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RETINAL CAPILLARY DENSITY IN PATIENTS WITH BIRDSHOT CHORIORETINOPATHY

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Abstract

Purpose—To quantify retinal capillary density and determine its correlation with visual acuity (VA) in patients with birdshot chorioretinopathy (BCR).

Methods—Patients with BCR and age-matched controls were imaged using a commercially available spectral-domain optical coherence tomography angiography (OCTA) system (RTVue-XR Avanti; Optovue, Inc., Fremont, CA). We used the integrated software of the OCTA device to analyze the foveal avascular zone area (FAZ) and the capillary density in the full retina as well as in the superficial (SCP) and deep capillary plexus (DCP). We assessed the correlation between these parameters and VA.

Results—Seventy-four eyes of 42 study participants (37 eyes of 21 BCR and 37 eyes of 21 healthy subjects) were included in this observational cross-sectional study. Capillary density of the full retina, SCP and DCP were significantly decreased in BCR compared with the healthy control group ($p < 0.01$). Visual acuity in BCR patients was significantly associated with the capillary density of the SCP, DCP and full retina ($p < 0.01$) but not with the area of the FAZ.

Conclusion—The decrease in visual acuity in BCR patients is associated with retinal vascular impairment. Vessel density of the retinal capillary plexuses may be a promising imaging biomarker for BCR disease severity.

Keywords

Birdshot chorioretinopathy; capillary plexus; deep capillary plexus; optical coherence tomography; optical coherence tomography angiography; vessel density

Introduction

Birdshot chorioretinopathy (BCR), first described in 1980 by Ryan and Maumenee, is a chronic bilateral disease, commonly affecting middle-aged, otherwise healthy patients.^{1, 2}

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Symptoms typically include floaters, nyctalopia, photopsias, decreased color vision and blurred vision.^{2, 3} While the pathologic mechanisms underlying BCR are not fully understood, it is generally considered an auto-immune disorder.⁴ It is characterized by bilateral yellow-white choroidal lesions, mild vitreous inflammation as well as retinal vasculitis and arteriolar narrowing, and is highly associated with the HLA-A29 haplotype. It has been hypothesized that inflammation in BCR evolves independently in the choroid and retinal vessels.^{5, 6} Sequelae of the disease include diffuse photoreceptor loss, cystoid macular edema (CME) (50%), epiretinal membranes (ERM) (8%) and choroidal neovascularization (CNV) (5–7.5%).^{2, 7}

Fluorescein angiography (FA) is considered the gold standard imaging modality for retinal vascular manifestation of BCR, highlighting findings of vasculitis, subclinical retinal capillary occlusion or vascular hyperpermeability.^{8, 9} As it is a strictly two-dimensional imaging modality, it is not possible to appreciate different retinal capillary plexuses on FA, precluding the distinction of ischemia at different levels within the retina.¹⁰ Furthermore, while FA has the advantage of imaging dye leakage as evidence of breakdown of the blood-retinal barrier, this feature also carries the disadvantage of obscuring underlying anatomic detail.

With this in mind, we chose to use the new and non-invasive optical coherence tomography angiography (OCTA), a functional extension of conventional optical coherence tomography (OCT). OCTA shows the retinal and choroidal vasculature by detection of blood flow within the vessels, while also depicting the retinal microstructure three-dimensionally (like conventional OCT). Previous studies have used OCTA to qualitatively characterize BCR eyes, however, significant questions remain regarding the quantitative changes at the different retinal capillary plexuses and their impact on visual acuity.¹¹ The aim of this study was to use OCTA to quantify the alterations in the different retinal capillary plexuses and their impact on visual acuity in patients with BCR.

