Advancements in ophthalmic imaging for better understanding of pachychoroid spectrum diseases: perspective

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Abstract

Pachychoroid disease spectrum encompasses entities with pathogenesis of choroidal circulatory dysfunction. Advancements in ophthalmic imaging enables better understanding of its structural and functional implications. This perspective article covers clinical features, ocular imaging findings, and management options of pachychoroid spectrum diseases including central serous chorioretinopathy, pachychoroid pigment epitheliopathy, pachychoroid neovasculopathy, polypoidal choroidal vasculopathy or aneurysmal type 1 neovascularization, focal choroidal excavation, and peripapillary pachychoroid syndrome.

Key words: Central serous chorioretinopathy; Choroidal neovascularization; Computed tomography angiography; Fluorescein angiography; Tomography, optical coherence

Introduction

Pachychoroid disease spectrum comprises entities with pathogenesis of choroidal hyperpermeability, increased choroidal thickness, and attenuated inner choroidal layers.[1] The choroid is a vascular structure primarily supplying blood to the outer retina. It consists of the avascular Bruch's membrane, choriocapillaris, Sattler's layer, and Haller's layer.[2] The choroid is bounded by the Bruch's membrane anteriorly and the suprachoroidal layer posteriorly.[3] In normal eyes, choroidal thickness is the distance between the outer retinal pigment epithelium (RPE) and the choroidal-scleral interface.[4-6] In eyes with retinal pigment epithelial detachment (PED) or double-layer sign, the boundary of choroid starts from the Bruch's membrane instead of the outer RPE.[7] Advancements in optical coherence tomography (OCT), in particular enhanced-depth imaging OCT and swept-source OCT, enable quantitative analysis of choroidal thickness.[4,7] Subfoveal choroidal thickness of >300μm is considered a pachychoroid phenotype,[8] in which vasculature in the Haller's layer is dilated with relative thinning and compression of the overlying Sattler's layer and choriocapillaris.[9] The loss of choriocapillaris results in a local ischemic environment leading to overexpression of angiogenic factors with subsequent neovascularization.[10] Dilation of the Haller's layer may also induce mechanical damage to the overlying RPE and Bruch's membrane, resulting in invasion of pathological vessels through focal defects.[7,11]

Pachychoroid spectrum diseases can occur in eyes with normal choroidal thickness.[12] Venous overload choroidopathy is increasingly associated with various entities of venous decompensation in the choroid.[12] Increased venous pressure secondary to outflow obstruction or increased inflow may result in pathological venous wall dilatation and increased capillary hydrostatic pressure with

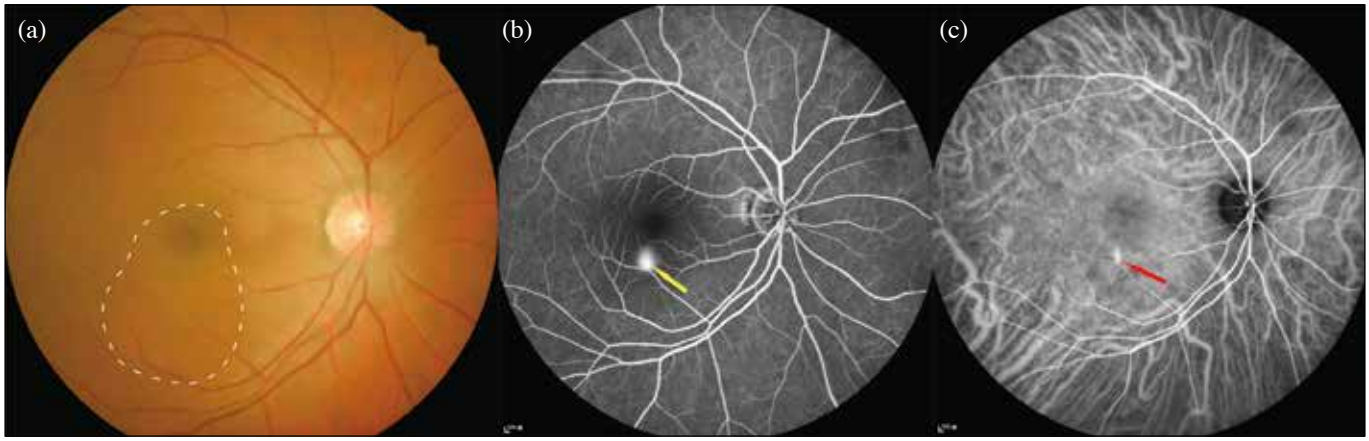

Figure 1. Central serous chorioretinopathy: (a) a fundus image showing the presence of subretinal fluid at the macular region (dashed line), (b) fluorescein angiography showing an inkblot leakage pattern (arrow), and (c) indocyanine green angiography showing hyperfluorescent areas of choroidal hyperpermeability (arrow) and dilatation of choroidal vasculature.

