Choroidal Vascular Features in Central Serous Chorioretinopathy: Widefield Multimodal Analysis

Características Vasculares na Coriorretinopatia Serosa Central: Análise por Imagem Multimodal de Campo Alargado

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ABSTRACT

INTRODUCTION: Our objective was to evaluate choroidal vascular features of patients with central serous chorioretinopathy (CSC) using widefield (WF) swept-source optical coherence tomography (SS-OCT) and ultra-widefield (UWF) indocyanine green angiography (ICGA).

METHODS: Observational study with a prospective design conducted in patients with CSC. All cases underwent UWF ICGA using a confocal scanning laser ophthalmoscopy (SLO) device and WF SS-OCT. WF *en face* OCT images of the choroid and mid-late UWF ICGA images were created using Photoshop. The image analysis protocol comprised the analysis of choroidal vascular features in UWF ICGA (symmetric vortex veins territories; pachyvessels crossing watershed territories; choroidal vascular hyperpermeability (CVH) and intervortex anastomosis) and WF *en face* SS-OCT images (pachyvessels crossing watershed areas and intervortex anastomoses). Correlation between the variables of interest was performed using the Pearson correlation coefficient. Statistical significance was set as <0.05.

RESULTS: A total of 23 eyes from 12 patients diagnosed with CSC were included in the analysis. Symmetry analysis in UWF ICGA showed asymmetric vortex vein territories in 16 eyes (70%). The most prevalent asymmetric territory was the inferior-nasal (10 eyes, 43%). Pachyvessels crossing choroidal watershed zones were present in 20 of eyes (87%) with a perfect agreement between UWF ICGA and *en face* UWF OCT (r = 1.0). Both horizontal and vertical watershed areas were crossed in 8 eyes (40%). Evaluation of intervortex anastomosis showed a higher prevalence when evaluated by *en face* WF OCT (26%, 6 eyes). A moderate correlation between asymmetric vortex vein territories and intervortex anastomoses was observed (r = 0.51). Mid-late CVH in ICGA was present in 19 cases (83%), among which 5 cases (26%) showed diffuse CVH. A moderate positive correlation (r = 0.53) was also observed between diffuse CVH and pachyvessels crossing both meridians.

CONCLUSION: WF *en face* SS-OCT can be used to detect non-invasively choroidal vascular anomalies in CSC. Pachyvessels crossing the horizontal and vertical meridians are moderately associated with diffuse CVH in ICGA, supporting its role as a non-invasive biomarker of choroidal venous insufficiency.

KEYWORDS: Angiography; Central Serous Chorioretinopathy; Indocyanine Green; Tomography, Optical Coherence.

RESUMO

INTRODUÇÃO: O nosso objetivo foi avaliar as alterações vasculares coroideias em doentes com coriorretinopatia serosa central (CSC) utilizando tomografia de coerência ótica *swept-source* de campo alargado (WF SS-OCT) e angiografia de verde de indocianina de campo ultra-alargado (UWF ICGA).

MÉTODOS: Estudo observacional prospetivo em doentes com CSC. Todos os doentes foram submetidos a UWF IGCA utilizando uma câmara de laser confocal e a WF SS-OCT. As imagens *en face* WF OCT da coróide e as imagens dos tempos tardios da UWF IGCA foram criadas utilizado *Photoshop*. O protocolo de análise de imagem consistiu na análise das características vasculares coroideias nas imagens de UWF IGCA (simetria dos territórios das veias vorticosas, paquivasos a cruzar os territórios de barragem, hiperpermeabilidade vascular coroideia (CVH) e anastomoses intervorticosas) e nas imagens de *en face* WF SS-OCT (paquivasos a cruzar os territórios de barragem e anastomoses intervorticosas). A correlação entre as variáveis em estudo foi realizada utilizado o coeficiente de correlação de Pearson. Definiu-se como estatisticamente significativo um valor <0,05.

RESULTADOS: Um total de 23 olhos de 12 doentes com o diagnóstico de CSC foram incluídos neste estudo. A análise da simetria dos territórios das veias vorticosas por UWF IGCA mostrou a presença de assimetria em 16 olhos (70%). O território assimétrico mais frequente foi o nasal-inferior (10 olhos, 43%). Foram identificados paquivasos a cruzar os territórios de barragem em 20 olhos (87%) com uma concordância perfeita entre a imagem UWF IGCA e a imagem *en face* WF OCT (r = 1,0). Em 8 olhos (40%) verificou-se o cruzamento simultâneo dos territórios de barragem horizontal e vertical. A prevalência de anastomoses intervorticosas foi superior quando avaliada por *en face* WF OCT (26%, 6 olhos). Foi observada uma correlação moderada entre a assimetria dos territórios das veias vorticosas e a presença de anastomoses intervorticosas (r = 0,51). Observou-se CVH na fase tardia da IGCA em 19 olhos (83%), dentro dos quais, 5 (26%) apresentavam CVH difusa. Foi também observada uma correlação moderadamente positiva (r = 0,53) entre CHV difusa e paquivasos a cruzar ambos os meridianos.