Methods

Study participants

The study protocol and procedures adhered to the ethics tenets of the Declaration of Helsinki and were approved by Northwestern University's Institutional Review Board. Informed consent was obtained from each participant before inclusion in this retrospective observational cross-sectional study. Healthy control participants as well as participants diagnosed with BCR were recruited at the Department of Ophthalmology of the Feinberg School of Medicine at Northwestern University, Chicago, IL, USA. Inclusion criteria for the BCR cohort were consistent with the international consensus conference research criteria for the diagnosis of BCR.¹² All patients were HLA-A29 positive. Eyes were not included in this study if they did not meet the criteria, had opacified ocular media or low quality imaging preventing a detailed analysis of retinal capillary plexuses. All patients had been diagnosed by a single uveitis specialist (D.A.G.) and were followed regularly for BCR at Northwestern University including best corrected visual acuity (VA) testing, complete ocular examination, OCT-imaging, color fundus photography, electroretinography (ERG) and Goldmann visual fields.

Imaging

For OCTA imaging and evaluation, a commercial SD-OCT device (RTVue- XR Avanti; Optovue, Inc., Fremont, CA) was used. The OCT uses a light beam with a center wavelength of 840nm and a full-width half maximum of 45 nm operating at an axial scan rate of 70,000 A-scans per second. The OCTA volume scans consisted of $304 \times 304 \times 512$ voxels and were acquired in 2.9 seconds. For the purpose of this study, angiographic *en face* OCT scans measuring $3\text{mm} \times 3\text{mm}$ ($X \times Y$) were evaluated using the incorporated Angiovue software. For detection of blood flow, the device acquires two consecutive B-scans at the same position in order to differentiate between bulk tissue and fluctuating particles (mostly erythrocytes in the blood stream). The machine uses split-spectrum amplitude-decorrelation angiography (SSADA) to improve the performance of the vessel segmentation algorithm. For the purpose of selecting images with a high enough image quality, we used the signal strength index (SSI), a measure automatically displayed with every volume scan. Images with a SSI below 50 were not included in our analysis.

Assessment of capillary density, retinal thickness and foveal avascular zone

We used the integrated Analytics software (version 2016.1.0.26) of the Angiovue device to evaluate the vessel density, retinal thickness and foveal avascular zone (FAZ). We used the preset segmentation of the SCP, where the inner and outer boundaries are set $3\mu\text{m}$ posterior to the internal limiting membrane (ILM) and $15\mu\text{m}$ posterior to the inner plexiform layer (IPL), respectively. In eyes with an ERM, the internal boundary was set $3\mu\text{m}$ posterior to the ERM and not the ILM. However, since the posterior boundary of the segmentation was dependent on the position of the IPL, the slab included the entire SCP and manual adjustment of the anterior boundary was not necessary.

For the DCP, the inner and outer boundaries are set $15\mu\text{m}$ posterior to the IPL and $70\mu\text{m}$ posterior to the IPL, respectively. To evaluate the vasculature of the entire retinal thickness, the inner boundary was set at $3\mu\text{m}$ posterior to the ILM (in cases with an ERM this was $3\mu\text{m}$ posterior to the ERM) and the outer boundary was manually set at the outer nuclear layer (ONL), posterior to the DCP. Depending on the retinal anatomy, the offset from the IPL differed individually, however, was always placed within the ONL and anterior to the hyper-reflective retinal pigment epithelium (RPE). We assessed SCP, DCP and full retinal vessel densities for the whole *en face* image ($3 \times 3\text{mm}$) as well as for the parafoveal area (ring with a diameter of 3 mm of the outer circle and a diameter of 1 mm of the inner circle).

The FAZ area was measured using the non-flow detection algorithm integrated in the analysis software. By clicking into the center of the FAZ in the *en face* angiographic image of the SCP, the software automatically extends the measured area to the vessels surrounding the FAZ (Figure 1).

Retinal thickness was automatically measured as the distance between the ILM and the RPE for the foveal (circle with a diameter of 1mm) and parafoveal areas.

Statistics

We used IBM SPSS statistics version 21 (IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA). The Shapiro-Wilk test was used to test for normal distribution of the parameters. We used a Mann-Whitney U test to compare the FAZ area, retinal thickness and the vessel densities of the SCP, DCP and full retina between the BCR and the control group. We used Spearman correlation analysis to study the correlations between VA and the following parameters: BCR disease duration, capillary density, FAZ area and retinal thickness. For these analyses, VA was converted from Snellen to the logarithm of the minimal angle of resolution (LogMAR).