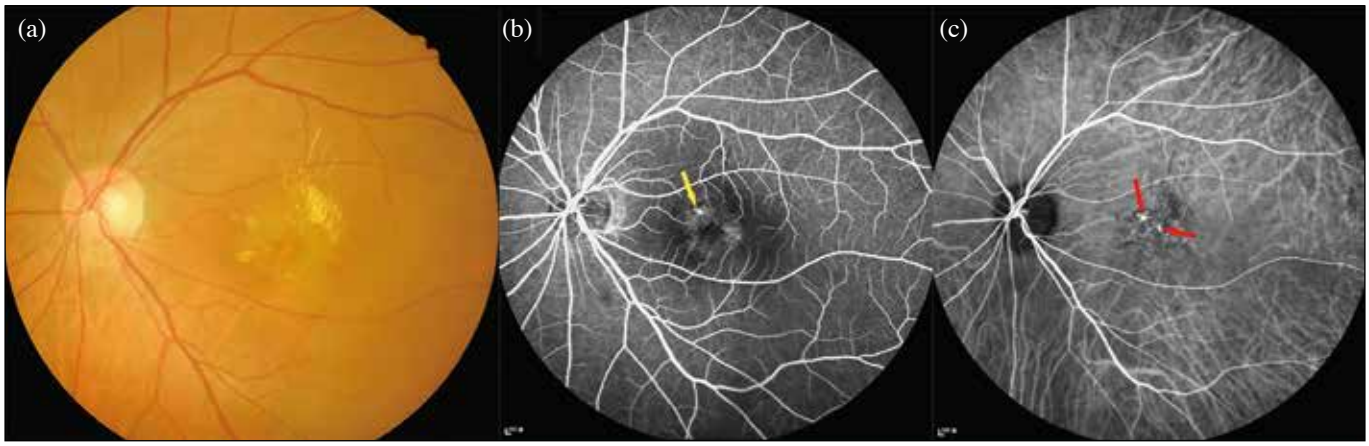

Figure 2. Polypoidal choroidal vasculopathy: (a) a fundus image showing subretinal fluid and hemorrhage with surrounding exudate, (b) fluorescein angiography showing the focal hyperfluorescent area (arrow) corresponding to (c) the region of polypoidal lesions (arrows) in indocyanine green angiography.

capillary leakage. Choroidal venous overload results in central serous chorioretinopathy (CSC) and peripapillary pachychoroid syndrome (PPS) akin to systemic chronic venous insufficiency in lower limbs, portal hypertension, and pulmonary vein varices.[12] Nonetheless, a thick choroid is not necessarily pathological, and choriocapillaris abnormalities may occur independent of choroidal thickness.[13] Ultra-widefield indocyanine green angiography (ICGA) enables identification of peripheral choroidal pathologies and their associations with macular abnormalities[7] as well as venous dilation along the entire course through the vortex vein ampulla.[14] OCT angiography enables detection of choriocapillaris signal void and vessel density for evaluation of choriocapillaris ischemia,[7] which may lead to secondary pathological neovascularization.

A classification system[4] is proposed for entities in the pachychoroid disease spectrum, which includes CSC, pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV), polypoidal choroidal vasculopathy (PCV) or aneurysmal type 1 neovascularization (AT1), focal choroidal excavation (FCE), and PPS (**Figures 1-4**). These entities are caused by choroidal dysfunction. Although there are overlapping features and progression from one entity to another, their manifestations are mutually exclusive.[1,4] Pachychoroid diseases are caused by chronic vortex vein stasis. Anastomoses can form between the vortex veins at the watershed zone to compensate for the stasis. These anastomotic vessels, known as pachyvessels, demonstrate dilation and hyperpermeability.[15] Vortex vein stasis results in choriocapillaris filling delay, which leads to occlusion of the choriocapillaris.[12] Choroidal neovascularization may arise at the site of the pachyvessels, in response to the ischemia.

