



Pachychoroid disease spectrum: how multimodal imaging and OCT angiography have improved our knowledge

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ABSTRACT

Pachychoroid spectrum disorders (PSDs) represent a group of chorioretinal disorders characterized by abnormal choroidal thickening and various pathological changes in the choroid, retinal pigment epithelium, and retina. This review provides a comprehensive analysis of current multimodal imaging techniques in the diagnosis and management of PSDs. We examine the role of various imaging modalities including optical coherence tomography (OCT), OCT angiography (OCTA), en face OCT, fluorescein angiography (FA), indocyanine green angiography (ICGA), infrared imaging (IR), and fundus autofluorescence (FAF) in evaluating PSDs. Each imaging modality provides unique insights: OCT reveals characteristic choroidal thickening and structural changes; OCTA demonstrates alterations in choroidal flow and neovascularization; en face OCT allows detailed visualization of choroidal vasculature and intervortex anastomoses; FA shows patterns of leakage; ICGA reveals choroidal hyperpermeability and pachyvessels; IR imaging assists in RPE evaluation; and FAF highlights RPE dysfunction. The integration of these imaging techniques has enhanced our understanding of the pathophysiology of PSDs and improved our ability to diagnose, monitor, and treat these conditions. This review particularly emphasizes how OCTA has advanced our knowledge of choroidal circulation and neovascularization in PSDs. We also discuss future directions in imaging technology and their potential impact on personalized therapeutic approaches, including optimized photodynamic therapy based on imaging biomarkers. The synergistic use of multimodal imaging represents a cornerstone in the management of PSDs, enabling more precise diagnosis and tailored treatment strategies.

1. Introduction

1.1. Definition, overview, and historical evolution of pachychoroid spectrum disease

The pachychoroid spectrum disease (PSD) represents a group of chorioretinal disorders characterized by abnormal choroidal thickening and various pathological changes in the choroid, retinal pigment epithelium (RPE), and retina (Cheung et al., 2024; Ming Gemmy Cheung et al., 2019). The pachychoroid spectrum encompasses several

conditions, initially including pachychoroid pigment epitheliopathy (PPE), central serous chorioretinopathy (CSC), pachychoroid neovascularopathy (PNV), and polypoidal choroidal vasculopathy (PCV) (Dansingani et al., 2016). More recently, the spectrum has expanded to include peripapillary pachychoroid syndrome (PPS) and pachyvilliform maculopathy (PVM) (Hilely et al., 2023; Phasukkijwatana et al., 2018).

The term "pachychoroid" was first introduced by Warrow and colleagues in 2013 to describe a constellation of retinal and choroidal findings observed in eyes with thickened choroids (Warrow et al., 2013). In their seminal paper, Warrow et al. (2013) described PPE as a

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Acronyms:

AMD	Age-related macular degeneration
AT1	Aneurysmal type 1 neovascularization
AACF	Asymmetric arterial choroidal filling
AVD	Asymmetric venous drainage
BVN	Branching vascular network
CC	Choriocapillaris
CFH	Complement factor H
CSC	Central serous chorioretinopathy
CT	Choroidal thickness
CVA	Choroidal venous anastomoses
CVH	Choroidal vascular hyperpermeability
CVI	Choroidal vascularity index
DARA	Diffuse atrophic RPE alterations
DLS	Double layer sign
DR	Diabetic retinopathy
DRPE	Diffuse retinal pigment epitheliopathy
EDI	Enhanced depth imaging
ELM	External limiting membrane
EZ	Ellipsoid zone
FA	Fluorescein angiography
FAF	Fundus autofluorescence
FCE	Focal choroidal excavation
ICGA	Indocyanine green angiography
IR	Infrared reflectance

IZ	Interdigitation zone
MNV	Macular neovascularization
NIR	Near-infrared reflectance
OCT	Optical coherence tomography
OCTA	Optical coherence tomography angiography
ONL	Outer nuclear layer
PCV	Polypoidal choroidal vasculopathy
PDT	Photodynamic therapy
PED	Pigment epithelial detachment
PNV	Pachychoroid neovasculopathy
PPE	Pachychoroid pigment epitheliopathy
PPS	Peripapillary pachychoroid syndrome
PSD	Pachychoroid spectrum disorder
PVM	Pachyvittelliform maculopathy
qAF	Quantitative autofluorescence
REwM	RPE elevation with microbreak appearance
RPE	Retinal pigment epithelium
SD-OCT	Spectral-domain optical coherence tomography
SHRM	Subretinal hyperreflective material
SLO	Scanning laser ophthalmoscope
SRD	Serous retinal detachment
SRF	Subretinal fluid
SS-OCT	Swept-source optical coherence tomography
TD-OCT	Time-domain optical coherence tomography
UWF	Ultra-widefield
VEGF	Vascular endothelial growth factor

condition characterized by:

1. Abnormal choroidal thickening, particularly of the outer choroidal layer (Haller's layer).
2. Thinning of the choriocapillaris and Sattler's layer overlying the thickened choroid.
3. RPE abnormalities in the absence of drusen.
4. Choroidal hyperpermeability on indocyanine green angiography.

Initially, the focus was primarily on increased choroidal thickness (CT), typically exceeding 300 μm (Ming Gemmy Cheung et al., 2019). However, our understanding has evolved since then, recognizing that the spectrum is not solely dependent on increased CT. The current definition has expanded to include:

1. Choroidal thickening: Often, but not always, present (Dansingani et al., 2016)
2. Pachyvessels: Dilated outer choroidal vessels, a critical diagnostic criterion even when overall choroidal thickness is not markedly increased (Lee et al., 2016)
3. Choriocapillaris thinning: Typically observed overlying the areas of dilated choroidal vessels (Balaratnasingam et al., 2016a; Dansingani et al., 2016).
4. Pachydrusen: A distinct type of drusenoid material associated with pachychoroid conditions, which may be present even in eyes with normal choroidal thickness (Baek et al., 2019; Ming Gemmy Cheung et al., 2019).
5. RPE and retinal changes: Various alterations depending on the specific condition within the spectrum (M. Giray Ersoz et al., 2018b).

Despite significant advances in our understanding of pachychoroid disorders, several controversies and knowledge gaps persist, highlighting the complexity of this disease spectrum. One fundamental debate concerns the diagnostic thresholds for choroidal thickness, with values ranging from 270 to 395 μm proposed in various studies (Chang and Cheng, 2020; Lehmann et al., 2015). This variability reflects the

challenges in establishing standardized criteria, especially considering the influence of age, axial length, and diurnal variations on choroidal measurements (Viggiano et al., 2025c).

Another significant area of contention involves the relationship between pachychoroid disorders and age-related macular degeneration (AMD). The distinction between pachychoroid neovasculopathy and neovascular AMD with thick choroids remains particularly challenging, with implications for treatment approaches and outcomes (Viggiano et al., 2025a). The pathophysiological mechanism underlying pachychoroid conditions also remains a subject of debate. While initial theories emphasized primary choroidal vascular abnormalities leading to secondary RPE dysfunction, recent evidence suggests a more complex interplay involving scleral biomechanics, choroidal venous outflow obstruction, and inflammatory processes (Bacci et al., 2022).

Perhaps most significantly, the current classification of pachychoroid disorders as distinct entities versus a continuous spectrum with overlapping features remains unresolved. The progression patterns between PPE, CSC, PNV, and PCV are not fully understood, and the role of genetic factors in determining disease phenotype needs further exploration (De Jong et al., 2015; Schubert et al., 2014). These knowledge gaps underscore the critical importance of advanced imaging techniques in refining our understanding of pachychoroid pathophysiology, improving diagnostic accuracy, guiding therapeutic decisions, and ultimately enhancing patient outcomes.

1.2. Epidemiology and risk factors

The majority of epidemiological data and risk factor analyses in the pachychoroid spectrum have historically focused on CSC. This condition, being the most clinically apparent and longest recognized within the spectrum, has been the subject of numerous studies over several decades. However, in recent years, the recognition of the broader pachychoroid spectrum, including entities such as PPE, PNV, PCV, PPS, and PVM, has significantly expanded our understanding of the epidemiology and risk factors associated with these conditions. This evolving conceptualization of pachychoroid disorders as a spectrum rather than

isolated entities has led to a more comprehensive approach in studying their prevalence, incidence, and associated risk factors. Researchers have begun to identify common threads running through these conditions, as well as distinguishing features that set them apart (Kunal K Dansingani et al., 2016; Ming Gemmy Cheung et al., 2019). The recognition of shared risk factors, such as increased choroidal thickness (Chung et al., 2011; Imamura et al., 2009), genetic predispositions (Miki et al., 2014; Schubert et al., 2014), and certain systemic associations like corticosteroid use (Haimovici et al., 2003) and hypertension (Eom et al., 2012; Rim et al., 2018), has provided new insights into the underlying pathophysiology of the pachychoroid spectrum. These commonalities suggest a shared pathogenic mechanism underlying the various manifestations of pachychoroid disease (Pang and Freund, 2015). While CSC remains the most extensively studied condition within this spectrum, emerging research on other pachychoroid entities is gradually filling the gaps in our knowledge. It's important to note that as our understanding of these conditions continues to evolve, so too may our perception of their epidemiology and associated risk factors.

1.2.1. Central serous chorioretinopathy

CSC ranks among the most common vision-threatening retinopathies after age-related macular degeneration (AMD), diabetic retinopathy (DR), and branch retinal vein occlusion (BRVO) (Wang et al., 2008). The epidemiology of CSC is characterized by significant gender and age-related patterns, as well as potential ethnic variations.

A higher prevalence among men has been consistently observed, with 72–88 % of cases occurring in male subjects (Liu et al., 2024; R. F. Spaide et al., 1996; Tittl et al., 1999). This gender disparity is further illustrated by a population-based study in Olmsted County, Minnesota, which reported an annual incidence of 9.9 per 100,000 for men compared to 1.7 per 100,000 for women, indicating a six-fold higher incidence in men (Kitzmann et al., 2008).

The age of onset for CSC shows considerable variability. Recent epidemiological data suggest a higher mean age than previously assumed, ranging between 39 and 51 years (Kitzmann et al., 2008; Liu et al., 2024; Tsai et al., 2013). Interestingly, CSC can occur at later ages, particularly in women and patients affected by atypical chronic forms (Kitzmann et al., 2008; Lafaut et al., 1998; Perkins et al., 2002; Quillen et al., 1996). It's worth noting that CSC has been rarely reported in children (Kim et al., 2012).

Ethnic variations in CSC incidence remain a subject of debate. Some studies have suggested a higher frequency among Asians, Caucasians, and Hispanics compared to African Americans (Chan et al., 2010; Yannuzzi, 1987), though this finding has not been consistently confirmed across all studies. When CSC does occur in African American subjects, it tends to present as a more severe form with lower visual acuity. In Asian populations, CSC is reported to be both frequent and severe, with bilateral and multifocal forms being more common than in other ethnic groups (How and Koh, 2006). A Taiwanese population-based study found a mean annual incidence of non-steroid induced CSC of 21 per 100,000, which is twice the incidence reported in Olmsted County, Minnesota. In this Asian cohort, the male-to-female ratio was 1.74, and the incidence peaked in the 35–39 year-old age group, followed by the 40–44 year-old group (Tsai et al., 2013).

The etiology of CSC is multifactorial, with a complex interplay of genetic predisposition and environmental factors. Evidence for a genetic component comes from several reported cases of familial CSC and the observation that over half of CSC patients' families have at least one relative with fundus lesions suggestive of chronic CSC (Weenink et al., 2001). Genetic studies have identified potential susceptibility genes (Schellevis et al., 2019), including polymorphisms in the Complement Factor H (CFH) gene and variants in ARMS2, suggesting a genetic overlap with age-related macular degeneration (De Jong et al., 2015; Miki et al., 2014). Interestingly, alleles conferring risk for AMD were found to be protective for CSC and vice versa. Additionally, variations in the cadherin 5 gene, which is involved in vascular endothelial adhesion,

have been associated with CSC in male patients (Schubert et al., 2014).

Beyond genetics, several systemic factors contribute to CSC risk. Cardiovascular health plays a significant role, with hypertension increasing the risk of CSC development (Eom et al., 2012; Tittl et al., 1999). Conversely, CSC itself has been identified as a potential risk factor for coronary heart disease in men and an independent risk factor for ischemic stroke (Chen et al., 2014; Tsai et al., 2013). This bidirectional relationship suggests that CSC may be part of a broader vascular dysfunction.

The autonomic nervous system's role in CSC is evident from the observed sympathetic-parasympathetic imbalance in patients, characterized by sympathetic over-activation and decreased parasympathetic activity (Tewari et al., 2006). This imbalance may influence choroidal blood flow regulation, contributing to CSC pathogenesis.

One of the most well-established risk factors for CSC is exposure to corticosteroids (Kang et al., 2022). Patients with CSC are more likely to have a history of corticosteroid use, and those under corticosteroid therapy are at higher risk of developing the condition (Carvalho-Recchia et al., 2002; Haimovici et al., 1997; Jampol et al., 2002). This association holds true for various routes of administration, including systemic, inhaled, and topical steroids. Steroid-induced CSC often presents with bilateral and atypical features, suggesting an idiosyncratic response in susceptible individuals rather than a dose-dependent effect (Bouzas et al., 1993; Han et al., 2014; Kang et al., 2022).

Endocrine factors also play a role in CSC risk. Pregnancy, particularly the third trimester, is associated with an increased risk of CSC (Haimovici et al., 2004). Additionally, CSC develops in a significant proportion of patients with endogenous Cushing syndrome, further highlighting the link between cortisol levels and CSC pathogenesis (Bouzas et al., 1993; Carvalho-Recchia et al., 2002).

Psychological factors contribute significantly to CSC risk. An association between CSC and "type-A" personality pattern has been long recognized (Yannuzzi, 1987). CSC patients often exhibit higher levels of emotional distress, somatization, depression, and hostility compared to controls (Conrad et al., 2007, 2014). The use of psychotropic medications and the presence of psychological stress have been identified as independent risk factors for CSC (Tittl et al., 1999).

Interestingly, gastroesophageal disorders have been linked to CSC. Patients with CSC have a higher risk of gastroesophageal reflux, and several studies have reported a high prevalence of *Helicobacter pylori* infection in CSC patients (Ahnouh-Zabsonre et al., 2004; Mansuetta et al., 2004). While the exact mechanism linking these conditions remains unclear, it may relate to shared risk factors or systemic inflammatory processes.

Various medications beyond corticosteroids have been associated with CSC. These include sympathomimetic drugs, phosphodiesterase-5 inhibitors, and MEK inhibitors used in cancer treatment (Aliferis et al., 2012; McCannel et al., 2014; Michael et al., 2003). The diverse nature of these medications suggests multiple pathways through which pharmacological agents can influence choroidal vasculature and RPE function.

Lastly, the role of sleep disturbances, particularly obstructive sleep apnea, in CSC remains a subject of debate. While some studies have reported a higher prevalence of sleep apnea in CSC patients, others have found no significant association when controlling for factors like body mass index (Brodie et al., 2015; Eom et al., 2012; Lee et al., 2022; Wu et al., 2018).

1.2.2. Pachychoroid pigment epitheliopathy

PPE is a relatively newly recognized entity within the PSDs. While specific epidemiological data for PPE are limited due to its recent identification, several studies have provided insights into its characteristics and associations.

PPE can be observed across a wide age range but is more commonly diagnosed in middle-aged patients. Warrow et al. (2013) reported that the mean age at diagnosis for PPE tends to be younger than that for CSC. Although specific gender ratios for PPE are not well-established,

Dansingani et al. (Kunal K Dansingani et al., 2016) observed a possible male predominance, similar to the pattern seen in CSC.

A significant association between PPE and CSC has been established. Warrow et al. (2013) observed that PPE is often present in the fellow eyes of patients with unilateral CSC. This finding suggests that PPE could potentially be a precursor to CSC in some cases.

Genetic factors appear to play a role in PPE development. Lehmann et al. (2015) conducted a study on families of CSC patients and found that 50 % of eyes from relatives had a choroid thicker than 395 μm . This observation suggests that pachychoroid, a key feature of PPE, could be an inherited condition with a possible dominant transmission pattern.

Importantly, PPE is often asymptomatic, which presents challenges for determining its true prevalence. While research on PPE-specific risk factors is still emerging, the established association with CSC and the inherited nature of pachychoroid suggest that there may be shared risk factors between these conditions. However, more targeted research is needed to elucidate PPE-specific risk factors and to understand its natural history and potential progression to other PSDs.

1.2.3. Polypoidal choroidal vasculopathy

PCV is a distinct form of choroidal neovascularization that has gained increasing attention due to its unique clinical and imaging characteristics. While considered a subtype of exudative AMD, accumulating evidence may suggest that PCV may represent a separate entity with its own epidemiological profile and risk factors. In details, while in Asian subjects PCV may effectively be considered as a subtype of AMD (Ricardi et al., 2024), in Caucasian subjects this entity may be effectively considered as a separate disease and mainly related to the pachychoroid spectrum.

The prevalence of PCV varies significantly across different ethnic populations. Studies have reported PCV prevalence rates of 10 %–54 % in Asian patients with presumed exudative AMD, compared to 8 %–13 % in Caucasian populations (Chang and Cheng, 2020; Cheung et al., 2018). This marked ethnic variation underscores the potential influence of genetic factors in PCV development. In particular, PCV is more common in pigmented races, with a higher prevalence observed in Asian and African populations compared to Caucasians (Baek et al., 2018).

Age plays a crucial role in PCV manifestation, but interestingly, the age distribution differs from typical AMD. Wang et al. (2024) identified 64.5 years as a significant threshold for distinguishing PCV characteristics, with patients below this age more likely to present with pachychoroid features. This finding aligns with observations that PCV can affect younger individuals compared to typical AMD, suggesting distinct pathogenic mechanisms. Baek et al. (2018) reported that the mean age of PCV patients in their study was 69.4 ± 9.3 years, which was significantly younger than patients with non-neovascular AMD (74.0 ± 6.0 years) or neovascular AMD (74.4 ± 6.0 years).

Gender also appears to influence PCV risk, with some studies reporting a male predominance. Baek et al. (2018) found that 78–79 % of PCV patients in their study were male, compared to only 34–47 % in AMD groups. This gender disparity suggests potential hormonal or lifestyle factors that may contribute to PCV development.

Recent research has highlighted the importance of choroidal characteristics in PCV, particularly choroidal thickness. Chang and Cheng (2020) proposed a cutoff of 267.5 μm subfoveal choroidal thickness to differentiate between pachychoroid and non-pachychoroid PCV subtypes. This classification not only reflects differences in choroidal morphology but also correlates with clinical features and treatment responses. Baek et al. (2018) further demonstrated that choroidal vascular density and the presence of pachyvessels differ between PCV, AMD, and CSC.

Systemic factors also contribute to PCV risk. Wang et al. (2024) found that younger PCV patients had a higher prevalence of diabetes, while older patients were more likely to have hypertension (Toto et al., 2020). Lifestyle factors such as smoking and staying up late were more prevalent in younger PCV patients, suggesting potential modifiable risk

factors. Additionally, features reminiscent of CSC, including choroidal vascular hyperpermeability, were more common in pachychoroid PCV, hinting at a possible pathophysiological link between these conditions (Baek et al., 2018).

The complex interplay of these epidemiological factors and risk elements underscores the heterogeneous nature of PCV. As our knowledge of PCV continues to evolve, it becomes increasingly clear that this condition represents a spectrum of choroidal vascular abnormalities with diverse clinical manifestations and treatment responses.

1.2.4. Pachychoroid neovascularopathy

PNV has emerged as a distinct clinical entity within the spectrum of chorioretinal vascular disorders. Since its initial description by Pang and Freund in 2015 (Pang and Freund, 2015), our understanding of PNV has evolved considerably. This condition, characterized by type 1 macular neovascularization (MNV) in eyes with pachychoroid features, challenges the traditional classification of neovascular macular disorders (Kuranami et al., 2023; Pang and Freund, 2015; Yanik et al., 2024). Importantly, PNV can present in either non-exudative or exudative forms. Non-exudative PNV features neovascular networks without active leakage or subretinal fluid, often detected incidentally during imaging studies. In contrast, exudative PNV demonstrates active leakage with subretinal and/or intraretinal fluid accumulation. The non-exudative form may remain stable for extended periods or may convert to the exudative form, particularly in the presence of additional risk factors (Sacconi et al., 2023).

The epidemiology of PNV reveals interesting patterns that distinguish it from neovascular AMD. Typically affecting a younger demographic, PNV patients are often in their mid-50s to early 60s, contrasting with the older age group commonly associated with nAMD (Arf et al., 2020; Kuranami et al., 2023; Miyake et al., 2015; Yanik et al., 2024). While some studies suggest a male predominance in PNV (Kuranami et al., 2023), others report no significant gender predilection (Riazi-Esfahani et al., 2023; Yanik et al., 2024). Intriguingly, a subset of PNV patients may share risk factors with CSC, such as a history of corticosteroid use or significant stress events (Pang and Freund, 2015; Sartini et al., 2020). Genetic studies have provided further insights into the unique nature of PNV. Unlike nAMD, individuals with PNV show a lower susceptibility to common AMD-associated gene variants, particularly ARMS2 and CFH (Cho et al., 2020; Miyake et al., 2015). This genetic distinction underscores the likelihood that PNV and nAMD are separate clinical entities with different underlying pathophysiological mechanisms (Chen et al., 2024; Cho et al., 2020; De Jong et al., 2015).

1.2.5. Peripapillary pachychoroid syndrome

PPS is a relatively newly described entity within the PSDs, characterized by choroidal thickening and vascular dilation predominantly in the peripapillary and nasal macular regions (Kumar et al., 2022a; Phasukkijwatana et al., 2018; Xu et al., 2022). The epidemiology and risk factors of PPS have been gradually elucidated through several recent studies, providing insights into this distinct clinical entity. PPS predominantly affects males, with studies reporting a male predominance of up to 81–82 % of cases (Phasukkijwatana et al., 2018; Xu et al., 2022). This striking gender disparity suggests a potential hormonal or genetic influence in the pathogenesis of the condition, although the exact mechanisms remain to be fully elucidated. The age of onset for PPS is typically later than that observed in other PSDs such as CSC. Patients with PPS are generally older, with a mean age of approximately 70–71 years reported in various studies (Phasukkijwatana et al., 2018; Xu et al., 2022). This contrasts with the younger age group typically affected by CSC, highlighting a potential difference in the underlying pathophysiology or risk factors between these conditions. PPS tends to be a bilateral condition, with studies reporting bilateral involvement in up to 94 % of cases (Xu et al., 2022). This high rate of bilaterality suggests a systemic or genetic predisposition. Refractive error and axial length have been identified as significant risk factors for PPS. Hyperopia is commonly

associated with PPS, with one study reporting its presence in 86 % of cases (Kumar et al., 2022a; Phasukkijwatana et al., 2018). A shorter axial length has been observed in a significant proportion of PPS cases, with 39 % of affected eyes having an axial length less than 23 mm (Phasukkijwatana et al., 2018). The presence of choroidal folds is another characteristic feature of PPS, observed in up to 77 % of cases (Phasukkijwatana et al., 2018). Optic disc characteristics are also associated with PPS, with many affected individuals exhibiting a crowded optic disc appearance or a small cup-to-disc ratio (Phasukkijwatana et al., 2018; Xu et al., 2022). Some patients may even develop chronic optic disc edema (Kumar et al., 2022a). Systemic vascular risk factors may play a role in the development of PPS, although their exact contribution remains unclear. Hypertension and other vascular pathologies have been reported in some cases (Phasukkijwatana et al., 2018). The use of corticosteroids and the presence of stress have been implicated as potential triggering factors for PPS in some cases (Phasukkijwatana et al., 2018). However, the prevalence of PPS in the general population remains uncertain.

1.2.6. Pachyvittelliform maculopathy

PVM is a rare and recently described condition within the pachychoroid spectrum of diseases (Hilely et al., 2023). While limited literature exists on this specific entity, recent study has provided some insights into its epidemiology and risk factors. The condition typically manifests in middle-aged to elderly individuals, with no clear gender predilection observed thus far (Hilely et al., 2023). Hilely et al. conducted a comprehensive analysis of PVM using optical coherence tomography (OCT), shedding light on its characteristics and potential risk factors (Hilely et al., 2023).

The study revealed that PVM is often associated with pachychoroid features, including increased choroidal thickness and the presence of dilated choroidal vessels. This suggests that the underlying pachychoroid phenotype may be a significant risk factor for developing this condition. Additionally, many patients exhibited hyperopic refractive errors, indicating a possible association between hyperopia and PVM (Hilely et al., 2023).

While the exact prevalence of PVM remains unknown due to its rarity and recent recognition, the condition appears to be bilateral in many cases, hinting at a potential genetic or systemic component (Hilely et al., 2023). However, no specific genetic markers have been identified to date. Age seems to play a role in the development of PVM, with most reported cases occurring in older adults. The study by Hilely et al. also noted that some patients with PVM had a history of CSC or other pachychoroid spectrum disorders (Hilely et al., 2023). This observation suggests that there might be a continuum or overlap between these conditions, with shared risk factors or pathophysiological mechanisms. Systemic factors such as hypertension have been reported in some cases, but their direct contribution to the development of PVM remains unclear and requires further investigation.

1.3. Multimodal imaging in pachychoroid spectrum disease

The diagnosis and management of PSDs rely heavily on various imaging modalities, which are crucial for visualizing the characteristic features of these conditions and differentiating them from other retinal disorders. OCT has revolutionized the assessment of PSDs by providing high-resolution cross-sectional images of the retina and choroid. This technology allows for precise measurement of choroidal thickness and visualization of pachyvessels (Spaide et al., 2008). Enhanced Depth Imaging OCT (EDI-OCT) further improves visualization of the choroid, enabling more accurate assessment of choroidal vasculature and morphology (Margolis and Spaide, 2009).

OCT Angiography (OCTA) has emerged as a powerful tool in the evaluation of PSDs. This non-invasive technique offers detailed visualization of retinal and choroidal vasculature, enabling detection of choroidal neovascularization and assessment of choriocapillaris flow

(Borrelli et al., 2019b; Novais et al., 2016; Viggiano et al., 2023d). OCTA has proven particularly valuable in identifying the subtle vascular changes characteristic of early stages of PSDs.

While newer technologies have advanced our diagnostic capabilities, traditional imaging modalities remain essential. Fluorescein Angiography (FA) continues to play a crucial role in identifying areas of leakage and evaluating retinal vasculature, particularly in conditions like CSC (Daruich et al., 2015). Indocyanine Green Angiography (ICGA) is particularly useful for visualizing choroidal vasculature, identifying pachyvessels, polypoidal lesions in PCV and detecting choroidal hyperpermeability (Fossataro et al., 2024; Ra et al., 2024).