Results

Our study included 74 eyes of 42 study participants (28 female, 14 male) with a mean age of 58 years (± 9 (SD)). Overall demographic and clinical characteristics are presented in table 1.

Representative examples of retinal capillary density and FAZ area are presented in figures 2–4.

Patients with BCR had a mean disease duration of 6 years (± 3.5 SD). Twenty-four eyes had an ERM, eight eyes had CME, two eyes had a CNV and one eye had subretinal fluid associated with CME. All except for two study patients with BCR (three study eyes) were receiving either local or systemic therapy including corticosteroids as well as other immunomodulators (Table 1).

SCP, DCP and full retinal vessel density were significantly lower in the BCR group compared to healthy controls. A significant difference was observed in the parafoveal retinal thickness between BCR and healthy controls but not in foveal retinal thickness. Details are presented in table 2.

The vessel densities of the SCP, DCP and full retina showed a significant (negative) correlation with best-corrected VA (LogMAR) in patients with BCR. In the control eyes, there was no significant correlation between best-corrected VA and any of the following parameters: vessel density, FAZ area, foveal and parafoveal retinal thickness (see table 3).

Discussion

In this study, we used OCTA to quantitatively analyze vessel densities of the retinal capillary plexuses in eyes with BCR and assess their correlation with VA. We found that the SCP and DCP vessel densities were significantly reduced in eyes with BCR when compared to an age-matched control group (Table 2). Vessel density in the different capillary plexuses was significantly associated with VA in BCR patients. This was not the case in the healthy control group (Table 3). The FAZ area and foveal retinal thickness were not significantly different between BCR and healthy controls. The parafoveal retinal thickness, however, was significantly thinner in the BCR group (Table 2). There were no significant correlations in either the BCR or healthy control groups between VA and any of the following parameters: FAZ area, foveal or parafoveal retinal thickness (Table 3).

The different retinal vascular plexuses show a non-uniform capillary distribution, which might be attributed to the metabolic demands of adjacent retinal tissue.¹³ It has been hypothesized that different vascular diseases could affect capillary networks differently, prompting us to separately examine the SCP and DCP in our study.^{14, 15} In a recent study, de Carlo et al. used OCTA in a series of four patients with BCR to show flow-void areas in the choroid in birdshot lesions and changes in the full retinal capillary network.¹¹ The retinal capillary changes detected in their study included abnormally tortuous vessels, capillary loops, focal dilatations and an increased intercapillary space, features typically seen in later stages of vasculitis.^{11, 16} This meticulous evaluation of micro-angiographic changes in the retina is, however, subjective in nature and would be challenging and time-consuming to perform in clinical practice as well as for the larger number of eyes and for the different retinal capillary plexuses. Therefore, we decided to use a quantitative and automated approach to assess microvascular damage. In our study, capillary density in the SCP, DCP and the full retina was significantly decreased in the BCR group, suggesting that microvascular inflammation and subsequent capillary closure are present throughout the retinal vasculature and not confined to a particular network in this disease.

In a histopathological study of BCR eyes, Gaudio et al. showed foci of lymphocytic aggregations along retinal vessels, but did not specify in which layer of the retina these were most numerous.⁶ They hypothesized that a progression from these perivascular lymphocytic infiltrations to ischemia of the inner retina might be expected in patients with BCR in later stages of the disease. In our series, we found a significant decrease of the retinal capillary density as well as retinal thickness in the parafoveal area in eyes of patients with BCR (with a mean disease duration of 6 years), which seems to support their hypothesis. Recently, Agrawal et al. measured retinal vascular calibers in BCR patients and reported significantly impaired calibers only in the retinal venules compared to a healthy control group.¹⁷ This finding suggests that microvascular inflammatory damage in BCR is primarily present in the venous arm.