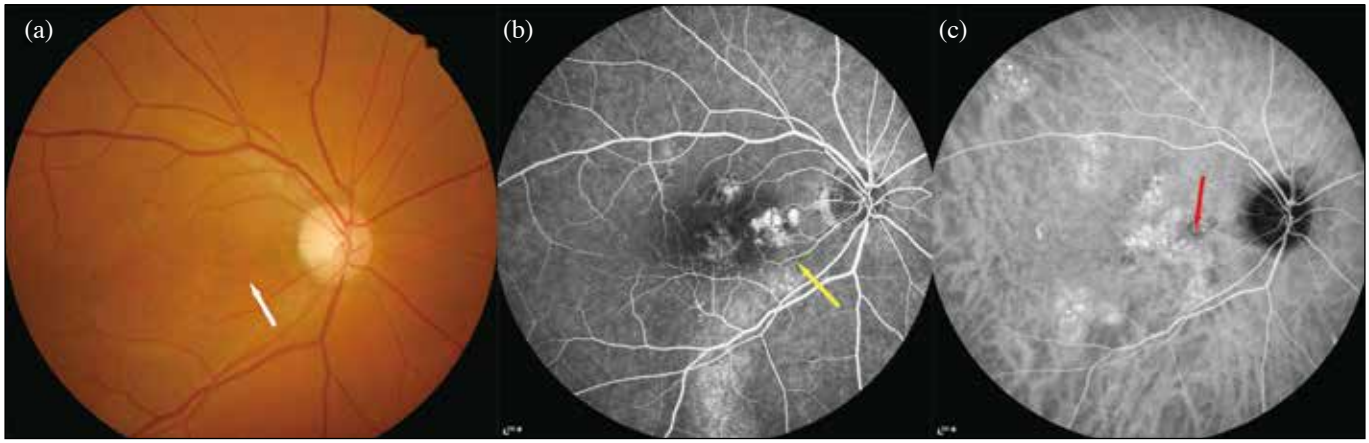

Figure 3. Peripapillary pachychoroid syndrome: (a) a fundus image showing subretinal fluid with associated mottled appearance in the retinal pigment epithelium (arrow), (b) fluorescein angiography showing multifocal hyperfluorescence and gravitational track near the optic disc (arrow), and (c) indocyanine green angiography showing pachyvessels and choroidal vascular hyperpermeability (arrow) around the optic nerve.

