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REVIEW

Current concepts in pachychoroid spectrum diseases: insights into the pathophysiology

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Abstract

The pachychoroid spectrum defines a group of diseases in which focal or diffuse thickness increase in the choroid layer is accompanied by dilated outer choroidal vessels and structural changes in the inner choroidal layers associated with it. This spectrum of diseases includes pachychoroid pigment epitheliopathy, central serous chorioretinopathy, pachychoroid neovascularopathy, polypoidal choroidal vasculopathy, focal choroidal excavation, peripapillary pachychoroid syndrome, and pachydrusen. Although these diseases have similar pachychoroid features, they have different clinical prognosis, ranging from a completely asymptomatic course to a very resistant clinical situation. The aim of this review is to summarize the current definition, underlying etiopathogenesis, examination findings, imaging features, differential diagnoses, and treatment approaches in light of current literature.

Keywords: Central serous chorioretinopathy; Pachychoroid neovascularopathy; Pachychoroid pigment epitheliopathy; Polypoidal choroidal vasculopathy.

The word “pachy” in Greek refers to “thick” and therefore “pachychoroid” literally means thick choroid. The choroid is a primarily vascular tissue with 3 layers found between the sclera and the retina, responsible for blood supply to the outer retina. These layers according to its proximity to Bruch’s membrane are, the choriocapillaris layer, the Sattler layer, which is observed as small oval vascular structures, and the Haller layer, which is the outermost large vascular structure.

The term “pachychoroid” was introduced by Warrow et al. in 2013, describing a group of macular diseases that presented a thick choroid.^[1] The definition of pachychoroid

and pachychoroid disease was introduced to describe a group of diseases characterized by a focal or diffuse increase in choroidal thickness and increased permeability of the choroidal vessels. It is a relatively new definition that refers to diseases with common phenotypic features such as thinning of the choriocapillaris and Sattler’s layer above these pachyvessels (dilated choroidal vessels) in the Haller layer, also associated retinal pigment epithelium (RPE) abnormalities and choroidal neovascularizations (CNVs). This spectrum of diseases includes pachychoroid pigment epitheliopathy (PPE), central serous chorioretinopathy (CSC), pachychoroid neovascularopathy (PNV), polypoidal



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choroidal vasculopathy (PCV), focal choroidal excavation (FCE), peripapillary pachychoroid syndrome (PPS), and pachydrusen.^[1-6]

The mechanism of development of pachychoroid disorders has not yet been clearly elucidated. The most commonly proposed mechanism is dilatation of the large choroidal vessels and increased choroidal permeability.^[7] Later, atrophy occurs in the overlying choriocapillaris and Sattler layers due to increased choroidal hydrostatic pressure. The increased sympathetic activity was also proposed as a possible mechanism of CSC.^[8,9]

AMD-susceptibility genes were evaluated for their associations with PNV development, and found most risk alleles for AMD in ARMS2 and CFH genes also contributed to the development of PNV. The risk allele frequencies of CFH and ARMS2/HTRA1 were highest in neovascular AMD, slightly lower in PNV, and significantly lower in normal controls, which suggests that the genetic characteristics of PNV stand between AMD and normal controls.^[10,11]

Recent technical improvements in ophthalmic imaging especially the optical coherence tomography (OCT) have led to the identification and understanding of etiopathogenesis of many chorioretinal diseases. With the discovery of enhanced depth imaging (EDI) and subsequent use of swept source OCT, the choroid has become more clearly visualized and these developments have allowed for qualitative and quantitative measurements of choroid. With the manual ruler of OCT devices, the thickness of the choroidal layer in the center of the macula and at different distances can be measured. More recently, software based on binarized OCT has been developed to quantify the ratio between the choroidal vascular luminal area to total choroidal area (choroidal vasculature index [CVI]), potentially representing a useful imaging biomarker for choroidal diseases.^[12] In pachychoroid disorders, CVI is found high both in diseased eyes and fellow eyes.^[13,14]

With the introduction of ultra-wide-field indocyanine green angiography (ICGA) into clinical use, vortex vessels have become better visualized. Recent publications suggest that intervortex congestion and anastomosis may be the keystones in the pathophysiology of poststroke depression (PSD) and the frequency of veno-venous intervortex anastomoses is increased in PSD.^[15]

