



# Pachychoroid spectrum disease and choriocapillary flow analysis in patients with Cushing disease: an optical coherence tomography angiography study

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## Abstract

**Purpose** To investigate the presence of pachychoroid spectrum disease (PSD) in patients with Cushing disease (CD) and to evaluate subfoveal choroidal thickness (SFCT) and choriocapillary flow using spectral domain OCT (SD-OCT) with the enhanced depth imaging (EDI) and optical coherence tomography angiography (OCT-A).

**Methods** Thirty-two patients with CD and 32 age- and sex-matched healthy volunteers were enrolled in this observational study. All participants had a complete ophthalmic examination including SD-OCT with EDI and OCT-A, and were subjected to the Perceived Stress Scale test (PSS). All patients with CD had hormone test including 24-h urinary-free cortisol (UFC) and plasma adrenocorticotrophic hormone (ACTH). We compared SFCT and choriocapillary vessel density (CVD) between the two groups and evaluated the presence of PSD. We investigated the association of hormone level, SFCT, CVD with the presence of CD; the association between the hormone level, SFCT, CVD, the CD disease activity, and duration with the presence of PSD in CD patients; and the association between SFCT and CVD with the hormone level, the CD disease activity, and duration in CD patients.

**Results** Higher values of SFCT and CVD were associated with CD ( $\beta$ : 0.028, 95% CI: 0.014; 0.041;  $\beta$ : 0.912, 95%CI: 0.205; 1.62, respectively). Twelve patients with CD (37.5%) reported a PSD in at least one eye, whereas no subject was found in control group ( $p < 0.001$ ); in particular, 11 CD patients (34%) presented pachychoroid pigment epitheliopathy (PPE) and 1 CD patient (3%) presented polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization (PCV/AT1). In patients with CD, a significant positive association between SFCT and PSD was found ( $\beta$ : 0.010, 95% CI 0.001; 0.019).

**Conclusion** A chronic state of hypercortisolism may have direct implications on the choroid. Patients with CD had higher SFCT values and a significant change in the choriocapillary flow compared to healthy controls. Moreover, PSD was observed only in CD patients.

**Keywords** Choroid · Cortisol · Cushing · Multimodal imaging · Neovasculopathy · Pachychoroid

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### Key message

- Several studies have already reported an increased choroidal thickness in patients with Cushing syndrome; the correlations with the levels of endogenous cortisol have not been clearly established yet.
- The current study is the first that quantitatively analyzes the characteristics of the choriocapillary flow using OCT-A in patients with Cushing Disease.
- Our study confirms that patients with increased endogenous cortisol levels have higher subfoveal choroidal thickness compared to controls and are more frequently affected by Pachychoroid Spectrum Disease.

## Introduction

In recent years, an increased interest in pachychoroid spectrum disease (PSD) has been shown by authors worldwide.

In 2013, Warrow described four groups of pathologies that seem to share characteristics and genesis: pachychoroid pigment epitheliopathy (PPE), central serous chorioretinopathy (CSC), pachychoroid neovascularopathy (PNV), and polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization (PCV/AT1) [1]. In a 2019 review by Cheung et al., two other clinical manifestations were included: focal choroidal excavation (FCE) and peripapillary pachychoroid syndrome (PPS) [2]. The main feature of all these pathologies is represented by focal or widespread choroidal thickness increase, i.e., vessels dilation in the Haller layer accompanied by a thinning of the Sattler layer and the choriocapillary with or without retinal pigment epithelium (RPE) alteration [2].

Choroidal thickness changes have been correlated to various anatomical and acquired factors such as ocular axial length, systemic pathologies, and age [3, 4]. Numerous pieces of evidence suggest that even the endocrine system can play a role in choroidal thickness variation [5–10].

Cushing syndrome is a condition characterized by a set of clinical signs and symptoms secondary to prolonged exposure to high levels of cortisol that can derive either from exogenous doses of corticosteroid drugs or from endogenous sources. Several studies have already reported an increased choroidal thickness in patients with Cushing syndrome, with a higher prevalence of PSD compared to healthy control [11–14].