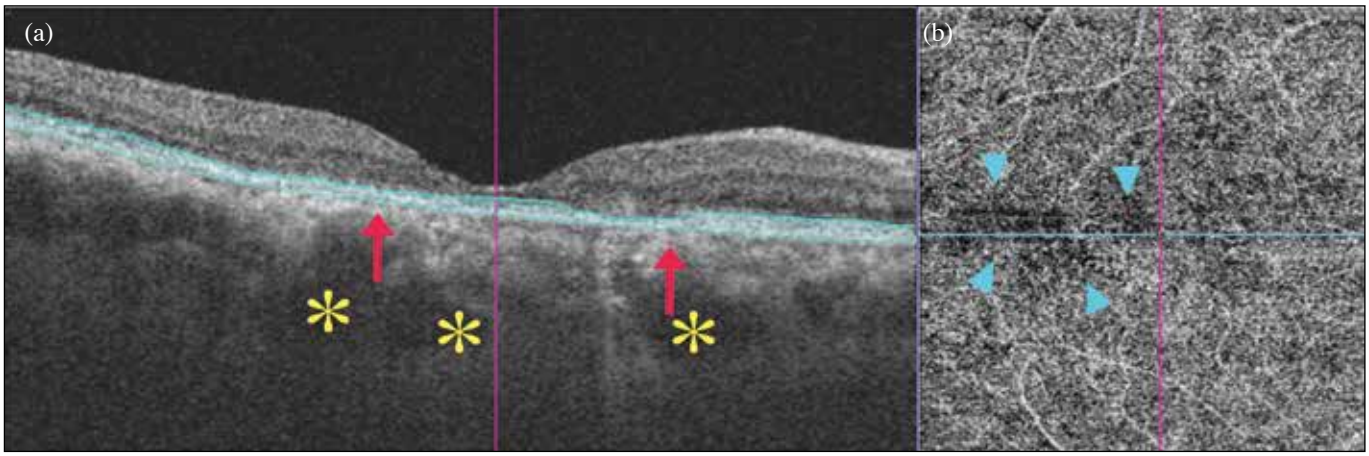

Figure 4. Chronic central serous chorioretinopathy: (a) swept-source optical coherence tomography showing pachyvessels as larger hyporeflective lumen (asterisks) and obliteration of overlying Sattler's layer and choriocapillaris (arrows). The dilated choroidal vessel from the deep layer (left arrow) appears to anteriorly impinge on the choriocapillaris layer, with the most significant flow deficit in the juxtafoveal region. The blue lines are segmentation lines that encompass the choriocapillaris just below the retinal pigment epithelium. (b) Optical coherence tomography angiography showing attenuation of flow signal within the choriocapillaris (arrowheads). Any overlying lesions on the retinal pigment epithelium such as drusen and pigment epithelial detachment may cast shadow artifact on the choriocapillaris. Blood vessels from the retina capillary plexus are superficial to the choriocapillaris secondary to projection artifact. Blood vessels situated in the choriocapillaris are normally in honeycomb configuration.

Central serous chorioretinopathy

As a prototypic disease of the pachychoroid spectrum, acute CSC is characterized by serous detachment of neurosensory retina with or without serous retinal PED.[1,16] Chronic CSC is defined as disease duration of >6 months or presence of atrophic changes in the outer retina and RPE.[4,17] A descending gravitational tract of RPE hypopigmentation may be visualized clinically or on fundus autofluorescence. Fundus fluorescein angiography typically shows an inkblot or smokestack pattern of leakage in acute CSC,[18] and multiple indistinct leaks within window defects in chronic CSC.[4] ICGA typically shows multifocal hyperfluorescent areas of choroidal hyperpermeability, dilatation of choroidal vasculature, and delayed choroidal filling.[4] The areas of hyperfluorescence are usually more extensive on ICGA than on fundus fluorescein angiography.[17] OCT (in particular enhanced-depth imaging OCT and swept-source OCT) is an invaluable tool to visualize the abnormally thickened choroid and the extent of subretinal fluid. Acute CSC typically shows well-defined areas of serous retinal detachment and PEDs, whereas chronic CSC typically shows shallow and broad subretinal fluid, intraretinal cystoid changes, subretinal hyper-reflectivities, and outer retinal atrophy.[4,16,17] The Central Serous Chorioretinopathy

International Group classifies CSC into simple and complex depending on the extent of involvement, disease course, anatomical alterations, and presence of complications.[19]

Most acute CSC resolve spontaneously; treatment is usually reserved for chronic or visually disabling CSC. The treatment goal is to maintain complete subretinal fluid resolution and avoid irreversible damage to the photoreceptors.[17,20] Photodynamic therapy (PDT) and subthreshold micropulse laser are the mainstay of treatment.[1,4,17] Half-dose or half-fluence PDTs are preferred owing to reduced risk of angiographic closure and systemic adverse effects.[17] In the PLACE trial, half-dose PDT is superior to high-density subthreshold micropulse laser treatment in patients with chronic CSC after 7 to 8 months of treatment. A significantly higher proportion of patients achieves complete resolution of subretinal fluid (67% vs 29%) and significantly more improvement in retinal sensitivity on microperimetry (3.2 vs 1.4 dB).[21] PDT is more effective in reducing choroidal vascular hyperpermeability and choroidal thickness than micropulse laser treatment.[4] Mineralocorticoid antagonists such as eplerenone and spironolactone have also been used to treat symptomatic CSC,[22] but no significant benefits of eplerenone are found compared with placebo.[23] Risk factors associated with CSC include corticosteroid usage, Cushing's syndrome, and psychological stress.[17] Creation of scleral windows and vortex vein decompression for treating the underlying choroidal venous overload should be reserved for recalcitrant CSC.[12]

Pachychoroid pigment epitheliopathy

PPE is considered to be 'forme fruste' of CSC,[4] but the natural course of eyes with PPE is highly variable and may remain stable for years. The presence of pachydrusen, which is scattered or isolated yellow white sub-RPE lesions of >125 μm in a thickened choroid, is predictive of disease progression.[24] Clinical features of PPE include focal RPE mottling and drusenoid RPE elevation over regions of choroidal thickening.[9] Subretinal fluid or exudation is typically absent. Patients with PPE may be misdiagnosed as having dry age-related macular degeneration, but patients with PPE are usually younger and absent of soft drusen. OCT features of PPE include RPE elevation and sub-RPE drusenoid deposit, with a thickened choroid directly underneath the RPE changes.[9] Small serous PEDs are occasionally present.[1] Fundus autofluorescence typically shows mixed stippled hyper- and hypo-autofluorescence. Choroidal hyperpermeability in the distribution of pigment epitheliopathy is well demonstrated with ICGA.[4] As most patients are asymptomatic, regular monitoring for any progression to symptomatic pachychoroid diseases such as CSC, PNV, and PCV is needed.[25]