Fundus Autofluorescence (FAF) has added another dimension to our understanding of PSD by aiding in the assessment of RPE changes and identifying areas of chronic disease (Warrow et al., 2013). This technique provides valuable information about the metabolic state of the RPE, offering insights into disease progression and prognosis.

The integration of these various imaging techniques provides a comprehensive view of the structural and functional changes occurring in PSD. This multimodal approach has not only enhanced our understanding of disease pathophysiology but also improved our ability to diagnose these conditions at earlier stages and monitor treatment response more effectively.

The primary aim of this review is to consolidate insights regarding the utilization of multimodal imaging in eyes afflicted by PSDs and to elucidate how OCTA has improved our knowledge in this field. We will explore the various imaging modalities used in the diagnosis and management of PSDs, with a particular focus on the role of OCTA in enhancing our understanding of these conditions. By synthesizing the latest research and clinical findings, this review aims to provide a comprehensive overview of the current state of imaging in PSDs, highlight the unique contributions of each imaging modality, and discuss how the integration of these technologies has advanced our diagnostic and therapeutic approaches. Furthermore, we will explore future directions in imaging technology and their potential impact on the management of PSDs, ultimately aiming to improve patient care and outcomes (Fig. 1 and Table 1).

2. Imaging techniques

2.1. Dye-based imaging

2.1.1. Fluorescein angiography

Flocks et al. documented the initial application of fluorescein angiography (FA) in ophthalmology in 1959, using fluorescein to visualize the retinal circulation in a cat (Flocks et al., 1959). With advancements in fundus photography, Novotny and Alvis extended this technique to human subjects in 1961. They employed FA to examine healthy individuals and patients with hypertension and diabetic retinopathy, demonstrating distinct arteriolar and venous filling phases, arteriovenous shunts, sluggish choroidal circulation, neovascularization, and cotton-wool patches (Novotny and Alvis, 1961). In 1965, Maumenee was the first to describe RPE leaks in CSC using FA (A E Maumenee, 1965). FA is integral to both clinical practice and research for the identification, management, and monitoring of treatment outcomes in retinal and choroidal diseases, including hypertensive retinopathy, diabetic retinopathy, vascular occlusions, age-related macular degeneration (AMD), and CSC (Bennett et al., 2001; Kornblau and El-Annan, 2019).

Fluorescein sodium, a hydrocarbon salt of sodium with a molecular weight of 376.67 Da and the chemical formula $C_{20}H_{10}Na_2O_5$, is a highly water-soluble dye (Hurley and Regillo, 2009). Fluorescence is a form of photoluminescence where blue light (465–490 nm) is absorbed and then re-emitted as yellow-green light (520–530 nm). The intensity of fluorescence is influenced by both dye concentration and pH levels. For angiographic purposes, the pH of fluorescein sodium is adjusted to a range of 8.0–9.8, resulting in an orange-red appearance (Bennett et al.,

Pachychoroid Spectrum Disorders: Diagnostic and Management Approach

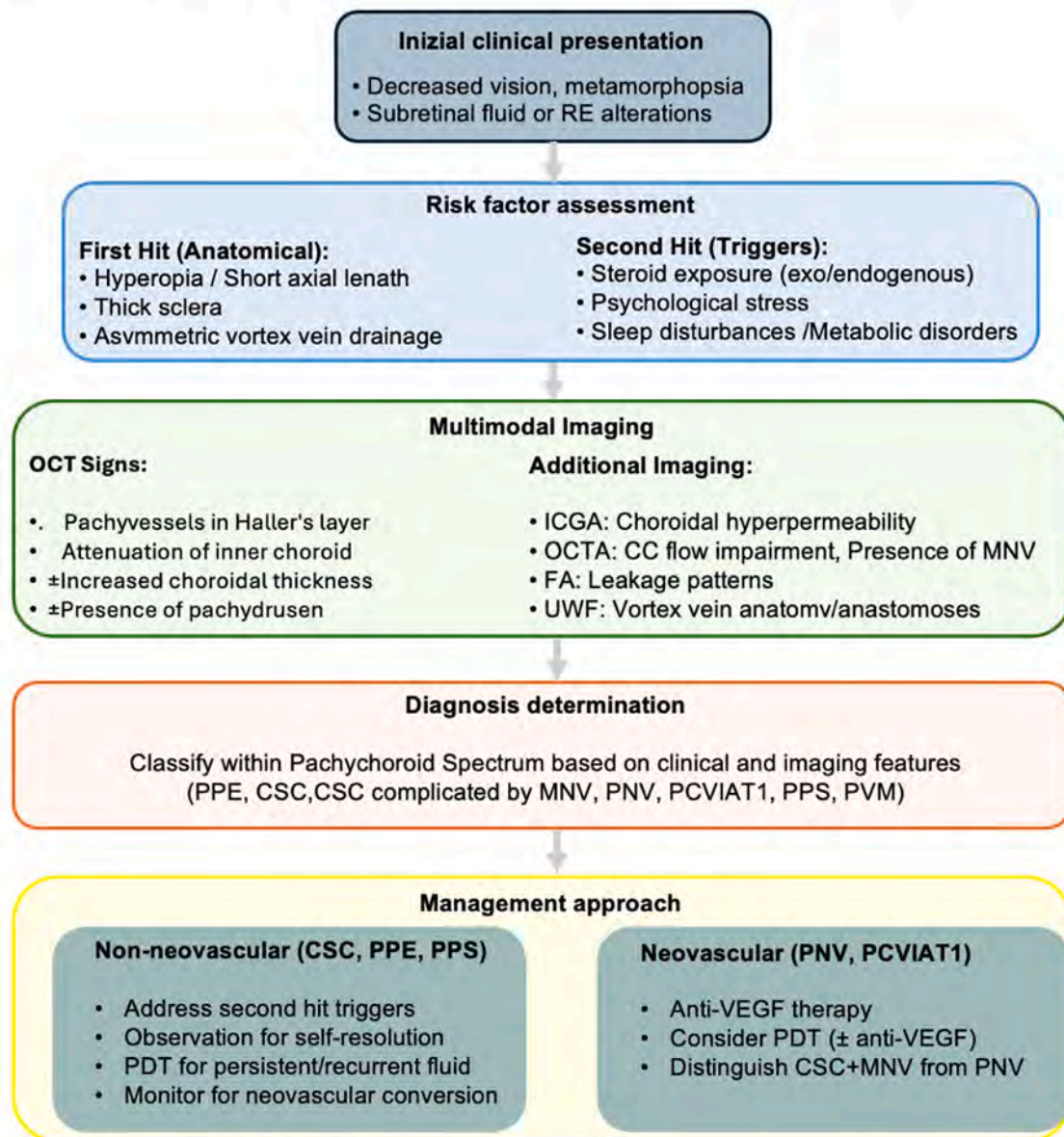


Fig. 1. Flowchart for the diagnostic and management approach to pachychoroid spectrum disorders. This algorithm demonstrates the integration of clinical presentation, risk factor assessment, multimodal imaging, and treatment strategies for various conditions within the pachychoroid spectrum. PPE = pachychoroid pigment epitheliopathy; CSC = central serous chorioretinopathy; MNV = macular neovascularization; PNV = pachychoroid neovascularization; PCV/AT1 = polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization; PPS = peripapillary pachychoroid syndrome; PVM = pachyvittelliform maculopathy; ICGA = indocyanine green angiography; OCTA = optical coherence tomography angiography; FA = fluorescein angiography; UWF = ultra-widefield; CC = choriocapillaris; PDT = photodynamic therapy; VEGF = vascular endothelial growth factor.

2001). About 80 % of the dye binds to plasma proteins, and only the unbound molecules fluoresce (Wolfe, 1986). As it is metabolized by the kidneys, intravenous fluorescein commonly causes urine to change color for 24–36 h. It may also cause a temporary yellow tint to the skin, which usually fades within a few hours (Bennett et al., 2001). In 1986, Yannuzzi categorized the side effects of intravenous fluorescein into three levels: mild, moderate, and severe. Mild reactions, which usually resolve quickly without needing treatment, include symptoms such as nausea, vomiting, dye extravasation, accidental injection into an artery, sneezing, itching, tingling sensations in the tongue or lips, and abdominal cramps. Moderate reactions, which might need medical intervention and tend to resolve over time, include fever, syncope, localized tissue

necrosis, skin rashes, thrombophlebitis, and nerve palsy. Severe reactions, which demand intensive medical care, include heart attacks, anaphylaxis, bronchospasm, acute pulmonary edema, respiratory arrest, seizures, and even death (Yannuzzi et al., 1986). It is classified as a category C drug in pregnancy (Kornblau and El-Annan, 2019).

Fluorescein angiography starts with a bolus injection of 500 mg (5 ml of 10 % or 2 ml of 25 %) from a peripheral vein. In pediatrics, the dosages are adjusted to 35 mg per 10 pounds of body weight (Bennett et al., 2001). The retinal circulation undergoes several dye-transit phases, starting with the prearterial (choroidal flush), around 1 s earlier than in the retina circulation, to show the choriocapillaris and larger choroidal vessels (Tsang and Sharma, 2018). In 10 s post-injection, the

Table 1
Multimodal imaging features of pachychoroid spectrum disorders.

Imaging Modality	Pachychoroid Pigment Epitheliopathy	Central Serous Chorioretinopathy (CSC)	CSC Complicated by MNV	Pachychoroid Neovascularopathy	Polypoidal Choroidal Vasculopathy	Peripapillary Pachychoroid Syndrome	Pachyvittelliform Maculopathy
Fluorescein Angiography	Minimal to no leakage; Subtle RPE changes	Classic "inkblot" or "smokestack" pattern of leakage in acute form; Multiple indistinct leaks with granular window defects in chronic form	Occult leakage pattern (from MNV) alongside CSC-related leakage patterns; Difficult to distinguish from each other	Occult leakage pattern with stippled hyperfluorescence; Can be masked by RPE window defects	Occult leakage pattern; Hyperfluorescent nodules; Late leakage from polypoidal lesions	Minimal to no leakage in macular region; May show peripapillary leakage	Minimal to no leakage; RPE window defects
Indocyanine Green Angiography	Choroidal vascular hyperpermeability (CVH); Dilated choroidal vessels; No active leakage	CVH; Delayed choroidal filling; Mid-phase geographic hyperfluorescence; Late-phase centrifugal displacement or wash-out	CVH; May lack typical late hyperfluorescence associated with MNV; MNV network often masked by underlying hyperpermeability	CVH; Late-staining plaque indicative of type 1 MNV; Early-to-mid phase hypercyanescence with late wash-out	Early hyperfluorescent polypoidal lesions with surrounding hypofluorescence; BVN visible as network; Late-phase washout of polyps	Peripapillary CVH; Dilated choroidal vessels in nasal macular and peripapillary regions	Focal areas of CVH corresponding to vitelliform material
Optical Coherence Tomography (OCT)	Pachyvessels; Inner choroidal thinning; RPE irregularities without SRF; RPE elevations with microbreak appearance (REwM)	SRF; PEDs; Increased choroidal thickness; Elongated photoreceptor outer segments; Pachyvessels; Hyperreflective dots in choroid and retina	SRF; Flat irregular PED with double-layer sign; PEDs; Evidence of both CSC and MNV features	Shallow irregular PEDs (double-layer sign); Pachyvessels; Inner choroidal attenuation; Minimal to moderate SRF	Sharply peaked PEDs (thumb-like polyps); PED notch; Ring-like lesions; Multiple/multilobular PEDs; Double-layer sign	Peripapillary SRF and/or intraretinal fluid; Peripapillary and nasal macular choroidal thickening	Vitelliform (hyperreflective) material above RPE with underlying pachychoroid features
En-face OCT	Dilated outer choroidal vessels corresponding to pachyvessels; Subtle RPE alterations	Focal choroidal thickening corresponding to leakage sites; Dilated choroidal vessels; Intervortex venous anastomoses	Similar to CSC with additional findings of MNV network corresponding to SIRE	Dilated outer choroidal vessels; RPE and sub-RPE irregularities corresponding to MNV	RPE ring-like elevations (polyps); Geographic RPE elevations (BVN); Large round RPE elevations (serous PEDs)	Dilated peripapillary choroidal vessels; Nasal choroidal thickening	Dilated choroidal vessels beneath area of vitelliform material
OCT Angiography (OCTA)	Areas of choriocapillaris flow impairment; Altered CC flow pattern with hyper- and hypoperfused areas	CC flow impairment corresponding to areas of CVH on ICGA; Reduced CC vessel density	Tangled vascular network between RPE and Bruch's membrane; Better visualization of MNV network than ICGA	Tangled vascular network corresponding to SIRE; Clear visualization of type 1 MNV; CC flow impairment	BVN clearly visible; Polypoidal lesions variably visible (some with flow, others without); CC flow impairment	CC flow alterations in peripapillary and nasal macular regions	CC flow impairment beneath vitelliform material
Fundus Autofluorescence (FAF)	Subtle areas of hyper- or hypoautofluorescence; May be normal in early stages	Initially decreased FAF in areas of SRF; Increased patchy FAF in persistent cases; Gravitational tracks in chronic cases	Mixed pattern with hypoautofluorescence from RPE atrophy and hyperautofluorescence from chronic disease	Patchy granular hypoautofluorescence with hyperautofluorescent specks	Confluent hypoautofluorescence at polyp sites with hyperautofluorescent ring ("punched-out" appearance); Granular BVN hypoautofluorescence	Peripapillary RPE mottling and hypoautofluorescence	Hyperautofluorescence corresponding to vitelliform material
Infrared Reflectance (IR)	Reduced fundus tessellation; Hyperreflective drusenoid lesions	Initially decreased reflectivity; May evolve to granular pattern in chronic cases	Similar to CSC with additional findings corresponding to MNV	Hyporeflective lines/ streaks corresponding to pachyvessels	Variable reflectivity at polyp sites; Helps estimate lesion boundaries	Hyperreflective choroidal vessels in peripapillary region	Hyperreflective area corresponding to vitelliform material

Abbreviations: RPE = retinal pigment epithelium; SRF = subretinal fluid; CVH = choroidal vascular hyperpermeability; MNV = macular neovascularization; PED = pigment epithelial detachment; CC = choriocapillaris; SIRE = shallow irregular RPE elevation; BVN = branching vascular network.

arterial phase shows the retinal arteries, then moves to the arteriovenous phase, where arteries and capillaries are filled, and veins exhibit laminar flow with peak fluorescence in both arteries and veins. Then enter the transit phase, which is the complete passage of fluorescein through the retina and choroid; approximately 10 min after injection, during the late phase, most vessels lose the dye, leaving large choroidal vessels visible as dark silhouettes against the brighter choroid and stained sclera (Kulkarni et al., 2024; Tsang and Sharma, 2018). In 1980, Kelley et al. (1980) demonstrated that sodium fluorescein can be safely administered orally, producing angiograms that effectively document dye leakage similar to venous injection. This is particularly beneficial for children and patients with difficult vein access.

Hypofluorescence lesions result from vascular filling defects in retinal vascular occlusions and capillary non-perfusion in ischemic retina or from blocked fluorescence due to hemorrhage, exudates, and inflammatory debris (Kulkarni et al., 2024). In contrast, hyperfluorescence lesions arise from autofluorescence, window defects in RPE atrophy, abnormal vessels, dye leakage, or staining (Kulkarni et al., 2024). In the pachychoroid spectrum, FA reveals varying features depending on disease duration, RPE damage, and leakage patterns. Acute CSC may present with specific dye leakage patterns such as ink-blot or smoke-stack, whereas chronic CSC often shows multiple indistinct leaks within granular window defects (Ming Gemmy Cheung et al., 2019).

However, FA interpretation faces several specific challenges. The identification of leakage points in CSC can be difficult, particularly in chronic cases where multiple areas of window defects may obscure the actual source of subretinal fluid (Daruich et al., 2015). Additionally, the presence of diffuse RPE alterations in chronic CSC can create widespread background hyperfluorescence that masks focal leakage sites, potentially leading to underestimation of disease activity or misdiagnosis of disease chronicity.

2.1.2. Indocyanine green angiography

Indocyanine green angiography (ICGA) was initially utilized by Kogure and Choromokos in 1969 to investigate pial circulation in canines (Kogure and Choromokos, 1969). Subsequently, the same researchers adapted this technique for fundus angiography in primates, employing intracarotid injection of indocyanine dye and high-speed infrared film with a standard fundus camera. This approach enhanced the visualization of choroidal filling, as it was not obstructed by the pigment epithelium (Kogure et al., 1970). In 1971, David pioneered the use of intraarterial ICG infrared absorption choroid angiography in humans (Kogure et al., 1970). By 1986, Hayashi et al. (1986) had identified a link between CSCR and choroidal circulatory insufficiency, highlighting the role of choroidal ischemia in RPE disturbances. Today, ICGA is employed in various applications, including iris and anterior segment angiography, AMD, choroidal neovascularization, inflammatory choroiditis, and choroidal tumors (Stanga et al., 2003).

ICGA, a tricarboyanine dye with a molecular weight of 775 g/mol and the chemical formula $C_{43}H_{47}N_2NaO_6S_2$, exhibits distinct properties compared to sodium fluorescein. Notably, ICGA has a significantly higher plasma protein binding rate of 98 %, in contrast to sodium fluorescein's 70–90 % (CHERRICK et al., 1960). Additionally, ICG's absorption and fluorescence peaks are in the near-infrared spectrum, with maximum absorption at 805 nm and maximum fluorescence at 835 nm, which is markedly different from sodium fluorescein. Consequently, ICG is minimally absorbed by macular xanthophyll pigments and the RPE, with only 10 % absorption by the latter (Destro and Puliafito, 1989). These attributes render ICGA particularly advantageous for visualizing choroidal vascular structures, especially in the submacular region, where sodium fluorescein's efficacy is limited (Gelişken, 2024a). ICG is known for its excellent tolerance and robust safety record. Potential side effects range from mild issues like nausea, vomiting, and itchiness to more serious conditions such as fever, hives, skin eruptions, anaphylaxis, bronchospasm, seizures, shock, or even death. Due to its

iodine content (approximately 5 %), it should be used cautiously in individuals with iodide allergies, and those with seafood allergies may also experience crossover reactions (Hope-Ross et al., 1994). It is classified as a category C drug in pregnancy (Fineman et al., 2001).

The concentration of ICG for intravenous injection varies with the instrument and other factors, typically involving 20–50 mg dissolved in 2–5 mL of solvent, injected slowly, followed by a 5 mL saline flush, with a maximum dose of 2 mg/kg. The required excitation and barrier filters depend on the imaging system and other factors, typically using an excitation filter peaking at 805 nm and a barrier filter peaking at 835 nm for image acquisition (Delgado-Tirado et al., 2022). A preinjection infrared fundus photograph showing pseudofluorescence or autofluorescence can help prevent misinterpretation of the angiograms (Piccolino et al., 1996). ICGA photographs progress through three phases: the early phase (seconds post-injection), where choroidal arteries, choriocapillaris, and veins fill; the middle phase (up to 10 min), marked by the late venous phase and reduced contrast between choroidal vessels and background fluorescence; and the late or inversion phase (10–20 min), which reveals hypofluorescent silhouettes of large choroidal veins on an iso-fluorescent fundus (Soubrane et al., 2000).

Hypofluorescent lesions manifest as dark regions resulting from filling defects in the choriocapillaris due to pathological conditions or blockages caused by pigmented lesions, choroidal stroma infiltrations, or subretinal hemorrhage. Hyperfluorescent lesions appear as white areas resulting from leakage due to stromal choroiditis, window defects due to RPE or choriocapillaris atrophy, or abnormal vessel formations such as choroidal hemangioma or PCV (Gelişken, 2024a). In pachychoroid spectrum diseases, ICGA reveals several characteristic features, including pachyvessels, choroidal hyperpermeability, polypoidal lesions, choroidal vessel filling defects, delayed arterial filling, and patchy hyperfluorescent areas (Akkaya, 2018; Safi et al., 2022), which will be elaborated upon in subsequent sections.

Despite its utility in visualizing choroidal vasculature, ICGA interpretation in PSDs presents several challenges. Choroidal hyperpermeability, a hallmark of pachychoroid disorders, can obscure the visualization of neovascular networks. This is particularly problematic in PNV and PCV/AT1, where ICGA demonstrates lower sensitivity (66 %) compared to OCTA (97 %) for detecting neovascularization (Demirel et al., 2022). Furthermore, the distinction between pachyvessels and a branching vascular network in early PCV/AT1 requires significant expertise.

2.2. Non-dye-based imaging techniques

2.2.1. Infrared and near-infrared reflectance

Near-infrared (NIR) imaging is a noninvasive and noncontact imaging technique for in vivo examination widely utilized in contemporary ophthalmological practice (Elsner et al., 1996). This technique operates within the wavelength spectrum of 804–895 nm (Elsner et al., 1996). This technique can be conducted through a non-dilated pupil, as infrared (IR) illumination does not induce pupil constriction. Additionally, it can penetrate cataracts and hemorrhages, particularly at wavelengths exceeding 820 nm (Elsner et al., 1996; Ly et al., 2016). Additional benefits include seamless integration with SD-OCT, improved patient comfort compared to the bright flash of fundus photography or FAF imaging, and the ability to capture images through opacities like dense cataracts, vitreous and retinal hemorrhages, or exudation (Hassenstein and Meyer, 2009).

The extended wavelength employed in NIR imaging allows deep penetration into intraocular structures and remains unaffected by melanin. This characteristic endows NIR imaging with the capability to detect pathologies in the outer retina and choroid (Hassenstein and Meyer, 2009). Although images often correlate with blue-light fundus autofluorescence (FAF), NIR imaging is particularly adept at revealing sub-RPE lesions. NIR imaging primarily captures reflected light from melanin-containing structures in the RPE and choroid, providing

structural information based on tissue reflectivity properties. In contrast, NIR-AF detects the emission of light from endogenous fluorophores such as melanin and melanilipofuscin after excitation in the near-infrared spectrum (787 nm), offering insights into the metabolic state and composition of RPE and choroidal tissues. This superiority is due to the greater absorption of shorter wavelength monochromatic light (480 nm) by melanin and lipofuscin granules at the RPE level (Issa et al., 2009; Weinberger et al., 2006).

When infrared illumination is applied to a material, it interacts by being absorbed, reflected, or scattered to varying degrees. In the ocular environment, the principal absorbers encompass the lens, melanin, water, macular pigment, and hemoglobin, leading to hyporeflectivity in the fovea, the optic disc, and major blood vessels. In contrast, the surrounding fundus demonstrates moderate reflectivity (Sukkarieh et al., 2023). To mitigate contrast loss caused by scattering within fundus structures, a scanning laser ophthalmoscope (SLO) was developed. This device illuminates a small fundus region and captures the returning light simultaneously. The resulting image is an en-face representation of the fundus, formed by the cumulative reflectance from multiple sources (Ly et al., 2016; Sukkarieh et al., 2023). Wide-field NIR imaging is a recent advancement with significant potential for distinguishing and documenting the extent and progression of various retinal diseases (Ho et al., 2016).

NIR has been observed in a wide range of conditions, including inflammatory chorioretinal diseases, vascular disorders, degenerative diseases, tumors, systemic illnesses, toxic and traumatic injuries, and abnormalities related to the optic nerve head (Fazelat et al., 2012). In acute CSC with neurosensory detachment, NIR levels were initially decreased but fluctuated as the disease progressed (Ayata et al., 2009). Additionally, resolved CSC with an atrophic ellipsoid zone exhibited abnormalities in NIR images (S.-K. Kim et al., 2013b), which is associated with decreased retinal sensitivity (Soga et al., 2021). Furthermore, the hypofluorescent spot observed in NIR images of CSCR corresponded to the leakage site identified in FA (Lindner et al., 2012).

2.2.2. Fundus autofluorescence

Fundus autofluorescence (FAF) imaging is a noninvasive technique for topographically mapping the metabolic activity of fluorophores. These fluorophores, such as lipofuscin, accumulate naturally within the lysosomal storage bodies of postmitotic RPE cells. Pathological accumulation of these substances in vivo can yield valuable diagnostic and prognostic insights into various retinal diseases (Schmitz-Valckenberg et al., 2021). The advantages of this imaging modality include its rapid execution and non-invasive nature, eliminating the need for intravenously injected agents. Additionally, it offers valuable information regarding the health of the RPE and the outer retina (Schmitz-Valckenberg et al., 2021).

FAF signals are emitted over a broad spectral range, spanning from 500 to 800 nm. Typically, excitation is achieved using blue light at a wavelength of 488 nm. A barrier filter above 500 nm is employed to detect the emitted autofluorescence signal (Jorzik et al., 2005). The ultra-widefield imaging system by Optos® integrates confocal scanning laser technology with an ellipsoid mirror to capture an extensive view of the ocular fundus, covering up to 200°, corresponding to approximately 82.5 % of the retinal surface area (Yung et al., 2016).

Clinically, this imaging modality is utilized for various retinal diseases, including inflammatory diseases, macular and retinal degenerations and dystrophies, toxic retinopathies, and retinal tumors (Yung et al., 2016). Hyper-autofluorescence lesions are due to increased RPE lipofuscin, including Stargardt, and pattern Hyper-autofluorescence can be observed in various retinal conditions. In vitelliform dystrophies, subretinal autofluorescent material can result in hyper-autofluorescent lesions. Other causes include window defects due to the loss of luteal or photopigments, as seen in white dot syndrome, CSCR, and Macular Telangiectasia type 2. Additionally, astrocytic hamartomas and optic disc drusen are known to cause hyper-autofluorescent lesions. RPE tears,

particularly those with retracted borders, can also present with hyper-autofluorescence (Yung et al., 2016). Structures outside the retinal plane can scatter signals, artificially elevating the FAF signal. This phenomenon is referred to as pseudo-autofluorescence (Lois et al., 2004). Hypo-autofluorescence lesions can arise from several factors. One primary cause is the reduction or absence of RPE lipofuscin, which may occur in conditions such as geographic atrophy. Blockage from materials anterior to the RPE, such as media opacities, macular pigments, intraretinal or subretinal hemorrhage, or fibrotic scars, can lead to hypo-autofluorescence (Yung et al., 2016).

In pachychoroid spectrum diseases, FAF imaging offers valuable insights into the health of RPE cells. Changes in FAF images can be indicative of RPE atrophy and the presence of subretinal hyperreflective material, which are common features in these conditions (Yung et al., 2016), and will be explained in subsequent sections.

