Assessment of Macular Capillary Perfusion by Optical Coherence Tomography Angiography on Quiescent Unilateral Anterior Pediatric Uveitis

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Research Article

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Abstract

Purpose: Using spectral domain optical coherence tomography angiography (SD-OCTA) to evaluate tomographic and microvascular parameters in the macula in quiescent unilateral anterior pediatric uveitis (APU) patients.

Methods: Forty-two eyes of 21 patients diagnosed with unilateral APU and 21 eyes of 21 normal controls (NC) were included in this study. 6*6 mm macular scanning mode of SD-OCTA was used for all subjects. The central macular thickness (CMT), subfoveal choroidal thickness (SFCT), vascular density (VD) of superficial capillary plexus (SCP) and the deep capillary plexus (DCP), the foveal avascular zone (FAZ) area, and choriocapillary flow density (CFD) were analyzed and compared among affected, fellow, and NC eyes. Correlation analysis were used to evaluate the potential correlating factors with CFD.

Results: DCP VD and CFD were significantly lower in quiescent affected eyes as compared to fellow and NCs eyes (DCP VD both $p<0.001$; CDF1.0: $p=0.012$ and $p=0.003$; CDF1.5: $p=0.015$ and $p=0.006$; CDF3.0: $p=0.036$ and $p=0.010$, respectively). SCP VD, DCP VD and CMT were significantly lower in the fellow eyes as compared to NC eyes ($p=0.021$; $p<0.001$; $p=0.037$, respectively); CFD was negatively correlated with FAZ and CMT in affected eyes and fellow eyes. No significant differences were detected in FAZ among the 3 groups ($p > .05$).

Conclusions: As compared to NC eyes, both retinal and choroidal microvasculature were impaired in eyes with quiescent APU; retinal microvasculature in unaffected fellow eyes of unilateral APU was also impaired. OCTA is a useful technology for detection of subclinical microvascular changes in APU and may be useful as an additional prognostic tool.

Background

Pediatric uveitis (PU), which accounts for 5-10% of all uveitis[1], is a topic of particular concern to uveitic specialists due to its unpredictability and intractability. PU is a group of heterogenous disease entities with epidemiology, etiology and clinical patterns vary among studies from different areas worldwide, and anterior uveitis is the most frequent ophthalmic manifestation of the PU[2–7]. The pathogenesis of PU remains incompletely understood and PU is more likely to be asymptomatic than uvetis in adults. Uveitis is usually associated with disruption of retinal microvascular system, leading to macular edema, retinal ischemia and retinitis that cause visual impairment[8, 9]. Spectral-domain optical coherence tomography (SD-OCT) and fundus fluorescein angiography (FFA) are commonly used to detect these changes[10, 11]. However, standard FFA is an invasive procedure and cannot provide images of the distinct layers of choroidal and retinal blood vessels. The results of FFA needs to be interpreted by experienced ophthalmologists and only permit subjective assessments that could not provide quantitative data for academic communication[12, 13].

On the other hand, OCT angiography (OCTA) is a non-invasive imaging method with good repeated ability and a high resolution of retinal and choroidal capillary[14, 15]. While changes in retinal capillary perfusion had been described in previous stuides[16, 17], whether and how the choroidal circulation was affected in anterior pediatric uveitis (APU) has not been addressed. In recent years, choriocapillaris flow density (CFD) has been widely investigated as a potential indicator of choroidal perfusion in a variety of retinal diseases, which showed good value for disease assessment[18–20]. The purpose of this study was to evaluate tomographic and microvascular parameters in the macula by OCTA in quiescent unilateral APU patients, and to explore potential clinical value of these parameters.

Methods

Patients

This cross-sectional observational study included clinical data from medical records of unilateral APU patients who underwent at least one OCTA scan between January 2019 and July 2021 at our center. The normal control (NC) group were the age-matched healthy volunteers with no ophthalmological and/or systemic disease who were recruited at the same period. The study protocol was approved by the institutional review board (No. S-K1722) and followed the Declaration of Helsinki. Before the study, written informed consent was acquired from the parents of the participant.