Cushing disease (CD), first described by Harvey Cushing in 1932 [15], is a term that refers specifically to adrenocorticotropic hormone (ACTH)-secreting pituitary gland adenoma which is the most frequent endogenous cause of Cushing syndrome. CD could represent a suitable model of study to understand and clarify the correlation between high endogenous cortisol levels and choroidal structural changes.

The aim of this study is to investigate the presence of PSD in patients with CD and to evaluate subfoveal

choroidal thickness (SFCT) and choriocapillary flow using spectral domain optical coherence tomography (SD-OCT) with enhanced depth imaging (EDI) and optical coherence tomography angiography (OCT-A).

## Methods

The observational, prospective study protocol was approved by the Ospedali Riuniti of Ancona Local Scientific committee and conducted in line with the Helsinki Declaration agreements for research involving human subjects. All participants gave their written informed consent.

Consecutive patients diagnosed with CD followed by the Department of Endocrinology and Metabolic Diseases of the Ospedali Riuniti of Ancona from January to December 2020 were enrolled and formed the first group.

A second group made by sex- and age-matched healthy volunteers who had not used exogenous corticosteroids in the past 2 years served as the control group.

For all participants, both eyes were enrolled in the study.

Patients were excluded if they presented one of the following characteristics: (1) a refractive defect greater than or equal to 6 diopters or the presence of 2 diopters of astigmatism; (2) history of glaucoma, uveitis, and retinal diseases such as diabetic retinopathy, venous occlusion, age-related macular degeneration, and macular pucker; (3) history of eye surgery such as laser photocoagulation, intravitreal injections, phacoemulsification, and vitrectomy; (4) other systemic diseases except for controlled secondary hypertension in patients with CD; (5) media opacity that compromised the visualization of the fundus oculi or did not allow a good quality OCT acquisition.

## Ophthalmic examination

All participants underwent complete ophthalmic examination including best-corrected visual acuity (BCVA), Goldmann applanation tonometry, and slit-lamp biomicroscopy of the anterior and posterior segment.

**Table 1** Specific EDI-OCT and OCT-A features and biomarkers of pachychoroid spectrum disease

Pachychoroid spectrum disease features	EDI-OCT	OCT-A
Pachychoroid pigment epitheliopathy (PPE)	<ul style="list-style-type: none"> <li>• Focal RPE abnormalities overlying pachychoroid disease changes</li> <li>• Absent subretinal fluid</li> </ul>	<ul style="list-style-type: none"> <li>• No evidence of choroidal neovascularization</li> </ul>
Central serous chorioretinopathy (CSC)	<ul style="list-style-type: none"> <li>• Well-defined or shallow serous retinal detachment</li> <li>• Pigment epithelial detachment (PED)</li> <li>• Elongated photoreceptor outer segments</li> <li>• Disruption or thinning of outer retinal layers</li> </ul>	<ul style="list-style-type: none"> <li>• No evidence of choroidal neovascularization</li> </ul>
Pachychoroid neovascularopathy (PNV)	<ul style="list-style-type: none"> <li>• Type 1 neovascularization overlying pachychoroid disease changes appearing as shallow irregular RPE detachment (double-layer sign)</li> </ul>	<ul style="list-style-type: none"> <li>• “Tangled network” of flow signal corresponding to type 1 neovascularization</li> </ul>
Polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization (PCV/AT1)	<ul style="list-style-type: none"> <li>• Type 1 neovascularization with aneurysmal lesions is located between RPE and the inner layer of Bruch’s membrane</li> <li>• Exudative changes from aneurysms</li> </ul>	<ul style="list-style-type: none"> <li>• Flow signal representing type 1 neovascularization</li> <li>• Variable flow signal within aneurysm</li> </ul>
Focal choroidal excavation (FCE)	<ul style="list-style-type: none"> <li>• Abrupt changes of choroidal thickness</li> <li>• Increased choroidal thinning with highly reflective choroidal tissue</li> <li>• Normal, smooth inner scleral surface suggesting an absence of scleral excavation or ectasia</li> <li>• Conforming no separation between photoreceptor tips and RPE</li> <li>• Non-conforming photoreceptor tips appear detached from underlying RPE, with a hyporeflexive intervening space</li> </ul>	<ul style="list-style-type: none"> <li>• No evidence of choroidal neovascularization</li> </ul>
Peripapillary pachychoroid syndrome (PPS)	<ul style="list-style-type: none"> <li>• Maximal choroidal thickness occurs close to the optic nerve rather than subfoveally</li> <li>• Nasal macular intraretinal and/or subretinal fluid</li> </ul>	<ul style="list-style-type: none"> <li>• No evidence of choroidal neovascularization</li> </ul>

All participants had a 12.0-mm macular line scan and a 6.0-mm macular radial scan with SD-OCT in EDI-OCT mode (RS-3000 Advance 2, Nidek CO., LTD.).