2.2.3. Optical coherence tomography

Ocular imaging is pivotal in clinical diagnosis and treatment. As a non-invasive technology, optical coherence tomography (OCT) has transformed ophthalmology by continuously enhancing image quality, speed, and resolution during this time, making it an indispensable tool for diagnosing a wide range of ocular pathologies in the anterior and posterior segments (Borrelli et al., 2019a; Boscia et al., 2024; Viggiano et al., 2023c, 2024a; Zeppieri et al., 2023). Using this technology, several eye structures, including the cornea, iris, iridocorneal angle, retina, choroid, and optic nerve, can be quantitatively assessed (Remlinger et al., 2023; Viggiano et al., 2023b). This method is an extension of low-coherence interferometry, originally used in ophthalmology to measure the eye's axial length in vivo (Gabriele et al., 2011). Intra-operative OCT, including hand-held, probe-integrated, and microscope-integrated OCT, helps in surgical decision-making (Sadeghi et al., 2023). (48).

The first commercially available OCT device in 1996 was time-domain OCT (TD-OCT) (Bhende et al., 2018), which involves splitting light and directing it to both a reference arm with a mirror and the sample. When the path lengths to the reference mirror and tissue match within the coherence length of the light source, the recombined reflected beams produce interference. Adjusting the position of the reference mirror enables the detection of backscattered tissue intensity levels from various depths within the tissue sample (Gabriele et al., 2011; Qin and An, 2021). With a bandwidth of 20 nm (Forte et al., 2009), wavelength frequency of 810 nm (Forte et al., 2009), and axial resolution of 8–10 μm (Singh and Chhablani, 2022), this device is capable of performing 400 A-scans per second (Adhi and Duker, 2013).

The next generation was spectral-domain OCT (SD-OCT), which became commercially applicable in 2006 (Bhende et al., 2018). In this device, the sensor is upgraded to a spectrometer, and the acquisition speed has improved considerably by detecting backscattered signals in the frequency domain. This allows for collecting backscattered depth information without the movement of a reference mirror and improves signal-to-noise ratio (de Boer et al., 2003; Zhao et al., 2023). With a bandwidth of 150 nm (Forte et al., 2009), wavelength frequency of 840 nm, and axial resolution of 5–7 μm (Singh and Chhablani, 2022), this device is capable of performing A-scans 20,000–52,000 per second (Adhi and Duker, 2013). Positioning the objective lens closer to the eye enhances depth sensitivity, allowing for improved visualization of deeper ocular structures such as the choroid. This technique is known as Enhanced Depth Imaging (EDI) OCT (Enaholo et al., 2024; Spaide et al., 2008).

Using a single wavelength of light led to the introduction of swept-source OCT (SS-OCT) (Qin and An, 2021; Viggiano et al., 2022a), which became commercially applicable in 2012 (Bhende et al., 2018). With a bandwidth of ~1040–1080 nm, wavelength frequency of ~1050 nm, and axial resolution of 5.3 μm (Singh and Chhablani, 2022), this device is capable of performing A-scans 100,000–236,000 per second (Adhi and Duker, 2013; Chen et al., 2022).

As a non-contact and non-invasive imaging technique, OCT is extensively utilized for evaluating retinal diseases by providing critical insights into disease pathophysiology and facilitating patient follow-up (Sakata et al., 2009).

Beyond diagnostic applications, several OCT biomarkers have demonstrated clinical utility in risk stratification and treatment response prediction in PSDs. Larger pachyvessel diameter ($>250\ \mu\text{m}$) correlates with increased risk of progression from PPE to CSC (Kunal K Dansingani et al., 2016), while the presence of intervortex venous anastomoses exceeding $350\ \mu\text{m}$ in diameter is associated with recurrent or chronic disease (Matsumoto et al., 2020). Regarding treatment outcomes, eyes with subfoveal choroidal thickness above $400\ \mu\text{m}$ show superior response to half-dose photodynamic therapy in CSC (Maruko et al., 2011a), whereas relatively thinner choroids ($<300\ \mu\text{m}$) demonstrate better response to anti-VEGF therapy in cases with neovascularization (Pitcher et al., 2015). The presence of subretinal hyperreflective material, particularly when thick ($>100\ \mu\text{m}$) or heterogeneous, serves as a predictor of neovascular transformation (Maruyama-Inoue et al., 2023). Moreover, outer retinal integrity markers, including outer nuclear layer thickness and ellipsoid zone continuity, reliably predict visual outcomes (Matsumoto et al., 2009; Ooto et al., 2015). The choroidal vascularity index, calculated as the ratio of luminal to total choroidal area, may serve as a quantitative marker of disease activity and treatment efficacy (Ersoz et al., 2021). While these biomarkers show promise for clinical application, most supporting evidence comes from retrospective studies, highlighting the need for prospective validation.

2.2.4. En-face optical coherence tomography

En-face OCT is a fast, noninvasive, high-resolution imaging technique that has recently become a standard tool for assessing and monitoring various vitreoretinal diseases (Oribio-Quinto et al., 2022). In en-face OCT, the primary scanning direction is lateral rather than in-depth (Leitgeb, 2019). With ultrafast Fourier domain OCT systems, en-face image slices can be retrospectively driven from fully recorded volumes or calculated by depth projection across selected depth ranges (Leitgeb, 2019). En-face OCT images offer high-resolution frontal views of the retina and choroid, enabling detailed assessment and valuable information on the severity of vitreoretinal interface pathologies such as epiretinal membranes, macular holes, vitreomacular traction, and retinoschisis (Oribio-Quinto et al., 2022). In AMD it provides valuable detail on drusens and geographic atrophy extension (Moult et al., 2016; Voichanski et al., 2024). In PDS, en-face images highlight abnormal changes in choroidal vasculature, pigment epithelial hyperplasia linked to FA leakage needing treatment, polypoidal lesions, dilated or displaced choroidal vessels, and extensive venous anastomoses (Dansingani et al., 2016; Lehmann et al., 2013a; Spaide et al., 2021).

2.2.5. Optical coherence tomography angiography

Optical coherence tomography angiography (OCTA) generates high-resolution volumetric blood flow data by analyzing the decorrelation signal between sequential OCT b-scans captured at the same cross-sectional location. The motion detected between these repeated OCT b-scans exclusively reflects erythrocyte movement within retinal blood vessels. It necessitates higher imaging speeds compared to most current OCT systems (Borrelli et al., 2019b, 2020b; Carlo et al., 2015; Schwartz et al., 2014).

In comparison to FA and ICG, OCTA is a non-invasive, non-expensive, and non-time-consuming technique that does not require intravenous dye injection, especially for patients who need frequent follow-up. It can localize the axial location of the lesion and measure the size of the lesions which is not possible in FA and ICG due to the 2-dimensional nature of the images and dye leakage. The en-face OCT angiograms can show the individual vascular plexus and segment the inner retina, outer retina, choriocapillaris, or other areas of interest. It provides both structural and functional information in the same scan (Carlo et al., 2015; Johnson et al., 2012). OCTA has been demonstrated to offer

valuable insights into ocular diseases such as AMD, diabetic retinopathy, and retinal vascular occlusion (Antonio et al., 2020; Borrelli et al., 2020c; Brinkmann et al., 2024a; Mastropasqua et al., 2020; Ong et al., 2023).

2.2.5.1. Evaluation of choroidal blood flow using optical coherence tomography angiography. Given its ability to overcome significant limitations of previous dye-based techniques, OCTA has emerged as a crucial technological tool for choroidal evaluation, providing novel and critical insights into the pathogenesis of various choroidal disorders (Brinkmann et al., 2024b; Viggiano et al., 2022c; Zouache et al., 2016).

En face choriocapillaris (CC) OCTA images are derived from a 10–30 μm slab under the Bruch's membrane, as a dense, mesh-like capillary bed, where dark areas indicating signal voids represent intercapillary spaces that expand with age and disease (Borrelli et al., 2018; D. Y. Kim et al., 2013a; Spaide, 2017). OCTA can visualize vascular layers at various depths but struggles with deeper choroidal layers due to pigment scattering, vessel interference, and signal attenuation, resulting in projection artifacts and silhouette-like images at greater depths (Borrelli et al., 2019c).

2.2.5.2. Artifacts in optical coherence tomography angiography images.

Current OCTA technology is susceptible to image artifacts. Factors such as media opacity, dry eye, and defocus, resulting from incorrect positioning, astigmatism, or operator error, contribute to low signal strength. This diminished signal strength can cause smaller vessels to be obscured by background noise, and efforts to reduce noise may further attenuate lower signals. Enhancing signal strength may be achieved through reimaging with ocular lubrication and refining imaging techniques (Spaide et al., 2017).

OCTA captures motion between sequential B-scans to create angiographic images. However, eye movements, especially in cases of poor visual acuity, amblyopia, and scotomas, and internal eye movements from the choroid's pulsatile expansion and intraocular pressure changes during the cardiac cycle can cause motion artifacts, shearing distortions, or gaps in en-face images. Utilizing eye tracking and software-based motion correction can help minimize these artifacts (Spaide et al., 2017).

To image deeper structures like photoreceptors or the RPE, the OCT beam must pass through retinal blood vessels, causing time-varying fluctuations due to flowing blood. This fluctuating illumination can create decorrelation between B-scans, falsely indicating blood flow in deeper layers called projection artifacts. Projection-resolved OCTA (PR-OCTA) mitigates these artifacts by normalizing OCTA decorrelation with OCT intensity and setting values deeper than the peak level to zero, preserving the continuity of deeper vascular layers (Zhang et al., 2016).

Segmentation artifacts, primarily due to segmentation errors, can cause serious inaccuracies in OCTA data, especially in eyes with disrupted retinal architecture. While many manufacturers offer software for manual correction of these errors, the process is time-consuming, and ongoing research aims to address the complexities of retinal pathology and advanced disease (Spaide et al., 2015, 2017).

Pachychoroid spectrum disorders present unique challenges for OCTA imaging. Extensive subretinal fluid, common in CSC and other PSDs, causes significant signal attenuation as light passes through fluid-filled spaces, creating shadow artifacts that obscure underlying choroidal vasculature. This can lead to apparent flow voids in the choriocapillaris that may be misinterpreted as areas of impaired perfusion rather than imaging artifacts (Ricardi et al., 2024; Viggiano et al., 2024b). Swept-source OCTA, with its longer wavelength, offers better penetration through fluid and can partially mitigate this limitation (Mastropasqua et al., 2019; Viggiano et al., 2025b). Large pigment epithelial detachments (PEDs) in chronic CSC, PNV, and PCV/AT1 pose additional challenges by causing both projection artifacts and segmentation errors. The curved surface of PEDs creates irregular reflections

that can appear as false flow signals beneath the detached RPE (Spaide et al., 2017). Automated segmentation algorithms often fail to correctly identify retinal layers around PEDs, requiring manual adjustment to properly visualize the choriocapillaris and potential neovascularization. The double-layer sign, characteristic of type 1 neovascularization in PSDs, can be particularly difficult to interpret on OCTA due to signal attenuation from overlying subretinal material and projection artifacts. Careful correlation with structural OCT and examination of segmentation boundaries on corresponding B-scans is essential before interpreting en face OCTA images in these challenging cases.

3. Pathogenesis and histopathology

3.1. Choroidal vascular abnormalities

3.1.1. Pachyvessels

PSDs are characterized by distinctive choroidal vascular abnormalities that play a central role in their pathogenesis. These abnormalities primarily involve the Haller's layer of the choroid and have far-reaching effects on the overlying choriocapillaris, Bruch's membrane, and RPE (Pauleikhoff et al., 2024; Spaide et al., 2022a). The hallmark feature of PSDs is the presence of pachyvessels, which are dilated choroidal vessels primarily located in the Haller's layer (Fig. 2). These vessels are typically larger than 300 μm in diameter and can be readily visualized on EDI-OCT and en face OCT (Dansingani et al., 2016). Pachyvessels are not merely dilated normal vessels but represent a pathological entity with altered flow dynamics and permeability characteristics (Spaide et al., 2022a). Unlike regular choroidal vessels that gradually taper as they approach the posterior pole, pachyvessels maintain their enlarged caliber and terminate abruptly. This atypical vascular pattern can

manifest either focally or diffusely across the choroid, contributing to the overall pachychoroid phenotype (Hua et al., 2021; Kishi and Matsumoto, 2022; Matsumoto et al., 2020). The presence of these non-tapering, abruptly terminating vessels serves as a key diagnostic feature in identifying PSDs, even in cases where overall CT may not be significantly increased.

These vessels appeared as hyporeflective, round, oval, or elongated shapes on en face scans through the choroid (Tomasso et al., 2018; Toto et al., 2022; Viggiano et al., 2023a). The distribution of pachyvessels varies among different PSDs. In CSC, pachyvessels are often localized to the macular area (Agrawal et al., 2016; Boscia et al., 2023; Chhablani et al., 2020; Viggiano et al., 2023a), while in PPS, they are predominantly found in the peripapillary region (Kumar et al., 2022a; Phasukkijwatana et al., 2018; Xu et al., 2022). This spatial variability suggests that local factors may influence the development and progression of choroidal vascular abnormalities in PSDs.

3.1.2. Inner choroid attenuation

A key feature of pachychoroid disorders is the attenuation of the inner choroidal layers, which includes both the CC and Sattler's layer. The CC, which lies immediately beneath Bruch's membrane, undergoes significant changes in PSDs. Thinning or attenuation of the CC can be focal or diffuse and is commonly observed overlying areas of dilated pachyvessels (Tagawa et al., 2022) (Fig. 2). This phenomenon, known as "choriocapillaris compression," is thought to result from the mechanical effects of the enlarged deeper choroidal vessels and altered hemodynamics (Spaide et al., 2022a). Spaide et al. (Ricardi et al., 2024) used OCTA to investigate choriocapillaris flow in eyes with pachychoroid features. They found that areas of choriocapillaris flow deficits corresponded to the locations of pachyvessels, suggesting a potential ischemic

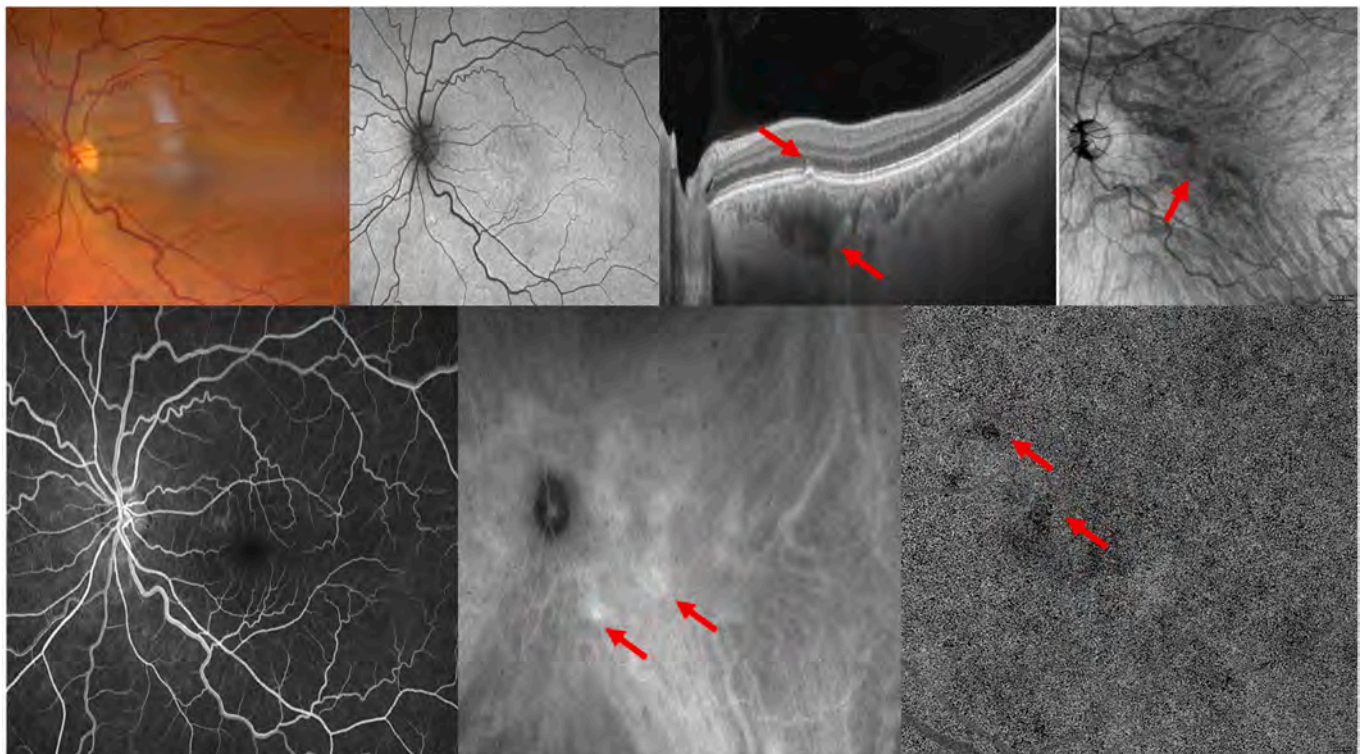


Fig. 2. Multimodal imaging of pachychoroid pigment epitheliopathy in a 38-year-old male. The color fundus photograph (top left) shows subtle retinal pigment epithelium alterations in the macula without subretinal fluid. Fundus autofluorescence (top, second from left) reveals patchy areas of mild hyperautofluorescence indicating RPE stress. OCT B-scan (top, third from left) demonstrates pachyvessels in Haller's layer (lower red arrow) and pachydrusen (upper red arrow) without subretinal fluid accumulation. En face OCT of the choroid (top right) displays dilated choroidal vessels and intervortex anastomoses (red arrow). Fluorescein angiography in late phase (bottom left) shows slight window defects without active leakage. Indocyanine green angiography in the intermediate phase (bottom, middle) reveals areas of choroidal hyperpermeability (red arrows). OCT angiography of the choriocapillaris (bottom right) demonstrates flow deficits (red arrows) corresponding to areas of pachyvessels, indicating attenuation of the inner choroidal layer.

component in the pathogenesis of PSDs. Gal-Or et al. (2018) conducted a comprehensive study using OCTA to examine inner choroidal flow patterns in eyes with pachychoroid disease. They identified zones of reduced inner choroidal flow signal, which they interpreted as areas of flow attenuation. Interestingly, the study found that these zones of reduced flow were not always directly attributable to structural changes visible on OCT. Only 42 % (62 out of 146) of the flow attenuation zones showed overlap or proximity with areas of structural inner choroidal thinning. This suggests that functional changes in choroidal blood flow may precede or occur independently of visible structural alterations.

The progression of PSD often leads to a gradual thinning of the inner choroidal layers. Initially, this may manifest as a subtle compression of the CC and Sattler's layer above the enlarged Haller's layer vessels. Over time, as the condition advances, the pachyvessels may expand to occupy an increasingly larger proportion of the CT (Demirel et al., 2021; Yun et al., 2019). This expansion can lead to significant reduction and, in severe cases, near-complete atrophy of the inner choroid. Importantly, recent research demonstrated that even in eyes with relatively normal overall choroidal thickness, the ratio of choriocapillaris to total choroidal thickness can be reduced, highlighting the importance of assessing choroidal flow and structure rather than relying solely on thickness measurements (Imamura et al., 2009; Ricardi et al., 2024).

Recent advancements in imaging analysis have led to the development of software-based techniques to quantify these structural and vascular changes. One such method involves the calculation of the choroidal vasculature index (CVI), which measures the ratio of choroidal vascular luminal area to total choroidal area using binarized OCT images (Boscia et al., 1941; Ersoz et al., 2021; Iovino et al., 2020; Viggiano et al., 2021, 2022b). This index has emerged as a potentially valuable imaging biomarker for PSDs, offering a more nuanced assessment of choroidal vasculature beyond simple thickness measurements (Agrawal et al., 2016; Toto et al., 2022).

The chronic changes in choroidal structure and perfusion associated with PSDs can have far-reaching effects beyond the choroid itself. Studies have observed thinning of the outer nuclear layer (ONL) in eyes with PSDs, even in the absence of subretinal fluid (Matsumoto et al., 2011). This finding suggests that the altered choroidal structure and blood flow may lead to degenerative changes in the photoreceptors and RPE over time, potentially contributing to vision loss even in seemingly uncomplicated cases (Gujar et al., 2022; S.-K. Kim et al., 2013b; Matsumoto et al., 2011).

3.1.3. Intervortex venous anastomoses

Intervortex venous anastomoses have emerged as a key anatomical feature in PSDs, particularly CSC. These anastomoses represent connections between different vortex vein drainage systems, most commonly observed between the superotemporal and inferotemporal vortex veins in the macular region (Bacci et al., 2022) (Fig. 2).

Spaide et al. (2021) first highlighted the significance of these anastomoses in PSDs, noting their presence in CSC, PPS, and PNV. They proposed that these anastomoses may develop as a compensatory mechanism in response to venous outflow obstruction or congestion in the choroid. Matsumoto et al. (2020) conducted a comprehensive study comparing the prevalence of intervortex anastomoses across different PSDs. They found that anastomoses were present in 90.2 % of eyes with CSC, 95.1 % of eyes with PNV, and 100 % of eyes with PCV. Importantly, they also observed anastomoses in 36.4–48 % of age-matched healthy control eyes, suggesting that while these anastomoses are significantly more common in PSDs, they can also be present as a normal anatomical variant (Matsumoto et al., 2020). Building on these findings, Demirel et al. (2024) performed a quantitative assessment of intervortex anastomoses in CSC, fellow eyes, and healthy controls. They not only confirmed the higher prevalence of anastomoses in CSC eyes (75.4 %) and fellow eyes (61.5 %) compared to healthy controls (36.4 %), but also measured the diameters of these anastomotic vessels. Interestingly, they found that the diameter of the widest anastomotic Haller vessel passing

through the watershed zone was significantly larger in CSC eyes (0.40 ± 0.10 mm) compared to fellow eyes (0.35 ± 0.11 mm) and healthy controls (0.30 ± 0.09 mm). This suggests that not only the presence but also the size of these anastomoses may be relevant to the pathophysiology of CSC (Demirel et al., 2024). Recent work by Matsumoto et al. (2024) has further elucidated the dynamic nature of choroidal vascular changes in pachychoroid disorders. Their study of eyes with retrograde pulsatile vortex venous flow revealed cases where the contralateral vortex veins were more dilated than those showing retrograde flow. This suggests a compensatory mechanism where congested venous blood is redirected via intervortex anastomoses, leading to secondary dilatation of initially unaffected vessels. This phenomenon, which they term 'inversion of asymmetric vortex vein dilatation,' highlights the complex and adaptive nature of choroidal venous drainage in PSDs (Matsumoto et al., 2024). These studies collectively support the concept of venous outflow dysfunction as a key mechanism in PSDs (Spaide et al., 2022a). The development of intervortex anastomoses appears to be a compensatory response to this outflow obstruction, potentially serving as an alternative drainage route. However, the presence of these anastomoses in a significant proportion of healthy eyes indicates that their mere presence is not pathognomonic for PSDs. Instead, the increased frequency and enlarged size of these anastomoses in CSC and other PSDs suggest a more severe or chronic venous congestion in these conditions. The identification and characterization of these anastomoses have been made possible by advances in imaging technology, particularly en-face OCT and wide-field ICGA.

3.1.4. Choroidal vascular hyperpermeability

CH is considered a manifestation of structural CC damage, resulting in increased extravasation of fluids and lipoprotein-bound molecules visible on ICGA (He et al., 2023). The pathophysiology of CH in pachychoroid diseases is thought to involve a combination of factors, including vascular congestion, increased hydrostatic pressure, and alterations in choroidal vessel wall permeability (Shinojima et al., 2016; Spaide et al., 2022b; Teussink et al., 2015). CH is typically defined as patches of hyperfluorescence with blurred contours during the middle phase (8–15 min) of ICGA after indocyanine green injection (Ricardi et al., 2024) (Fig. 2). This phenomenon is variably present across pachychoroid disorders, including CSC, PNV, and PCV (Han et al., 2023; Ming Gemmy Cheung et al., 2019).

Previous studies have identified distinct patterns of choroidal vein (ChV) alterations associated with CH areas, observable within the first minute after dye injection (He et al., 2023). These patterns include ChV fusiform (choroidal vessel dilation less than twice the diameter of the host vessel), ChV bulbosity (dilation twice or more than twice the host vessel diameter), and ChV sausageing (a segment with three or more contiguous fusiform dilations differing by at least 50 % in diameter) (Spaide et al., 2022b). Additionally, ChV anastomoses (intervortex venous anastomoses) and ChV confluence (the junction between a main vessel and its branches) have been described (Demirel et al., 2024; Spaide et al., 2021). Importantly, ICGA hyperfluorescent spots can be detected even in fellow eyes without active disease, suggesting a bilateral predisposition to pachychoroid-related changes (Sakurada et al., 2020). CH might precede clinically detectable features, later correlating with areas of RPE alterations and focal choroidal thickening (Sasahara et al., 2006; Yannuzzi et al., 2000). These specific vascular alterations provide valuable insights into the underlying pathophysiology of CH and may serve as early markers for pachychoroid-related changes.

ICGA not only highlights pachyvessels but can also demonstrate choroidal filling defects, delayed arterial filling, and patchy hyperfluorescence areas that usually correspond to leakage sites on FA (He et al., 2023). These findings may persist in eyes with CSC even after the resolution of subretinal fluid, supporting the hypothesis that choroidal changes represent the primary etiology of PSDs (Fossataro et al., 2024; Han et al., 2023). It is important to note that while eyes with CH generally exhibit increased CT, not all eyes with thickened choroids

show CH, indicating a complex relationship between these features (Journal et al., 2014). Furthermore, advances in OCTA have provided new perspectives on the microvascular changes associated with CH, revealing alterations in CC flow and vessel density in areas of hyperpermeability (Nicolò et al., 2017; Shinojima et al., 2016; Teussink et al., 2015).

Understanding the role of CH in PSDs has significant implications for both diagnosis and treatment. Early detection of CH using advanced imaging techniques may allow for earlier intervention and potentially prevent progression to more severe manifestations of PSDs (Sasahara et al., 2006; Siedlecki et al., 2019; Yannuzzi et al., 2000). Moreover, the presence of CH may influence treatment decisions, as eyes with significant hyperpermeability may respond differently to various therapeutic modalities (Fossataro et al., 2024; Han et al., 2023).

3.1.5. Choroidal thickness

The concept of CT in PSDs has undergone significant evolution since the introduction of EDI-OCT by Spaide et al. (2008). This technological advancement allowed for detailed visualization and measurement of the choroid, leading to initial observations of increased CT in CSC and PCV by Imamura et al. (2009). Early studies consistently reported thicker choroids in PSDs compared to healthy controls, often exceeding 300 μm subfoveally. This led to the initial concept that pachychoroid was primarily defined by increased CT. Chung et al. (Chung et al., 2011, 2016) reported a mean subfoveal CT of 438.5 μm in eyes with PCV, significantly thicker than the 203.6 μm observed in normal eyes.

