Evaluation of Macular Vessel Densities in Patients with Birdshot Chorioretinopathy Using Optical Coherence Tomography Angiography

M Seminel

Hôpital Cochin, Assistance Publique- Hôpitaux de Paris, Université Paris 5, Sorbonne Paris Cité

C Mehanna

Hôpital Cochin, Assistance Publique- Hôpitaux de Paris, Université Paris 5, Sorbonne Paris Cité

M Gerardy

Hôpital Cochin, Assistance Publique- Hôpitaux de Paris, Université Paris 5, Sorbonne Paris Cité

F Hoogewoud

Hôpital Cochin, Assistance Publique- Hôpitaux de Paris, Université Paris 5, Sorbonne Paris Cité

A Touboul

Hôpital Cochin, Assistance Publique- Hôpitaux de Paris, Université Paris 5, Sorbonne Paris Cité

S Somisetty

University of California

D Monnet

Hôpital Cochin, Assistance Publique- Hôpitaux de Paris, Université Paris 5, Sorbonne Paris Cité

A Brezin

Hôpital Cochin, Assistance Publique- Hôpitaux de Paris, Université Paris 5, Sorbonne Paris Cité

E Bousquet (✉ elodie.bousquet@aphp.fr)

Hôpital Cochin, Assistance Publique- Hôpitaux de Paris, Université Paris 5, Sorbonne Paris Cité

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Abstract

Objective

to quantify macular vessel densities (VD) in patients with birdshot chorioretinopathy (BSCR) and investigate the correlation of these parameters with other features of the disease.

Design

Single-center cross-sectional study

Method

Patients with BSCR and healthy controls underwent projection-resolved OCT-angiography (PR-OCTA, RTVue XR Avanti, Optovue). The foveal avascular zone (FAZ) area, the macular VD in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) were recorded. Univariate and multivariate analyses were performed to evaluate the association between PR-OCTA parameters and other clinical and imaging findings.

Results

seventy-five patients (138 eyes) with BSCR and 27 healthy age and sex-matched controls (27 eyes) were included in the study. The VD in both SCP and DCP were significantly lower in the BSCR group compared to the control group ($p < 0.001$). The FAZ area was similar between both groups. Multivariate analysis showed visual acuity and visual field mean defects to be associated with VD in the SCP, while central macular thickness and the visual field were associated with VD in the DCP. Eyes with a disrupted macular ellipsoid zone had a lower VD in the SCP and DCP ($p < 0.001$).

Conclusions

Quantitative evaluation of the macular vessel density might be a new promising tool for monitoring BSCR severity.

Introduction

Birdshot chorioretinopathy (BSCR) is a chronic, bilateral, posterior uveitis characterized by multiple hypopigmented choroidal spots, vitritis, retinal vasculitis and macular edema.¹ The disease is strongly associated with the human leucocyte antigen (HLA)-A29 allele.¹ The exact pathogenesis remains poorly understood, but histopathologic studies show multiple foci of lymphocytes in the deep choroid near the choroidal vessels and surrounding retinal vessels.^{2,3} The range of BSCR phenotypes varies between a benign form of the disease with an excellent prognosis to sight-threatening, progressive chorioretinal atrophy. Monitoring the disease activity and progression remains difficult. Indeed, visual acuity is a poor indicator of disease severity⁴ and other disease-monitoring methods require the use of visual field,

