDdp

(F1ch: flow in the central 1 mm-radius-circle of the choriocapillaris, VDdp: vascular density of parafoveal in the deep capillary network).

By choosing a threshold of 26.2, this parameter provides an AUC: 0.979, 95% lower: 0.948, sensitivity 0.98, specificity: 0.923, positive predictive value: 0.97, negative predictive value: 0.947 and accuracy: 0.964.

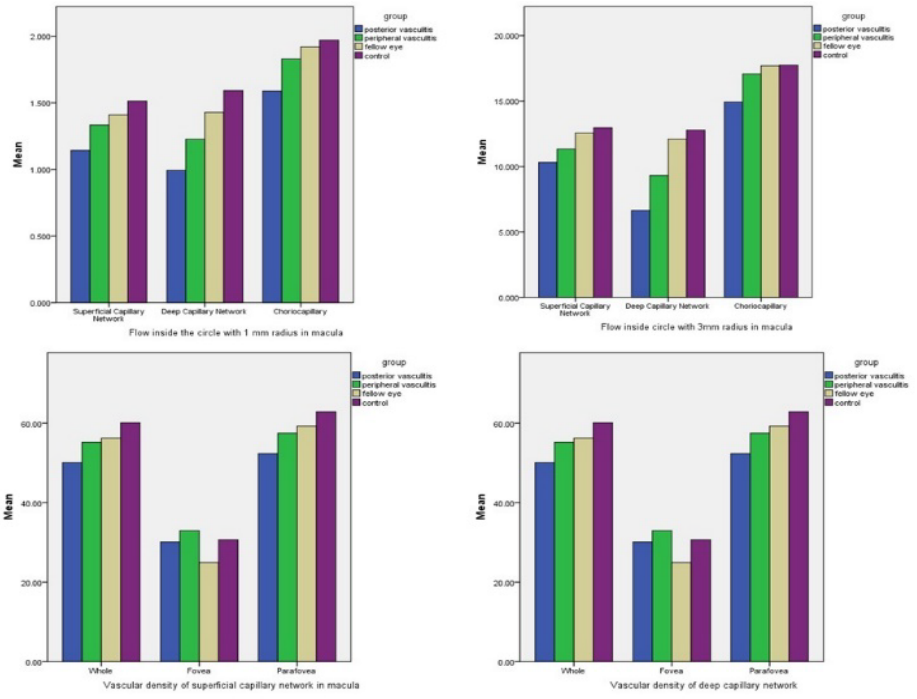

Figure 3: The graphs of flow and vascular density in eyes with posterior uveitis, eyes with peripheral vasculitis, fellow eyes of patients without uveitis and healthy eyes.

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Table 3: Correlation between visual acuity and OCT-angiography parameters of retina and choriocapillaries in eyes with posterior vasculitis.

Parameter	r	P
Flow in the circle with 1 mm radius in macula in superficial capillary network	-0.431	0.001
Flow in the circle with 1 mm radius in macula in deep capillary network	-0.447	0.001
Flow in the circle with 1 mm radius in macula in choriocapillaris	-0.515	<0.001
Whole vascular density in superficial capillary network	-0.353	0.008
Vascular density in superficial capillary network in foveal area	0.07	0.611
Vascular density in superficial capillary network in parafoveal area	-0.32	0.017
Whole vascular density in deep capillary network	-0.556	<0.001
Vascular density in deep capillary network in foveal area	0.252	0.063
Vascular density in deep capillary network in parafoveal area	-0.567	<0.001
Flow in the circle with 3 mm radius in macula in superficial capillary network	-0.646	<0.001
Flow in the circle with 3 mm radius in macula in deep capillary network	-0.482	<0.001
Flow in the circle with 3 mm radius in macula in choriocapilaries	-0.639	<0.001

Table 4: Mean ratio of vascular density and flow between eyes with posterior vasculitis (case) compared to healthy eyes (control).

Parameters	Mean Ratio	SD	Median	Percentile 25	Percentile 75
Flow in the circle with 1 mm radius in macula in superficial capillary network	0.75	0.21	0.81	0.62	0.92
Flow in the circle with 1 mm radius in macula in deep capillary network	0.62	0.31	0.71	0.46	0.85
Flow in the circle with 1 mm radius in macula in choriocapillary	0.8	0.24	0.9	0.74	0.95
Whole vascular density in superficial capillary network	0.84	0.1	0.87	0.77	0.92
Vascular density in superficial capillary network in foveal area	0.95	0.25	0.89	0.85	1.01
Vascular density in superficial capillary network in parafoveal area	0.83	0.11	0.84	0.74	0.92
Whole vascular density in deep capillary network	0.83	0.1	0.84	0.77	0.9
Vascular density in deep capillary network in foveal area	0.98	0.32	0.93	0.75	1.12
Vascular density in deep capillary network in parafoveal area	0.83	0.1	0.84	0.79	0.9
Flow in the circle with 3 mm radius in macula in superficial capillary network	0.8	0.21	0.81	0.74	0.96
Flow in the circle with 3 mm radius in macula in deep capillary network	0.52	0.34	0.53	0.24	0.84
Flow in the circle with 3 mm radius in macula in choriocapillary	0.84	0.19	0.92	0.79	0.96
Note-Mean Ratio: the mean ratio of each eye compared to the average of control group, SD: standard deviation.					