Pachychoroid neovasculopathy

PNV refers to choroidal neovascularization in eyes with thick choroid.[26] It is considered a late complication of PPE or chronic CSC.[1] The presence of neovascularization is confirmed by fundus fluorescein angiography, typically in the form of late leakage, with plaque-like hyperfluorescence on ICGA.[4] Dilated choroidal vasculature and choroidal hyperpermeability in late phases of ICGA differentiates PNV from other causes of choroidal neovascularization including myopic degeneration and posterior segment inflammation.[10] OCT features of PNV include shallow irregular separation of RPE from Bruch's membrane (also known as double layer sign), hyper-reflective materials in the sub-RPE space (denoting area of neovascularization), and development of small peaked PEDs near the lesion.[4,27] Diagnosis of PNV can be made by OCT angiography, which readily identifies a tangled network of flow signal between the RPE and Bruch's membrane resembling the area of neovascularization.[28,29] Treatment options for PNV include intravitreal injection of anti-vascular endothelial growth factors (anti-VEGF), PDT, and a combination of both.[30-33] Although there are studies evaluating treatment efficacy of PNV,[34-37] randomized controlled studies to identify the optimal treatment regimen are limited.[30,37] Intravitreal injection of anti-VEGF is the usual treatment for PNV.[38] PNV requires a fewer number of injections than neovascular age-related macular degeneration, with longer treatment-free period of up to 36 months.[39,40] PDT of various dosage and fluence is effective on improving visual acuity, central macular thickness, and choroidal thickness.[26,30] PDT enables fluid absorption in patients non-responsive to anti-VEGF.[38]

Polypoidal choroidal vasculopathy or aneurysmal type 1 neovascularization

PCV is characterized by nodular dilatation of choroidal vessels and is a variant of type 1 macular neovascularization, which accounts for up to 50% of neovascular age-related macular degeneration cases in Asia.[41] PCV is increasingly known as AT1, which more accurately describes its vascular nature.[1,41] PCV/AT1 typically presents with a serosanguineous exudative maculopathy along with intraretinal/subretinal fluid and serous or fibrovascular PEDs.[42] Sudden vision loss may occur secondary to spontaneous rupture of polypoidal lesions, followed by submacular hemorrhage or breakthrough vitreous hemorrhage.[1] Its diagnosis is based on the EVEREST criteria and the Japanese Study Group Guideline,[42,43] in which ICGA is the gold standard and typically shows focal hyperfluorescent polypoidal lesions in early phases with or without branching vascular network.[42] Fundus fluorescein angiography is of limited use owing to inability to visualize sub-RPE structures,[42] but it may be used to detect and monitor leakage from pathological choroidal vessels. For non-ICGA diagnostic criteria,[41] OCT is commonly used owing to its accessibility and non-invasive nature. Swept-source OCT typically shows sub-RPE ring-like lesions, sharp-peaked PEDs, double-layer sign, and complex RPE elevations,[41,42] as well as thickening of the choroidal layer with dilated Haller's vessels (as opposed to choroidal thinning that is more typical of neovascular age-related macular degeneration).[4,41] Together with subretinal or sub-RPE hemorrhage and orange nodules on clinical examination or on color fundus photograph, PCV/AT1 can be detected independent of angiogram with high accuracy.[41] OCT angiography usually shows flow signals indicating type 1 macular neovascularization, but the detection rate of

OCT angiography for polypoidal lesions is lower than that of ICGA.[44,45]