electroretinography, OCT, fluorescein angiography (FA), and indocyanine green angiography (ICG-A). Macular thinning and disruption of the photoreceptor ellipsoid zone on macular OCT have been associated with a poor visual prognosis.^{5,6} Fluorescein angiography (FA) has been widely used to evaluate the inflammatory activity of the disease and provides a good visualization of the retinal vascular leakage, attesting the breakdown of the blood-retinal barrier.⁵ Nevertheless, FA fails to image the deep capillary network⁷ and the leakage of dye can limit the visualization of capillary non-perfusion. Additionally, FA is an invasive, time-consuming test requiring the injection of intravenous dye, which can lead to rare adverse effects.⁸ Optical coherence tomography angiography (OCTA) is a new imaging modality that detects erythrocyte movement, allowing the visualization of blood flow in vivo, without the use of intravenous dye, showing the retinal vasculature.⁹ The projection-resolved OCTA (PR-OCTA) suppresses artefacts in the deep capillary plexus.¹⁰ Moreover, PR-OCTA allows for segmentation of retinal layers and generates quantitative measurements such as vessels densities (VD) and foveal avascular zone (FAZ) area. Interestingly, Roberts PK et al reported a decreased density in both, superficial and deep plexus, in patients with BSCR, which correlated with visual acuity.¹¹ The aim of this study was to quantify the macular retinal capillary density in a large cohort of patients with BSCR and to investigate the correlation of these parameters with other features of the BSCR.

Methods

Study design and population

This is a single center non-interventional cross-sectional study on a longitudinal cohort of patients with birdshot chorioretinopathy. All patients underwent a standardized, prospectively defined evaluation at Hôpital Cochin in Paris, France. The diagnosis of the disease was made based on the criteria described by Levinson et al¹² and all patients were HLA-A29 allele carriers. Patients with cystoid macular edema greater than 300 µm were excluded due to the limitations of OCTA imaging as detailed below. Other additional eye diseases such age-related macular degeneration, diabetic retinopathy, retinal vascular occlusion, and high myopia were excluded from the study.

In addition, we enrolled a group of age and sex-matched healthy participants with a normal ocular exam and refraction within -3 and +2 diopters of refractive error and without any known systemic or ocular disease.

Ethic Statement

Informed signed consent was obtained from all subjects. All research adhered to the tenets set forth in the Declaration of Helsinki. Patients acknowledged that they cannot be identified via the paper and that we have fully anonymized them. All study-related data acquisitions were approved by our institutional review board (CERB d'Ile de France, Paris, France) and registered on clinicaltrials.gov (identifier NCT05153057).

Study protocol

The research protocol for our cohort of BSCR has been described in detail in our previous publications.^{4,5}

Data collection was recorded using a standardized form. The ophthalmological history was systematically recorded and included: treatment modalities and duration of the disease since the first uveitis related symptoms.

In brief, all patients underwent a complete ophthalmologic examination on a single day, including assessment of best-corrected visual acuity, anterior segment examination, dilated fundus biomicroscopy, fluorescein angiography (Spectralis, Heidelberg Engineering, Heidelberg, Germany), and spectral domain OCT (SD-OCT, Spectralis) with EDI (enhanced depth imaging) acquisition. Choroidal thickness was manually measured between the outer portion of the retinal pigment epithelium and the inner surface of the sclera on EDI horizontal B-scans, as previously described.¹³ The ellipsoid zone was analyzed on the EDI-SD-OCT-scan crossing the fovea. The EZ line was classified as “continuous” or “disrupted” (supplementary Figure). Two independent masked graders (MS and MG) analyzed the EZ line integrity. In situations of disagreement between readers, consensus was reached by an open discussion. Visual field testing was performed using automated perimetry with the Humphrey visual field analyzer, using the FastPac full-threshold 30-2 program (Zeiss-Humphrey, San Leandro, CA).

The presence of vitritis was quantified as described by Nussenblatt et al.¹⁴ Intraocular inflammation was defined by the presence of ≥ 1 + of vitritis, and/or vasculitis, and/or papillitis.

OCTA images acquisition and analysis

All subjects were imaged by the AngioVue OCT-Angiography system on the commercially available RTVue XR Avanti device (Optovue, Inc, Fremont, CA). OCT angiography (OCTA) device was used to obtain amplitude decorrelation angiography images. This instrument has an A-scan rate of 70,000 scans per second to acquire OCTA volumes consisting of 304X304 A-scans. Orthogonal registration and merging of 2 consecutive scan volumes were used to obtain 3X3 mm OCTA volumes centered on the fovea. The projection-resolved (PR-OCTA) was used to suppress projection artefacts, thus allowing for proper segmentation of retinal structures.¹⁰ The proportion of retinal area occupied by blood vessels was automatically calculated and defined as the macular vessel density (VD). The images were automatically segmented into the superficial capillary plexus (SCP) and deep capillary plexus (DCP). Automated segmentation was verified for each eyes and manual correction was performed in cases of segmentation errors. The foveal avascular zone (FAZ) was measured in the SCP using the no-flow measurement tool of the software and was adjusted manually if necessary. Two experienced readers (MS and MG) analyzed the images. Poor quality images, defined as scans with signal strength less than 50 (maximum: 100), saccade or blinking artifacts disturbing micro vascularization analysis, were excluded.