CONCLUSÃO: A WF *en face* SS-OCT pode ser utilizada para identificar de forma não invasiva as alterações vasculares coroideias presentes na CSC. A presença de paquivasos a cruzar os meridianos horizontais e verticais está moderadamente associada à presença de CHV difusa na IGCA, o que suporta o seu papel com biomarcador não invasivo de insuficiência vascular coroidea.

PALAVRAS-CHAVE: Angiografia; Corioretinopatia Serosa Central; Tomografia de Coerência Ótica; Verde de Indocianina.

INTRODUCTION

As firstly hypothesized by Gass, choroidal abnormalities, i.e. choroidal thickening, capillary and venous congestion, and hyperpermeability, are thought to be the primary pathophysiology of central serous chorioretinopathy (CSC).[1] Choroidal blood supply originates from the posterior ciliary arteries (PCA) and venous drainage is performed by four vortex veins, each of which drains a symmetric quadrant.[2] In healthy subjects, choroidal vortex veins have independent drainage territories which translate into physiologic horizontal and vertical watershed zones between the four quadrants.[3]

Imaging of the choroid by traditional photographic and angiographic modalities is impeded by the relative opacity of the retinal pigment epithelium (RPE) to visible light.[4] Indocyanine green angiography (ICGA) uses longer wavelengths that penetrate deeper into the RPE, making this method the current gold standard to evaluate the choroidal vasculature.[5] Various studies have shown that ICGA is the method of choice to evaluate choroidal vascular anomalies in patients with CSC, i.e. vascular filling delay, large, dilated, and densely packed choroidal vessels, and choroidal vascular hyperpermeability revealed by late focal hyperfluorescent staining.[6-8] However, ICGA is a time-consuming and expensive procedure, and its routine application in clinical practice is not sustainable.

Optical coherence tomography (OCT) was one of the biggest advances in ophthalmology, allowing the obser-

vation of the structure and flow of the human retina with unprecedented speed and resolution. The development of *swept-source* OCT (SS-OCT), with a longer wavelength and higher scanning speed, has improved depth imaging and enabled the acquisition of high-resolution volumetric cubes of the choroid, from which *en face* sections can be constructed.[4] Several studies have described *en face* SS-OCT features of the choroidal vasculature in chronic CSC, most notably choroidal thickening and dilated choroidal vessels occupying the full thickness of the choroid, i.e. pachyvessels.[4,7,9] Recently, Ramtohul *et al* have shown the ability of ultra-widefield SS-OCT (UW-OCT) to replicate some of the choroidal venous insufficiency features identified by ICGA.[11] Choroidal venous insufficiency can impact clinical management not only in patients with CSC but also in patients with other retinal diseases concurrent with subretinal fluid, i.e. some forms of retinal dystrophies and age-related macular degeneration.[6] Thereby, the ability to identify choroidal venous insufficiency features non-invasively might impact daily clinical practice.

The aim of this study was to investigate whether *en face* WF SS-OCT using a simple imaging protocol can non-invasively replicate features observed using UWF IGCA in patients with CSC.