Foveal retinal thickness was not significantly different between the BCR and healthy control group in our study, nor was the FAZ area. However, parafoveal retinal thickness was significantly decreased in the BCR eyes. Retinal thinning in this area may be caused by retinal atrophy secondary to capillary loss in the macula. Since the fovea contains no inner retinal layers and, therefore, no capillary network, the foveal zone (circle with a 1mm diameter) may be less susceptible to retinal vasculitis and subsequent retinal atrophy. The choroidal perfusion could be sufficiently robust to support the fovea, which would explain the non-significant difference in foveal retinal thickness between the groups in this study. Furthermore, the presence of intraretinal cysts and/or an ERM is likely to distort the foveal contour, resulting in thickening of the fovea in the BCR eyes. In fact, when we compared the healthy controls and BCR eyes (excluding eight eyes with CME), the mean foveal thickness in both groups was surprisingly similar ($259.9 \pm 31.3 \mu\text{m}$ vs $259.9 \pm 32.4 \mu\text{m}$). An important consideration, however, is that diffuse retinal thickening without the presence of intraretinal cysts may be present in the fovea secondary to subtle capillary leakage in BCR. The actual foveal retinal tissue thickness may, therefore, be thinner in BCR patients than in healthy controls but this might not be obvious due to overall retinal (non-cystic) swelling.

Best-corrected visual acuity was significantly correlated with capillary density in the SCP, the DCP and the full retina in the BCR group. In the healthy control group, however, we did not observe a significant correlation between VA and retinal capillary densities. Previous studies in BCR have shown disruption of photoreceptor bands and outer retinal atrophy on OCT associated with vision loss.^{2, 18–21} An association of photoreceptor layer disruption on OCT with retinal vasculitis has been suggested.²¹ These findings might be explained by the important role of the DCP in maintaining a functional outer retinal metabolism. Recently, our group has shown an association between DCP non-perfusion and photoreceptor disruption in patients with diabetic macular ischemia, highlighting the important role of the DCP for oxygen needs of the outer retina.¹⁴ In BCR, the correlation between vessel density and VA may be caused by one of the following mechanisms or a combination of these. Since the plexiform layers of the retina are known to be highly metabolizing regions and dependent on sufficient oxygen supply, retinal vascular impairment could lead to ischemia and subsequent dysfunction of signal transmission within the parafoveal inner retina.²² Another possibility is that, even though primarily nourished by the choroidal vasculature, foveal cones may be dependent on lateral diffusion of oxygen from the surrounding retinal capillary plexuses.²³ Finally, it is plausible that there is no direct cause-and-effect relationship between VA and retinal vessel density. In this scenario, retinal vessel density may be a significant, but indirect biomarker for global retinal damage including photoreceptor compromise, caused by the underlying inflammatory mediators in BCR. We cannot rule out that choriocapillaris and choroidal changes, which we did not assess in this study, could account for photoreceptor and VA deterioration in BCR patients. Previous studies, however, based on indocyanine green angiography, OCT and histopathology, have suggested there may be differential inflammatory involvement of the retina and choroid in BCR.^{5, 6, 20} Furthermore, current SD-OCT-based OCTA devices have limited penetration depth into the choroid, making an accurate evaluation of miniscule abnormalities particularly challenging.¹¹ For these reasons, we think that future studies using swept-source OCT-based OCTA operating at longer wavelengths are necessary to comprehensively investigate the relationship between retinal and choroidal vascular damage.

There was no significant difference in the FAZ area between the two groups. This finding stands in contrast to other retinal vascular diseases such as diabetic retinopathy or retinal vein occlusion, where enlargement of the FAZ is a typical finding that is associated with structural damage to inner and outer retinal layers.^{14, 24} The FAZ area in the general population, however, is highly variable, which may reduce the predictive value of this parameter for an individual patient.²⁵ Using the implemented software of the OCTA instrument for automated measurement of the FAZ, we observed FAZ area sizes in both groups that were similar to a recent report of healthy eyes by Shahlaee et al., who used a manual method for FAZ delineation in OCTA images.²⁶ Given that the control and BCR groups were age-matched in our study, we do not believe that age could have had any role as a potential confounder in the correlation between FAZ area and VA, a finding previously shown in eyes with retinal ischemic vascular disease.²⁴