Moreover, intraretinal cysts frequently cause inaccurate segmentation of the software and assessment of vessel densities. Thus, we excluded all patients with cystoid macular edema on SD-OCT and those with a

central macular thickness greater than 300 μm .

Statistical analysis

Statistical analyses were performed using R version 3.5.0 (R foundation for Statistical Computing, Vienna, Austria). Best-corrected visual acuity was converted to the logarithm of the minimal angle of resolution (logMAR). Descriptive data is presented as the mean $\pm$ standard deviation for the quantitative variables. For the categorical variables, data is presented as counts and percentages. Comparisons between variables were performed using Mann-Whitney U test or Chi-square tests when appropriate. Univariate and multivariate generalized linear regression analyses were performed to assess the association between macular vessel densities and other ocular factors. Correlations between both eyes were eliminated using the marginal model generalized estimating equations. Factors showing significant associations in univariate analysis ($p < 0.05$) were included in the multivariate regression model. All P-values were 2-sided and were considered significant if $p \leq 0.05$.

Results

Demographic, Clinical and Imaging Patient characteristics

Overall, 75 patients (138 eyes) with BSCR met the inclusion criteria and 27 healthy, age and sex-matched controls (27 eyes) were included in the study (Table 1). Indeed, among the 86 patients (159 eyes) seen at the time of the study, 11 patients (21 eyes) were excluded: diabetic retinopathy (2 eyes), macular neovascularization (2 eyes), macular edema with CMT $> 300 \mu\text{m}$ (8 eyes), poor image quality due to artefacts, movement, or signal strength index (SSI) < 50 (9 eyes).

Table 1

Demographic, clinical and imaging data of birdshot chorioretinopathy and healthy control groups.

	Birdshot Patients (n= 138 eyes from 75 patients)	Healthy Controls (n= 27 eyes from 27 patients)	P value
Demographic and clinical data			
Age (years), mean $\pm$ SD	60.7 $\pm$ 10.1	60.5 $\pm$ 12.5	0.5 ^a
Gender, females, n (%)	47 (62.7%)	16 (59.3%)	0.7 ^b
Disease duration (years), mean $\pm$ SD	9.7 $\pm$ 6.4	-	
Treatment :			
Never treated (systemic, locally), n patients (%)	15 (20%)	-	
Current Immunosuppressive treatment, n patients (%)	30 (40%)	-	
Current systemic corticosteroids without immunosuppressive treatment, n patients (%)	5 (6.7%)	-	
Previous corticosteroids subtenon or intravitreal injection, n eyes (%)	69 (50%)	-	
Best-Corrected Visual Acuity, logMAR, mean $\pm$ SD	0.12 $\pm$ 0.28	0 $\pm$ 0	< 0.001 ^a
Disease inflammatory activity* , n eyes (%)	46 (33.8%)	-	
Vitreous haze: 1 + or more	11 (8%)	-	
Retinal vasculitis based on FA	34 (25%)	-	
Papillitis based on FA	24 (17.6%)	-	
SD-OCT			
Central macular thickness, mean $\pm$ SD, μ m	226 $\pm$ 44	-	
Previous macular edema, n eyes (%)	63 (45.7%)		
Subfoveal choroidal thickness, mean $\pm$ SD, μ m	238.7 $\pm$ 104.2	-	

SD: standard deviation; LogMAR: logarithm of the Minimal Angle of Resolution; FA: fluorescein angiography; SD-OCT: spectral domain optical coherence tomography; dB: decibel; FAZ : foveal avascular zone.