However, as research progressed, it became clear that CT alone was insufficient to fully characterize PSDs. Dansingani et al. (Dansingani et al., 2016) introduced the concept of PPE, emphasizing that the pachychoroid phenotype could exist without increased CT. They described eyes with pachyvessels, compression of inner choroidal layers, and RPE abnormalities, even in the absence of significant choroidal thickening. The limitations of using CT as the sole diagnostic criterion for PSDs have been further highlighted in recent years. Cheung et al. (Ming Gemmy Cheung et al., 2019), in their 2019 review, emphasized that the key features of pachychoroid include dilated outer choroidal vessels, thinning of the choriocapillaris and Sattler's layer, and choroidal hyperpermeability on ICGA, which can be present even in eyes with normal or subnormal CT.

Complicating matters further, factors such as age, axial length, refractive error, and gender can all influence CT, making comparisons between studies and individuals challenging (Fujiwara et al., 2009; Goldenberg et al., 2012; Ikuno et al., 2010; Karapetyan et al., 2016; Tuncer et al., 2015). This variability underscores the importance of considering these factors when interpreting CT measurements and emphasizes the need for standardized approaches in research and clinical practice.

More recent studies have focused on the clinical significance of CT changes in PSDs and the importance of evaluating choroidal morphology beyond just subfoveal CT. Matsumoto et al. (2020) used wide-field OCT to map CT across the posterior pole in PSD patients, finding that focal areas of choroidal thickening often corresponded to sites of disease activity, even when subfoveal CT was within normal limits. This highlights the importance of evaluating choroidal morphology across a wider area. Furthermore, the term "uncomplicated pachychoroid" has been introduced to describe eyes that present these specific choroidal changes in the absence of RPE or neurosensory retinal alterations (Siedlecki et al., 2019).

The relationship between CT and disease chronicity remains unclear, while some studies have observed a reduction in CT following the resolution of CSC or after various therapeutic interventions (Hua et al., 2014; Maruko et al., 2011a; Pitcher et al., 2015), the relationship between CT and treatment outcomes is not straightforward. This variability underscores the complex nature of choroidal changes in PSDs and suggests that other factors, such as the presence of pachyvessels, changes in CC and Sattler's layer, and CH, may be equally important in

understanding disease activity and progression.

While CT remains an important parameter in the study of PSDs, current understanding emphasizes the need for a comprehensive, multimodal evaluation of choroidal morphology. This approach, which goes beyond simple thickness measurement, is crucial for the correct identification and management of PSDs, while also considering potential secondary causes of increased CT.

3.2. RPE and outer retinal changes

3.2.1. RPE alterations in pachychoroid spectrum disorders

The RPE and outer retinal layers undergo significant alterations in PSDs, playing a crucial role in the pathogenesis and clinical manifestations of these conditions. One of the most striking features is the development of pigment epithelial detachments (PEDs). These detachments are observed in 53–100 % of CSC-affected eyes, with a higher prevalence in chronic cases (Ahlers et al., 2009; Mitarai et al., 2006). PEDs can occur both within and outside areas of subretinal fluid accumulation, indicating a widespread dysfunction of the RPE that extends beyond clinically apparent areas of fluid retention (Van Velthoven et al., 2005). The formation of PEDs is closely associated with choroidal vascular abnormalities, often co-localizing with areas of dilated choroidal vessels, increased CT, and CH as demonstrated by SD-OCT and ICGA (Hirami et al., 2007; Yang et al., 2013). This spatial correlation suggests that PED formation may be a direct result of choroidal flow dysregulation, supporting the primary role of choroidopathy in the pathogenesis of PSDs. Several types of PEDs have been described in PSDs, each potentially reflecting different underlying mechanisms. Dome-shaped PEDs are characterized by a sharply demarcated, protruding appearance without signs of RPE hyperplasia (Fujimoto et al., 2008). En face OCT imaging reveals these PEDs as homogenous hyporeflective circular areas with hyperreflective borders (Shin and Lee, 2012). In contrast, irregular or wavy flat PEDs are more commonly observed in chronic CSC cases (Darwich et al., 2015). Of particular interest are irregular PEDs with hyperreflective content overlying an intact thin hyperreflective layer (attributed to Bruch's membrane), creating a "double layer sign" (Pang and Freund, 2015). This appearance may result from a loss of elasticity in the adjacent RPE basement membrane due to chronic elevation. The exact mechanisms underlying PED formation in PSDs are likely multifactorial, involving mechanical stress from increased intrachoroidal pressure or dilated choroidal vessels, reduced RPE adhesion, alterations in hydro-ionic RPE regulation, and RPE atrophy secondary to choriocapillaris hypoperfusion (Baek et al., 2018). The presence and characteristics of PEDs not only aid in diagnosing and monitoring pachychoroid disorders but also provide valuable insights into the underlying disease mechanisms.

While PEDs are a prominent feature of PSDs, a wider range of RPE alterations have been described, reflecting the complex and progressive nature of these conditions. These changes include focal RPE tears, areas of RPE atrophy, and RPE hypertrophy, which collectively contribute to a spectrum of localized and diffuse epitheliopathy involved in the different stages of CSC and related disorders. Focal RPE tears are a less common but significant finding in CSC. These tears can occur spontaneously or as a complication of PED progression. Research has indicated that in CSC patients, RPE tears are more likely to occur in association with more extensive PEDs. The presence of such tears can have important clinical implications, potentially leading to persistent accumulation of subretinal fluid and adversely affecting visual outcomes (Gupta et al., 2008; Lim and Wong, 2008).

RPE atrophy in PSDs has been associated with a reduction in choroidal permeability, manifesting as hypofluorescence on ICGA (Ricardi et al., 2024). This alteration in permeability is thought to result from long-term remodeling of the CC, a consequence of prolonged disease duration and chronic RPE atrophy. The relationship between RPE health and CC integrity is underscored by the role of VEGF released by the RPE in maintaining CC homeostasis and structure (Bhutto and Luty,

2012). The compromised choroidal circulation may lead to increased hydrostatic pressure on the RPE, potentially impairing its function and contributing to subretinal fluid accumulation (Maruko et al., 2011b; Yannuzzi et al., 2000). The extent of secondary RPE damage can vary widely, ranging from localized lesions to extensive degeneration. In cases of widespread RPE involvement, terms such as diffuse atrophic RPE alterations (DARA) and diffuse retinal pigment epitheliopathy (DRPE) have been employed to describe these advanced stages of epithelial dysfunction (Laatikainen, 1994; Mohabati et al., 2018; Polak et al., 1995; von Winning et al., 1982). Conversely, areas of RPE hypertrophy can also be observed in CSC, often in proximity to regions of atrophy or detachment. Fujimoto et al. (2008) used Fourier-domain OCT to demonstrate focal RPE thickening in CSC patients, which they hypothesized might represent a compensatory response to chronic stress. These hypertrophic changes can appear as hyperautofluorescent areas on FAF imaging.

The progression of RPE alterations in CSC follows a temporal pattern. Yalcinbayir et al. (2014) studied the correlation between RPE changes and visual acuity in CSC patients, finding that the extent of RPE damage increased with disease duration. They observed that eyes with CSC duration of less than 6 months predominantly showed PEDs, while those with longer disease durations exhibited more widespread RPE alterations, including atrophy and irregularities. In chronic cases, the persistent course of the disease, often in conjunction with aging, leads to more extensive RPE changes. Piccolino et al. (2005) described a spectrum of RPE alterations in long-standing CSC, including widespread atrophy, irregular PEDs, and areas of RPE mottling. These changes were associated with reduced visual acuity and altered macular sensitivity on microperimetry.

3.2.2. RPE barrier function and consequences on the outer retina

The RPE serves as a critical component of the outer blood-retinal barrier, regulating the movement of fluid, nutrients, and waste products between the choroid and the neurosensory retina (Strauss, 2005). This barrier function is maintained through tight junctions between RPE cells and active transport mechanisms that control fluid movement across the epithelium (Rizzolo, 2007). In PSDs, the RPE barrier function is compromised through various mechanisms. The mechanical stress induced by choroidal hyperpermeability and subretinal fluid accumulation can disrupt RPE tight junctions, leading to increased paracellular permeability (Desjardins et al., 2016; Marmor, 1999). Additionally, the accumulation of fluid in the subretinal space may overwhelm the RPE's capacity for active fluid transport, further compromising its barrier function (Zhao et al., 2012). The breakdown of the RPE barrier has significant consequences for the outer retina. The accumulation of subretinal fluid alters the ionic and metabolic environment of the photoreceptors, potentially leading to oxidative stress and cellular dysfunction (Darwich et al., 2015). Furthermore, the disruption of the RPE's role in retinoid metabolism can impair the visual cycle, affecting photoreceptor function and outer segment renewal (Wang et al., 2008).

3.2.3. Subretinal fluid accumulation and its implications

The formation of subretinal fluid in PSDs is thought to result from a complex interplay between CH, RPE dysfunction, and altered fluid dynamics at the outer retina-choroid interface (Darwich et al., 2015). In CSC, focal areas of RPE dysfunction allow for the accumulation of fluid in the subretinal space, leading to neurosensory retinal detachment (Nicholson et al., 2013). As the disease progresses to PNV and PCV, the presence of choroidal neovascularization and polypoidal lesions can further contribute to fluid accumulation through vascular leakage (Ming Gemmy Cheung et al., 2019).

The presence of SRF has significant implications for photoreceptor function and visual acuity, both in the short and long term. Prolonged detachment of the neurosensory retina from the RPE can lead to photoreceptor outer segment elongation, a phenomenon observed in OCT studies of CSC patients (Matsumoto et al., 2008). This elongation is

thought to represent a compensatory mechanism to maintain contact with the RPE, but it may also indicate cellular stress and impaired outer segment renewal (Maruko et al., 2009).

The impact of subretinal fluid on visual function appears to be related to both its duration and volume. Recent long-term studies have provided crucial insights into the impact of subretinal fluid on visual outcomes in PSDs. A large-scale study by Azuma et al. (2023) demonstrated that CSC and PNV were associated with worse long-term visual prognosis compared to focal choroidal excavation (FCE) and PPE. Importantly, this study identified the duration of subretinal fluid existence as a critical factor affecting long-term visual outcomes in CSC patients without the development of macular neovascularization. The impact of subretinal fluid on visual function appears to be related to both its duration and volume. Azuma et al. found that patients with subretinal fluid duration ≥ 12 months (whether continuous or intermittent) had significantly worse visual prognosis compared to those with < 12 months (Azuma et al., 2023). This suggests that the 1-year mark may be an important time limit for subretinal fluid duration in terms of impact on visual outcomes. Notably, even intermittent presence of subretinal fluid, when summed to exceed 1 year, was associated with poorer visual prognosis.

These findings are consistent with earlier studies showing that persistent subretinal fluid is associated with worse visual outcomes in CSC patients, likely due to chronic photoreceptor stress and potential apoptosis (Aggio et al., 2010). However, the relationship between fluid persistence and visual prognosis is not always straightforward, as some patients with chronic CSC maintain relatively good visual acuity despite long-standing subretinal fluid (Darwich et al., 2017).

Interestingly, Azuma et al. found no significant association between different treatments (observation, laser photocoagulation, photodynamic therapy, anti-VEGF) and visual prognosis in CSC patients (Azuma et al., 2023). This highlights the complex nature of CSC and suggests that the duration of subretinal fluid may be a more critical factor in long-term visual outcomes than the specific treatment modality used. These findings have important implications for the management of CSC and other PSDs. They suggest that early and effective management of subretinal fluid, aiming to resolve it within 12 months, may be crucial for preserving long-term visual function. Furthermore, they underscore the importance of careful monitoring and potential intervention in cases of recurrent or persistent subretinal fluid, even if intermittent.

3.2.4. Photoreceptor and outer nuclear layer changes

The photoreceptors and outer nuclear layer (ONL) undergo significant structural and functional changes in PSDs. OCT studies have revealed thinning of the ONL in chronic CSC, particularly in areas of persistent subretinal fluid (Yalcinbayir et al., 2014). This thinning is thought to represent photoreceptor cell loss due to chronic detachment and metabolic stress (Fujita et al., 2012). In addition to ONL thinning, alterations in the ellipsoid zone (EZ) and interdigitation zone (IZ) have been observed in PPE (M. Giray Ersoz et al., 2018b). Disruption or loss of the EZ and IZ on OCT imaging is associated with worse visual acuity and may indicate photoreceptor dysfunction or loss (Ooto et al., 2015). These changes are often more pronounced in PNV and PCV, where the presence of CNV and polypoidal lesions can cause more severe damage to the outer retinal layers (Cho et al., 2013). The relationship between structural changes in the photoreceptors and ONL and visual function is complex. While some studies have shown a correlation between ONL thickness and visual acuity in CSC patients (Hata et al., 2014), others have found that visual function can be preserved even in the presence of significant structural alterations (Fung et al., 2012). This discrepancy may be explained by the adaptive mechanisms of the photoreceptors and the potential for functional recovery. Following the resolution of subretinal fluid, the photoreceptors and ONL demonstrate remarkable capacity for adaptation and regeneration. Studies using adaptive optics scanning laser ophthalmoscopy have shown that cone density can recover to near-normal levels in some CSC patients after fluid resolution

(Vogel et al., 2017). However, the extent of recovery appears to be dependent on the duration of detachment, with prolonged fluid persistence associated with less complete structural and functional restoration (Chung et al., 2018).

3.3. Post-mortem histological findings

Post-mortem histological studies have provided invaluable insights into the structural and cellular changes underlying PSDs. These studies offer a unique perspective that complements *in vivo* imaging techniques, allowing for a more comprehensive understanding of the pathophysiology of these conditions.

3.3.1. General histological findings in the choroid

Histological studies of the choroid, conducted on both animal models and human specimens, have provided fundamental insights into its structure and function. Early studies by Hogan and Alvarado described the basic anatomy of the human choroid, identifying its distinct layers: Bruch's membrane, CC, Sattler's layer, and Haller's layer (Hogan, 1967). They noted the dense vascular network of the CC and the larger vessels in the deeper layers. Subsequent studies focused on the unique features of choroidal endothelial cells. Spitznas et al. (Spitznas and Reale, 1975) demonstrated the presence of fenestrations in the CC endothelium, which play a crucial role in the exchange of nutrients and waste products between the choroid and the RPE. These fenestrations were found to be more abundant on the retinal side of the capillaries, suggesting a polarity in their distribution (Nagy and Ogden, 1990).

Investigations into the extracellular matrix of the choroid revealed its complex composition. Marshall et al. identified various types of collagen (I, III, IV, and V) and elastin in Bruch's membrane and the choroidal stroma, highlighting their importance in maintaining the structural integrity of the choroid (Marshall et al., 1992).

3.3.2. Histological findings related to the pachychoroid spectrum

Histological studies specifically focusing on PSDs are limited. However, some valuable insights have been gained from the few available studies. The foundation for understanding these changes was laid by Gass in 1967, who conducted one of the earliest and most significant post-mortem studies on eyes with CSC. Gass observed focal areas of RPE detachment and atrophy, correlating with the clinical findings of CSC (Gass, 1967). This study laid the groundwork for understanding the structural changes in the RPE and choroid associated with PSDs. Building on Gass's work, Yannuzzi et al. (1984) performed histopathological examinations on eyes with chronic CSC, revealing significant alterations in the choroidal vasculature. They noted dilated choroidal vessels, particularly in Haller's layer, and areas of CC atrophy (Yannuzzi et al., 2012). These findings correlated well with the concept of pachychoroid, which would be more fully developed in subsequent years.

While human histological studies specifically focusing on CSC are limited due to the rarity of obtaining specimens from patients with active disease, animal models have provided valuable insights into the pathophysiology of pachychoroid conditions. Zhao et al. (2012) developed a rat model of CSC by systemic administration of glucocorticoids and mineralocorticoids. Histological examination of the choroid in these animals revealed significant dilation of choroidal vessels, particularly in Haller's layer, mirroring the pachychoroid features observed in human CSC patients. This model has been instrumental in understanding the role of corticosteroids in the development of pachychoroid features. In a groundbreaking study, Zhao et al. (2010) further investigated the effects of high-dose glucocorticoids on choroidal vasculature using a monkey model. They found that systemic glucocorticoid administration led to dilation of choroidal vessels, particularly in Haller's layer, and thinning of the CC. These changes were associated with increased expression of endothelial nitric oxide synthase (eNOS) in choroidal vessels, suggesting a potential mechanism for

glucocorticoid-induced choroidal hyperpermeability.

The combination of these human histopathological findings and animal studies has significantly advanced our understanding of the PSDs. They have elucidated potential mechanisms underlying choroidal vessel dilation and hyperpermeability, providing valuable insights into the effects of current and potential future therapies. These studies have collectively demonstrated the central role of choroidal vascular changes in the pathogenesis of PSDs, highlighting the importance of targeting these vascular alterations in therapeutic approaches.

3.3.3. Correlation with *in vivo* imaging

The comparison of histological findings with *in vivo* imaging has been crucial in validating and interpreting clinical observations of PSDs. EDI-OCT has been particularly valuable in this regard. While direct correlative studies between histological findings and OCT in PSDs are limited, the available post-mortem results appear to be consistent with our current understanding of choroidal anatomy and pathology based on *in vivo* imaging. This consistency lends credibility to the few histological studies that exist, suggesting that they provide valuable insights into the structural changes associated with PSDs.

3.3.4. Limitations and challenges of post-mortem studies

Post-mortem histological studies in PSDs, despite their value, face several limitations and challenges. The scarcity of available specimens, particularly from eyes in the early stages of disease, makes it difficult to understand the initial pathological changes and disease progression. This limitation is compounded by the fact that most histological specimens come from advanced or end-stage cases, potentially skewing our understanding towards later disease manifestations. The interpretation of histological findings is further complicated by post-mortem changes and fixation artifacts, which can alter the structure of the choroid. These changes may affect the appearance of tissues, potentially leading to misinterpretation of findings. Additionally, the static nature of histological preparations cannot fully capture the dynamic aspects of choroidal blood flow and fluid dynamics, which are crucial in understanding PSDs. These challenges underscore the need for caution in interpreting histological findings and highlight the importance of correlating these findings with *in vivo* imaging and functional studies.

3.4. Proposed pathophysiological mechanisms

The understanding of choroidal dysfunction has undergone significant evolution over the past few decades. From early observations of choroidal thickening to the development of sophisticated theories explaining the underlying pathophysiology, our comprehension of these disorders has grown exponentially. Understanding the pathogenesis of choroidal dysfunction is crucial not only for academic interest but also for developing effective treatment strategies for PSDs related disorders.

3.4.1. The pachychoroid concept

The pachychoroid phenotype is characterized by several key features: increased choroidal thickness, pathologically dilated outer choroidal vessels (pachyvessels), thinning of the inner choroid (Sattler's layer and choriocapillaris), and various RPE abnormalities (Ming Gemmy Cheung et al., 2019). Several hypotheses have been proposed to explain the pathogenesis of PSDs. One prevalent theory suggests that the expansion of Haller's layer vessels leads to mechanical compression of the overlying Sattler's layer and choriocapillaris. This compression is thought to cause ischemia and dysfunction of the RPE, ultimately leading to the clinical manifestations of PSDs (Journal et al., 2014). Chronic inflammation involving the CC has also been implicated in the pathogenesis. Some researchers propose that this inflammatory process may be responsible for abnormal angiogenesis seen in more advanced stages of pachychoroid disease (Sartini et al., 2020; Terao et al., 2018). There is also evidence suggesting a genetic predisposition to PSDs. Studies have observed that relatives of CSC patients often present with

significantly increased choroidal dysfunction, even in the absence of clinical disease (Lehmann et al., 2015).

3.4.2. The two-hit mechanism

Building on the pachychoroid concept, recent research has proposed a "Two-Hit Mechanism" to explain the development and progression of pachychoroid disorders 2. (Hirooka et al., 2022). This model suggests that two distinct pathophysiological processes must occur for the full expression of pachychoroid disease:

1. **First Hit (Anatomical Predisposition):** The presence of anatomical risk factors such as thick sclera, short axial length, and asymmetric vortex venous drainage (Imanaga et al., 2024). These features create a framework of vulnerability but may not alone lead to disease manifestation.
2. **Second Hit (Triggering Factors):** External or physiological triggers that activate disease expression in anatomically predisposed individuals. These may include:
 - Steroid exposure (endogenous or exogenous)
 - Psychological stress
 - Hormonal fluctuations
 - Autonomic nervous system imbalance
 - Sleep disturbances
 - Metabolic disorders

This two-hit mechanism explains why not all individuals with anatomical pachychoroid features develop clinical disease, and why disease manifestation can be episodic or fluctuating. It also accounts for the effectiveness of treatments targeting either the anatomical predisposition (e.g., PDT addressing choroidal hyperpermeability) or the triggering factors (e.g., stress reduction, steroid avoidance).

Evidence supporting this model comes from the observation that fellow eyes in unilateral CSC often display pachychoroid features without active disease (Cheung et al., 2024). Additionally, the efficacy of targeted interventions addressing either the first or second hit further validates this conceptual framework.

3.4.3. Limitations of the pachychoroid concept

While the pachychoroid concept has been instrumental in advancing our understanding of various chorioretinal disorders, it has several limitations. For instance, not all eyes with thickened choroids develop pathological changes, and some eyes with typical pachychoroid features may have normal choroidal thickness (Cheung et al., 2018). Additionally, the concept does not fully explain the mechanisms behind the development of complications such as choroidal neovascularization.

3.4.4. The choroidal venous overload theory

Recent research has proposed a new theory to explain the pathogenesis of pachychoroid-related disorders: the choroidal venous overload theory. This concept, introduced by Spaide et al., suggests that

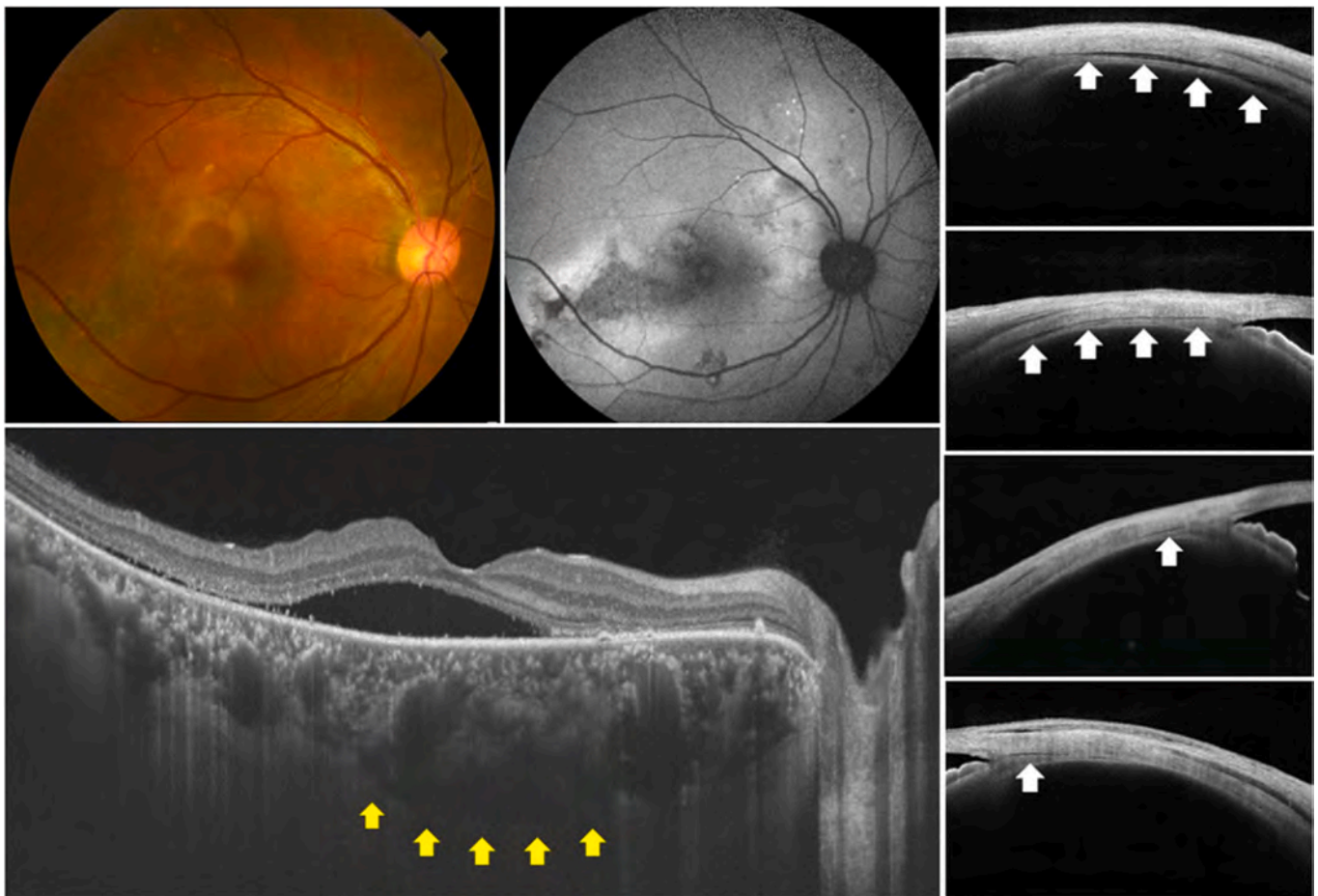


Fig. 3. Representative multimodal imaging of complex central serous chorioretinopathy (CSC) with pachychoroid features. The retinal imaging (top left/middle panels) shows serous retinal detachment and widespread RPE changes. The OCT (bottom left) demonstrates classic features of pachychoroid disease including thick choroid (502 μm), dilated choroidal vessels (yellow arrows), and subretinal fluid. The anterior segment OCT (right panels) reveals significantly thickened sclera (544–581 μm) across all quadrants with ciliochoroidal effusion (white arrows). These findings illustrate the association between scleral thickness and complex manifestations of CSC within the pachychoroid spectrum (Reproduced from Imanaga et al., American Journal of Ophthalmology, 2024; 261:103–111, under CC BY license.)."

abnormalities in choroidal venous drainage play a crucial role in the development of these conditions (Spaide et al., 2021). The anatomical basis for this theory lies in the unique structure of choroidal venous drainage. Unlike most vascular beds in the body, the choroid lacks a typical branching pattern of veins. Instead, it has numerous parallel vessels that drain directly into the vortex veins (Spaide, 2020). A key element of this theory is the role of the sclera in modulating choroidal venous outflow (Imanaga et al., 2024) (Fig. 3). The passage of vortex veins through the sclera is thought to act as a Starling resistor, a mechanism that helps maintain a constant outflow pressure despite variations in intraocular pressure (Bacci et al., 2022; Spaide et al., 2022a). Evidence supporting this theory includes observations of dilated choroidal veins, the presence of intervortex venous anastomoses, and alterations in CC structure in eyes with CSC and related disorders (Ricardi et al., 2024). These findings are analogous to changes seen in chronic venous insufficiency in other parts of the body (Spaide et al., 2022a).