The inclusion criteria were patients with unilateral APU (according to the criteria established by the Standardization of Uveitis Nomenclature international working group[12]) in a inactive state and with complete medical records. One eye of each NC subject was randomly selected for analysis. Exclusion criteria for APU patients and controls were (1) age older than 16 years at disease onset; (2) detectable anterior chamber cells and any sign indicative of posterior segment involvement (including optic disc edema and macular edema) in the involved eyes within 3 months; (3) spherical equivalent (SER) refraction≤− 3.0 diopters; (4) ocular media opacity that impede examination of the fundus; (5) a history of any intraocular surgery within the past 6 months; (6) the scan quality of OCTA was lower than 6; and (7) an infectious cause was identified or suspected.

Data Acquisition and Processing

APU and NC subjects all underwent a complete binocular evaluation, including best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp examination of the anterior segment and dilated posterior examination. Patients with definite or suspected posterior segment involvement also underwent FFA. An RT XR Avanti instrument (AngioVue; Optovue, Fremont, CA, USA) performed OCTA images. Two consecutive scans of each eye

were performed using automatic motion correction technology and 3D projection artifact elimination technology and analyzed using the highest quality scans. Central macular thickness (CMT), vascular density (VD) of superficial capillary plexus (SCP) and the deep capillary plexus (DCP), foveal avascular zone (FAZ), subfoveal choroidal thickness (SFCT) and choriocapillary flow density (CFD) were recorded for all participants.

VD was measured in the “HD Angio Retina, macular, 6*6 mm” scanning mode and defined as the percentage of vascular areas with blood flow on angiograms to the entire surface of the selected area. The software automated layer segmentation of the SCP and DCP in each scan. The FAZ was the area containing the central fovea that has no vessels[21]. The SFCT evaluation were manually evaluated by enhanced high-definition line scans, which are adjusted vertically from the outer edge of the retinal pigment epithelium to the choroid-scleral boundary in the fovea. Using the flow measurement tool of the software at the CC level, the flow area of CC with the radius of 1-, 1.5- and 3-mm were calculated as CFD-1.00, CFD-1.50, and CFD-3.00, representing the percentage of flow area to the whole selected area. Intergroup comparisons parameters, including CMT, SFCT, FAZ, SCP VD, DCP VD and CFD, were conducted among affected eyes, fellow eyes and NCs. The group information was blinded to the examiner.

Statistical analysis

Statistical analyses were performed with SPSS Statistics Premium v23.0 (IBM Corporation, Armonk, NY, USA). BCVA values were converted from Snellen to the Logarithm of the Minimum Angle of Resolution (logMAR) for statistical analysis. Kolmogorov-Smirnov test was used to verify the normality of the data. The independent sample t-test and the Mann–Whitney U test were used for normally distributed data and non-normally distributed data respectively. Spearman correlation coefficient and multivariate linear regression analyses were used to evaluate the potential correlating factors of CFD. P value was set at 0.05 for statistical significance.

Results

In this study, 21 patients with unilateral APU (10 male, 11 female) and 21 age-matched NC were included. The mean age was 10.9 ± 2.7 years in the APU group and 11.0 ± 2.5 years in the NC group. Of the 21 patients, 17 were idiopathic and 4 were JIA-associated uveitis. All included OCT and OCTA scans had complete retinal and choroidal structures and correct automatic segmentations obviating the need for additional manual adjustments. For affected eyes, the mean duration of remission was 10.47 ± 6.69 (range, 3–22) months. The mean BCVA was 0.06 ± 0.11 log MAR in the affected group, -0.01 ± 0.04 logMAR in the fellow eye group, and 0.00 ± 0.06 logMAR in the NC group (all *p* values > 0.05). The demographic information is presented in Table 1.

Table 1

The demographics and clinical characteristic of the participants.

	APU	Fellow	NC	*p* value	*p* value	*p* value
Characteristic	(*N*=21)	(*N*=21)	(*N*=21)	(APU vs. fellow)	(APU vs. NC)	(Fellow vs. NC)
Age, y mean (SD)	10.9 (2.7)	10.9 (2.7)	11.0 (2.5)	1.000	0.900	0.900
Gender□female (N) (%)	11 (52.4)	11 (52.4)	14 (66.7)	1.000	0.351	0.351
logMAR BCVA	0.06±0.11	-0.01±0.04	0.00±0.06	0.114	0.106	0.115
Side, right (N) (%)	13 (61.9)	8 (38.1)	11 (52.4)	0.129	0.538	0.358
Remission time (months)	10.47±6.69	-	-	-	-	-
SD Standard deviation, NC Normal control, logMAR Logarithm of the minimal angle of resolution, BCVA Best-corrected visual acuity. *Statistically significant *p* value.						