The choroidal blood empties through the vortex vein systems in a quadratic fashion. In each quadrant, the vortex veins course toward the vortex vein ampulla and exit the eye near the equator independently and there is a watershed zone between them. The vortex vein penetrates

sclera obliquely and actually pass 4 mm through it.^[16] A thick sclera cause an obstruction to venous passage through it and affected vortex veins showing dilatation and hyperpermeability, converging to the dilated ampulla suggesting stasis of the vortex veins. Dilated vortex veins under the fovea seem to contribute to the choroidal thickening noted in the PSD. In eyes with PSD, venous engorgement, increased venous pressure, and venous outflow impediment from the choroid leading the remodeling of choroidal drainage routes. Remodeling of the vortex veins due to the long-standing asymmetric congestion of the choroid during the progression of PSD has been suggested as the cause of the development of anastomosis.^[15] Intervortex vein anastomosis was observed in 90.2% of eyes with CSC, 95.1% of eyes with PNV, and 100% of eyes with PCV.^[17]

PPE

It is a relatively newly defined entity with characteristic imaging features observed in the macula. PPE refers to a usually asymptomatic condition characterized by RPE changes and choroidal thickening. It differs from CSC by the absence of detectable subretinal fluid, despite the presence of irregularities in the RPE. It is also called the “*formae frustae*” form of the CSC. It is a finding that is usually seen in the other asymptomatic eyes of the eyes with CSC.^[18] These patients may progress to CSC over time or can develop type 1 neovascularization, so constant evaluation of these patients is suggested.

Fundus examination often reveals the loss of fundus mosaicism and a red diffuse posterior pole appearance due to the pachychoroid feature. RPE changes are often found in the macula and sub-RPE deposits described as pachydrusen may underlie these changes. Pachydrusen may be confused with AMD, pattern dystrophy, or inflammatory lesions involving the RPE, however pachydrusen formation is more scattered and ovoid in nature, unlike cluster-shaped drusen seen in AMD. In contrast to AMD, PPE patients are relatively young, and the pachydrusen are usually in extrafoveal location. Typical OCT finding is characterized by RPE changes, which are often localized on the compressed choriocapillaris on pachyvessels (Fig. 1a-c). The choriocapillaris and Sattler layers can be completely disappeared on OCT sections due to the compression of the dilated large vessel in the underlying Haller layer, and the pachyvessels and Bruch's membrane contact directly with each other. In ICGA studies, mid-phase hyperfluorescence caused by large choroidal vessels in this area and increased choroidal permeability were identified in 91.7% of the cases.^[19] Typ-