We have defined the presence of PSD features (codified as presence = 1/absence = 0) when a clinical condition such as PPE, CSC, PCV/AT1, PNV, PPS, and FCE was detected with EDI-OCT and OCT-A according to previous definitions [2]. Specific features and biomarkers for each condition are summarized in Table 1. Fluorescein and indocyanine green angiography was performed to confirm the suspicion of a choroidal neovascularization.

SFCT was measured between the hyperreflective outer edge of the retinal pigment epithelium (RPE) and the internal hyperreflective line of the scleral interface at the central fovea, calculating the distance perpendicularly. All participants had also 6 × 6-mm macular angioscan with fine OCT sensitivity and wide SLO setting (RS-3000 Advance 2, Nidek CO., LTD.). We used the OCT software (NAVIS-EX 1.8.0.14, Nidek CO., LTD.) to calculate choriocapillary vessel density (CVD, “linear mm of vessels/mm<sup>2</sup>”). We used a preset segmentation at 20 microns below the hyperreflective line of the retinal pigment epithelium (RPE) to define the

choriocapillary level according to the manufacturer’s default choriocapillary slab. A manual modification was carried out by the operator in case of an incorrect segmentation in the B-scan image of the OCT-A.

All acquisitions were made by a single skilled operator between 1 and 5 PM to avoid possible interferences due to the choroid circadian rhythm [16]. OCT images were then analyzed by two experienced operators. A third opinion was evaluated when the two operators disagreed.

## Endocrinological evaluation

The diagnosis of CD was carried out by the Department of Endocrinology and Metabolic Diseases of the Ospedali Riuniti of Ancona based on the guidelines of the Endocrine Society [17]. With “duration of the disease,” we have defined the months passed between the diagnosis and the enrollment in the study, while with “adjusted duration of the disease,” we have defined the period between the onset of symptoms and the enrollment in the study. For the severity of the pathology, we have defined two different groups: not active disease and active disease. Not active disease stands

for all patients with 24-h urinary-free cortisol (UFC) < 110 mcg/24 h for at least 12 months, while active disease refers to all patients with at least 2 non-consecutive 24-h UFC measurements > 110 mcg/24 h.

On the day of the ophthalmological examination, all patients with CD performed a serum ACTH dosage (ECLIA Cobas and 601, ROCHE electrochemiluminescence test, reference values 8–60 pg/ml) and presented 2 samples of the 24-h UFC (ECLIA Cobas and 601, ROCHE electrochemiluminescence test, reference values 10–110 mcg/24 h) achieved at least 2 days before the examination. During the visit, blood pressure reading and routine blood chemistry were carried out. For blood pressure value, we calculated the mean arterial pressure (MAP), estimated using the following formula:  $MAP = DP + 1/3(SP - DP)$ , where DP is the diastolic blood pressure and SP is the systolic blood pressure.

All the study participants underwent a Perceived Stress Scale test (PSS—Sheldon Cohen) [18]. Individual scores on the PSS can range from 0 to 40, with higher scores indicating higher perceived stress.

### Statistical analysis (GEE)

A descriptive analysis of the baseline characteristics of subjects was performed. The Shapiro–Wilk test was used to assess the normality of measurements. Median and interquartile range (IQR), absolute, and percentage frequencies were used to summarize quantitative and qualitative variables respectively. Wilcoxon-sum-rank test and chi-square test were used to compare age and gender, respectively, between the CD and control group. The presence of PSD, codified as presence = 1/absence = 0, was compared in CD patients and the control group; the comparison was evaluated using the Fisher exact test.