*defined by the presence of macular edema and/or $\geq 1+$ of vitritis and/or vasculitis and/or papillitis

^a Mann-Whitney U test; ^b Chi2 test

	Birdshot Patients (n= 138 eyes from 75 patients)	Healthy Controls (n= 27 eyes from 27 patients)	P value
Visual field mean deviation, mean $\pm$ SD, dB	- 5.1 $\pm$ 5.6	-	
OCT-Angiography			
Signal Strength Index, mean $\pm$ SD	68 $\pm$ 9.3	72 $\pm$ 19	0.002
Macular Vessel Density, mean $\pm$ SD			
Superficial Capillary Plexus	41.8 $\pm$ 4.8	46.1 $\pm$ 4.1	< 0.001 a
Superficial Capillary Plexus parafovea	44.1 $\pm$ 5	48.8 $\pm$ 4.5	< 0.001 a
Deep Capillary Plexus	43.9 $\pm$ 6	50.1 $\pm$ 4.4	< 0.001 a
Deep Capillary Plexus parafovea	45.3 $\pm$ 6.2	52 $\pm$ 4.9	< 0.001 a
FAZ area, mm ² mean $\pm$ SD	0.27 $\pm$ 0.14	0.26 $\pm$ 0.13	0.83 ^a
SD: standard deviation; LogMAR: logarithm of the Minimal Angle of Resolution; FA: fluorescein angiography; SD-OCT: spectral domain optical coherence tomography; dB: decibel; FAZ : foveal avascular zone.			
*defined by the presence of macular edema and/or ≥ 1 + of vitritis and/or vasculitis and/or papillitis			
^a Mann-Whitney U test; ^b Chi2 test			

The demographic, clinical, and imaging data are summarized in Table 1.

In the BSCR group, patient's mean age was 60.7 $\pm$ 10.1 years and 47 patients were female (62.7%). The mean disease duration was 9.7 years. Systemic and ocular treatments are described in Table 1. The mean best-corrected visual acuity (BCVA) was 0.12 $\pm$ 0.28 logMAR. Inflammatory disease activity was detected in 46 (33.8%) patients (Table 1).

Comparison Between Birdshot Chorioretinopathy And Healthy Control Groups

The age and sex-matched healthy control group consisted of 27 eyes from 27 participants (Table 1). The signal strength index was slightly lower in the BSCR group than in control patients ($p=0.002$). The vessel density in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) was significantly lower in the BSCR group compared with the control group ($p< 0.001$, Table 1 and Figure). There was no significant difference in the Foveal avascular zone (FAZ) area between both groups.

Factors associated with the Superficial Capillary Plexus densities in univariate and multivariate analysis

In univariate analysis, SSI, age, BCVA, previous macular edema, and visual field mean defect were associated with SCP vascular density (Table 2). In multivariate analysis, a decrease in SSI, visual acuity, and visual field mean defect were associated with a lower SCP (Table 2).

Table 2

Generalized Linear Regression Analyses of factors associated with superficial vascular plexus density in patients with Birdshot Chorioretinopathy.

Variables	Univariate		Multivariate	
	Standardized Coefficient β	P value	Standardized Coefficient β	P value
Signal Strength Index	0.526	< 0.001	0.432	< 0.001
Age	- 0.277	0.004		
Gender (male vs females)	- 0.144	0.2		
Estimated disease duration	- 0.183	0.1		
Current Immunosuppressive treatment (no vs yes)	0.082	0.4		
Previous corticosteroids subtenon or intravitreal injection (no vs yes)	- 0.068	0.5		
Best-corrected visual acuity	- 0.392	0.047	- 0.198	< 0.001
Disease Inflammatory activity* (no vs yes)	0.082	0.3		
Previous macular edema (no vs yes)	0.211	0.03		
Central macular thickness	0.156	0.3		
Subfoveal choroidal thickness	0.04	0.6		
Visual field Mean Defect	0.384	< 0.001	0.234	0.006
* Disease Inflammatory activity defined by the presence of vitritis and/or papillitis and/or retinal vasculitis				

Factors associated with the deep capillary plexus densities in univariate and multivariate analysis

In univariate analysis, SSI, disease duration, immunosuppressive treatment, previous macular edema, central macular thickness, and visual field mean defect were associated with DCP vascular density (Table 3). In multivariate analysis, a decrease in SSI, central macular thickness, and visual field mean defect were associated with a lower DCP (Table 3).