Table 5: AUC (Area under curve) of vascular density and flow in distinguish vasculitis.

Parameters	AUC	95% Lower	95% Upper
Flow in the circle with 1 mm radius in macula in superficial capillary network	0.93	0.872	0.988
Flow in the circle with 1 mm radius in macula in deep capillary network	0.945	0.905	0.986
Flow in the circle with 1 mm radius in macula in choriocapillary	0.965	0.926	1
Whole vascular density in superficial capillary network	0.949	0.906	0.991
Vascular density in superficial capillary network in foveal area	0.639	0.526	0.752
Vascular density in superficial capillary network in parafoveal area	0.959	0.928	0.991
Whole vascular density in deep capillary network	0.969	0.939	0.999
Vascular density in deep capillary network in foveal area	0.57	0.457	0.683
Vascular density in deep capillary network in parafoveal area	0.972	0.94	1
Flow in the circle with 3 mm radius in macula in superficial capillary network	0.846	0.759	0.932
Flow in the circle with 3 mm radius in macula in deep capillary network	0.918	0.864	0.972
Flow in the circle with 3 mm radius in macula in choriocapillary	0.912	0.845	0.979

Discussion

Although FA is the most valuable method in diagnosing vasculitis, the leakage, and staining obscure the boundaries of vessels. Although, FA can best demonstrate the superficial macular capillary network in early phases after that it was difficult to obtain perifoveal microvascular alterations, especially due to early dye leakage from the capillaries. OCTA provides clear details of small vessels in three different layers in the macula and as there is no dye injection involved, leakage or staining does not obliterate the visibility of deeper structures [7-14].

OCTA as a non-invasive tool adds detailed quantitative information about the vascular density and flow of retinal and choroidal vessels [13]. However, OCTA's inability in showing leakage accounted as one of its most important drawbacks for the diagnosis of vasculitis [12].

In addition, it has a relatively small (8 × 8 mm) field of view. In this study, we found quantitative indices, which are deranged in vasculitis involving posterior pole as well as vasculitis not affecting the posterior pole.

The whole vascular density and parafoveal vascular density in both superficial and deep capillary plexuses were reduced significantly in eyes with vasculitis compared to healthy control subjects. These reductions were significantly more in eyes with posterior vasculitis versus eyes with only peripheral vasculitis. Similarly, vascular flow reduced in three capillary layers including superficial, deep and choriocapillaris in these eyes. The detection of retinal vasculature

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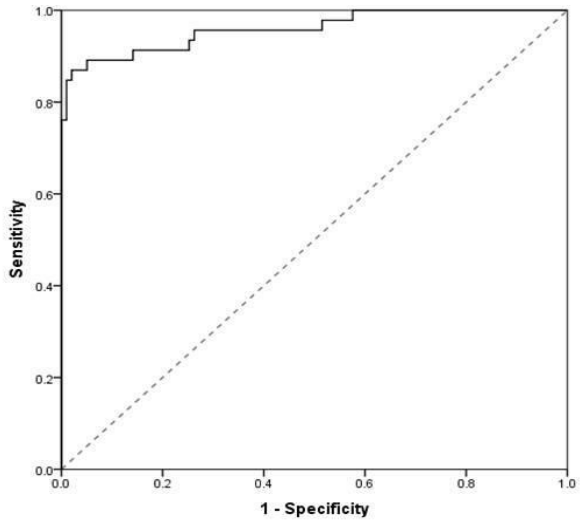

Figure 4: ROC curve of best combination of parameters using optical coherence tomography angiography in diagnostic ability of vasculitis.

defined by OCTA is dependent on the detection of the decorrelation signal from the moving structures, especially red blood cells in the blood column. Inflammation of the vessel will result in capillary disruption, which leads to diminished flow. Therefore, the no perfusion area defined by OCTA in our study is more likely caused by real no perfusion or too low retinal capillary flow [14-16].