Retinal Analysis

SCP VD and DCP VD were significantly decreased in all eyes in affected APU eyes compared with NCs (both $p < .001$). However, the CMT and FAZ were not statistically different between APU and NC groups ($p = 0.880$ and $p = 0.297$). All fellow eyes of APU patients also had a significantly lower SCP VD and DCP VD ($p = .021$ and $p < .001$) compared with the NC group, however, the decrease of SCP VD was less than that in the affected eye. The CMT had a significant decrease in the fellow eye compared to the NC group ($p = 0.037$). The FAZ did not differ significantly between the fellow eye group and NC group ($p = 0.651$). (Table 2)

Choroidal Analysis

The SFCT of the affected APU eyes was significantly thicker than that of the NC eyes but was not significantly different from the fellow eyes (306.9±49.0 μm vs 254.1±48.7 μm and 279.6±56.1 μm, p = 0.003and p = 0.101, respectively). The mean CFD-1.00, 1.50, and 3.00 of the affected eyes were 66.0%, 66.2%, and 67.4%, respectively, which were significantly lower than those of the fellow eyes (p = 0.012, p = 0.015, and p = 0.036, respectively) and the NC eyes (p = 0.003, p = 0.006, and p = 0.010, respectively). However, there was no significant difference between the fellow eye group and the NC group. (Table 2)

Table 2

Comparisons of OCTA and OCT parameters among affected APU eyes, the fellow eyes and NCs.

	APU	fellow	NC	p value	p value	p value
Parameters	(N=21)	(N=21)	(N=21)	(APU vs. fellow)	(APU vs. NC)	(Fellow vs. NC)
CMT (μm)	212.1±21.7	205.9±18.3	212.5±10.3	0.320	0.880	0.037*
SCP VD (%)	44.4±4.9	47.0±4.8	49.7±1.9	0.072	<0.001*	0.021*
DCP VD (%)	47.9±4.4	52.8±3.2	56.4±2.3	<0.001*	<0.001*	<0.001*
FAZ area, mm^2	0.282±0.133	0.280±0.122	0.261±0.067	0.953	0.297	0.651
SFCT (μm)	306.9±49.0	279.6±56.1	254.1±48.7	0.101	0.003*	0.199
CDF1.0 (%)	0.660±0.048	0.696±0.039	0.703±0.030	0.012*	0.003*	0.763
CDF1.5 (%)	0.662±0.050	0.698±0.040	0.705±0.022	0.015*	0.006*	0.744
CDF3.0 (%)	0.674±0.042	0.699±0.031	0.708±0.021	0.036*	0.010*	0.513

NC Normal control, CMT Central macular thickness, SCP Superficial capillary plexus, DCP Deep capillary plexus, VD Vascular density, FAZ Foveal avascular zone, SFCT Subfoveal choroidal thickness, CFD Choriocapillaris flow density.

*Statistically significant p value.

Correlation Analysis

Univariate analysis (Table 3) revealed that FAZ and SFCT were both negatively correlated with CFD1.0, CFD1.5, CFD3.0 (p = .001, p < .001, p = .007; p = .004, p = .004, p = .004, respectively). The DCP VD was positively correlated with CFD1.0, CFD1.5, CFD3.0 (p = .013; p = .023; p = .021, respectively). According to multiple linear regression, CFD1.0, CFD1.5, CFD3.0 were statistically correlated with FAZ (p = 0.015, p = 0.009, and p = 0.010, respectively), CMT (p = 0.026, p = 0.002, and p = 0.028, respectively). CFD1.0, CFD1.5 were statistically correlated with DCP VD (p = 0.047 and p = 0.045, respectively). (Table 4)

Table 3

Univariate analysis of potential correlation factors with CFD-1.00, CFD-1.50, and CFD-3.00 as dependent variable.

Table 4

Multiple linear regression analysis of related factors was conducted CFD as dependent variables.