3.4.5. Integration of concepts: from pachychoroid to multi-hit model

The various theories described above are not mutually exclusive but rather complementary, providing a more comprehensive understanding of pachychoroid disorders. The venous overload theory dovetails with the first hit of the two-hit mechanism, explaining how anatomical predispositions create the foundation for disease. Similarly, the second hit concept explains why only some individuals with pachychoroid features develop clinical disease, and why disease manifestation can be episodic.

This integrated view allows for a more nuanced approach to diagnosis and treatment. For patients with primarily anatomical factors (first hit), interventions targeting choroidal vascular abnormalities like PDT may be most effective. For those where triggering factors (second hit) play a dominant role, addressing these factors through lifestyle modifications or pharmacological interventions might be prioritized.

3.4.6. Implications for clinical practice

The evolution in our understanding of choroidal dysfunction pathogenesis has significant implications for both clinical practice and research. From a diagnostic perspective, it highlights the importance of comprehensive choroidal imaging, including evaluation of choroidal vasculature and flow patterns, rather than relying solely on CT measurements (Dansingani et al., 2015). Therapeutically, this new understanding opens up possibilities for novel treatment approaches. For instance, interventions aimed at improving choroidal venous drainage or modulating scleral permeability could potentially be effective in managing these disorders (Spaide and Ryan, 2015).

4. Multimodal imaging application in different pachychoroid disorders

4.1. Pachychoroid pigment epitheliopathy

PPE represents the earliest manifestation within the PSDs. Its diagnosis and characterization heavily rely on multimodal imaging techniques, each offering unique insights into the condition's pathophysiology and clinical presentation (Fig. 2).

4.1.1. Dye-based imaging techniques

In the diagnosis and monitoring of PPE, dye-based imaging techniques play a crucial role. The two primary methods used are FA and ICGA, each offering unique insights into the vascular and structural changes associated with PPE.

4.1.1.1. Fluorescein angiography. FA is a well-established technique that has been used for decades in retinal imaging. In the context of PPE, FA typically shows minimal to no leakage, which is a key distinguishing feature from more advanced conditions in the PSDs, particularly CSC

(Warrow et al., 2013). This lack of significant leakage is crucial in differentiating PPE from CSC, where FA often reveals one or more focal points of leakage in classic "smokestack" or "inkblot" patterns (Chhablani et al., 2020; Feenstra et al., 2024). In PPE, FA may reveal subtle RPE changes, which can appear as areas of mild hyperfluorescence or hypofluorescence (Yagi et al., 2022). These changes are typically more subtle and less extensive than those seen in more advanced PSDs. The absence of subretinal fluid, a hallmark of PPE, is also confirmed by the lack of pooling or leakage on FA (Fig. 2).

4.1.1.2. Indocyanine green angiography. ICGA has become an invaluable tool in the evaluation of choroidal disorders, including PPE. This technique uses indocyanine green dye, which binds strongly to plasma proteins and thus remains largely within the choroidal vasculature, allowing for detailed imaging of choroidal structures.

In PPE, ICGA often reveals CVH, which is a key feature of PSDs (Borooah et al., 2021; Dansingani et al., 2016). This hyperpermeability is typically observed as multifocal areas of hyperfluorescence in the mid to late phases of the angiogram (Sakurada et al., 2020; Yagi et al., 2022) (Fig. 2). These areas of increased choroidal permeability are thought to represent regions of increased hydrostatic pressure within the choroid, which is central to the pathophysiology of PSDs (Demirel et al., 2021).

The study by Yagi et al. (2022) highlighted the significance of CVH in predicting the progression of PPE to CSC. They found that 100 % of PPE eyes that developed CSC had CVH at baseline, compared to only 52.1 % of those that did not develop CSC. This underscores the importance of ICGA in not only diagnosing PPE but also in assessing the risk of progression to more advanced PSDs (M Giray Ersoz et al., 2018).

ICGA in PPE also typically shows dilated choroidal vessels, particularly in the Haller's layer. These dilated vessels, often referred to as "pachyvessels," are a characteristic feature of pachychoroid disorders and are more readily visible on ICGA than on other imaging modalities (M. Giray Ersoz et al., 2018a). Another important feature that can be observed on ICGA in PPE is the presence of areas of delayed choroidal filling. This delayed filling, when present, is thought to reflect alterations in choroidal blood flow dynamics associated with the pachychoroid phenotype (M. Giray Ersoz et al., 2018a). Sakurada et al. (2018) also demonstrated a significant association between choroidal caverns and areas of CVH on ICGA. They found that 88 % of choroidal caverns were located within areas of CVH, suggesting a potential relationship between these structural changes and the vascular abnormalities observed in PSDs. The late phase of ICGA can also reveal the hypofluorescent silhouettes of pachyvessels traversing the areas of CVH, providing a unique perspective on the relationship between these dilated vessels and the surrounding hyperpermeability (M. Giray Ersoz et al., 2018a; Yagi et al., 2022).

The combination of FA and ICGA provides complementary information that is crucial for a comprehensive evaluation of PPE. While FA helps in ruling out active leakage and assessing RPE integrity, ICGA provides detailed information about choroidal vasculature and permeability. This multimodal approach not only aids in the accurate diagnosis of PPE but also helps in differentiating it from other macular disorders and in monitoring for progression to more advanced stages of PSDs.

4.1.2. No dye-based imaging techniques

In the diagnosis and monitoring of PPE, no dye-based imaging techniques have become indispensable tools. These modalities, including structural OCT, FAF, and IR imaging, each contribute unique insights into the structural and functional changes associated with this condition.

4.1.2.1. Optical coherence tomography. OCT, particularly SD-OCT with EDI, has revolutionized our understanding of PPE. This imaging modality provides high-resolution, cross-sectional images of the retina and

choroid, revealing subtle structural changes that are characteristic of PPE.

One of the most striking features observed on OCT in PPE is the increased CT. This thickening is primarily due to dilation of the large choroidal vessels in Haller's layer, referred to as pachyvessels (Fig. 2). These pachyvessels are often accompanied by thinning or compression of the overlying Sattler's layer and choriocapillaris, creating a characteristic choroidal architecture (Borrelli et al., 2022; M. Giray Ersoz et al., 2018b; Warrow et al., 2013).

The study by Karacorlu et al. (2018) provided valuable insights into the various types of RPE lesions observed in PPE and their evolution over time. They identified three distinct types of RPE lesions on OCT: RPE elevation with microbreak appearance (REwM), pigment epithelium detachment (PED), and RPE thickening.

The REwM is a novel finding. It appears as a slight detachment of the RPE from Bruch's membrane at one or both sides, accompanied by a very small fissure-like appearance between RPE cells. This lesion type was found to be the most common initial presentation, accounting for 41.9 % of all initial PPE lesions in their study (Karacorlu et al., 2018).

Pigment epithelium detachments (PEDs) were the second most common lesion type, seen in 36.5 % of initial PPE lesions. These appear as elevations of the RPE with obvious sub-RPE fluid. The third type, RPE thickening, was observed in 21.6 % of initial lesions and is characterized by thickening of the hyperreflective RPE layer without disruption of the ellipsoid zone and external limiting membrane. Importantly, Karacorlu et al. observed that these lesions can evolve over time. REwMs were found to progress to PEDs in 41.9 % of cases, and to RPE thickening in 38.7 % of cases. Some REwMs (6.5 %) progressed directly to CSC. This longitudinal data provides valuable insights into the natural history of PPE lesions (Karacorlu et al., 2018; Yagi et al., 2022).

Another significant finding was the development of hyperreflective RPE spikes from areas of RPE thickening (Lee et al., 2019; Wong et al., 2023). These spikes were associated with focal disruption of the ellipsoid zone or even the external limiting membrane and outer nuclear layer. Interestingly, when these spikes regressed, they left behind focal loss of the ellipsoid zone, interdigitation zone, and external limiting membrane, but without RPE atrophy (Lee et al., 2019). The study also highlighted the importance of the external limiting membrane (ELM) in PPE. The ELM remained intact in all lesions throughout the follow-up period, which may explain the generally good visual prognosis in these patients.

SD-OCT provides invaluable information about the choroidal and retinal changes in PPE. It allows for detailed characterization of RPE lesions, monitoring of their evolution over time, and assessment of choroidal thickness and architecture.

4.1.2.2. Structural en face OCT. Structural en face OCT has emerged as a valuable imaging technique in the evaluation of PPE. This modality provides a unique perspective by offering a planar view of different retinal and choroidal layers, complementing the cross-sectional information obtained from traditional B-scans. In PPE, en face OCT is particularly useful for visualizing and characterizing choroidal vascular changes. Dansingani et al. (Dansingani et al., 2016) demonstrated that en face OCT can clearly delineate the pachyvessels characteristic of PPE, allowing for precise mapping of their distribution and extent. This technique also aids in identifying areas of choriocapillaris thinning overlying the pachyvessels, a key feature of the PPE. Furthermore, en face OCT can reveal subtle RPE alterations associated with PPE, such as small elevations or undulations, which might be less apparent on B-scans alone. Matsumoto et al. (2008) used en face OCT to study choroidal vascular patterns in PPE, identifying distinctive features such as dilated choroidal veins and their anastomoses (Fig. 2). These findings not only enhance our understanding of the choroidal vascular architecture in PPE but also provide potential biomarkers for disease progression and differentiation from other pachychoroid spectrum disorders. The ability of

structural en face OCT to provide detailed, layer-specific information makes it an invaluable tool in the comprehensive evaluation and management of PPE.

4.1.2.3. Fundus autofluorescence. FAF provides valuable information about the metabolic state of the RPE in PPE. FAF may reveal areas of subtle hyper- or hypoautofluorescence, indicating early RPE dysfunction or stress. Some PPE lesions may appear as patchy areas of increased autofluorescence, potentially corresponding to areas of RPE stress or lipofuscin accumulation. Conversely, regions of RPE atrophy or damage may appear as hypoautofluorescent areas (Wong et al., 2023). It's important to note, however, that some PPE eyes may show normal FAF patterns, especially in early stages of the disease, as observed by Warrow et al. (2013) (Fig. 2).

4.1.2.4. Infrared reflectance. IR imaging is particularly useful in visualizing choroidal and RPE changes in PPE. IR imaging often shows reduced fundus tessellation, reflecting the increased choroidal thickness characteristic of PPE (Yagi et al., 2022). Drusenoid lesions associated with PPE may appear as round hyperreflective lesions on IR imaging, as noted by Karacorlu et al. (2018). Regions of RPE alteration or atrophy may appear as hyporefective areas. Additionally, IR imaging can sometimes provide enhanced visualization of dilated choroidal vessels (pachyvessels), offering another perspective on the choroidal changes in PPE.

4.1.3. Enhanced insights provided by OCT angiography

OCTA, in particular swept-source OCTA (SS-OCTA), has emerged as a powerful non-invasive imaging technique that provides valuable insights into the vascular changes associated with PPE. This technology allows for detailed visualization of blood flow in different retinal and choroidal layers without the need for dye injection, offering unique perspectives on the pathophysiology of PPE.

4.1.3.1. Choriocapillaris flow alterations. One of the most significant contributions of OCTA in the study of PPE is its ability to reveal changes in choriocapillaris flow. Lee et al. (2019) demonstrated that OCTA can detect areas of reduced flow in the choriocapillaris in eyes with PPE. These flow void areas are often more extensive and numerous compared to those observed in normal eyes. The presence of these flow deficits suggests that CC ischemia or attenuation may play a role in the pathogenesis of PPE (Fig. 2).

Interestingly, Saito et al. (2020) reported that CC flow alterations in PPE are not uniform. Their study using laser speckle flowgraphy showed that choroidal blood flow velocity can actually increase in some areas of PPE lesions. This variability in flow patterns highlights the complex vascular dynamics in PPE and suggests that both hypoperfusion and hyperperfusion may be involved in its pathophysiology.

4.1.3.2. Correlation with structural changes. OCTA studies have also shed light on the relationship between CC flow and CT in PPE. Lee et al. (2023) found that eyes with PPE often show increased CT along with areas of CC flow impairment. This observation supports the hypothesis that the thickening of the choroid in PPE may be due to dilation of larger choroidal vessels rather than an increase in CC perfusion. Moreover, studies have shown that areas of CC flow impairment often correspond to regions of RPE abnormalities visible on structural OCT. This correlation suggests a close relationship between choroidal circulation and RPE health in PPE (Lee et al., 2019).

4.1.3.3. Variability in choriocapillaris perfusion. A particularly intriguing finding from recent OCTA studies is the variability in CC perfusion in PPE. Lee et al. (2023) reported both hyper- and hypoperfusion areas in the CC of eyes with PPE. They found that the CC vessel density showed higher variability in PPE eyes compared to control eyes, with

significantly higher maximum vessel density and lower minimum vessel density. This variability may reflect the dynamic nature of the vascular changes in PPE and could potentially be used as a marker for disease activity or progression.

4.1.3.4. Longitudinal changes. While limited longitudinal data are available, some studies have used OCTA to track changes in choriocapillaris flow over time in PPE. Saito et al. (2020) observed fluctuations in choroidal blood flow that corresponded with the clinical course of PPE and its progression to CSC. These observations suggest that OCTA could be a valuable tool for monitoring disease activity and predicting progression in PPE.

Definitely, OCTA has provided unprecedented insights into the vascular changes associated with PPE. The ability to visualize and quantify CC flow non-invasively has enhanced our understanding of the disease's pathophysiology and may lead to improved diagnostic and monitoring strategies. However, it's important to note that interpretation of OCTA findings in PPE can be challenging due to potential artifacts and the complex, three-dimensional nature of choroidal vasculature.

4.2. Central serous chorioretinopathy

CSC is a well-recognized entity within the pachychoroid spectrum disorders, characterized by serous detachment of the neurosensory retina and/or RPE. Multimodal imaging plays a pivotal role in the diagnosis, management, and monitoring of CSC. It provides crucial insights into the structural and functional changes occurring in the retina, RPE, and choroid. The combination of various imaging modalities allows for a comprehensive assessment of the disease, helping to differentiate CSC from other macular disorders and guide treatment decisions.

4.2.1. Dye-based imaging techniques

In the evaluation of CSC, dye-based imaging techniques are essential for visualizing the vascular abnormalities and pinpointing areas of leakage. FA and ICGA are the primary dye-based methods used, each offering unique and complementary information about the retinal and choroidal vasculature in CSC.

4.2.1.1. Fluorescein angiography. FA plays a crucial role in the diagnosis and management of CSC. While not mandatory for diagnosis, FA helps confirm CSC and guides potential laser treatment for eccentric leaks (Yannuzzi et al., 2000).

In acute CSC, FA typically reveals one or several leakage points within or adjacent to areas of serous retinal detachment (SRD). Most acute cases present with a single leakage site, though multiple sites can occur (Burumcek et al., 1997; KOGO et al., 2024). When multiple leaks are present, usually one site is primarily responsible for the ongoing episode.

The leakage patterns in acute CSC can be categorized as follows:

1. Pinpoint leakage: The most common pattern, appearing as points of increasing fluorescence throughout the angiogram sequence.
2. "Ink-blot" pattern: Characterized by progressive expansion of a circular hyperfluorescence from a central pinpoint.
3. "Smokestack" pattern: The fluorescein ascends with slight lateral diffusion, creating a mushroom-like appearance above the leaking point. This pattern is observed in about 14 % of cases and is associated with early acute forms, typically seen around 15 days from symptom onset (Bujarborua et al., 2010).

In mid to late phases of FA, dye pooling into the SRD results in diffuse circular hyperfluorescence within the detached area. PEDs, a common feature in CSC, appear as early fluorescein pooling with persistent hyperfluorescence in late phases (Bujarborua et al., 2005; Feenstra et al.,

2024; Rijssen et al., 2019).

Chronic CSC presents differently on FA. Diffuse RPE defects lead to multifocal leakage points visible in mid- and late phases as patches of granular hyperfluorescence (Yannuzzi et al., 1984, 2012). Additionally, sequelae of unnoticed extramacular episodes in affected or fellow eyes appear as hyperfluorescent areas due to increased transmission through localized RPE atrophy (Fig. 4).

However, the traditional classification of CSC into acute and chronic forms based solely on the duration of subretinal fluid has been refined by Chhablani and colleagues, who propose a more comprehensive approach using multimodal imaging (Chhablani et al., 2020). This new classification system categorizes CSC into simple and complex subtypes, providing a more nuanced understanding of the disease's progression and severity. It provides a more comprehensive assessment of the disease, including the extent of choroidal involvement, outer retinal changes, and the presence of complications like choroidal neovascularization.

4.2.1.2. FA in CSC complicated by MNV. A particular challenge in CSC management is the identification of macular neovascularization (MNV) that may complicate chronic or recurrent cases. This complication, distinct from pachychoroid neovascularopathy, represents a significant diagnostic challenge. On FA, MNV secondary to CSC often presents as occult or type 1 neovascularization with ill-defined areas of leakage. However, FA has limited specificity in this setting as the MNV-related leakage can be difficult to distinguish from the RPE window defects and leakage points typically seen in chronic CSC (Kilgaard et al., 2024) (Fig. 5). The presence of a double-layer sign (DLS) on OCT—a shallow irregular PED with hyperreflective material between the RPE and Bruch's membrane—may suggest the presence of MNV in CSC. However, this sign alone lacks specificity, as similar appearances can occur in chronic CSC without neovascularization (Hagag et al., 2022).

It is important to clarify the distinction between CSC complicated by MNV and PNV, as these represent related but conceptually different entities within the pachychoroid spectrum. CSC complicated by MNV typically presents as a secondary complication in eyes with long-standing or recurrent CSC, where chronic RPE damage and choriocapillaris ischemia eventually trigger neovascular growth. The neovascularization develops in an eye with established CSC, pre-existing subretinal fluid, and often a history of multiple CSC episodes. In contrast, PNV represents a primary entity characterized by type 1 neovascularization developing in eyes with pachychoroid features (pachy-vessels, choroidal thickening, and/or choroidal hyperpermeability) but without a definitive prior history of active CSC (Pang and Freund, 2015). While both conditions involve type 1 neovascularization in the context of pachychoroid, PNV may represent a more advanced stage in the pachychoroid disease spectrum, potentially evolving from asymptomatic PPE without necessarily passing through a classic CSC phase (Cheung et al., 2024). This distinction has implications for understanding disease pathogenesis and potentially for therapeutic approach, though the treatment principles often remain similar.

4.2.1.3. Indocyanine green angiography. ICGA has become an indispensable tool in the diagnosis and management of CSC since its introduction in the early 1990s. The unique properties of indocyanine green, including its higher molecular weight and amphiphilic nature, allow for superior visualization of choroidal vasculature compared to FA (Desmettre et al., 2000).

ICGA in CSC reveals crucial information about choroidal changes contributing to the disease process. These changes can be observed in three main phases:

1. Early phase: There's a delayed initial filling of arteries and CC (Prünte, 1995), with hypofluorescent areas resulting from decreased

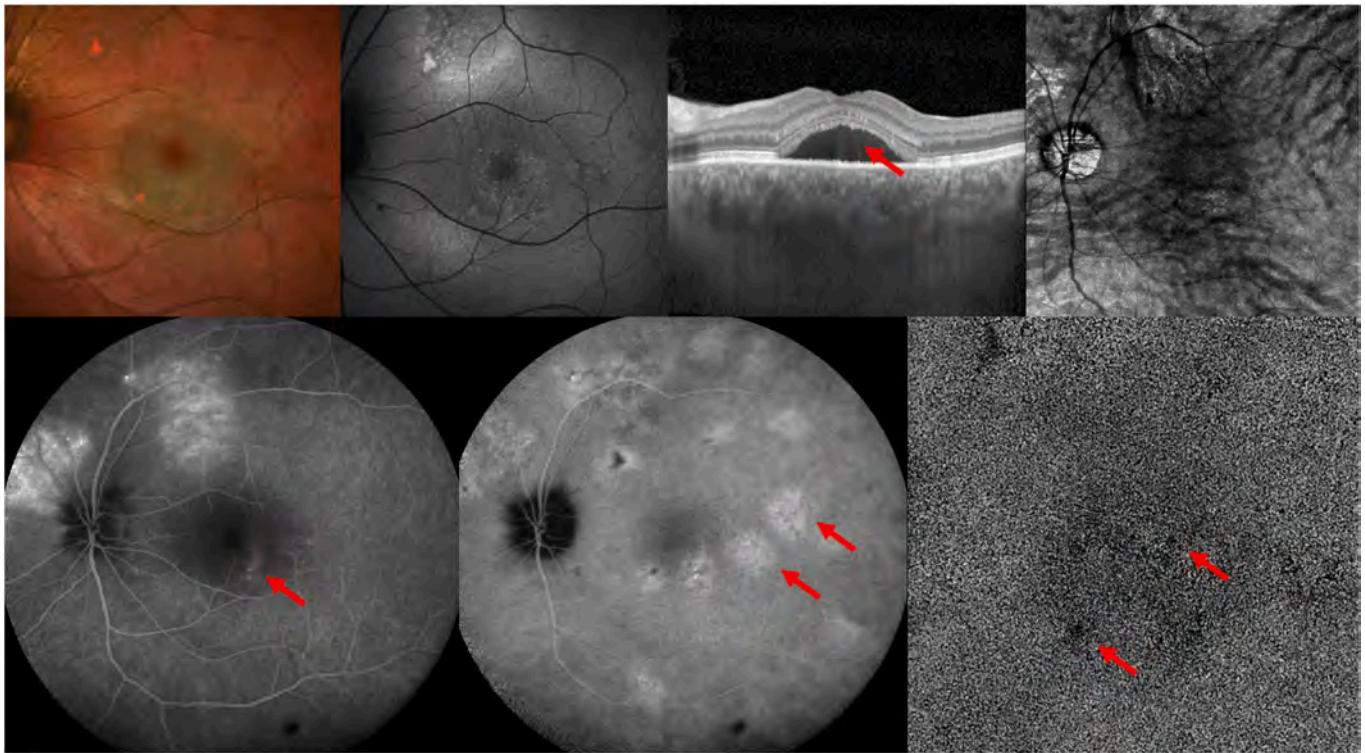


Fig. 4. Multimodal imaging of chronic central serous chorioretinopathy in a 52-year-old female with a 14-month history of decreased vision and metamorphopsia. Color fundus photograph (top left) shows a circular area of RPE alteration in the macula with pigmentary changes. Fundus autofluorescence (top, second from left) reveals a mottled pattern of hyper- and hypoautofluorescence consistent with chronic RPE damage. Structural OCT (top, third from left) demonstrates shallow subretinal fluid accumulation (red arrow) and RPE irregularities with pachyvessels in the underlying choroid. En face OCT (top right) clearly shows dilated choroidal vessels (red arrow) beneath the area of RPE alteration. Fluorescein angiography in late phase (bottom left) demonstrates multiple areas of window defect and granular hyperfluorescence (red arrows) characteristic of chronic RPE damage. Indocyanine green angiography in the intermediate phase (bottom, middle) reveals areas of choroidal hyperpermeability (red arrows). OCT angiography of the choriocapillaris (bottom right) shows multiple flow voids (red arrows) corresponding to areas of dilated pachyvessels and attenuation of the inner choroidal layers.

choriocapillaris filling, persisting into mid- and late phases (Kitaya, 2003).

2. Mid-phase: Large choroidal veins appear dilated in areas correlating to atrophic or elevated RPE on OCT (Hirami et al., 2007). Geographic areas of hyperfluorescence with blurred contours, classically interpreted as choroidal vascular hyperpermeability, are observed as a hallmark of CSC imaging (Fossataro et al., 2024; Guyer, 1994; Piccolino et al., 1995; PICCOLINO and BORGIA, 1994).
3. Late-phase: The mid-phase hyperfluorescent areas evolve into either persistent hyperfluorescence, wash-out, or centrifugal displacement of the hyperfluorescence, forming hyperfluorescent rings (Kim et al., 2015; Tsujikawa et al., 2010).

The essential role of choroidal hyperpermeability in CSC pathogenesis is underscored by the persistence of hyperfluorescent areas in the mid-phase of ICGA after leakage ceases on FA (Scheider et al., 1993), and the recurrence of CSC with new leakage in areas of persistent mid-phase ICG hyperfluorescence (IIDA et al., 1999) (Fig. 4).

PEDs in CSC also exhibit a characteristic pattern on ICGA:

- Early phase: mild hyperfluorescence
- Mid-phase: variable hyperfluorescence
- Late phase: marked hypofluorescence surrounded by a possible hyperfluorescent ring, attributed to ICG affinity to fibrin deposits at the PED margins (Guyer, 1994; Mrejen and Spaide, 2013).

4.2.1.4. ICGA in CSC complicated by MNV. In CSC complicated by MNV, ICGA often fails to show the typical late-phase hyperfluorescence associated with classic MNV, making diagnosis challenging (Demirel et al.,

2022). The neovascular network in CSC-related MNV may appear less prominent on ICGA compared to MNV in age-related macular degeneration. Additionally, the underlying choroidal hyperpermeability characteristic of CSC can mask the ICGA features of MNV, further complicating the diagnostic process (Demirel et al., 2022). Kiilgaard et al. (2024), in their systematic review and meta-analysis, reported that ICGA shows a sensitivity of 75 % and a specificity of 87 % for detecting MNV in CSC. Although these values are reasonably high, ICGA still demonstrates significant limitations in identifying MNV in a CSC context, primarily due to masking from the underlying choroidal hyperpermeability (Fig. 5).