Table 3

Generalized Linear Regression Analyses of factors associated with deep vascular plexus density on OCT angiography in patients with Birdshot Chorioretinopathy.

Variables	Univariate		Multivariate	
	Standardized Coefficient β	P value	Standardized Coefficient β	P value
Signal Strenght Index	0.414	< 0.001	0.390	< 0.001
Age	-0.215	0.07		
Gender (male vs females)	- 0.047	0.64		
Disease duration	-0.223	0.018		
Current Immunosuppressive treatment (no vs yes)	0.199	0.046		
Previous corticosteroids subtenon or intravitreal injection (no vs yes)	0.082	0.4		
Best-corrected visual acuity	-0.263	0.027		
Disease Inflammatory activity* (no vs yes)	0.052	0.58		
Previous macular edema (no vs yes)	0.212	0.025		
Central macular thickness	0.384	< 0.001	0.289	<0.001
Subfoveal choroidal thickness	0.076	0.42		
Visual field Mean Defect	0.538	< 0.001	0.318	<0.001
* Disease Inflammatory activity defined by the presence of vitritis and/or papillitis and/or retinal vasculitis				

Macular Ellipsoid Zone (Ez) Analysis

A disrupted macular EZ was detected in 37/138 eyes (26.8%) (Table 4). A lower BCVA and higher mean defect on visual field were detected in eyes with a disrupted EZ compared to eyes with continuous

macular EZ ($p < 0.001$). The CMT was thinner in eyes with a disrupted EZ ($p < 0.001$). Macular vessel densities were decreased in both, SCP and DCP, in eyes with a disrupted macular EZ compared to eyes with a continuous macular EZ ($p < 0.001$, Table 4).

Table 4

Clinical and Imaging data of patients with Birdshot Chorioretinopathy in respect to the macular Ellipsoid zone on SD-OCT.

	Continuous macular EZ n=101	Disrupted macular EZ n=37	P value*
Best-Corrected Visual Acuity , logMAR, mean $\pm$ SD	0.07 $\pm$ 0.15	0.27 $\pm$ 0.45	< 0.001
Visual field mean deviation, mean $\pm$ SD, dB	-3.2 $\pm$ 3.1	-10.6 $\pm$ 7.3	< 0.001
SD-OCT			
Central macular thickness, mean $\pm$ SD, μ m	274.8 $\pm$ 36.3	236.3 $\pm$ 43.7	< 0.001
Subfoveal choroidal thickness, mean $\pm$ SD, μ m	248.8 $\pm$ 106.3	212.1 $\pm$ 95	0.11
OCT-Angiography			
Signal Strength Index, mean $\pm$ SD	68.8 $\pm$ 9.5	64.3 $\pm$ 8	0.009
Macular Vessel Density, mean $\pm$ SD			
Superficial Capillary Plexus	42.3 $\pm$ 5.7	39.2 $\pm$ 5.1	0.001
Deep Capillary Plexus	45.6 $\pm$ 5.1	39 $\pm$ 5.8	< 0.001
SD: standard deviation; LogMAR: logarithm of the Minimal Angle of Resolution			
* Mann-Whitney U test			