The generalized estimation equation (GEE) model was used to evaluate associations in order to take into account the presence of the inter-eye correlation. The association between CD and each ophthalmological (SFCT, CVD, IOP, PSD, BCVA) and endocrinological (PSS, MAP) characteristic was evaluated considering CD as dependent variable (CD patients vs. control group); in patients with CD, the association between the PSD and SFCT, CVD, UFC, ACTH, DD, ADD, and active CD was analyzed using PSD (presence vs absence) as a dependent variable. Finally, the association between SFCT and CVD with UFC, ACTH, DD, ADD, and active CD was investigated.

Results were expressed as regression coefficients and 95% confidence interval (95% CI).

Statistical analyses were carried out using R 4.0.3 (R Foundation for Statistical Computing). The significance level was set at 0.05.

**Table 2** Association between CD and ophthalmological and endocrinological characteristics of patients

	$\beta$ (95% CI)	<i>p</i>
Ophthalmological data		
SFCT ( $\mu\text{m}$ )	0.028 (0.014; 0.041)	< <b>0.001</b>
CVD ( $\text{mm}^2$ )	0.912 (0.205; 1.62)	<b>0.012</b>
IOP (mmHg)	−0.062 (−0.25; 0.127)	0.523
Endocrinological data		
PSS (score)	0.084 (−0.5; 0.217)	0.220
MAP (mmHg)	0.07 (−0.085; 0.224)	0.378

$\beta$ , regression coefficient; 95% CI, 95% confidence interval; *p*-values refer to the Wald test in generalized estimation equation model; CD patients were compared to the control group; CD, Cushing disease; SFCT, subfoveal choroidal thickness; CVD, choriocapillary vessel density; IOP, intraocular pressure; PSS, Perceived Stress Scale; MAP, mean arterial pressure

Boldface values when  $p \leq 0.05$

### Results

Thirty-four patients with CD were screened and 32 patients (64 eyes) were enrolled in this study and formed the CD group. Two patients were excluded from analysis because one suffered from high myopia while the other patient was discarded for previous anti-VEGF intravitreal injections and laser photocoagulation to treat a PNV.

Thirty-two healthy volunteers (64 eyes), with gender and age comparable to the first group, formed the control group.

A median age of 48 years was reported in both groups ( $p = 0.469$ ) with a higher percentage of females (84.4% in the CD group, 85.7% in the control group,  $p = 1$ ).

None of the subjects in the control group suffered from PSD, while 12 patients in the CD group (37.5%) reported a PSD in at least one eye ( $p < 0.001$ ); 4 of them reported PSD in only one eye. Eleven CD patients (34%) presented PPE and 1 CD patient (3%) presented PCV/AT1.

Only two patients in the CD group had a BCVA (log-MAR: 0.10) value different from zero.

In the CD group, the mean duration of the disease was 95 months (IQR = 68.5), while the adjusted duration of the disease was 98.6 months (IQR 78.5); 22 patients (68.8%) had an active disease.

Table 2 shows the association between CD and ophthalmological and endocrinological characteristics of patients. Higher values of SFCT and CVD were significantly associated with the presence of CD (respectively,  $\beta = 120$ , 95% CI: 88; 151,  $p < 0.001$ ;  $\beta = 0.912$ , 95% CI: 0.205; 1.62,  $p = 0.012$ ).

Table 3 reports the association between PSD, SFCT, and CVD with ophthalmological and endocrinological characteristics of patients with CD. A significantly positive association was found between PSD and SFCT ( $\beta = 0.01$ , 95% CI: 0.001; 0.019,  $p = 0.027$ ).