4.2.1.5. Ultra-widefield indocyanine green angiography. The advent of ultra-widefield ICGA (UWF-ICGA) has revolutionized our understanding of choroidal vascular changes in CSC. Recent studies have provided crucial insights into the extent and nature of choroidal involvement in this condition. Pang et al. (2014) first demonstrated that UWF-ICGA could reveal more widespread disease than standard field imaging, with 83.3 % of eyes showing dilated vessels associated with congested vortex vein ampullae. This finding suggested a potential role for outflow congestion in CSC pathogenesis. Building on this, Jeong et al. (2022) conducted a quantitative analysis of choroidal vascular alterations using UWF-ICGA, revealing that CVH and dilated choroidal vessels in CSC extend far beyond the posterior pole, with a predilection for the superior quadrant. Their observation of similar, albeit less pronounced, changes in clinically unaffected fellow eyes supported the concept of CSC as a bilateral condition with asymmetric manifestations. Most recently, a landmark study by Pauleikhoff et al. (2024) examined 178 eyes of 91 CSC patients using UWF-ICGA, providing crucial insights into the extent

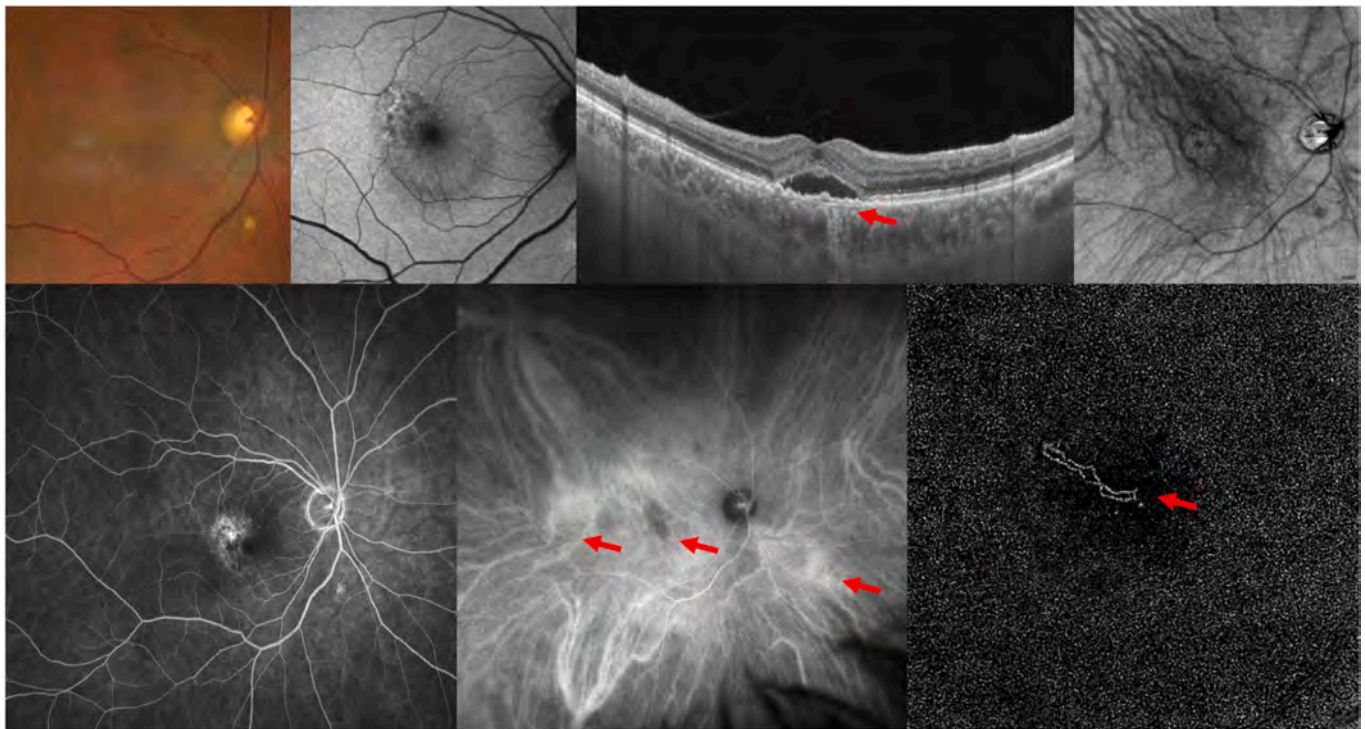


Fig. 5. Multimodal imaging of central serous chorioretinopathy complicated by macular neovascularization in a 58-year-old male with a history of recurrent visual distortion and progressive central vision loss for 8 months. Color fundus photograph (top left) reveals a yellowish subretinal lesion with surrounding pigmentary changes in the macula. Fundus autofluorescence (top, second from left) demonstrates a central hypoautofluorescent area surrounded by a ring of hyperautofluorescence, indicating chronic RPE damage. Structural OCT (top, third from left) shows a shallow irregular pigment epithelial detachment with hyperreflective material beneath the RPE (red arrow), consistent with type 1 macular neovascularization. En face OCT (top right) clearly shows dilated choroidal vessels beneath the area of RPE alteration. Fluorescein angiography in late phase (bottom left) demonstrates an area of irregular hyperfluorescence consistent with occult-type leakage from the neovascular network. Indocyanine green angiography in the intermediate phase (bottom, middle) shows areas of choroidal hyperpermeability (red arrows) characteristic of CSC, with evidence of washout at the macular neovascular lesion site. OCT angiography (bottom right) clearly delineates the type 1 neovascular network (red arrow) between the RPE and Bruch's membrane, confirming the diagnosis of CSC complicated by macular neovascularization.

and nature of choroidal involvement in this condition. The study evaluated several signs of choroidal venous overload, including asymmetric arterial choroidal filling (AACF), dilated choroidal vessels ("pachyvessels"), choroidal venous anastomoses (CVA), asymmetric venous drainage (AVD), and CVH. Their findings revealed a high prevalence of these features in both affected and fellow eyes: AACF was present in 85 % of gradable affected eyes, pachyvessels in 88 % of affected and 94 % of fellow eyes, CVA in 94 % of affected and 90 % of fellow eyes, AVD in 74 % of affected and 67 % of fellow eyes, and notably, CVH in 100 % of affected and 85 % of fellow eyes. Interestingly, CVH showed the highest intergrader agreement (94 %) compared to other features (74–82 %). The study also found that the presence of pachyvessels or AVD in one eye significantly increased the odds of the same feature in the fellow eye. These comprehensive findings support the concept of choroidal venous overload as a major factor in CSC pathogenesis and suggest that CSC may be considered a bilateral condition with asymmetric manifestations. The authors conclude that while various signs of venous overload are common in CSC, CVH, evaluated using UWF-ICGA, stands out as a key diagnostic feature due to its consistent presence and high intergrader reliability.

4.2.2. No dye-based imaging techniques

4.2.2.1. Optical coherence tomography. SD-OCT has become the primary imaging modality for diagnosing and monitoring CSC. It provides rapid, non-invasive, and reproducible high-definition images of retinal layers and pathological modifications in the macular area. Recent advancements in EDI and swept-source technologies have allowed full-depth visualization of the choroid, improving morphological analysis of

retinal and choroidal layers. SD-OCT has revealed numerous changes in CSC that extend beyond the commonly observed subretinal fluid and PEDs, which may or may not be associated with RPE leakage sites. These additional alterations have provided valuable insights into the pathogenesis of CSC. In the following sections, we will present a comprehensive review of the retinal and choroidal alterations identified by SD-OCT with EDI technology and SS-OCT in CSC patients (Figs. 4 and 5). This detailed examination will cover a wide range of structural changes observed in various layers of the retina and choroid, offering a deeper understanding of the disease process and its progression.

4.2.2.1.1. Choroid. Increased choroidal thickness is a hallmark of CSC, observed in both affected and fellow eyes of patients compared to healthy subjects (Imamura et al., 2009; Jirattanasopa et al., 2012; Kim et al., 2012). Affected eyes in unilateral cases typically demonstrate greater choroidal thickness than fellow eyes (Goktas, 2014; Maruko et al., 2011b; Oh et al., 2014). While the exact threshold for "normal" choroidal thickness remains to be determined, considering various factors such as axial length, age, and circadian rhythm, a value of 395 μm has been proposed as a sensitive threshold for diagnosing "thick choroid" or "pachychoroid" (Lehmann et al., 2015).

Choroidal thickening in CSC can result from focal or diffuse dilation of large choroidal vessels. These dilated vessels often correspond to areas of increased choroidal vascular permeability on ICGA (Jirattanasopa et al., 2012; Maruko et al., 2011a). Interestingly, the inner choroidal layer above these dilated vessels, which includes medium and small vessels, is often thinner than in adjacent areas (Yang et al., 2013). This thinning could be due to primary atrophy of the CC or compression by the enlarged vessels in the outer choroid.

Other choroidal features observed on SD-OCT include:

1. Hyperreflective dots in the choroid, particularly in the inner choroid, which seem to disappear with subretinal fluid resolution (Ruiz-Medrano et al., 2017).
2. Hyperreflective choroidal vessel walls, more frequently observed in affected eyes than unaffected eyes (Ruiz-Medrano et al., 2017).
3. In chronic cases, large vessel walls may exhibit a granular hyperreflectivity, suggesting possible changes in vascular wall structure.

It's important to note that while increased choroidal thickness is associated with CSC, it is not mandatory for diagnosis, as typical cases may present without increased thickness (Jirarattanasopa et al., 2012). These preliminary findings indicate that, in addition to increased CT, other qualitative alterations within the choroid may be indicative of ongoing disease activity in CSC. The full clinical significance of these changes and their potential value as prognostic indicators have yet to be thoroughly evaluated through prospective studies.

4.2.2.1.2. Retinal pigment epithelium. PEDs are a common finding in CSC, observed in 53–100 % of affected eyes (Ahlers et al., 2009; KOGO et al., 2024; Mitarai et al., 2006; Yang et al., 2013). PEDs are more frequently reported in chronic CSC and can be found both inside and outside the subretinal fluid area. They often co-localize with areas of dilated large choroidal vessels, thickened choroid on SD-OCT, and vascular hyperpermeability on ICG angiography (KOGO et al., 2024).

Different types of PEDs have been described in CSC:

1. Dome-shaped PEDs: These have a sharply demarcated and protruding appearance, lacking signs of RPE hyperplasia. En face OCT reveals a homogenous hyporeflective circular area with a hyperreflective border (Ahlers et al., 2009; Lehmann et al., 2013b; Van Velthoven et al., 2005).
2. Irregular or wavy flat PEDs: These are more commonly observed in chronic CSC.
3. Shallow irregular PEDs with hyperreflective content: These create a "double layer sign" overlying an intact thin hyperreflective layer attributed to Bruch's membrane (Cho et al., 2020; Hwang et al., 2020; Shin and Lee, 2012).

The formation of PEDs appears to be closely associated with choroidopathy, as they frequently co-localize with areas of choroidal vascular anomalies on SD-OCT and ICGA. A recent study using swept-source en face OCT found RPE changes overlying areas of choroidal vascular dilatation in all examined eyes, further supporting the correlation between epitheliopathy and choroidopathy (Ferrara et al., 2014; Lee et al., 2017).

4.2.2.1.3. Neurosensory retina. The neurosensory retina in CSC exhibits various structural changes that can be observed through structural OCT. In acute CSC, while the overall morphology of retinal layers typically remains intact, several notable alterations can be detected. One of the most characteristic findings is the elongation of photoreceptor outer segments in the area of macular serous retinal detachment (Matsumoto et al., 2008). This elongation is often accompanied by the presence of hyper-reflective dots, frequently observed in the subretinal space below the detached neurosensory retina and within several retinal layers. These dots co-localize with hyper-autofluorescent areas on fundus autofluorescence imaging, suggesting a correlation with cellular debris or inflammatory processes (KON et al., 2008; Maruko et al., 2011a; Matsumoto et al., 2011; SPAIDE and KLANCNIKJR, 2005).

As the disease progresses, more significant structural changes may occur. Intraretinal cysts can form after several years of disease duration, potentially indicating a compromised RPE allowing fluid passage. These cysts may fluctuate or disappear over time. In chronic cases, disruption of the ellipsoid zone, external limiting membrane, and thinning of the outer nuclear layer can be observed, all of which correlate with poor visual prognosis (EANDI et al., 2005; Matsumoto et al., 2009; Ojima et al., 2007).

A rare but significant variant of CSC is the bullous form,

characterized by an unusually large and often inferior accumulation of subretinal fluid. This results in a dramatic, dome-shaped elevation of the neurosensory retina that can extend to the peripheral retina, sometimes reaching the ora serrata (Bautista Salamanca et al., 2024; Kang et al., 2022; Ou et al., 2023; Tsui et al., 2023). OCT imaging in these cases reveals a remarkably elevated retina with a large optically empty space beneath it (Bautista Salamanca et al., 2024). The bullous variant is often associated with more severe visual symptoms and a potentially worse prognosis (Chatziralli et al., 2017).

Another important OCT biomarker in CSC is the subretinal hyperreflective material (SHRM), which appears as a hyperreflective deposit between the neurosensory retina and the RPE. SHRM is more commonly observed in chronic CSC cases with long-standing subretinal fluid and is associated with worse visual outcomes (Feo et al., 2024). While its exact composition remains unclear, SHRM is thought to consist of accumulated photoreceptor outer segments, inflammatory cells, fibrin, or other proteins (Feo et al., 2024; Maruyama-Inoue et al., 2023). The presence of SHRM may indicate a critical point in disease progression, potentially signaling the transition from acute to chronic stages or an increased risk for complications such as choroidal neovascularization (Dansingani et al., 2016).

These various neurosensory retinal changes observed in CSC provide valuable insights into the disease's pathophysiology and progression. Their identification through OCT imaging plays a crucial role in diagnosis, prognostication, and guiding treatment decisions in CSC management.

4.2.2.2. OCT findings in CSC complicated by MNV. In CSC complicated by type 1 MNV, OCT typically reveals a flat irregular PED with a "double-layer sign" (DLS), characterized by hyperreflective material between the RPE and Bruch's membrane. However, the DLS has limited specificity for confirming MNV in this setting, as similar findings can be observed in chronic CSC with RPE irregularities without neovascularization (Hagag et al., 2022) (Fig. 5). Recent work from our group demonstrated that CSC eyes with neovascular complications exhibit significant thinning of both the choriocapillaris-Sattler complex and Haller's layer beneath flat irregular pigment epithelial detachments compared to uncomplicated CSC eyes (Viggiano et al., 2025b). These findings suggest that progressive choroidal thinning, rather than thickening alone, may represent a key feature in neovascular transformation. This observation could serve as a valuable biomarker for identifying eyes at elevated risk for developing neovascular complications and may help guide clinical monitoring strategies in chronic CSC cases.

Additional OCT features that may suggest MNV in CSC include:

- Shallow, irregular PEDs with heterogeneous reflectivity
- Subretinal hyperreflective material adjacent to PEDs
- Intraretinal fluid combined with subretinal fluid
- Disruption of external limiting membrane and ellipsoid zone over areas of suspected neovascularization

It's important to note that these OCT findings alone are insufficient for definitive diagnosis of MNV complicating CSC, necessitating correlation with other imaging modalities, particularly OCTA (Kiilgaard et al., 2024).

4.2.2.3. Structural en-face OCT. En face OCT has emerged as a crucial imaging modality in the evaluation and management of CSC. This technique provides horizontal slices of the retina and choroid at various depths, offering unique insights into choroidal vascular changes, particularly in assessing intervortex veins. Pang et al. demonstrated that en face OCT can effectively visualize choroidal vasculature, revealing dilated Haller's layer vessels characteristic of CSC (Pang et al., 2014). The role of en face OCT in evaluating intervortex veins has been further elucidated in recent studies. Dansingani et al. used en face OCT to

identify and characterize dilated choroidal veins in CSC patients, noting their correspondence with areas of choroidal hyperpermeability (Dansingani et al., 2016). Spaide et al. emphasized the importance of en face OCT in mapping choroidal venous patterns and delineating inter-vortex anastomoses (Spaide et al., 2021). Building on this, Demirel et al. conducted a quantitative assessment of intervortex anastomosis in CSC and fellow eyes, suggesting that the characteristics of these vessels may serve as a diagnostic marker for CSC (Demirel et al., 2024). Oribio-Quinto et al. utilized en face OCT to evaluate changes in choroidal macular anastomoses following photodynamic therapy (PDT), demonstrating its utility in monitoring treatment response (Oribio-Quinto et al., 2023). Hwang et al. focused on hyperreflective foci in the CC using en face OCT, providing new insights into micro-structural changes associated with CSC (Hwang et al., 2023). Ramtohul et al. employed ultrawidefield en face OCT to examine the vortex vein system in CSC, offering a broader perspective on choroidal vascular changes (Ramtohul et al., 2023). Additionally, a recent study explored the use of en face OCT transillumination for evaluating RPE alterations in CSC, underlining the technique's value in assessing RPE integrity (D. S. et al., 2022). These studies collectively demonstrate the versatility and importance of en face OCT in CSC, from diagnosing and monitoring treatment response to providing detailed insights into choroidal and RPE changes associated with the disease. The enhanced visualization of intervortex veins and choroidal vascular patterns through en face OCT not only aids in diagnosis but also provides crucial information for targeted treatments such as photodynamic therapy, potentially improving outcomes in CSC management (Fig. 4).

4.2.2.4. Fundus autofluorescence. FAF has emerged as valuable non-invasive techniques for evaluating CSC. Short-wavelength FAF, primarily originating from RPE lipofuscin, provides crucial information about RPE health and allows for the detection of various changes across different phases and forms of CSC (Delori et al., 1995).

In acute CSC, focal areas of hypo-autofluorescence at leakage points are observed in 70–100 % of cases, supporting the hypothesis of focal RPE defects or detachment (Ayata et al., 2009; EANDI et al., 2005; Iacono et al., 2016). Initially, a diminished FAF is seen in the area corresponding to the SRD. This may return to normal after SRD resolution or progress to increased FAF in episodes persisting beyond four months (Framme et al., 2005). The initial decrease in FAF can be attributed to masking by the SRD and elongated photoreceptor outer segments, while the subsequent increased patchy FAF in non-resolving cases may result from accumulation of non-shed fluorophores in these elongated segments (Matsumoto et al., 2011) (Fig. 4).

Interestingly, a residual granular increased FAF may persist after resolution, correlating with intraretinal hyper-reflective dots on SD-OCT (Iacono et al., 2016). Moreover, Freund et al. propose that this residual hyper-autofluorescence might originate from a loss of photoreceptor outer segments, which normally contain photopigments that partially block RPE autofluorescence (Freund et al., 2013).

Recent studies have further elucidated its role and potential in this condition. Weber et al. (2024) introduced quantitative autofluorescence (qAF) as a novel approach in CSC evaluation. Their study demonstrated that qAF levels were significantly increased in CSC patients compared to healthy controls, particularly in areas of subretinal fluid accumulation. This quantitative method may provide a more objective assessment of RPE metabolism and damage in CSC, potentially aiding in monitoring disease progression and treatment response. Mohabati et al. (2023) investigated the predictive value of FAF abnormalities for FA findings in chronic CSC. They found that specific FAF patterns, particularly descending tracts and granular hypo-autofluorescence, were strongly associated with FA abnormalities. This suggests that FAF could potentially be used as a non-invasive alternative to FA in some cases, reducing the need for invasive procedures in the management of chronic CSC.

The study by Bindewald-Wittich et al. (2023) focused on blue-light

FAF imaging of PEDs, a common feature in CSC. They observed distinct FAF patterns associated with different types of PEDs, providing insights into the underlying pathophysiology of these lesions. In CSC, this could be particularly relevant for understanding the evolution of PEDs and their relationship to disease progression.

These recent studies highlight the evolving role of FAF in CSC management. From quantitative assessments to predictive capabilities and detailed lesion characterization, FAF continues to prove its worth as a non-invasive, informative imaging modality in CSC.

4.2.2.5. Infrared reflectance. IR is an innovative, non-invasive imaging modality that has gained attention in the evaluation of CSC. IR primarily captures signals emanating from melanin in the choroid and RPE (Keilhauer and Delori, 2006). This unique characteristic allows for a different perspective on the structural changes occurring in CSC.

In acute CSC cases, IR typically shows an initial decrease in reflectivity. This initial change is thought to be related to the displacement of melanin-containing RPE cells by subretinal fluid. As the disease progresses, two primary patterns have been observed:

1. Complete resolution: In some cases, the IR signal returns to normal as the subretinal fluid resolves and the RPE regains its normal configuration (S.-K. Kim et al., 2013b). This pattern is often associated with better visual outcomes and may indicate a more favorable prognosis.
2. Granular pattern: In other cases, particularly those with prolonged or recurrent episodes, IR may evolve to exhibit a granular pattern. This granularity is believed to represent long-term changes in RPE melanin distribution following a CSC episode (Ayata et al., 2009; Sekiryu et al., 2010). The presence of this pattern might indicate more significant RPE damage and could be associated with a higher risk of recurrence or chronic disease.

While NIR-AF is not yet routinely employed in the evaluation of CSC patients, its unique ability to visualize melanin distribution makes it a promising tool for assessing RPE integrity and choroidal changes. This could be particularly useful in monitoring disease progression, evaluating treatment efficacy, and predicting long-term outcomes.

4.2.3. Enhanced insights provided by OCT angiography

OCTA has emerged as a revolutionary non-invasive imaging technique that provides enhanced insights into the pathophysiology and management of CSC. This technology offers detailed visualization of retinal and choroidal vasculature without the need for dye injection, overcoming limitations of traditional angiography methods.

4.2.3.1. OCTA in CSC complicated by MNV. OCTA has revolutionized the detection of MNV complicating CSC by providing direct visualization of neovascular networks without the confounding effect of dye leakage. OCTA can identify type 1 MNV appearing as networks of high-flow vessels between the RPE and Bruch's membrane in areas corresponding to flat irregular PEDs on structural OCT (Demirel et al., 2022; Hagag et al., 2022) (Fig. 5).

However, OCTA has certain limitations in detecting MNV in CSC. Kiilgaard et al. (Kiilgaard et al., 2024; Ng et al., 2021) in their systematic review and meta-analysis, reported that while OCTA demonstrates high sensitivity for MNV detection in CSC, false negatives can occur, particularly in cases with:

- Small or immature neovascular networks
- Low-flow lesions
- Suboptimal image quality due to subretinal fluid or dense subretinal material
- Projection artifacts from overlying retinal vessels

The differential diagnosis between MNV complicating CSC and

neovascular AMD is critical, as misdiagnosis can lead to inappropriate treatment strategies. [Borrelli et al. \(2020a\)](#) demonstrated that a correct diagnosis impacts clinical outcomes, with different patterns of response to anti-VEGF therapy observed between these entities. The study highlighted that eyes with MNV complicating CSC typically require fewer anti-VEGF injections and show better visual outcomes compared to neovascular AMD.

4.2.3.2. OCTA insights into choriocapillaris circulation. OCTA also provides unique insights into CC circulation in CSC. [Teussink et al. \(2015\)](#) observed that OCTA can reveal areas of choriocapillaris flow impairment in CSC patients, which correlate with regions of CH seen on ICGA. OCTA has also proven invaluable in assessing CC ischemia in the fellow eyes of CSC patients. [Yun et al. \(2019\)](#) demonstrated that OCTA can reveal subtle CC flow alterations in the apparently unaffected fellow eyes of acute CSC patients. Likewise, [Lin et al. \(2024\)](#) utilized quantitative OCTA to assess vascular changes in fellow eyes of patients with unilateral CSC. Their study revealed significant reductions in superficial and deep retinal vascular density, along with increased choroidal flow area in fellow eyes compared to healthy controls.

4.2.3.3. OCTA for evaluating treatment response. OCTA has also proven invaluable in guiding treatment strategies and evaluating treatment response in CSC. [Li et al. \(2023\)](#) conducted a randomized trial comparing OCTA-guided versus ICGA-guided half-dose PDT for acute CSC. Their results demonstrated that OCTA-guided PDT was non-inferior to ICGA-guided PDT in terms of treatment efficacy at 6 months, highlighting the potential of OCTA as a non-invasive alternative for guiding PDT treatment. Furthermore, OCTA has shown its utility in assessing treatment response. [Costanzo et al. \(2015\)](#) used OCTA to evaluate changes in choroidal vasculature following PDT in CSC patients, observing a reduction in choroidal vascular flow area post-treatment that correlated with clinical improvement. Similarly, our previous papers ([Boscia et al., 2023](#); [Viggiano et al., 2023a](#)) employed OCTA to assess long-term effects of eplerenone treatment on CC reperfusion in resolved chronic CSC cases, demonstrating OCTA's capability to detect subtle improvements in CC perfusion over time.

4.2.3.4. Widefield and ultra-widefield OCTA. The advent of widefield and ultra-widefield OCTA has further expanded our understanding of CSC. Widefield OCTA allows for a broader view of the retinal and choroidal vasculature, extending beyond the posterior pole. [Meng et al. \(2022\)](#) utilized widefield OCTA to demonstrate that choroidal vascular abnormalities in CSC often extend beyond the clinically apparent areas of involvement. Ultra-widefield OCTA has provided even more comprehensive insights. Recent papers ([Luo et al., 2023](#); [Zeng et al., 2022b](#)) used this technology to investigate the choroidal vortex vein drainage system in CSC, revealing extensive alterations in the choroidal vascular network extending far beyond the macula. This broader view is particularly relevant in CSC, where choroidal changes can be widespread and not limited to the posterior pole. Finally, [Zeng et al. \(2022a\)](#) utilized ultra-widefield swept-source OCTA to evaluate the three-dimensional choroidal vascularity index (CVI) in CSC. Their study demonstrated significant differences in CVI between CSC eyes and healthy controls, with CSC eyes showing increased choroidal vascularity.

4.3. Pachychoroid neovascularopathy

PNV is a distinct entity within the PSDs, characterized by the presence of type 1 MNV in eyes with pachychoroid features. This condition represents a progression from PPE and/or CSC, sharing common underlying choroidal abnormalities but with distinct clinical and imaging features that differentiate it from both CSC complicated by MNV and from neovascular AMD. ([Pang and Freund, 2015](#)). It is important to

distinguish between two related but distinct clinical entities: PNV and MNV complicating CSC. As highlighted by [Cheung et al. \(2024\)](#), PNV represents a distinct phenotype characterized by alterations in choroidal vasculature that result in outer retinal and choriocapillaris damage, ultimately leading to the development of type 1 MNV.

4.3.1. Dye-based imaging techniques

4.3.1.1. Fluorescein angiography. FA plays a role in the evaluation of PNV, although its utility is limited compared to other imaging modalities. In PNV, FA typically reveals a pattern of occult leakage characteristic of type 1 MNV, appearing as a stippled hyperfluorescence with ill-defined borders in the late phases ([Kuranami et al., 2023](#); [Riazi-Esfahani et al., 2023](#)). However, this pattern can be difficult to distinguish from the multiple leakage points often seen in chronic CSC ([Fig. 6](#)).

The conventional appearance of stippled, granular hyperfluorescence and occult leakage of type 1 MNV in FA can be masked by multifocal leakages and stains from RPE and window defects, making the detection of neovascularization challenging ([Fung et al., 2012](#)). This limitation is particularly pronounced in PNV due to the underlying choroidal thickening, which can further obscure the visualization of neovascular networks. A significant study by [Ng et al. \(2021\)](#) compared OCTA with multimodal imaging, including FA, for diagnosing neovascular CSC, a condition closely related to PNV. While FA demonstrated high sensitivity in detecting neovascularization, it showed lower specificity compared to OCTA. The study underscored that FA's leakage patterns, while indicative of neovascularization, can sometimes be misleading in pachychoroid conditions due to the underlying choroidal hyperpermeability.