We are aware of certain limitations of this study. The cross-sectional observational study design limited our observations to only one point in time within the disease process. As well, the study did not stratify BCR patients based on disease severity, duration or control. Larger,

longitudinal studies would allow for better understanding of the vascular pathology and the chain of events that eventually lead to retinal damage and visual impairment, but the rarity of this diagnosis may make this a difficult goal to achieve. Because of the small field of view of the OCTA (and focusing on correlations with VA), we only analyzed vessel densities in the macula in our study. We predict that similar vascular damage occurs outside the arcades, given electroretinographic findings and Goldmann visual field test results that are suggestive of global retinal functional changes⁷, but repeated OCTA measurements outside of the macula are necessary to confirm this theory. Furthermore, exclusion of OCTA scans of low quality and scans with severe motion artifacts may have led to exclusion of the most severe cases of BCR. Strengths of our study include a rather large number of study eyes, an age-matched control group and automated analyses.

In conclusion, our study showed decreased capillary density in all retinal vascular plexuses in eyes with BCR compared to healthy controls, a finding which was significantly correlated with BCVA in BCR. The FAZ area was not different in eyes with BCR compared to healthy controls and did not correlate with vision. Retinal capillary density measured automatically by OCTA might be a promising new parameter to monitor during follow-up and management of BCR and may be a useful biomarker in future longitudinal studies.

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Summary statement

In this study we examined patients with birdshot chorioretinopathy (BCR) using optical coherence tomography angiography (OCTA). Vessel density of the different capillary plexuses, area of the foveal avascular zone and retinal thickness were assessed and correlated with best-corrected visual acuity.

Figure 1.

Color fundus photography (a) and OCT angiography *en face* maps (b-f) of the left eye of a healthy control participant showing vessel density maps of the superficial capillary plexus (SCP; b), the deep capillary plexus (c) and the full retina (d). The color legend illustrates vessel density in percent. The blue overlay on the *en face* OCT angiography of the SCP (e) shows the foveal zone (central circle with 1mm diameter) and the parafoveal zone (ring surrounding the foveal zone with a 3mm diameter). The foveal avascular zone, automatically measured by the OCTA device, is highlighted in yellow in (f).

Figure 2.

Color fundus photography (a) and OCT angiography *en face* maps (b-f) of the right eye of a BCR patient showing vessel density maps of the superficial capillary plexus (b), the deep capillary plexus (c) and the full retina (d). Note the pronounced choroidal changes surrounding the optic disc in (a), as well as the almost confluent appearing birdshot lesions. Mild changes in vessel density are observed in (b-d). The color legend illustrates vessel density in percent.

Figure 3.

Color fundus photography (a) and OCT angiography *en face* maps (b-f) of the right eye of a BCR patient showing vessel density maps of the superficial capillary plexus (b), the deep capillary plexus (c) and the full retina (d). Classic creamy ill-defined birdshot lesions appearing to radiate from the optic nerve are seen in (a), as are a few more atrophic lesions nasal to the nerve. Moderate changes in vessel density are noted in (b-d). The color legend illustrates vessel density in percent. Note the telangiectatic vessels temporal to the fovea in the superficial capillary plexus in (e) and (f).

Figure 4.

Color fundus photography (a) and OCT angiography *en face* maps (b-f) of the right eye of a BCR patient with late stage disease showing vessel density maps of the superficial capillary plexus (b), the deep capillary plexus (c) and the full retina (d). Pigmentary changes can be observed in and around the macula in (a). Distinct birdshot lesions are harder to appreciate, and the retina appears atrophic. Vessel density is severely impaired in the capillary plexuses (b-d). The color legend illustrates vessel density in percent. Note the capillary dropout and the distorted foveal avascular zone in the superficial capillary plexus in (e) and (f).