The treatment goal for PCV/AT1 is to preserve vision and achieve polyp closure.[1] Focal laser has variable efficacy and a higher risk of adverse effects, and its use is thus limited to extrafoveal polyps or when other treatment options are not available. PDT and anti-VEGF treatment achieve significant visual gain and reduction in disease activity.[1,41,42] In the EVEREST-II trial, compared with ranibizumab alone, combination of PDT and ranibizumab achieves greater improvement in best-corrected visual acuity (8.3 vs 5.1 letters), higher polyp closure (69.3% vs 34.7%), and fewer number of injections (5.2 vs 7.3).[46] With the previous global suspension of verteporfin supply, anti-VEGF monotherapy is increasingly used. In the PLANET study involving eyes with PCV/AT1 treated with intravitreal injection of aflibercept with and without PDT, >85% of patients have improvement in visual function and >80% of patients have no signs of leakage from polypoidal lesions after aflibercept monotherapy.[47] The mean visual acuity improvement and polyp closure rate are similar between the two groups. The functional and anatomical improvements at 52 weeks are maintained up to 96 weeks.[48] However, aflibercept monotherapy usually results in a lower polyp closure rate and requires a higher number of anti-VEGF injections.[42]

Heterogeneity is high among patients with PCV/AT1 and thus variations in treatment responses are expected.[49] Differences in baseline ocular characteristics such as choroidal vascular hyperpermeability and choroidal thickness affect treatment response.[25] Future research to identify clinical and imaging biomarkers may provide guidance on the optimal management for PCV/AT1.[49]

Focal choroidal excavation

FCE is a localized choroidal concavity without posterior staphyloma or scleral ectasia occurring in patients with no secondary cause of choroidal thinning identified.[4,50] FCE is usually unilateral and more common in myopic eyes.[51] Most patients are asymptomatic, but mild blurring of vision or metamorphopsia is sometimes reported.[4] Fundus examination may appear normal or show indistinct pigmentary RPE changes in the affected area.[50] In conforming FCE, the photoreceptor tips and RPE are in direct contact, whereas in non-conforming FCE the photoreceptor tips are detached from the underlying RPE, with a hyporeflective space representing subretinal fluid.[50] OCT is the preferred diagnostic imaging modality, as it can show abrupt changes of choroidal thickness and poorly defined choroidal-scleral interface beneath the FCE.[4] Fundus fluorescein angiography shows hyperfluorescence in mid or late phase corresponding to transmission defects associated with RPE atrophy. Leakage is absent unless it is complicated by choroidal neovascularization or CSC.[4] ICGA shows filling defect in early phase and punctate hyperfluorescence in late phase.[51] Most eyes have a relatively stable clinical course, and conservative management should suffice. However, FCE can be associated with CSC, PCV, and secondary choroidal neovascularization.[4,52,53] Treatment with anti-VEGF and/or PDT may be beneficial for these conditions.[51]

Peripapillary pachychoroid syndrome

In PPS, maximal choroidal thickness occurs close to the optic nerve head rather than subfoveally.[4,54] Intervortex venous anastomoses and venous overload are found in the peripapillary region.[12] Hypermetropic eyes with short axial length and crowded discs are commonly affected.[54] Clinical features of PPS include intraretinal/subretinal fluid in the nasal macula and peripapillary region, optic nerve head edema, and chorioretinal folds.[4,51] Fundus autofluorescence shows mottled hypoautofluorescence and occasionally gravitational tracks in the peripapillary area, especially in chronic cases.[1,4] ICGA shows pachyvessels and choroidal hyperpermeability around the optic nerve, which can distinguish PPS from uveal effusion syndrome.[54] Fundus fluorescein angiography shows speckled hyperfluorescent window defects and staining typically in area between the optic disc and fovea. Disc leakage is sometimes present. Treatments for PPS include anti-VEGF injection, PDT, and use of topical and oral carbonic anhydrase inhibitors, but treatment responses vary.[1,54] In a multicenter study, PDT significantly decreases both subretinal fluid height and central macular thickness and improves visual acuity after 3 months.[55] However, in another multicenter study with a mean follow-up of 27 months, no significant visual improvement is found in patients with PPS treated with anti-VEGF injection or PDT, despite a decrease in retinal edema and choroidal thickening.[56]

Conclusion

Advancements in enhanced-depth imaging OCT, swept-source OCT, OCT angiography, and ultra-widefield ICGA enable better understanding of the pachychoroid disease spectrum by demonstrating choroidal circulatory dysfunction. Recognition of the pachychoroid state is essential for disease prognostication and management guidance. Treatment is recommended for those with symptomatic conditions and at risk of vision loss such as chronic or complex CSC, PVN, and PCV/AT1. Management options include conventional or subthreshold micropulse laser treatment, PDT, and intravitreal injection of anti-VEGF. Treatment responses vary across different clinical entities. Further studies are warranted to determine factors associated with various pachychoroid states and transition from quiescent entities to neovascular forms of PCV/AT1.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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