	SCP VD		DCP VD		CFD1.0		CFD1.5		CFD3.0	
Characteristic	Correlation Coefficient	*p* value[a]	Correlation Coefficient	*p* value[a]	Correlation Coefficient	*p* value[a]	Correlation Coefficient	*p* value[a]	Correlation Coefficient	*p* value[a]
Age	-0.109	0.491	0.113	0.476	0.046	0.770	0.032	0.839	0.125	0.431
Gender（female	-0.169	0.284	-0.061	0.701	-0.256	0.102	-0.181	0.251	-0.173	0.273
log MAR BCVA	-0.209	0.184	-0.279	0.073	-0.256	0.102	-0.278	0.066	-0.181	0.251
FAZ	0.145	0.361	-0.158	0.318	-0.477	0.001*	-0.411	0.007*	-0.439	0.004*
CMT	-0.091	0.565	-0.021	0.895	-0.160	0.311	-0.263	0.093	-0.177	0.263
SFCT	0.121	0.445	-0.397	0.009*	-0.514	<0.001*	-0.432	0.004*	-0.431	0.004*
SCP VD	1.000	——	0.081	0.611	0.159	0.314	0.213	0.175	0.084	0.559
DCP VD	0.174	0.271	1.000	——	0.382	0.013*	0.349	0.023*	0.355	0.021*

logMAR Logarithm of the minimal angle of resolution, BCVA Best-corrected visual acuity, FAZ Foveal avascular zone, CMT Central macular thickness, SFCT Subfoveal choroidal thickness, SCP Superficial capillary plexus, DCP Deep capillary plexus, VD Vascular density, CFD Choriocapillaris flow density.

*Statistically significant *p* value. [a] Spearman correlation analysis.

	CFD1.0		CFD1.5		CFD3.0	
	β	*p* value	β	*p* value	β	*p* value
Age	-0.021	0.902	0.042	0.807	0.093	0.619
BCVA	0.030	0.825	0.065	0.629	0.086	0.562
FAZ	-0.494	0.015*	-0.527	0.009*	-0.566	0.010*
CMT	-0.322	0.026*	-0.466	0.002*	-0.342	0.028*
SFCT	-0.182	0.215	-0.131	0.364	-0.070	0.654
SCP VD	0.102	0.462	0.181	0.191	0.064	0.667
DCP VD	0.277	0.047*	0.275	0.045*	0.283	0.059

logMAR Logarithm of the minimal angle of resolution, BCVA Best-corrected visual acuity, FAZ Foveal avascular zone, CMT Central macular thickness, SFCT Subfoveal choroidal thickness, SCP Superficial capillary plexus, DCP Deep capillary plexus, VD Vascular density, CFD Choriocapillaris flow density.

*Statistically significant *p* value.

Discussion

In this study, retinal and choroidal macular capillary perfusion changes in patients with quiescent unilaterally APU eyes were assessed by OCTA and compared to the contralateral eyes and NCs. To our knowledge, this is the first study that demonstrated significant decrement in retinal and choroidal capillary perfusion in patients with quiescent APU using OCTA.

Our research revealed that, compared with NCs, all eyes in the affected group and the fellow eye group had a significantly lower SCP VD and DCP VD, and the decrease of SCP VD in the fellow eye was less than that in the affected group. This demonstrated the presence of impaired retinal capillary perfusion of quiescent APU patients in both affected and fellow eyes, which was consistent with the studies that inactive VKH patients also had macular circulation disorder[22]. Moreover, the DCP of patients with quiescent APU is more profoundly reduced than the SCP, which is consistent with previous findings described by Kim et al. and Tian et al.[16, 23]. The possible reason is that, unlike the superficial retinal capillaries, the deep retinal vessels are more vulnerable to ischemia since they are not directly connected to arterioles[24]. Besides, there have been studies [25]demonstrating that the underlying intraocular inflammation can lead to macular edema regardless of anatomical location[16, 26, 27]. For example, relative retinal and choroidal thickening and relative choroidal vascular engorgement in fellow eyes of patients with HLA-B27-associated uveitis have been described. This phenomenon was presumed to be due to the release of inflammatory cytokines of prolonged anterior uveitis that disrupt the internal and external blood-retinal barrier[28] Therefore, ocular inflammation may occur in both eyes despite the normal clinical appearance of the unaffected fellow eye.