Despite its historical significance, FA faces considerable limitations in the context of PNV, and the literature specifically addressing its role in PNV is notably sparse. The limitations of FA in PNV are multifaceted and significant. The thickened choroid characteristic of PNV often obscures the visualization of the underlying neovascular networks, making it difficult to accurately assess the extent and nature of the neovascularization. Furthermore, the CH common in pachychoroid conditions can lead to diffuse hyperfluorescence that may be mistaken for or mask true neovascular leakage, potentially resulting in misdiagnosis or overestimation of disease severity. The dynamic nature of PNV, with its fluctuating subretinal fluid levels, can also complicate FA interpretation, as the fluid itself can alter the appearance of fluorescein leakage patterns. Additionally, FA's two-dimensional nature limits its ability to provide depth information, which is crucial in understanding the layered pathology of PNV. The invasive nature of FA, requiring dye injection, also poses risks of adverse reactions and limits its frequent use for disease monitoring.

4.3.1.2. Indocyanine green angiography. ICGA continues to be a crucial tool in the diagnosis and characterization of PNV, building upon its established role in other pachychoroid spectrum disorders. Key findings include the presence of dilated choroidal vessels prominently visible in the Haller's layer. These pachyvessels often correspond to areas of CH, appearing as regions of diffuse hypercyanescent. Additionally, ICGA reveals plaques or focal areas of hypercyanescent, indicative of type 1 neovascularization, a hallmark of PNV ([Dansingani et al., 2016](#)). ICGA plays a vital role in differentiating PNV from neovascular AMD. In contrast, neovascular AMD typically exhibits persistent late plaque hypercyanescence ([Cheung et al., 2024](#)). Unlike AMD, PNV typically lacks drusen and widespread retinal pigment epithelium atrophy, features readily apparent on ICGA ([Kuranami et al., 2023](#)) ([Fig. 6](#)).

Additionally, ICGA plays a crucial role in differentiating PNV from other related conditions, particularly PCV and non-exudative MNV AMD-related. In PNV, ICGA typically reveals a late-staining plaque, characteristic of type 1 neovascularization. This feature contrasts

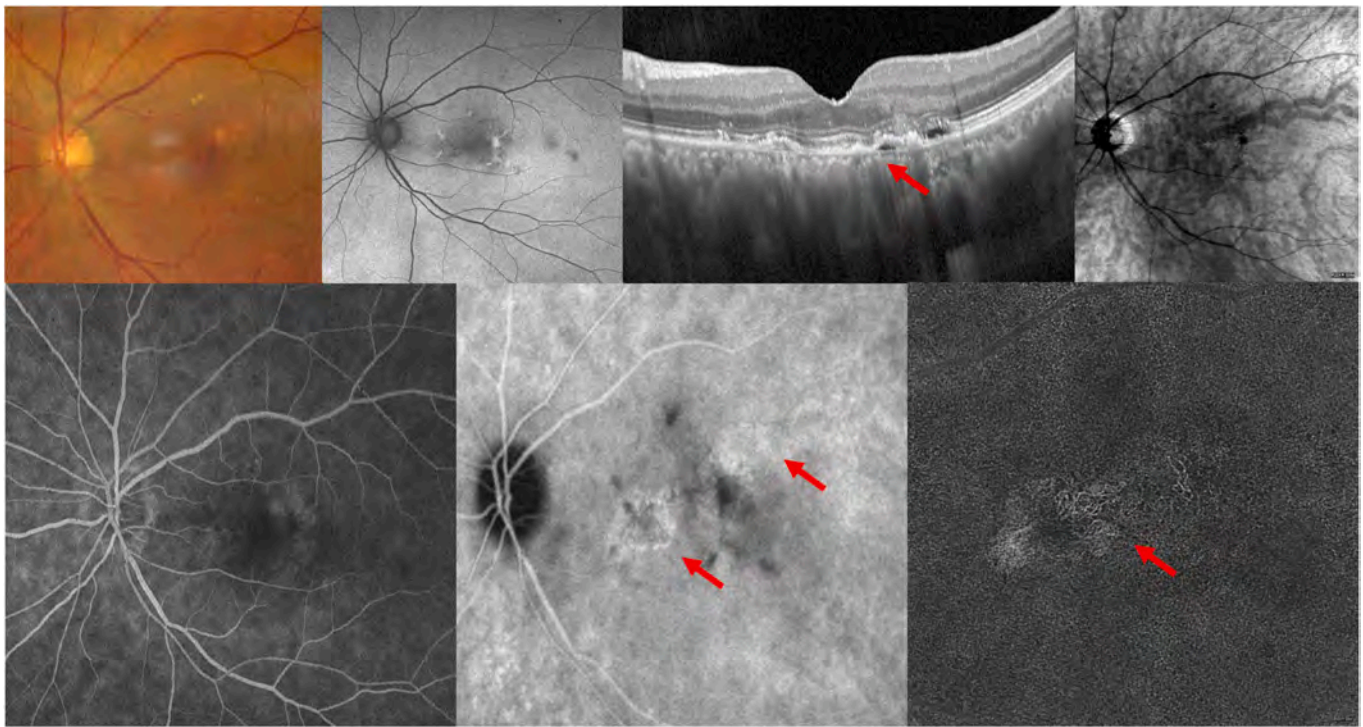


Fig. 6. Multimodal imaging of pachychoroid neovascularopathy in a 61-year-old female with gradual vision decline over the past year. Color fundus photograph (top left) shows subtle RPE alterations in the macula with minimal pachydrusen. Fundus autofluorescence (top, second from left) displays a mixed pattern of hypo- and hyperautofluorescence, indicating chronic RPE changes. Structural OCT (top, third from left) demonstrates a shallow irregular pigment epithelial detachment with subretinal hyperreflective material (red arrow) characteristic of type 1 neovascularization, overlying prominent pachyvessels in the Haller's layer. En face OCT (top right) clearly shows dilated choroidal vessels. Fluorescein angiography in late phase (bottom left) reveals ill-defined late leakage. Indocyanine green angiography in the intermediate phase (bottom, middle) demonstrates dilated choroidal vessels (red arrows) with areas of choroidal hyperpermeability. OCT angiography (bottom right) clearly visualizes the neovascular network (red arrow) beneath the RPE, confirming the presence of type 1 macular neovascularization in the context of pachychoroid features.

sharply with PCV, where ICGA shows hypercyanescent nodules surrounded by hypocyanescence in the early phase, evolving into hypercyanescent areas in the mid-late phase due to leakage from terminal aneurysmal dilations (Bijer et al., 2018; Cheung et al., 2024). Furthermore, ICGA aids in distinguishing PNV from neovascular AMD in cases of non-exudative MNV. While neovascular AMD exhibits late plaque hypercyanescence, PNV demonstrates a unique pattern of hypercyanescence in the early to mid-phase, followed by a distinctive late wash-out phenomenon. These nuanced differences in ICGA findings are instrumental in accurate diagnosis and appropriate management strategies for PNV (Querques et al., 2013; Sacconi et al., 2023).

Recent research, however, has highlighted some limitations of ICGA when compared to newer imaging modalities, particularly OCTA. Previous papers (Borrelli et al., 2023; Kiilgaard et al., 2024; Ng et al., 2021) et al. found that while ICGA remains valuable, it may not provide the same level of detail and accuracy as OCTA in detecting neovascularization in conditions related to PNV. Nevertheless, ICGA still holds value, especially in cases where media opacities or patient factors may limit OCTA image quality, and in providing a wide-field view of choroidal changes.

4.3.2. No dye-based imaging techniques

4.3.2.1. Optical coherence tomography.

OCT plays a crucial role in diagnosing and characterizing PNV, offering high-resolution cross-sectional images of the retina and choroid. In PNV, several distinctive features can be observed on OCT.

One of the most characteristic findings is the presence of shallow, irregular PEDs. These PEDs, often referred to as "double-layer signs" or "flat irregular PEDs," are typically broader and less elevated compared to

those seen in AMD (Kuranami et al., 2023; Miyake et al., 2015; Riazi-Esfahani et al., 2023). They represent the space between the RPE and Bruch's membrane, occupied by type 1 neovascularization (Cheung et al., 2024; Dansingani et al., 2016). In particular, the presence of heterogeneously hyperreflective material in the sub-RPE space further suggests the presence of neovascularization. More-over, small peaked PED may develop at the margin of PNV, within which aneurysmal lesions may be identified with OCT or ICGA. It is important to note that areas of type-1 neovascularization are spatially correlated with areas that display pachychoroid feature (Sartini et al., 2020). Subretinal fluid may be present, though it's often less pronounced than in CSC. The presence of SRF can fluctuate over time, reflecting the dynamic nature of PNV. OCT also reveals characteristic changes in the outer retinal layers. These may include elongation of photoreceptor outer segments in areas of SRF, disruption of the ellipsoid zone, and thinning of the outer nuclear layer in chronic cases (Cheung et al., 2024; M. Giray Ersoz et al., 2018b) (Fig. 6).

Regarding CT, it's crucial to note that in PNV, it may not always exceed the 300 μ m threshold traditionally associated with pachychoroid conditions. The key feature is the presence of pachyvessels, typically in Haller's layer. These pachyvessels can be readily identified on OCT even in cases where overall choroidal thickness is not markedly increased (Cheung et al., 2024; Dansingani et al., 2016). Importantly, PNV is characterized by a distinctive choroidal vascular pattern. While the outer choroid shows dilation of large vessels, there is often a concurrent thinning of the inner choroid, particularly the choriocapillaris and Sattler's layer (Dansingani et al., 2016). Lastly, another characteristic OCT sign of PNV is the presence of pachydrusen. On OCT, they present as focal elevations of the RPE, generally broader and less numerous than conventional drusen (Spaide, 2018).

Recent research by Baek et al. (2019) has provided further insights into pachydrusen distribution across the pachychoroid spectrum. In PNV, pachydrusen are more commonly located in peri- or parafoveal areas rather than subfoveally, with a particular prevalence of perifoveal lesions. Interestingly, PNV and PCV tend to have a higher number of pachydrusen per eye compared to other PSDs. This combination of dilated outer choroidal vessels, attenuated inner choroid and the presence and distribution of pachydrusen is a crucial diagnostic feature of PNV, potentially more significant than absolute CT. Importantly, PNV typically lacks the drusen and widespread RPE atrophy characteristic of AMD, helping to differentiate between these conditions. However, focal areas of RPE atrophy may develop over time in chronic PNV.

4.3.2.2. Structural en-face OCT. In PNV, en face OCT is particularly useful for visualizing the characteristic choroidal vascular changes. At the level of the outer choroid, en face imaging clearly delineates the dilated choroidal vessels (pachyvessels) typical of PSDs. These appear as large, hyporeflective channels, often more prominent and numerous than in normal eyes (Dansingani et al., 2016). At the level of the CC and Sattler's layer, en face OCT may reveal areas of reduced vessel density or flow voids, corresponding to the attenuation of these layers often seen in PNV. This pattern contrasts with the more uniform appearance of the choriocapillaris in healthy eyes (Spaide et al., 2017). En face OCT is also valuable in assessing the RPE and sub-RPE space. It can clearly demonstrate the presence and extent of shallow irregular PEDs, a hallmark of PNV. These appear as irregularly shaped areas of elevation, often with a stippled or granular internal reflectivity pattern, representing type 1 neovascularization (Borrelli et al., 2018). Moreover, en face OCT can help in identifying and characterizing pachydrusen. These appear as focal, round or oval elevations of the RPE, typically larger and less numerous than conventional drusen (Baek et al., 2019). Another advantage of en face OCT in PNV is its ability to map the distribution and extent of subretinal fluid, when present. This can be particularly useful in monitoring disease activity and treatment response over time.

Ultimately, En face OCT allows for precise correlation of structural findings with other imaging modalities like OCTA, FAF, and ICGA enhancing our understanding of the relationship between choroidal vascular changes and overlying retinal alterations in PNV (Fig. 6).

4.3.2.3. Fundus autofluorescence. In PNV, FAF typically displays a characteristic pattern that reflects the underlying choroidal and RPE changes. The imaging shows patchy areas of granular hypoautofluorescence, interspersed with scattered, distinct hyperautofluorescent specks. These changes are often observed overlying pachyvessels, mirroring patterns seen in other pachychoroid spectrum diseases (Cheung et al., 2024) (Fig. 6).

The granular hypoautofluorescence may indicate areas of RPE stress or subtle atrophy, while the hyperautofluorescent specks could represent areas of increased lipofuscin accumulation or focal RPE hyperplasia. This pattern differs from the more uniform hypoautofluorescence seen in geographic atrophy of AMD, helping to differentiate PNV from AMD. In cases where PNV is associated with recent or ongoing subretinal fluid, FAF may show broader areas of hyperautofluorescence, reflecting the accumulation of fluorophores in the outer retinal layers. As the disease progresses or in chronic cases, areas of more pronounced hypoautofluorescence may develop, indicating more severe RPE damage or atrophy (Pang et al., 2014; Pang and Freund, 2015; Warrow et al., 2013).

4.3.2.4. Infrared reflectance. Infrared reflectance imaging, another non-invasive technique, can also provide useful information in PNV. This modality is particularly effective in visualizing choroidal vessels and subtle RPE changes. In PNV, infrared imaging often reveals a pattern of hyporeflective lines or streaks corresponding to dilated choroidal vessels (pachyvessels). These appear as dark bands against a lighter

background, reflecting the increased light absorption by the engorged choroidal vessels (Pang et al., 2014).

Additionally, infrared imaging can highlight areas of RPE alteration, which may appear as subtle variations in reflectivity. This can be particularly useful in detecting early or subtle changes that might not be apparent on other imaging modalities.

4.3.3. Enhanced insights provided by OCT angiography

This non-invasive imaging modality excels in detecting and characterizing type 1 neovascularization, a hallmark of PNV, revealing the full extent of these networks as a fine, lacy pattern of vessels between the RPE and Bruch's membrane (Azar et al., 2017; Biçer et al., 2018) (Fig. 6). Demirel et al. (2022) demonstrated OCTA's superior sensitivity (97 %) compared to ICGA (66 %) in detecting MNV in pachychoroid eyes. This heightened sensitivity is particularly valuable in PNV, where low-grade neovascularization may be challenging to differentiate from choroidal hyperpermeability on ICGA. The diagnosis of PNV is confirmed when OCTA reveals a tangled vascular network corresponding to the shallow irregular PEDs seen on structural OCT. Interestingly, type 1 MNV in pachychoroid disease is often more clearly visualized on en face OCTA compared to neovascular AMD. This enhanced visibility may be attributed to the gradual onset allowing for network maturation, the planar geometry of the lesions, and the absence of drusenoid material that might otherwise obscure the OCT signal.

OCTA also offers unprecedented insights into choroidal vasculature, clearly demonstrating the dilated outer choroidal vessels characteristic of PNV and allowing for quantitative assessment of choroidal blood flow and vascular density. Moreover, it can reveal areas of CC flow impairment or attenuation, often seen in PNV, providing crucial insights into the disease's pathophysiology (Cheung et al., 2024; Viggiano et al., 2025a).

Recent studies have focused on differentiating PNV from other conditions, particularly type 1 MNV in AMD (Altinisik et al., 2022; Arf et al., 2020; Biçer et al., 2020; Riazi-Esfahani et al., 2023; Viggiano et al., 2025a). Yanik and colleagues (Yanik et al., 2024) conducted a comprehensive analysis comparing the morphological characteristics of neovascular networks in PNV and AMD using OCTA. Their findings revealed distinct differences in the vascular patterns, with PNV typically showing a more uniform, a smaller and less complex structure compared to the heterogeneous, often tangled appearance in AMD. This distinction aids in accurate diagnosis and tailored management strategies.

OCTA's value extends to treatment monitoring, showing changes in neovascular network size and flow characteristics following interventions like photodynamic therapy (Hikichi et al., 2023). Advanced OCTA software enables quantitative analysis of vascular parameters, providing objective measures for disease monitoring and prognostication. Furthermore, recent advancements in wide-field OCTA have expanded our ability to assess peripheral choroidal and retinal vasculature, offering a more comprehensive view of vascular changes in PNV (Meng et al., 2022). OCTA has become an indispensable tool in the diagnosis, characterization, and management of PNV, offering unique insights that complement and often surpass traditional imaging modalities.

4.4. Polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization

PCV was first described by Yannuzzi et al. as idiopathic polypoidal choroidal vasculopathy (Yannuzzi et al., 1990). Although the initial description considered PCV to be a distinct entity arising from the inner choroid, advanced multimodal imaging has transformed our understanding of this condition. Current evidence demonstrates that PCV is in fact a variant of type 1 (sub-RPE) neovascularization with aneurysmal lesions (Balaratnasingam et al., 2016b; Cheung et al., 2024).

In 2017, Dansingani et al. proposed the term "aneurysmal type 1 neovascularization" (AT1) as a more accurate descriptor to reflect the

neovascular nature of these lesions (Dansingani et al., 2017). This terminology acknowledges that the lesion is fundamentally vascular (an aneurysmal dilatation) rather than epithelial (a solid or fleshy polyp). The term AT1 serves as a descriptive designation that is not disease-specific, recognizing that aneurysmal lesions can occur in neovascularization associated with various conditions, including pachychoroid disease, typical drusen-associated AMD, myopic staphyloma, radiation retinopathy, and angioid streaks (Balaratnasingam et al., 2016b). The Asia-Pacific Ocular Imaging Society (APOIS) PCV workgroup has contributed significantly to standardizing the nomenclature. They recommended the terms "polypoidal lesion" and "branching neovascular network" for the two key components of PCV/AT1 (Cheung et al., 2021a). While acknowledging the merits of the term "aneurysmal," they retained "polypoidal lesion" until more universal evidence becomes available. The workgroup also recognized that the branching vascular network in PCV/AT1 and the neovascular network in PNV likely represent a continuum of the same pathological process, further supporting the neovascular nature of these conditions.

4.4.1. Dye-based imaging techniques

4.4.1.1. Fluorescein angiography. FA has been widely used as routine imaging technique for PCV/AT1 diagnosis. The EVEREST study reported the FA features distinguishing PCV/AT1 from nAMD including the presence of hyperfluorescent nodules and areas of blockage secondary to subretinal hemorrhage (Tan et al., 2019). However, these findings have

low specificity, as similar characteristics may also be present in eyes with neovascular AMD (Tan et al., 2019). Thus, performing FA, it's frequently not sufficient for a complete PCV/AT1 diagnosis. Moreover, FA presents additional drawbacks in PCV/AT1 evaluation. Indeed, FA uses a wavelength of about 465–490 nm that doesn't pass through that RPE, and, consequently, is unable to capture the choroidal abnormalities (Kumar et al., 2019). Moreover, the dye leakage through the choriocapillaris fenestrations may cover the presence of the underlying PCV/AT1 (Kumar et al., 2019) (Fig. 7).

4.4.1.2. Indocyanine green angiography. ICGA is considered the gold-standard for the definitive diagnosis of PCV/AT1 (Sen et al., 2023). ICGA may reveal the presence of single or multiple polypoidal lesions, generally located in the macular area or in the peripapillary region. There are two main PCV/AT1 findings on ICGA: the branching vascular network (BVN) beneath the Bruch's membrane, and the aneurysmal dilatation at the border of the network (Spaide et al., 1995). Typically, PCV/AT1 appearance changes following ICGA phases (Ciardella et al., 2004):

1. Early phase: the early stages show the filling of the vascular network followed by the appearance of an hyperfluorescent nodule corresponding to the polyp. The area surrounding the polyps appears hypofluorescent.
2. Mid-phase: during the mid-phase the border of the lesion tend to expand (Fig. 7).

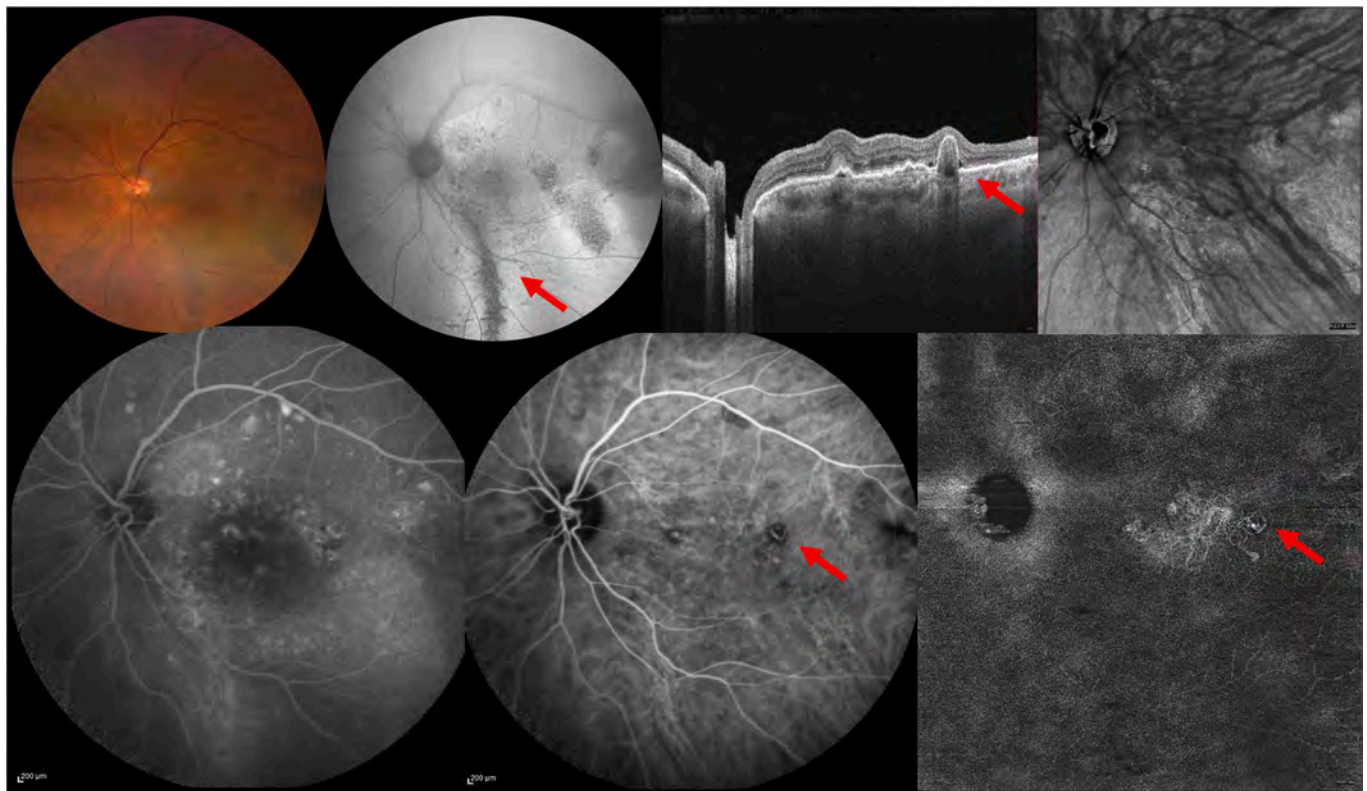


Fig. 7. Multimodal imaging of polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization (PCV/AT1) in a 68-year-old male presenting with acute vision decline and metamorphopsia. Color fundus photograph (top left) reveals orange-red subretinal nodular lesions and RPE alterations in the macula. Fundus autofluorescence (top, second from left) demonstrates a mix of hypo- and hyperautofluorescence patterns (red arrow), showing both typical PCV features as well as surrounding RPE alterations characteristic of pachychoroid phenotype. Structural OCT (top, third from left) displays a sharply peaked pigment epithelial detachment (red arrow) containing a hyperreflective ring-like lesion consistent with a polypoidal lesion, overlying dilated pachyvessels in Haller's layer. En face OCT (top right) clearly shows dilated choroidal vessels. Fluorescein angiography in late phase (bottom left) demonstrates multiple areas of hyperfluorescence with stippled leakage corresponding to the neovascular network. Indocyanine green angiography in intermediate phase (bottom, middle) reveals distinct nodular hyperfluorescence (red arrow) representing the aneurysmal dilatation characteristic of PCV/AT1, surrounded by a branching vascular network. SS-OCT angiography (bottom right) clearly visualizes the neovascular network with terminal aneurysmal dilatations (red arrow), confirming the diagnosis of PCV/AT1 in the context of pachychoroid features.

3. Late phase: there is the reversal of the pattern observed initially. Indeed, the border of the lesions become hyperfluorescent and the central part hypofluorescent. In the very late stages, the non-leaking PCV/AT1 shows the complete dye disappearance from the lesion. The latter phenomenon is known as “wash out”. Conversely, in the leaking polyps the hyperfluorescence persists.

It is important to note that in PCV/AT1 forms associated with pachychoroid spectrum, ICGA characteristically reveals diffuse choroidal hyperpermeability (Sasahara et al., 2006). This feature reflects the increased choroidal thickness and vascular alteration typical of pachychoroid, distinguishing these forms of PCV/AT1 from those not associated with pachychoroid. Hyperpermeability is generally visible in the intermediate and late phases of ICGA as an area of diffuse hyperfluorescence that extends beyond the boundaries of the polypoidal lesion and the BVN (Kim et al., 2015; Sasahara et al., 2006) (“[Criteria for diagnosis of polypoidal choroidal vasculopathy].,” 2005). A ICGA-based diagnostic protocol of PCV/AT1 was reported in the EVEREST study report 2 (Tan et al., 2015). The authors described PCV/AT1 as an early hyperfluorescent lesion appearing in the earliest 5 min of ICGA, with one of the additional following characteristics: 1) a nodular stereoscopic appearance; 2) a surrounding hypofluorescent halo; 3) the pulsatility of the lesion on dynamic ICGA; 4) visualization of BVN; 5) the lesion appearance as an orange subretinal nodule; 6) the presence of a massive submacular hemorrhage. In this way, ICGA plays a crucial role in PCV/AT1 assessment, and is still recognized as the gold-standard for diagnosis. Despite that, when compared to newer imaging modalities such as OCTA, ICGA presents some drawbacks. Indeed, ICGA is an invasive exam with several potential side effects, and is time consuming in comparison to OCTA (Gelişken, 2024b; Teo and Cheung, 2019). In addition, OCTA allows the visualization of the different vascular layers, including choriocapillaris and choroid (Teo and Cheung, 2019). Furthermore, same researches that compared OCTA to ICGA showed the former to be equal or superior in the BVN assessment (Kim et al., 2016; Wang et al., 2016). For instance, Wang and coworkers reported that the BVN was imaged more clearly by OCTA than ICGA (Wang et al., 2016). By contrast, the polyp identification rate is still superior on ICGA; (Wang et al., 2016; Singh et al., 2020). Thus, the substitution of ICGA with OCTA in the diagnosis of PCV/AT1 is still not recommended (Gu et al., 2023; Teo and Cheung, 2019).