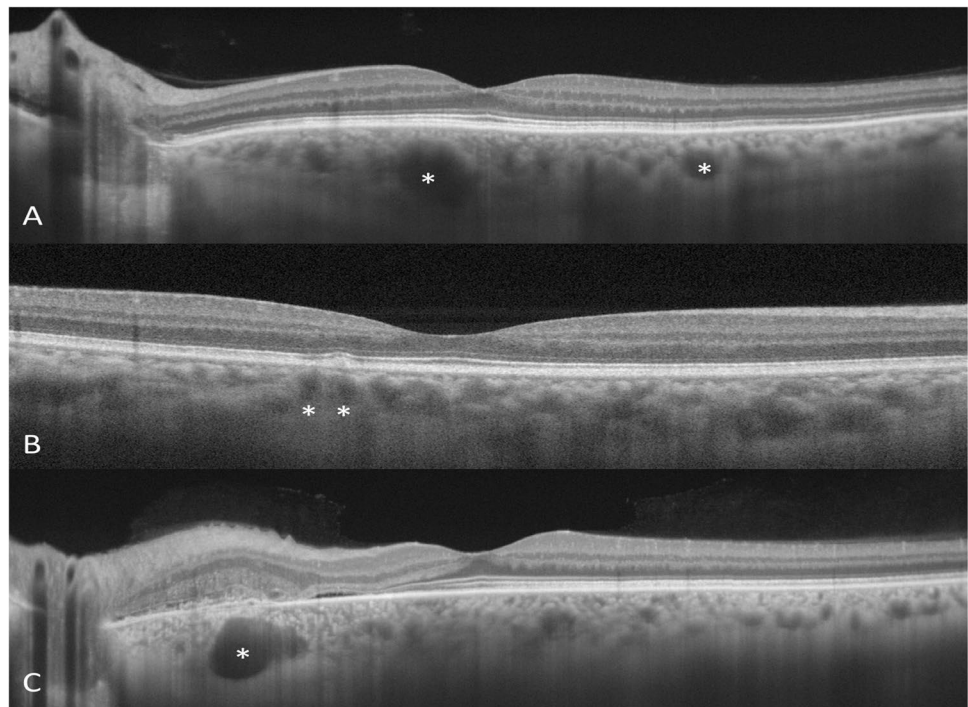
**Table 3** Association between PSD, SFCT, and CVD with ophthalmological and endocrinological characteristics of patients with CD

	PSD (yes vs. no)		SFCT ( $\mu\text{m}$ )		CVD ( $\text{mm}^2$ )	
	$\beta$ (IC 95%)	<i>p</i>	$\beta$ (IC 95%)	<i>p</i>	$\beta$ (IC 95%)	<i>p</i>
<b>Ophthalmological data</b>						
SFCT ( $\mu\text{m}$ )	0.010 (0.001; 0.019)	<b>0.027</b>				
CVD ( $\text{mm}^2$ )	-0.037 (-0.777; 0.703)	0.922	19.8 (-18.6; 58.2)	0.312		
<b>Endocrinological data</b>						
UFC ( $\mu\text{g}/24\text{ h}$ )	0.0001 (-0.004; 0.004)	0.960	0.08 (-0.001; 0.161)	0.052	-0.0001 (-0.001; 0.001)	0.867
ACTH (pg/ml)	0.005 (-0.003; 0.012)	0.199	-0.088 (-0.338; 0.163)	0.492	0.001 (-0.002; 0.003)	0.575
DD (month)	-0.002 (-0.012; 0.008)	0.668	0.194 (-0.206; 0.593)	0.342	0.001 (-0.002; 0.004)	0.574
ADD (month)	0.001 (-0.010; 0.011)	0.878	0.187 (-0.259; 0.633)	0.410	0.001 (-0.002; 0.004)	0.370
Active CD (yes vs. no)	1.27 (-0.475; 3.02)	0.154	40 (-9.91 (89.9)	0.116	0.168 (-0.348; 0.684)	0.523

$\beta$ , regression coefficient; 95% CI, 95% confidence interval; *p*-values refer to the Wald test in generalized estimation equation model; SFCT: subfoveal choroidal thickness; CVD, choriocapillary vessel density; PSD: pachychoroid spectrum disease; UFC, urinary-free cortisol; ACTH, adrenocorticotropic hormone; DD, duration of the disease; ADD, adjusted duration of the disease; CD, Cushing disease

Boldface values when  $p \leq 0.05$

**Fig. 1** Enhanced depth imaging-OCT scan of three different patients with Cushing disease. **A** Patient with uncomplicated pachychoroid showing pachyvessels (asterisks), localized dilated Haller's layer, and compressed Sattler's layer and choriocapillary. **B** Patient with pachychoroid pigment epitheliopathy showing retinal pigment epithelial irregularities above pachyvessels (asterisks). **C** Patient with polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization showing peripapillary irregular RPE elevation with subretinal fluid overlying a large pachyvessel (asterisk)



An example of EDI-OCT scans of three different CD patients with uncomplicated pachychoroid, PPE and PCV/AT1, and their relative OCT-A map is shown in Figs. 1 and 2.