METHODS

This was an observational study that included patients diagnosed with CSC at Hospital Garcia de Orta from the practice of two retina specialists (AMP and DC), between June 2022 and September 2022. The study was conducted by the principles of the Declaration of Helsinki, written informed consent was obtained from each participant and IRB approval was obtained from Hospital Garcia de Orta Ethics Committee for Health (Almada, Portugal). CSC diagnosis was based on the clinical history, ophthalmoscopic examination, and retinal imaging using multimodal imaging (presence of serous retinal detachment on SS-OCT, typical dye leakage on FA, choroidal vascular hyperpermeability (CVH) on mid- to late-phase ICGA, focal or diffuse increased choroidal thickness and absence of macular neovascularization on SS-OCTA. We excluded patients with any ocular or systemic condition possibly affecting the diagnosis of CSC, including a history of ocular trauma, choroidal neovascularization, uveitis, retinal surgery, glaucoma filtration surgery, extreme axial lengths and/or refractive error inferior to - 6 or superior to + 3 diopters and/or choroidal tumors. All patients underwent UWF ICGA using a confocal scanning laser ophthalmoscopy (SLO) platform coupled with a widefield adapter with 163º field of view (Mirante, Nidek Co. Ltd., Gamagori, Japan). UWF ICGA images were acquired after intravenous administration of 0.2 mg/kg of indocyanine green at the early (up to 3 minutes after injection), middle (5 to 10 minutes), and late phases (10 to 20 minutes) of the angiogram. Widefield acquisitions were done to observe the four vortex veins (two acquisitions per angiographic phase) and merged into a single UWF image using the Photomerge™ command in Photoshop (versions 21.1.3, Adobe, Inc., San 143 Jose, CA, USA).

SS-OCTA data was acquired using PLEX Elite 9000 SS-OCTA (Carl Zeiss Meditec, Inc., Dublin, CA, USA) with a scanning speed of 100 000 A-sans/s, lateral resolution of 20 µm, axial resolution of 6.3 µm, with a near-infrared illumination of 1040 - 1060 nm. Images with a quality index ≥ 7 were selected. WF OCT scans of 15 x 15 mm using a scanning speed of 200KHz were obtained. Segmentation of the choroid was performed automatically using the built-in software and manual correction when required. The Bruch's membrane and choroidal-scleral junction were set as inner and outer segmentation boundaries, respectively. WF SS-OCT scans were performed at two fixation points (central and nasal) to create a composite WF *en face* OCT image of the choroid with a field of view of approximately 15 x 20 mm. Photomontage was performed using the Photomerge™ command in Photoshop.

WF ICGA (early and late phases) images and *en face* WF OCT images were automatically registered and aligned prior to grading. ICGA and *en face* SS-OCT images were registered using the plugin landmark correspondences for Fiji (U. S. National Institutes of Health, Bethesda, Maryland) by selecting 6 corresponding points for each pair of images and employing a similarity algorithm.[10]

The image analysis protocol comprised the analysis of choroidal vascular features in UWF ICGA (symmetric vortex veins territories (present/absent; when absent, the asymmetric quadrant was identified); pachyvessels crossing watershed territories (present/absent; when present, the watershed territory crossed was annotated); choroidal vascular hyperpermeability (CVH, present/absent; when present, location per quadrant was itemized) and intervortex anastomosis (present/absent; when present, the location per quadrant was listed). The presence of pachyvessels crossing watershed areas and intervortex anastomoses were also assessed in WF *en face* SS-OCT images obtained after photomontage. Images were assessed by two groups of graders (UWF ICGA: PC and PR; WF *en face* SS-OCT: DC and RL). Disagreements over readings were resolved by open adjudication. The symmetry of vortex vein territories, pachyvessels and choroidal vascular hyperpermeability were defined as previously described.[211] Summarizing, vortex veins territories were considered asymmetric when there was a difference superior or equal to 20% in the surface area drained by the vortex vein of one quadrant in comparison to the territory of the dominant vortex vein; pachyvessels were defined as dilated and tortuous choroidal vessels observed in the venous phase of ICGA; choroidal vascular hyperpermeability was defined as hyperfluorescent spots different from the background fluorescence in mid-late ICGA images and not attributable to choroidal neovascularization (eyes presenting ill-defined or larger areas of hyperfluorescence were labeled as having "diffuse" CVH); intervortex venous anastomoses were defined as two anastomotic vessels (greater than or equal to the size of a retinal arcade vein at the border of the optic disc) connecting two separate vortex vein systems. Fig. 1 shows an example of image analysis of UWF ICGA and *en face* SS-OCT. Statistical analysis was performed using SPSS

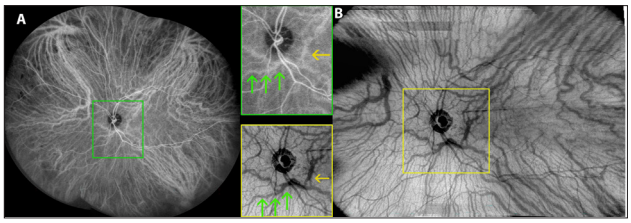

Figure 1. Multimodal analysis of left eye of a 75-year-old man with central serous chorioretinopathy: (A) Mid-phase widefield indocyanine green angiography and (B) photomontage of *en face* OCT image (15x20 mm) showing intervortex venous anastomoses (yellow arrow) and pachyvessels crossing watershed areas (green arrow).

software statistical software (version 25, SPSS Inc, Chicago, IL). All values are expressed as the mean ± standard deviation. Correlation between pachyvessels crossing the watershed zones identified on UWF ICGA and *en face* WF OCT images was performed using the Pearson correlation coefficient. Statistical significance was defined as <0.05.