In this study, the main level of impairment in patients with posterior pole vasculitis was deep retinal capillary plexus. It is consistent with a recent study by Emre at al. that showed that deep capillary plexus was affected more than superficial capillary plexus in 16 patients with Bechet uveitis [15]. It has been shown that macular ischemia and DCP loss can be found earlier in the course of retinal vasculitis and can explain vision loss in these situations [16] it is presumed that deep capillary plexus is more sensitive to ischemia due to being not directly connected to arterioles and indeed considered as an intraretinal watershed zone between inner and outer retinal circulation [16].

The presence of cystoid macular edema in patients with uveitis can cause a signal void area in OCTA. These no perfusion areas should be discriminated from the cystoid spaces which are due to the total absence of flow signal [16,17] assessed 25 eyes of 14 uveitis patients using OCTA. Eight eyes had macular edema, five eyes showed resolved edema and five eyes did not have uveitis associated macular edema. They observed diminished capillary density and absence of normal vascular tapering accompanied by irregularity and tortuosity in those who had persistent macular edema or resolved macular edema. In our study, 22.2% (10/45) of patients with vasculitis had cystoid macular edema. we omitted these patients to reanalysis the findings; however, our results were consistent with reduced parameters of vascular density and flow and excluding the eyes with cystoid macular edema, did not significantly change the results.

The foveal vascular density showed no difference in superficial and deep capillary plexuses between the vasculitis and control group. This can be explained by sparse vasculature in the foveal area [18] evaluated the feature of OCTA in posterior uveitis in 14 eyes from 9 patients and compared them with 30 normal controls. Four eyes had simultaneous vasculitis. They found deep capillary plexus especially in the parafoveal area as the most damaged layer. Our results are consistent with their findings. In addition, by calculating the mean ratio of vascular density and flow parameters, we found that the flow inside the central circle with a 3 mm radius in the deep retinal capillary network is the most damaged parameter, followed by flow inside the central circle with 1 mm radius in the deep capillary network. It may be explained partly with the existence of the more vessels in 3 mm central. This finding is consistent with other disorders like diabetic retinopathy and retinal vein occlusion, as deep capillary plexus may be more vulnerable to inflammatory or ischemic events [14-20].

Our analysis showed that the peripheral vasculitis group has some reduced macular OCTA parameters like capillary density in comparison to healthy eyes. Likewise, OCTA of the uninvolved fellow eyes showed that the capillary density and fellow were significantly reduced compared to healthy control subjects. It can be explained with the presence of inflammatory mediators in vitreous and their effects on macular microvasculature and resultant decreased flow before it can be visible in fluoresce in angiography [14-16]. Although our cases are limited in number, the result suggests that OCTA can be helpful in finding the early changes of posterior pole vessels in a patient with retinal vasculitis before it becomes evident in fluorescein angiography. As FA has some limitations to detect deep capillary plexus, it can underestimate macular ischemia due to the presence of the perifoveal leakage or pooling of dye in cystoid spaces. Our study showed that deep capillary plexus can be affected based on OCTA even in the eye with normal FA. Therefore, no perfusion could happen in any stage of ocular vasculitis especially in the deep capillary plexus, which can reflect the pathogenesis of central visual loss in patients with uveitis [16].

We found the best combination of parameters for distinguishing the vasculitis with the threshold of 26.2 and 98% AUC with high sensitivity, specificity and accuracy. Based on this model, it can be assumed that OCTA may diagnose vasculitis correctly in the early stages and maybe a suitable replacement for FA in some situations. This theory needs to be confirmed by complementary larger studies.

Our investigation had some limitations. OCTA cannot use in patients with significant media opacity and poor fixation in contrast to fluorescein angiography. A limited sample size is another limitation of our study. Future studies with larger sample size or using wide-field OCTA are required to confirm our results.

Conclusion

OCTA can be a helpful tool to give us additional information about the macular microvasculature changes under inflammatory conditions even before fluorescein angiography. The most involved parameters in eyes with vasculitis were vascular density and flow in deep capillary network although superficial and choriocapillaris layers were also impaired. More precise conclusions are precluded by the limitations of the current data. A further larger trial is necessary to clarify the situation.

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Not applicable

Conflict of interest

None of the authors have any proprietary interests or conflicts of interest related to this submission.

Informed consent

Informed consent was obtained from all individual participants included in the study before operation.

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Availability of data and material

The data generated during or/and analysed during the current study are available from the corresponding author.

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Authors' contributions

Concept and design (RR, FB); data acquisition (FB, BI, MR, MS); data analysis/interpretation (FB, MS); drafting of manuscript (MS, FB); critical revision of the manuscript (MZ, FB, NE, HR); supervision (RR, MZ); statistical analysis (FB, MS). All authors read and approved the final manuscript.

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