## Discussion

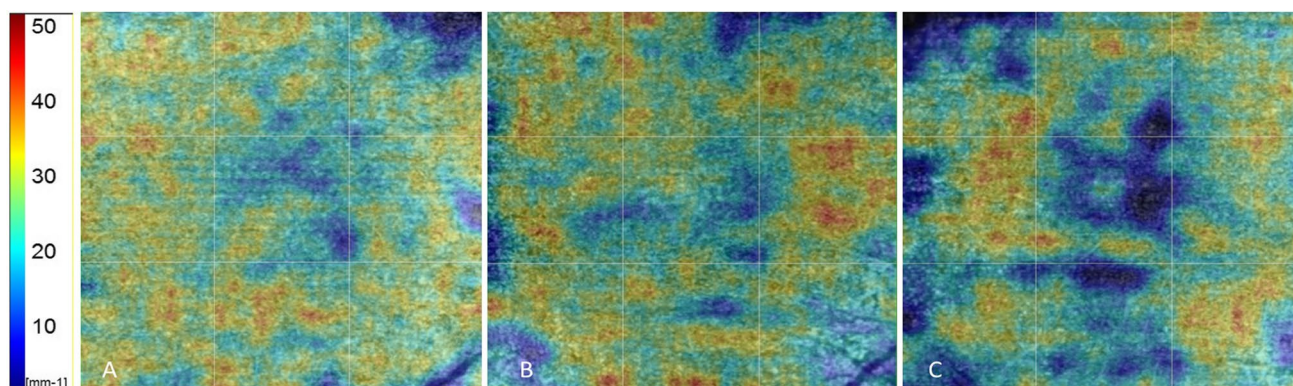
### Analysis of plasmatic hormone levels

In 1993, Bouzas documented 3 cases of CSC in 60 patients with CD [19]. It is well known that active CSC is usually

concurrent with increased endogenous cortisol levels [6] and presents a higher risk of recurrence during periods of intense psychological stress, sleep deprivation, or pregnancy [20]. Patients with type A personality, one of the most important risk factors in CSC [21], present chronically elevated plasma and urinary levels of catecholamines and cortisol [22].

Several studies have already reported an increased choroidal thickness in patients with Cushing syndrome, but the correlations with the levels of ACTH and endogenous cortisol have not been clearly established yet [11–13].

Plasmatic ACTH was not significantly associated with the presence of PSD features. The association between ACTH



**Fig. 2** Optical coherence tomography angiography vessel density maps of patients discussed in Fig. 1. **A** Patient with uncomplicated pachychoroid showing quite uniform choriocapillary vessel density with small flow voids. **B** Patient with pachychoroid pigment epitheliopathy showing increased choriocapillary vessel density that sur-

rounds a central area with flow voids. **C** Patient with polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization showing major alteration of the choriocapillary vessel density uniformity with a deep area without flow surrounded by areas with reactive hyperperfusion

overproduction and choroid thickening is questionable according to previously published data. While Karaca in his study reported an increased choroidal thickness in patients with Cushing syndrome, probably correlated with the levels of ACTH [12], Wang did not find any correlation [13].

The other hormone tested, 24-h UFC, did not show any significant association with SFCT and with the presence of PSD features. In Wang's study [13], 24-h UFC values were significantly related to choroidal thickness; however, in a more recent study by Eymard et al., no statistical association was found between 24-h UFC and SFCT [14]. A possible explanation for these controversial results might be that, despite the fact that the choroid is an extremely dynamic tissue, the fluctuation of cortisol levels could take time to result in choroidal thickness change [13]. Otherwise, the RPE morphological changes following an intense and prolonged state of hypercortisolism could be, as a matter of fact, an irreversible effect of a protract ischemic insult due to a change in choroidal flow.

### Analysis of morphological parameters

Our study shows that the presence of CD was associated with higher values of SFCT ( $p \leq 0.001$ ): eleven patients with CD (34%) presented PPE in at least one eye and one patient presented PCV/AT1 in both eyes (3%). In a previous study by Abalem et al., the incidence of PPE in patients with an active Cushing syndrome was 9% [11], but the total number of patients analyzed was limited. In Eymard's study on 56 eyes from 28 Cushing syndrome patients, 17.9% had a PPE and 3.6% had a PCV/AT1 [14].