RESULTS

A total of 24 eyes from 12 patients diagnosed with CSC, 7 men (58.3%) and 5 women (41.6%) were initially enrolled. Following image acquisition, 1 eye was excluded from further imaging because medium opacities were difficult to circumvent by ICGA. The mean age in the cohort was 57.3 ± 14.7 (range 34 to 82) years. All patients in this series had a disease duration longer than 6 months.

Symmetry analysis in UWF ICG showed asymmetric vortex vein territories in 16 eyes (70%) (Fig. 2). The asymmetric territory was the inferior-nasal (IN) in 10 eyes (43%), the superior-nasal (SN) in 5 eyes (31%), and the inferior-temporal in one eye (4%).

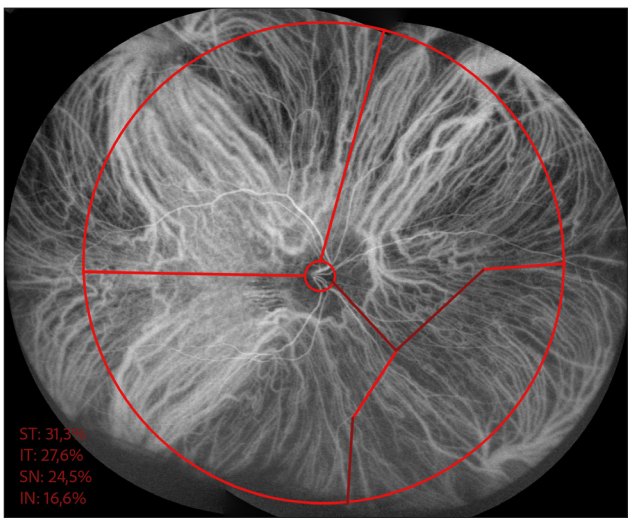

Figure 2. Mid-phase widefield indocyanine angiography image of the right eye of a 54-year-old man with chronic central serous chorioretinopathy. Manual demarcation of each vortex vein system was done for symmetry analysis (red markings) and expressed as a percentage of a circular area centered on the optic disc, with its circumference intersecting the vortex vein ampulla. The choroidal venous drainage is not evenly distributed into the 4 quadrants, being the inferior-nasal vortex vein territory asymmetric.

Pachyvessels crossing choroidal watershed zones were present in 20 eyes (87%), with a perfect agreement between UWF ICGA and *en face* UWF OCT grading (r = 1.0) (Fig. 3). Both horizontal and vertical watershed areas were crossed in 8 eyes (40%); in 8 eyes (40%) only the horizontal watershed zone was crossed, and the vertical watershed zone was crossed in 4 eyes (20%). The correlation between pachyvessels crossing watershed areas (present/absent) and asymmetric vortex vein territories (present/absent) was negligible (r = 0.30).

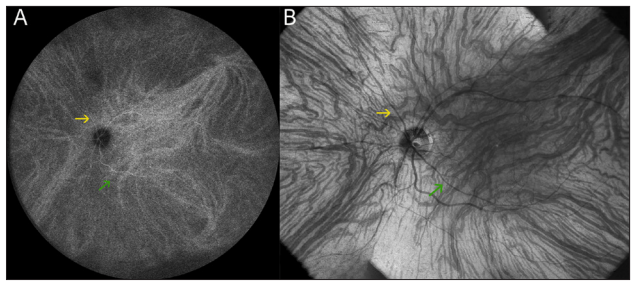

Figure 3. Multimodal analysis of left eye of a 40-year-old man with central serous chorioretinopathy: (A) Mid-phase widefield indocyanine green angiography and (B) photomontage of *en face* OCT image (15x20 mm) showing pachyvessels crossing vertical (yellow arrow) and horizontal choroidal watershed zones (green arrow).

The evaluation of intervortex anastomosis showed a prevalence of 26% (6 eyes) when assessed by UWF ICGA and 35% (8 eyes) when evaluated by *en face* WF OCT images (r = 0.84). In *en face* WF OCT images analysis, the anastomosis between superior and inferior vortex veins was the most frequently identified (4 eyes, 50% cases), followed by peripapillary anastomoses (3 eyes, 38% cases) and horizontal anastomosis (1 eye, 12.5%) (Fig. 4). The correlation between intervortex anastomosis (present/absent) and asymmetric vortex vein territories (present/absent) was moderate (r = 0.51).