Table 1

Characteristics of study participants:

	Healthy control participants (n=21)	BCR patients (n=21)
Female (n;%)	12 (57%)	16 (76%)
Eyes (n)	37	37
Age (years; mean±SD)	58 ± 9	57 ± 8
Visual acuity (LogMAR; mean±SD)	0.01 ± 0.06	0.10 ± 0.20
(mean Snellen equivalent)	(20/20)	(20/25)
Systemic IMT (n= patients):	0	13 (62%)
Local treatment (n= eyes):		
Fluocinolone acetonide implant	0	23 (62%)
PST triamcinolone acetonide	0	17 (46%)
Prednisolone acetate eye drops	0	8 (22%)
Dexamethasone intravitreal implant	0	3 (8%)
IVTA	0	2 (5%)
Anti-VEGF	0	1 (3%)
No treatment	0	3 (8%)
Eye findings (n= eyes):		
ERM	0	24 (65%)
CME	0	8 (22%)
CNV	0	2 (5%)
SRF	0	1 (3%)

Abbreviations: BCR = birdshot chorioretinopathy, LogMAR = logarithm of the minimal angle of resolution, IMT = immunomodulatory therapy, PST triamcinolone acetonide = posterior subtenon injection of triamcinolone acetonide, IVTA = intravitreal triamcinolone acetonide injection, anti-VEGF = anti-vascular endothelial growth factor ERM = epiretinal membrane, CME = cystoid macular edema, CNV = choroidal neovascularization, SRF = subretinal fluid.

Table 2

Vessel density, area of FAZ and retinal thickness in the BCR and control group

	Healthy controls (37 eyes)	BCR patients (37 eyes)	p-value
Vessel density (%; mean±SD)			
SCP	50.41 ± 3.01	46.39 ± 4.03	<0.01*
SCP parafovea	52.87 ± 3.05	48.32 ± 4.58	<0.01*
DCP	55.90 ± 3.14	51.64 ± 4.09	<0.01*
DCP parafovea	59.14 ± 3.22	54.37 ± 4.44	<0.01*
Full retina	53.09 ± 3.27	48.97 ± 4.58	<0.01*
Full retina parafovea	56.05 ± 3.29	51.35 ± 5.09	<0.01*
FAZ area (mm²; mean±SD)	0.275 ± 0.10	0.244 ± 0.10	0.196
Retinal thickness (µm; mean±SD)			
Fovea	259.9 ± 31.3	283.7 ± 104.0	0.417
Parafovea	319.1 ± 16.5	306.1 ± 62.0	<0.01*

Abbreviations: BCR = birdshot chorioretinopathy, FAZ = foveal avascular zone, SCP = superficial capillary plexus, DCP = deep capillary plexus. The foveal area was defined as a circle with a diameter of 1mm centered on the fovea. The parafoveal area was defined as a ring with a diameter of 3mm surrounding the foveal area. Statistically significant differences between the groups are highlighted by an asterisk.

Table 3

Correlation between disease duration, vessel density, FAZ area, retinal thickness and visual acuity (LogMAR):

Correlation of visual acuity with evaluated retinal parameters:	Healthy controls (n=37)		BCR (n=37)	
	R	p-value	R	p-value
Disease duration	–	–	0.184	0.276
Vessel density				
SCP	–0.117	0.492	–0.503*	<0.01*
SCP parafovea	–0.120	0.478	–0.527*	<0.01*
DCP	–0.144	0.396	–0.506*	<0.01*
DCP parafovea	–0.189	0.263	–0.463*	<0.01*
Retinal vessel density	–0.162	0.339	–0.516*	<0.01*
Retinal vessel density parafovea	–0.164	0.331	–0.517*	<0.01*
FAZ area	–0.135	0.425	0.127	0.455
Retinal thickness				
Foveal retinal thickness	–0.022	0.896	0.071	0.676
Parafoveal retinal thickness	0.021	0.902	–0.117	0.490

Abbreviations: LogMAR = logarithm of the minimal angle of resolution, BCR = birdshot chorioretinopathy, SCP = superficial capillary plexus, DCP = deep capillary plexus, FAZ = foveal avascular zone. The foveal area was defined as a circle with a diameter of 1mm centered on the fovea. The parafoveal area was defined as a ring with a diameter of 3mm surrounding the foveal area. Statistically significant correlations are highlighted by an asterisk.