Our study was the first one to investigate CFD in APU and demonstrated that CFD may be used as quantifiable markers related to disease prognostic. According to previous adult studies, SFCT may be related to disease activity[29–31]. In our study, the SFCT of the affected eye was found significantly thicker than those of the NCs but not with fellow eye. However, pediatric choroidal thickness is associated with several systemic or ocular parameters, especially the axial length and body mass index[32] which weakened its effectiveness as a biomarker. Interstingly, our study found that CFD in the affected eyes was lower than that of NCs and fellow eyes even in the quiescent stage, indicating the persistent choroidal perfusion impairment in the chronic disease course. The reason might be that, firstly, CFD by previous inflammation was partially irreversible. Secondly, even when the uveitis is clinically inactive, there may be an underlying subclinical inflammatory activity that continues to damage the choroid circulation. The use of CFD-1.5 and CFD-3.0 to assess changes in parafoveal capillary density may also provide a unique assessment of disease, which shows the consistency of blood flow density change between parafoveal and subfoveal in affected eyes. Although this was contradictory to the results reported by Karaca's[22] that no differences were detected on CFD between eyes of inactive uveitis and healthy controls. The possible reason is that the remission time of inactive VKH patients in their study was much longer than in our current study.

CFD was negatively correlated with FAZ and SFCT according to univariate analysis, indicating that choroidal perfusion was worse in patients with larger FAZ and thicker choroid. Thicker choroid indicated choroidal stroma edema, which due to the large amounts of inflammatory cells infiltrate the choroidal stroma[33, 34]. And choroidal stroma edema leading to the compression of the choriocapillaris further causes blood circulation disorder. Enlarged FAZ indicated macular ischemia, as reflected by decreased VDs of SCP and DCP in our research. Since the choroid provides blood and metabolic supply for the outer layer of the retina, decreased CFD reveals choroidal ischemia, which may also lead to impairment of retinal capillary perfusion. And consistent in our study that DCP VD was positively correlated with CFD. Further explorations of the influencing factors in the active period of APU are needed to figure out a more convincing conclusion.

Although corticosteroids remain to be the mainstay treatments for APU, they may cause significant side effects to pediatric patients. Currently, there is no reliable indicator to guide treatment duration[35], and patients are at risk of being treated inadequately or excessively. In our study, multiple linear regression revealed that FAZ, CMT, and DCP VD were factors strongly correlated with CFD. These correlations indicated that CFD might be a novel sensitive marker to evaluate APU patients even better than SFCT. With CFD, we can monitor patients' response to treatment by quantifying choroid changes without the interference of other systemic or ocular parameters. This study has some limitations. Since it is a retrospective and cross-sectional study, it has an inferior level of evidence compared to prospective studies. The projection artifacts inherent in OCTA can affect the accuracy of the data. And the sample size is relatively small because of the rarity of unilateral APU. However, despite these limitations, we believe that evaluating changes in macular capillary perfusion may provide valuable insights into the pathophysiology of PU.

In conclusion, our study revealed impairment of retinal microcirculation by OCTA in the affected eyes in clinically quiescent unilateral APU patients as well as the contralateral fellow eyes; CFD may serve as an additional noninvasive parameter for APU. Further prospective studies are needed to explore the values of quantitative OCTA parameters in monitoring disease activity and understanding the pathogenesis of APU.

Declarations

Funding:

None.

Conflicts of interest/Competing interests:

The authors declare no conflict of interest.

Availability of data and material:

Some or all data, models, or code generated or used during the study are available from the corresponding author by request.

Code availability:

Not applicable.

Authors' contributions:

Junyan Xiao acquired the clinical information, interpretation of data and wrote up the manuscript. Meifen Zhang carried out critical revision and reviewed the manuscript. Yi Qu, Chan Zhao, Hang Song, Anyi Liang and Jingyuan Yang participated in the data collection. All authors reviewed the manuscript.

Ethics approval:

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board of Peking Union Medical College Hospital approved this study (S-K1722).

Consent to participate:

Informed consent was obtained from the parents of each child included in the study.

Consent for publication:

All authors read and approved the final manuscript. The requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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