Assessment of areas of CVH mid-late phases of ICGA allowed its identification in 19 cases (83%), from which diffuse hyperpermeability was present in 5 cases (26%), peripapillary leakage was present in one case (5%), and the following cases showed focal hyperpermeability. Correlation

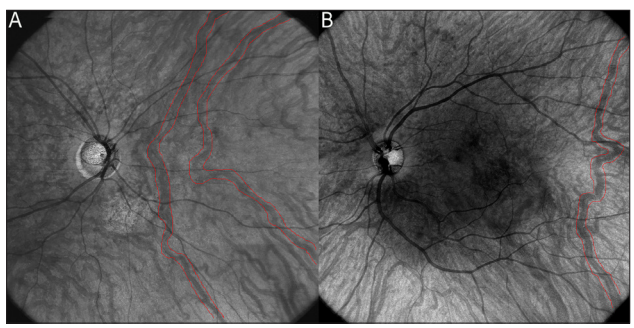

Figure 4. Different types of intervortex anastomoses as assessed by *en face* SS-OCT images (15x15 mm window size). (A) Intervortex anastomoses connect the superior-nasal and inferior-nasal vortex vein territories in an acquisition centered in the optic nerve head. (B) Intervortex anastomoses connect the superior-temporal and inferior-temporal vortex vein territories in a macula-centered acquisition.

analysis showed a negligible correlation (r = -0.19) between pachyvessels crossing choroidal watershed zones in UWF OCT and CVH, and a moderate positive correlation (r = 0.53) between pachyvessels crossing both meridians and diffuse CVH (Fig. 5).

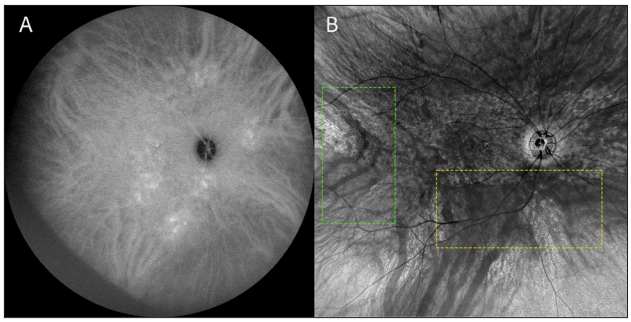

Figure 5. Multimodal analysis of the right eye of a 42-year-old woman with chronic central serous chorioretinopathy: (A) Late-phase widefield indocyanine green angiography showing diffuse areas of choroidal vascular hyperpermeability and (B) photomontage of *en face* OCT image (15x20 mm) showing pachyvessels crossing both vertical (yellow inset) and horizontal meridians (green inset).

DISCUSSION

In our analysis of 23 eyes from 12 patients with CSC, we observed a high agreement between non-invasively acquired *en face* SS-OCT and UWF ICGA to detect choroidal vascular anomalies in CSC, i.e. pachyvessels crossing choroidal watershed zones and intervortex anastomoses. A moderate correlation between pachyvessels crossing choroidal watershed zones and CVH was also established. If pachyvessles crossed both horizontal and vertical meridians, it was likely to observe diffuse CVH in UWF ICGA. Our findings support the usage of a simple and fast imaging protocol to identify the most prevalent features of choroidal venous insufficiency in clinical practice.

Abnormalities of the choroidal circulation are believed to play an important role in the pathophysiology of CSC.[12] Although a complete understanding of choroidal vascular hyperpermeability remains controversial, recent works support that venous outflow abnormalities are an intrinsic phenomenon in CSC.[13] The choroidal circulation accounts for 85% of the total blood flow in the eye through a high-flow system.[14] In the choroid, blood is drained in a lobular-shaped arrangement forming small diameter veins that merge eventually into larger ones that run in parallel groups to the equator before joining on a collector ampulla, forming an ensemble with a vortex-like shape. The drainage of each retinal quadrant is usually symmetric, even in the presence of 5 or more vortex veins. Thereby, it has been hypothesized that an imbalanced vortex vein drainage, i.e. underdevelopment of one or two vortex veins collector systems, could contribute to overwhelming adjacent vortex vein territories predisposing them to venous outflow abnormalities.[2] Bacci *et al* have shown a significant within-subject variance in the proportion of the post-equatorial fundus drained by each vortex vein system and suggested this might contribute to regional choroidal thickening, CVH, and remodeling of venous drainage routes.[2] In our series, we observed an imbalance of the vortex vein drainage in 70% of the cases, which is a much higher percentage than what has been described in eyes without a diagnosis of CSC (35%).[7] We also observed that the vortex vein territory more often underdevelopment was the inferior-nasal, in accordance with recent works.[2,11]