A significant positive association was also found between SFCT and the presence of PSD features in the CD group. PPE, CSC, PNV, and PCV/AT1 could represent a continuous

disease process ultimately triggered by choroidal malfunction [23]. It is believed that the primum movens lies in the choroid, most likely in a pathological dilation of Haller layer vessels; this dilatation leads to a compression of the overlying choriocapillary and subsequent modification of the RPE [24, 25]. The microtrauma of Bruch's membrane associated with ischemia, hypoxia, and vascular congestion of the choroid could then play a fundamental role in the genesis of neovascularization due to the increased production of pro-angiogenic factors such as the vascular endothelial growth factor (VEGF). Therefore, PPE diagnosis could become really important in order to prevent well-known complications.

### Analysis of vascular features

Gal-Or already reported in her study with OCT-A a high prevalence of attenuated flow areas in eyes affected by CSC or PPE, highlighting an anatomical correlation between these areas and the underlying presence of pachyvessels often associated with RPE alterations [26]. In 2019, Baek compared the choriocapillary flow (calculated with OCT-A) with the morphological aspect of the choroid: the number of choriocapillary blood flow attenuations was greater in eyes with pachychoroid and in patients with RPE alterations when compared to controls [27]. Teussink using OCT-A demonstrated irregular choriocapillary flow patterns in patients with chronic CSC, suggesting focal choriocapillary ischemia surrounded by areas with reactive hyperperfusion [28].

To the best of our knowledge, the current study is the first that quantitatively analyzed the characteristics of the choriocapillary flow using OCT-A in patients with CD, highlighting that higher values in CVD were significantly associated with the CD ( $p = 0.012$ ). This may be justified by the fact

that most of the eyes of CD patients enrolled in the study (those without PPE, CSC, PCV/AT1, PNV features) probably belong to a remodeling and redistribution phase. The increased choroidal thickness and the presence of pachyvesels in the Haller layer could represent a phase antecedent to choriocapillary ischemia, recently described with the name of uncomplicated pachychoroid [23, 29].

In 2019, Demirel compared CVD and choriocapillary flow area between patients with CSC, PPE, and uncomplicated pachychoroid by means of OCT-A [30]. It was found that the CVD was lower in eyes with CSC when compared to PPE and uncomplicated pachychoroid and that it was also reduced in the PPE group when compared to the uncomplicated pachychoroid group. Again, a continuum between these PSD entities was suggested and the amount of the choriocapillary ischemia seemed to reflect the clinical manifestations of the disease. It could be hypothesized that uncomplicated pachychoroid may represent a prodromal stage of PSD or could be its initial presentation.

## Conclusion

The results of this study, in line with those of previous works, suggest that a state of hypercortisolism may have direct implications on the choroid.

In our study, SFCT and CVD values are positively associated with CD, and also, SFCT is positively associated with the presence of PSD.

The current study has a number of limitations including the cross-sectional design and the small number of patients. We tried to minimize the confounding factors that could affect the choroidal thickness by excluding patients suffering from other retinal and/or systemic pathologies and by carrying out the OCT examination in the afternoon to reduce the influence of the circadian rhythm of cortisol. Other limits are to be found in the resolution of the OCT-A system, not free from artifacts. Despite these limitations, this study provides additional evidence that endogenous corticosteroid dysfunction can be related to PSD. Further studies will be useful to better understand the pathophysiological process that leads to entities such as PPE and the possible neovascular complications, in order to develop targeted and customized therapies.

**Author contribution** Nicola Vito Lassandro was involved in the study conception and design. Material preparation, data collection, and analysis were performed by Nicola Vito Lassandro, Michele Nicolai, Luca Cantini, Alessandro Franceschi, Rosaria Gesuita, and Andrea Faragalli. The first draft of the manuscript was written by Nicola Vito Lassandro and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## Declarations

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Ospedali Riuniti of Ancona Local Scientific committee.

**Consent to participate** Informed consent was obtained from all individual participants included in the study.

**Consent to publish** Patients signed informed consent regarding publishing their data and photographs.

**Conflict of interest** The authors declare no competing interests.

**Disclaimer** The principal investigator, Dr. Lassandro Nicola Vito had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

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