Discussion

In this cross-sectional study, we evaluate macular vessel densities using PR-OCTA in a large cohort of birdshot patients. Eyes with retinal cysts and CMT > 300 μ m were excluded to avoid segmentation errors and inaccurate vascular density values. We found that the vascular density is lower in BSCR eyes when compared with age-matched healthy eyes in both, the SCP and DCP. This result is in agreement with the study of Roberts et al evaluating 37 eyes of 27 patients with BSCR.¹¹ The reason for the decreased vascular density in patients with BSCR is unknown. Whether the capillary inflammation in BSCR leads to macular capillary occlusion is yet to be determined.¹¹ In a study of 4 patients with BSCR, De carlo et al¹⁵ found qualitative abnormalities on OCT angiogram such as capillary loops, focal dilatations and an increased intercapillary space, which may correspond to capillary inflammation. In the study of Forte R et al, these capillary abnormalities were found in about half the patients with BSCR. Whether these capillary

abnormalities are the consequence of macular capillary inflammation and secondary occlusions is yet to be determined. However, using ultrawide field angiography, Testi et al¹⁶ showed peripheral capillary non-perfusion in half the cases, suggesting vascular inflammation induced retinal vessel occlusion and ischemia in patients with BSCR.

Another interesting result from our study was the association between vascular density in the SCP and functional parameters such as visual acuity and visual field in multivariate analysis. Roberts et al¹¹ previously showed a correlation between visual acuity and vascular density in patients with BSCR. Vessel densities are also correlated with visual acuity in other retinal diseases which are characterized by occlusion of retinal capillaries.¹⁷

Nevertheless, we did not find any difference in the FAZ area between patients with BSCR and healthy control group, consistent with the study of Robert et al.¹¹ On the other hand, in diabetic retinopathy and retinal vein occlusion, the FAZ area is increased and correlated with visual acuity. The reason for the lack of increased FAZ area in patients with BSCR is unknown, but recent analyses using OCTA demonstrates high interindividual differences in FAZ area and shape in healthy subjects.^{18,19}

We further explored the macular ellipsoid zone (EZ) on SD-OCT scan. Interestingly, patients with disrupted macular EZ had a decreased CMT, SCP, and DCP compared to patients with a continuous foveal EZ. These results are in line with recent works suggesting that decreased perfusion in the DCP may play an important role in photoreceptor damage seen on SD-OCT. Recently, Forte et al showed a decrease in cone density using adaptative optics in the area of capillary abnormalities seen on OCTA in patients with BSCR, suggesting that capillary macular occlusion could lead to photoreceptor damage. However, if it is well established that most of the metabolic supply to the outer retina is provided by the choroidal circulation, recent studies suggest that the DCP could contribute to photoreceptor oxygen requirements, particularly during dark adaptation²⁰ and hypoxia.²¹ However, due to the cross-sectional design of our study, we are unable to determine if the decrease in VD precedes photoreceptor damage and macular thinning or if it is the other way around. Previous studies have revealed that macular ischemia, in the context of diabetic macular edema, may be associated with EZ zone disruption.^{22,23} We cannot exclude choroidal changes as a contributor to photoreceptor disruption on OCT even if we did not find an association between DCP and the choroidal thickness.

We acknowledge several limitations of our study. First, the evaluation of the intermediated capillary plexus was not available in the software of the Optovue at the time of the study. Second, the cross-sectional design limited our analysis to only one point in time. Third, we analyzed the vessel densities in a small field of view of the PR-OCTA (3mm x 3mm). Recent advances in OCT technology includes the introduction of OCTA swept-source technology and wide-field OCTA imaging beyond the macula²⁴, which could permit further studies on vascular alterations in BSCR disease and investigate the relationship between retinal and choroidal vascular damage. Finally, we excluded patients with macula edema since the presence of retinal cysts affects the quantification analysis of the OCTA. Most severe cases of BSCR were excluded due to poor fixation and low-quality scans.

However, there are strengths of this study such as a large sample size of patients with a rare disease and a prospective longitudinal cohort with a standardized clinical examination. Our results suggest that OCTA is a non-invasive exam which could monitor birdshot chorioretinopathy progression and could improve our understanding of the physiopathology of BSCR. Further longitudinal studies are warranted to confirm these results.

Declarations

All data generated analyzed during this study are included in this published article.

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Figures

Figure 1

Representative 3x3 mm OCTA angiograms of BSCR (birdshot chorioretinopathy) and control patients centered on the fovea. The vessel density is decreased at the level of both the superficial and deep capillary plexus.

Supplementary Files

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