Previous studies have shown that imbalanced vortex vein drainage can be appreciated non-invasively using UWF SS-OCT with the same accuracy as UWF ICGA.[7,11] However, these works are limited by the access to UWF wide-field OCT imaging in routine practice and a laborious process of multiple large acquisitions (23x20 mm) followed by photomontage.[11] Moreover, most OCT device optics have been designed to perform high-quality imaging of the posterior pole, with a maximum range of 15x15 mm scans centered in the fovea and/or the optic nerve. Thereby, the identification of choroidal circulatory insufficiency features through larger acquisition windows could be an important contribution to clinical practice. Kishi *et al* have shown that after the iatrogenic injury of a vortex vein by a scleral buckle there is remodeling of choroidal drainage with the development of anastomosis between vortex veins and large choroidal vessels crossing physiologic watershed territories.[7,15] Likewise, animal models of increased choroidal outflow have shown collateral formation and eventually choroidal venous anastomosis after surgical ligation of one vortex vein.[16] We observed a moderate correlation between the presence of intervortex veins anastomosis in *en face* SS-OCT and an imbalance of vortex vein drainage, supporting this might be a biomarker of imbalanced choroidal drainage. On the opposite side, we observed a negligible correlation between pachyvessels crossing watershed zones and imbalanced vortex vein drainage. This seems to suggest that the patterns herein described reflect different degrees of vascular remodeling in patients with choroidal venous insufficiency, intervortex anastomosis being the most severe.

Mid-late phase CVH in ICGA is a hallmark feature of CSC and has been considered a surrogate marker of choroidal venous congestion and a putative target for verteporfin photodynamic therapy.[1,7,6] In this series, CVH was observed in 83% of the cases, agreeing with previous studies that show interocular asymmetry of CSC features.[1,7] Correlation analysis showed a negligible correlation between the presence of CVH and pachyvessels crossing choroidal watershed zones or intervortex anastomosis in UWF OCT, supporting that, when taken into account separately, these features are not specific enough to infer on choroidal vascular congestion severity. However, interestingly, we detected a moderate positive correlation between pachyvessels crossing both meridians and diffuse CVH, which has been acknowledged as a biomarker of increased disease severity.[17] While this seems to suggest that this pattern might be a biomarker of severe choroidal venous congestion, we believe that the negligible correlation between CVH and other

en face OCT features, i.e. pachyvessels crossing only one of the watershed meridians and intervortex anastomosis, indicate that these features reflect different levels of choroidal vascular remodeling without a complete correlation with gold standard levels of diseases severity, and should not be taken in isolation to guide clinical decision making.

The main strengths of this study are the high signal-to-noise ratio of the multimodal imaging platforms employed and the accuracy of the image analysis protocol. Image analysis was based on a very reliable protocol, that included manual segmentation of the retinal layers of interest in each B-scan.

Limitations addressable in future studies include the small sample size, heterogeneity of the disease duration, the usage of non-built-in software to perform photomontages and the lack of choroidal vascular thickness analysis. Imaging studies have demonstrated a correlation between choroidal thickness, imbalanced choroidal venous drainage, and CVH in ICGA.[7,11] While this analysis could be a useful add-on to the current study, the software that enables this analysis is pending approval for usage in the European Union.

In conclusion, we observed a very high agreement between the UWF ICGA and WF *en face* SS-OCT to detect choroidal vascular anomalies in CSC, i.e. pachyvessels crossing choroidal watershed zones and intervortex anastomoses. Identification of pachyvessels crossing the horizontal and vertical meridians was associated with diffuse CVH in ICGA, which supports that these vessels might be a compensatory process for overcoming choroidal outflow resistance, eventually becoming a biomarker of choroidal venous insufficiency.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

PC, AS, ARC, AMP, NC, DC: Responsible for gathering the data.

PC, DC, PR, RL: Responsible for creating the manuscript.

DC, PR, RL: Supervised this project and contributed with their expertise to its conclusion.

All authors read and approved the final manuscript.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no financial or proprietary interest in the materials presented herein.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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