4.4.2. No dye-based imaging techniques

4.4.2.1. Optical coherence tomography. With its ability to acquire high-resolution, cross-sectional scans of the choroid and retina, OCT allows to capture some distinctive features of the PCV/AT1. One of the first tomographic characteristics of PCV to be reported is the sharply peaked PED with internal moderate reflectivity. The first report of the sharply peaked PED as OCT configuration of PCV/AT1 was published by Iijima and coworkers (Iijima et al., 2000). Following articles suggested that the dome-shaped PED corresponded to the polypoidal lesion, presenting a nodular appearance beneath the RPE (Otsuji et al., 2000). The name “sharp peaked PED” was reported by De Salvo and co-workers, which proposed such feature, along with the PED notch, the hyporeflective lumen within the hyperreflective lesion adherent to the RPE, and the presence of multiple PEDs as distinguishing feature of PCV/AT1 from occult CNV (De Salvo et al., 2014). The presence of three of these feature was indicative of PCV/AT1 with a sensitivity of 94.6 % and a specificity of 92.9 % (De Salvo et al., 2014). Subsequently, Liu and associates named “thumb-like polyp” the OCT appearance of PED related to the polyps, and included this finding as one of the three distinguish features of PCV/AT1 from nAMD, along with PED and the double-layer sign (Liu et al., 2016) (Fig. 7). The presence of at least two out of 3 of these signs was positive for the presence of PCV/AT1 with a sensitivity of 89.4 % and specificity of 85.3 % (Liu et al., 2016).

As stated above, another important feature of PCV/AT1 was the PED notch. The PED notch was described for the first time by Sato and coworkers as the “V-shaped depression” between the dome-shaped PED and the adjacent smaller PED (Sato et al., 2004). Subsequently, Tsujikawa and coworkers showed that the “notch” at the margin of PED corresponded to the polypoidal lesion on ICGA (Tsujikawa et al., 2007). Following articles included the PED notch as distinctive for the presence of PCV/AT1 (De Salvo et al., 2014).

Another important characteristic of PCV/AT1 is the hyporeflective lumen, also termed “ring-like lesion” (De Salvo et al., 2014; Coscas et al., 2015). The hyporeflective lumen, corresponding to the lumen of the polyp, is a rounded hyporeflective structure located within the hyperreflective lesions adherent to external margin of RPE (De Salvo et al., 2014; Chang et al., 2016).

The presence of the “double layer sign” is also correlated to the PCV. It was firstly described in association to PCV/AT1 by Sato and coworkers as a fluid accumulation spreading the Bruch’s membrane from the RPE (Sato et al., 2007). Subsequently, Ojima and coworkers postulated that the low-lying elevation of the RPE corresponded to BVN on the angiogram (Ojima et al., 2009).

Another distinctive finding of the PCV/AT1 are the “multiple PEDs”, which correspond to the presence of several adjacent PED (De Salvo et al., 2014). The consensus nomenclature for PCV/AT1 of the Asia-Pacific Ocular Imaging Society proposed the convergence of the PED notch, multiple PED, and hemorrhagic PED into a single signed termed “multilobular PED” (Cheung et al., 2021a). They suggested a new scheme including the sharply peaked PED, the ring-like lesion, and the *en face* OCT complex RPE elevation, as major criteria for PCV diagnosis. The combination of these three features obtained an area under curve of 0.90 for PCV/AT1 diagnosis. Moreover, they included the choroidal thickening (≥ 300 μm), the orange nodule on color fundus photograph, the multilobular PED, and the double layer sign as minor diagnostics criteria (Cheung et al., 2021a) (Fig. 7).

4.4.2.2. Structural *en-face* OCT. The *en face* OCT is particularly useful in the PCV/AT1 assessment. Kameda and colleagues described the *en face* OCT configuration of the polypoidal lesion as round protrusions of the RPE, and the BVN as a slight elevation of the overlying RPE with a geographic shape (Kameda et al., 2007). In the same way, serous PED were described as larger round elevations of the RPE adjacent to the polypoidal lesions (Kameda et al., 2007). Sayanagi and coworkers used the high-penetration OCT to implement the visualization of the PCV/AT1 through the RPE (Sayanagi et al., 2015). The PCV/AT1 appeared as an RPE ring with inner reflectivity and was visible in 41 out of 43 cases previously assessed by ICGA. By contrast, the BVN presented an hyperreflective mesh-like configuration, and was visible in 15 eyes (Sayanagi et al., 2015). Subsequently, the consensus nomenclature for PCV/AT1 of the Asia-Pacific Ocular Imaging Society proposed the previously described *en face* OCT configuration as one of the criteria for the non-ICGA diagnosis of PCV/AT1 (Cheung et al., 2021b). At the choroidal level, *en face* OCT shows the dilated choroidal vessels, hyporeflective channels (Dansingani et al., 2016). Additionally, as for PNV, *en face* OCT may provide a map of the distribution and extent of subretinal fluid, resulting extremely useful along the treatment (Fig. 7).

4.4.2.3. Fundus autofluorescence. In PCV/AT1 diagnosis FAF plays a significant role, despite the PCV/AT1 pattern not always shows consistency. Yamagishi and colleagues reported two characteristics patterns of FAF: 1) a confluent hypoautofluorescence in the site of the polyp surrounded by a ring of hyperautofluorescence, the latter pattern referred to as “punched-out lesion”, and 2) a granular pattern of hypoautofluorescence in the site of BVN (Yamagishi et al., 2012). These findings indicate an important damage to the RPE in the site of the polypoidal lesion, and the RPE stress in the BVN area (Yamagishi et al., 2012). Suzuki and associates described the FAF changes along the PCV/AT1

follow-up (Suzuki et al., 2013). At baseline, the majority of cases displayed a confluent hypoautofluorescence surrounded by a ring of hyperautofluorescence. Another group of eyes showed a confluent hypoautofluorescence without the hyperautofluorescent ring, while another group showed no significant changes on FAF. The BVN showed a granular pattern of hypoautofluorescence (Fig. 7). Over the follow-up, the lesions trend was of increasing the hypoautofluorescent area, and of loosing of the hyperautofluorescent ring (Suzuki et al., 2013). They hypothesized that the hyperautofluorescent ring may be due to the aggregation of RPE cells in the steeply elevated areas. Conversely, the increased hypoautofluorescence area later in the follow-up may be caused by the continues RPE loss (Suzuki et al., 2013). Yamagishi and coworkers in a following paper reported the association between the fluid resolution and the hyperautofluorescent ring disappearance (Yamagishi et al., 2014). The granular hypoautofluorescence corresponding to the BVN remained unchanged. They suggested that the hyperautofluorescent ring corresponds to the RPE cells neighboring the polyp's protrusion. These cells present an impaired metabolism that results in the lipofuscin accumulation. The polyp's regression leads to the RPE cells normalization, and consequently, to the hyperautofluorescent ring disappearance (Yamagishi et al., 2014). Further possible FAF pattern in active PCV/AT1 were described by Zhao and coworkers (Zhao et al., 2018). Indeed, they showed three possible additional patterns in naïve PCV/AT1: 1) hyperautofluorescent lesions with hypoautofluorescent ring, 2) widespread granular hypoautofluorescence, and 3) blocked hypoautofluorescence due to the presence of a hemorrhage. The central hyperautofluorescence may be explained by the presence of new-developed PCV/AT1 lesion, with an initial impairment of the lipofuscin transportation. The evolution of the lesion leads to the irreversible RPE impairment, with the consequent hypoautofluorescence development. Another initial form of PCV/AT1 lesion may manifest with the granular hypoautofluorescence, corresponding to an alternate RPE damage (Zhao et al., 2018). However, also in the latter study, the most common FAF pattern is the confluent hypoautofluorescence surrounded by a ring of hyperautofluorescence.

4.4.2.4. Infrared reflectance. Infrared reflectance imaging may also be useful in PCV/AT1 diagnosis. As stated above, it may help in assessing some findings associated to PDS such as choroidal vessels dilatation and RPE alteration. Additionally, the Asia-Pacific Ocular Imaging Society, defining the non-ICGA criteria for the eyes with a PCV/AT1 with a suboptimal response to the anti-VEGF monotherapy, showed that infrared reflectance can reasonably estimates the boundaries of the lesion, and may be helpful in the OCT-guided PDT treatment (Yi et al., 2021).

4.4.3. Enhanced insights provided by OCT angiography

As for the other PDS-related disorders, OCTA has drastically improved the management and understanding of PCV/AT1. OCTA presents several advantages: it's a non-invasive, fast, and safer if compared to other imaging modalities. OCTA allows the acquisition and comparison of cross-sectional and *en face* images, and permits to assess the status of the regions surrounding the lesion (Inoue et al., 2015). Furthermore, it allows the correlation between the cross-sectional structure and the flow signal (Inoue et al., 2015).

Inoue and associates described the *en face* and structural OCTA findings correlated to PCV/AT1 (Inoue et al., 2015). The *en face* OCTA showed anatomical configurations of PCV comparable to those of ICGA, with a uniform signal intensity and well-defined borders. Furthermore, the loss of choriocapillaris and the presence of pachyvessels were visible beneath the BVN. Conversely, on the OCTA B-scan, both the polyps and the BVN were clearly visible to be located between the Bruch's membrane and RPE. The flow-signal was observed only in the polyp lumens (Inoue et al., 2015). Notably, recent high-resolution OCTA studies have revealed that polypoidal lesions often appear as tangled vascular

complexes rather than true polypoidal structures, suggesting that these lesions may represent focal aneurysmal dilations of neovascular networks rather than distinct polyps (Ahmed-Balestra et al., 2023). The main drawback of OCTA reported in this paper was the loss of signal in correspondence of serosanguineous fluid accumulation (Inoue et al., 2015). Srour et al. reported, at the level of choriocapillaris, BVN as an hyper-flow lesion, and the polyp as an hyper-flow structure, surrounded by an hypo-intense structure or, in some cases, as an hypo-flow round structure (Srour et al., 2016). The latter appearance is probably associated to an abnormal flow within some of the polyps. Wang and coworkers suggested to evaluate the polyps on the outer retina slab rather than the choriocapillaris, given that the polyps correspond to the PED apex (Wang et al., 2016). Several authors reported the OCTA to be not-inferior or superior in detecting BVN in comparison to ICGA (Singh et al., 2020; Fukuyama et al., 2018). Takayama and associates compared ICGA and OCTA in the detection of polyps and BVN (Takayama et al., 2017). They showed the OCTA superiority in detecting BVN (95.2 % vs 71.4 %), in contrast with the ICGA superiority in detecting polyps (100 % vs 75.2 %). The OCTA detection rate is reported to decrease for the polypoidal lesions (Chong Teo et al., 2021; Takayama et al., 2017) because of the reduced internal blood flow (Tomiyasu et al., 2016; Fukuyama et al., 2018) (Fig. 7). Thus, the replacement of ICGA with OCTA is still not suggested. Despite that, OCTA has drastically increased the understanding of PCV, as also improved the quality of the follow-up along the treatment. For instance, Teo and coworkers showed the efficacy of OCTA in assessing the flow signal within the polyps, in the choriocapillaris, and the caliber of choroidal vessels before and after the treatment of PCV (Teo et al., 2018). Another quality of OCTA is the possibility to assess the 3-dimensional (3D) structure of PCV. Using the 3D function, Chi and coworkers reported that the polypoidal lesions can be found at the mean height of 45.3 μm over the RPE, while the BVN at the mean depth of 28.6 μm below the RPE (Chi et al., 2017). The mean polyps' thickness was 38.4 μm , while the mean BVN thickness 60.2 μm . Furthermore, they showed the BVN location to be above, within or beneath the Bruch's membrane (Chi et al., 2017).

4.5. Pachyvittelliform maculopathy: a distinct novel entity

PVM is a new entity recently described by Hilely and colleagues (Hilely et al., 2023). Through an OCT-based analysis, they reported the association of pachychoroid and pachyvessels and the overlying vitelliform lesion in 17 eyes of 17 patients (Hilely et al., 2023). They found total choroidal area (TCA), stromal choroidal area (SCA), and luminal choroidal area (LCA) and SFCT to be significantly greater in PVM group compared to controls. Furthermore, they showed that the patients with PVM had a progressive decrease of BCVA at the end of follow-up. Indeed, as result of PVM involution, about 65 % of patients developed OCT signs of RPE break-down, while about 40 % of them presented macular atrophy (Hilely et al., 2023). Fundoscopically, PVM appears as a subfoveal round yellowish deposit, while at FAF the lesions appear hyperautofluorescent (Fig. 8). OCTA was performed to exclude the presence of a neovascularization (Hilely et al., 2023). The authors hypothesized that the combination of ageing mechanisms and Haller's layers vessels dilatation, may lead to the choriocapillaris flow impairment leading to a dysfunction of the RPE (Cicinelli et al., 2025; Hilely et al., 2023). As result, the RPE lose its ability to phagocytize photoreceptors debris with the consequent formation of vitelliform lesions (Hilely et al., 2023) (Fig. 8). Future OCTA analysis of the choroid and choriocapillaris flow, may implement our knowledge of the pathophysiological mechanisms of this new entity.

4.6. Peripapillary pachychoroid syndrome

Peripapillary pachychoroid syndrome (PPS) is a distinct entity of the PDS characterized by nasal macular and peripapillary fluid pockets, and a greater prevalence of IRF as compared to SRF (Phasukkijwatana et al.,

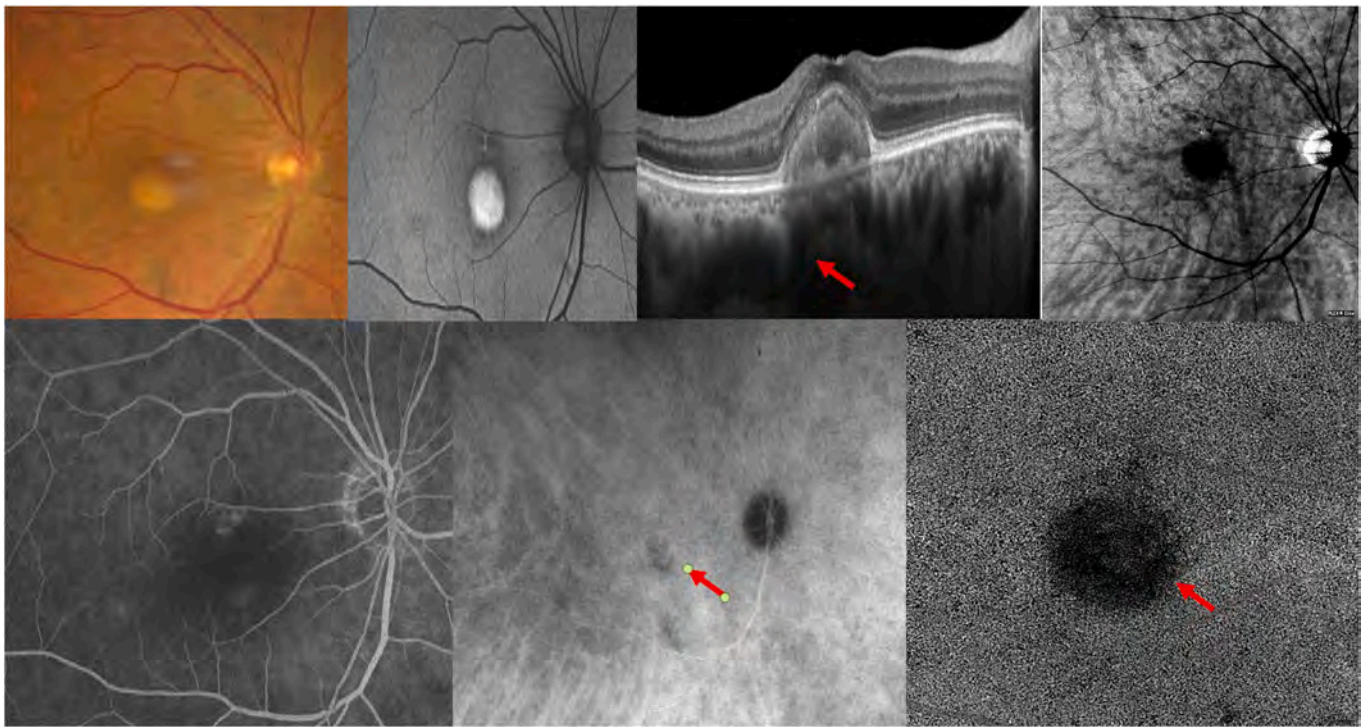


Fig. 8. Multimodal imaging of pachyvittelliform maculopathy in a 65-year-old female complaining of mild central visual distortion. Color fundus photograph (top left) demonstrates a yellowish round subretinal lesion in the macular area, resembling a vitelliform deposit. Fundus autofluorescence (top, second from left) shows intense hyperautofluorescence of the vitelliform material, consistent with accumulation of outer segment debris. Structural OCT (top, third from left) reveals a homogeneous hyperreflective subretinal deposit with underlying pachyvessels in Haller's layer (red arrow), without evidence of choroidal neovascularization or drusen. En face OCT (top right) clearly shows dilated choroidal vessels, intervortex anastomoses and a central hyporeflective area corresponding to the vitelliform lesion. Fluorescein angiography (bottom left) shows minimal hyperfluorescence without active leakage. Indocyanine green angiography (bottom, middle) demonstrates dilated choroidal vessels (red arrow) and areas of choroidal hyperpermeability characteristic of pachychoroid phenotype. OCT angiography of the choriocapillaris (bottom right) reveals flow voids (red arrow) corresponding to areas of attenuated inner choroidal layers overlying pachyvessels.

2018). Despite PPS shares some characteristics with CSC, such as gravitational tracks of RPE alteration, and serous pigment epithelial detachments (PED), the authors described a preferential peripapillary choroidal thickening (Phasukkijwatana et al., 2018) (Fig. 9). Further characteristics are peripapillary RPE mottling on FAF, the fluid accumulation nasally to the optic disc, the peripapillary choroidal vessels hyperpermeability showed by ICGA, and the absence of a significant leakage on FA in the majority of cases (Phasukkijwatana et al., 2018; Kumar et al., 2022b) (Fig. 9).

PPS is thought to result from the parapapillary Haller's layers vessels congestion, leading to an RPE dysfunction and the consequent peripapillary fluid accumulation (Phasukkijwatana et al., 2018). Spaide and coworkers showed the presence of anastomosis in the vortex vein complex around the optic disc, explaining the mechanism of choroidal vessels congestion in that area (Spaide et al., 2021; Nicholson et al., 2013). They imaged a group of patients with several pachychoroid related disorders with wide-field ICGA, showing a different patterns of anastomosis of PPS from the other PDS conditions (Ricardi et al., 2024). Indeed, differently from all the other disorders, the inferonasal vortex vein system was involved in all the PPS eyes, and the anastomosis occurred predominantly in the peripapillary area (Spaide et al., 2022a). Such anastomosis bypass the choriocapillaris, directing the arterial blood flow to the venous circulation, and potentially leading to the venous engorgement (Brinks et al., 2022). An in-depth analysis of pathophysiological mechanisms of PDS has been reported by Spaide and coworkers (Ricardi et al., 2024). By OCTA, they investigated choriocapillaris vessels parameters in healthy patients, in patients with a thick choroid, and in patients with pachychoroid related diseases such as CSC and PPS. They revealed that in affected eyes the choriocapillaris showed a reduced number of vessels, that appear wider, longer, and with a

greater standard deviation in comparison to the other groups (Ricardi et al., 2024). The authors concluded that a thicker choroid is not necessarily pathologic, but may rather be a part of a more complex pathophysiological mechanism involving the choriocapillaris flow impairment (Ricardi et al., 2024). Further studies, integrating different multimodal imaging techniques are necessary to better assess the pathophysiological mechanisms leading to the disease manifestation.

5. Conclusions and future directions

The evolution of multimodal imaging techniques has revolutionized our understanding and management of pachychoroid spectrum disorders. As we look to the future, the integration and refinement of these imaging modalities will continue to play a pivotal role in advancing our knowledge of PSDs. The synergistic use of OCT, OCTA, en face OCT, FA, ICGA, IR imaging, and FAF provides a comprehensive view of the structural and functional changes in PSDs, enabling earlier diagnosis, more accurate disease classification, and personalized treatment strategies. Artificial intelligence (AI) and automated image analysis represent promising avenues for advancing pachychoroid management. Deep learning algorithms may enhance diagnostic accuracy by automatically detecting pachyvessels, quantifying choriocapillaris flow deficits, and identifying subtle neovascular changes before they become clinically apparent. Machine learning approaches could improve the reproducibility of choroidal measurements and create standardized classification systems for PSDs. As these technologies mature, they may enable earlier detection of disease progression and more personalized treatment strategies based on comprehensive risk profiles derived from multimodal imaging data. Future research should focus on developing standardized multimodal imaging protocols for each PSD entity, which could lead to

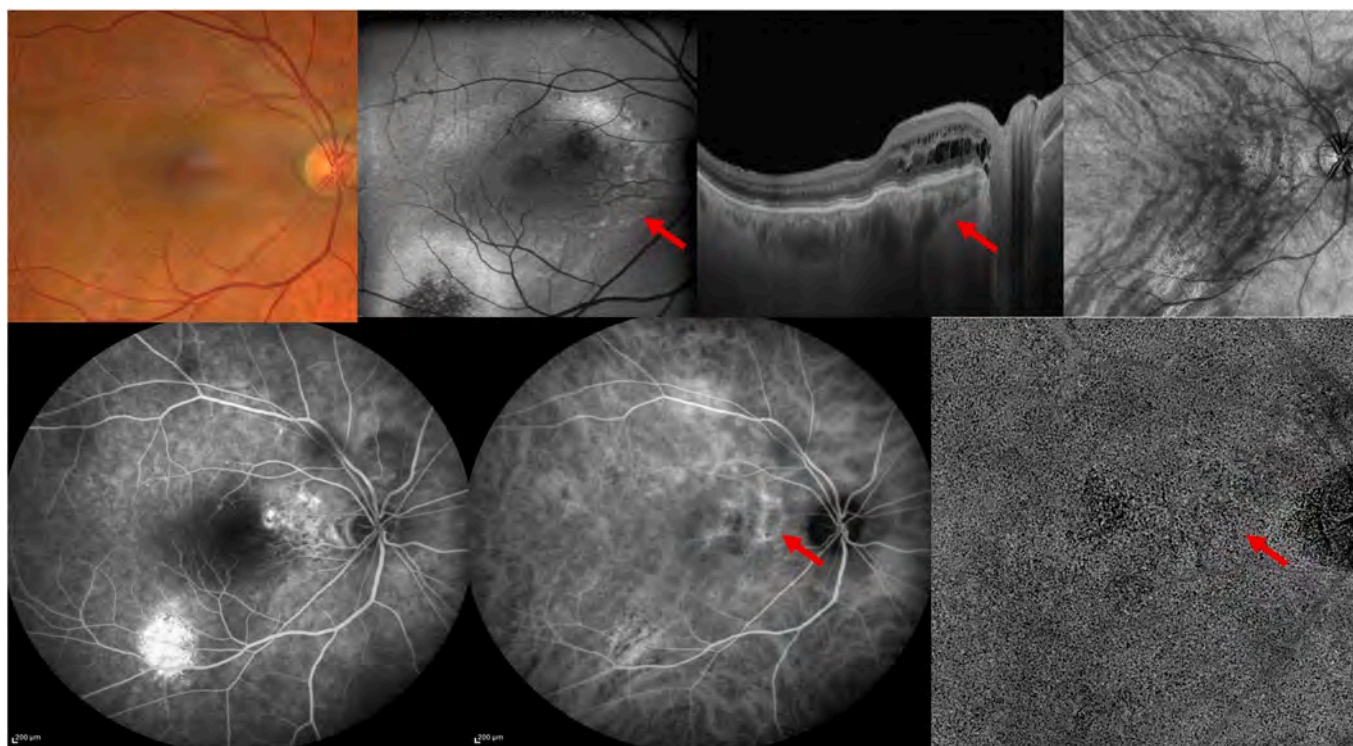


Fig. 9. Multimodal imaging of peripapillary pachychoroid syndrome (PPS) in a 72-year-old hyperopic male presenting with blurred vision and chronic metamorphopsia. Color fundus photograph (top left) shows subtle peripapillary and nasal macular RPE alterations. Fundus autofluorescence (top, second from left) demonstrates irregular hyper- and hypoautofluorescence in the peripapillary region extending toward the nasal macula (red arrow). Structural OCT (top, third from left) reveals intraretinal fluid with prominent pachyvessels in the choroid (red arrow) concentrated in the peripapillary and nasal macular region. En-face OCT (top right) shows choroidal vessels dilation in the peripapillary area with extension toward the macula. Fluorescein angiography (bottom left) displays granular hyperfluorescence with focal leakage in the affected area. Indocyanine green angiography (bottom, middle) demonstrates dilated choroidal vessels and hyper-permeability in the peripapillary region (red arrow). OCT angiography of the choriocapillaris (bottom right) reveals flow deficits (red arrow) corresponding to areas of attenuated inner choroidal layers above pachyvessels.

the identification of novel biomarkers for disease progression and treatment response. Artificial intelligence and machine learning algorithms applied to multimodal imaging data hold promise for automated diagnosis, risk stratification, and prediction of disease outcomes. Additionally, advancements in wide-field and ultra-wide-field imaging technologies will likely expand our understanding of the peripheral retinal and choroidal changes in PSDs, potentially uncovering new aspects of disease pathophysiology. In terms of therapy, while photodynamic therapy (PDT) remains the gold standard for many PSDs, particularly central serous chorioretinopathy, future research should explore how multimodal imaging can guide more precise and individualized PDT treatments. The optimization of PDT parameters based on specific imaging biomarkers could enhance treatment efficacy while minimizing collateral damage. Moreover, as our understanding of choroidal venous outflow and intervortex anastomoses in PSDs deepens through advanced imaging, novel therapeutic approaches targeting these vascular alterations may emerge. The development of new imaging modalities, such as adaptive optics combined with OCTA, may provide unprecedented insights into the cellular-level changes in PSDs, potentially leading to breakthrough therapies. Ultimately, the future of PSD management lies in the seamless integration of multimodal imaging with emerging treatments, creating a paradigm of precision medicine that tailors interventions to the unique characteristics of each patient's disease manifestation.

CRedit authorship contribution statement

Pasquale Viggiano: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration,

Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Giacomo Boscia:** Writing – original draft, Formal analysis. **Elham Sadeghi:** Writing – original draft, Methodology, Investigation, Funding acquisition. **Gemmy Cheung:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Enrico Borrelli:** Validation, Supervision, Resources. **Giovanni Alessio:** Project administration, Investigation, Formal analysis. **Jay Chhablani:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Francesco Boscia:** Validation, Supervision, Software, Resources.

Declarations of interest

None.

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none.

Data availability

No data was used for the research described in the article.

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