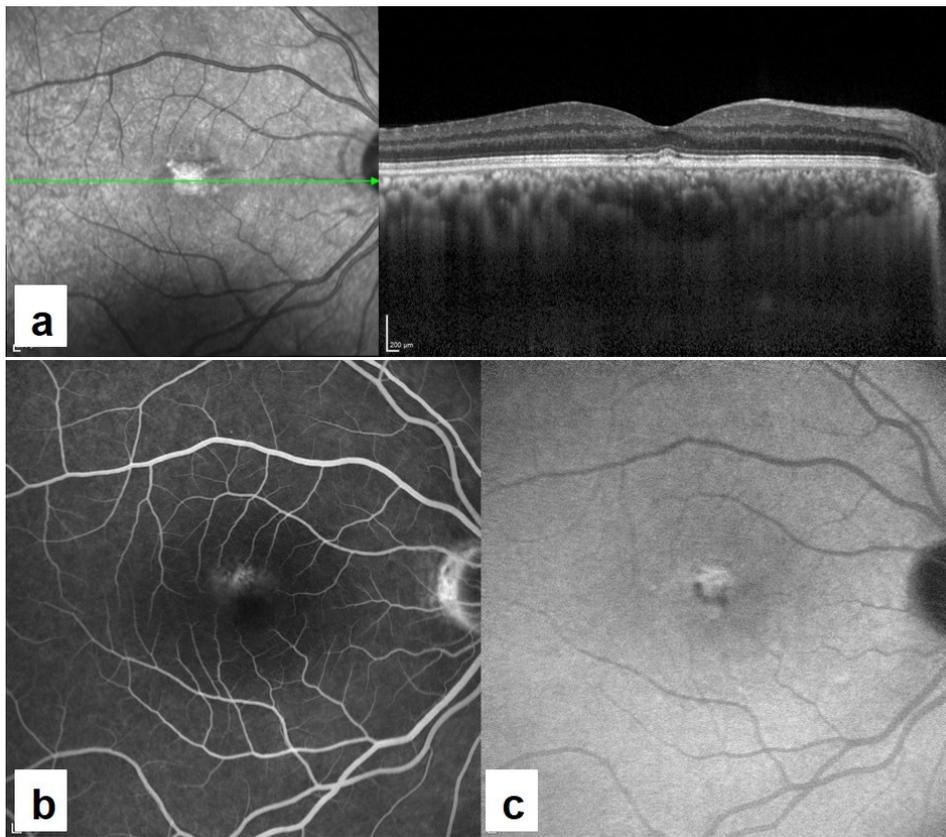


Fig. 1. Multimodal fundus images of a patient with pachychoroid pigment epitheliopathy: (a) Increased choroidal thickness, dilated Haller vessels, and central retina pigment epithelium irregularities on enhanced depth imaging optical coherence tomography. (b) Hyperfluorescence due to retina pigment epithelium alterations observed in fundus fluorescein angiography. (c) Hyperfluorescence due to increased permeability caused by large choroidal vessels in the mid-phase of indocyanine green angiography.

ical pachychoroid features are present, and mottled areas of both hypoautofluorescence and hyperautofluorescence in fundus autofluorescence (FAF) imaging can be seen within sites of RPE changes. Signs of previous subretinal fluid, such as gravitational tracks, are not described in PPE. In one study, the outer nuclear layer thickness in eyes with PPE was thinner than in eyes with uncomplicated pachychoroid, suggesting that photoreceptor and/or RPE degeneration may occur even in the absence of subretinal fluid.^[20] A recent study also reported that choriocapillaris density was strongly reduced in the area of choroidal hyperpermeability, highlighting compression over the choriocapillaris layer.^[21] Karacorlu et al. evaluated 46 eyes with PPE at least 3 years of follow-up and found that 17.4% of the eyes developed long-term CSC, and they did not find any PNV or PCV conversion of these eyes.^[22] Similarly, choriocapillaris perfusion was found to be lower in CSC patients compared to uncomplicated pachychoroid patients accordingly, CSC may be the long-term advanced stage of PPE or uncompli-

cated pachychoroid cases.^[23]

PPS

PPS is a new entity described by Phasukkijwatana et al.^[5] The choroidal thickness reaches its maximum thickness in the area close to the optic disc rather than in the subfoveal area. These patients are characterized by subretinal fluid, intraretinal cyst, and rarely optic disc edema, which often develops in the temporal region of the optic disc. Hyperopia, short axial length, and choroidal folds are other conditions that associated with PPS.^[5] Hyperautofluorescent gravitational tracks of pigmentary abnormalities of chronic fluid localized to the peripapillary area because of gravity on either FFA or FAF can be illustrated.^[24] ICGA illustrates peripapillary dilated choroidal vessels with multifocal hyperpermeability.^[24]

Clinical findings in PPS can have similarities with uveal effusion syndrome (UES). Gravitational tracks of RPE alterations are more common in PPS, in contrast to the leopard-spot pigmentary pattern of UES.^[25] To make this diagnosis, in-

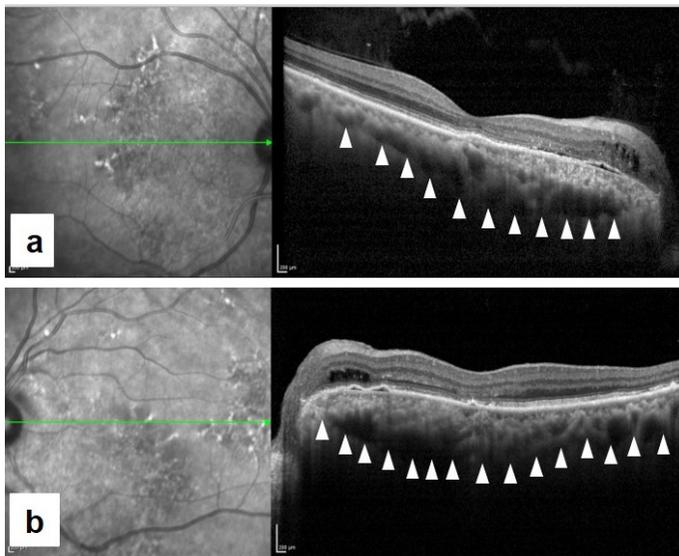


Fig. 2. Optical coherence tomography images of a case with peripapillary pachychoroid syndrome in both eyes: (a and b) Increasing choroidal thickness from temporal to nasal in both eyes (arrowhead) and dilated Haller veins on enhanced depth imaging optical coherence tomography.

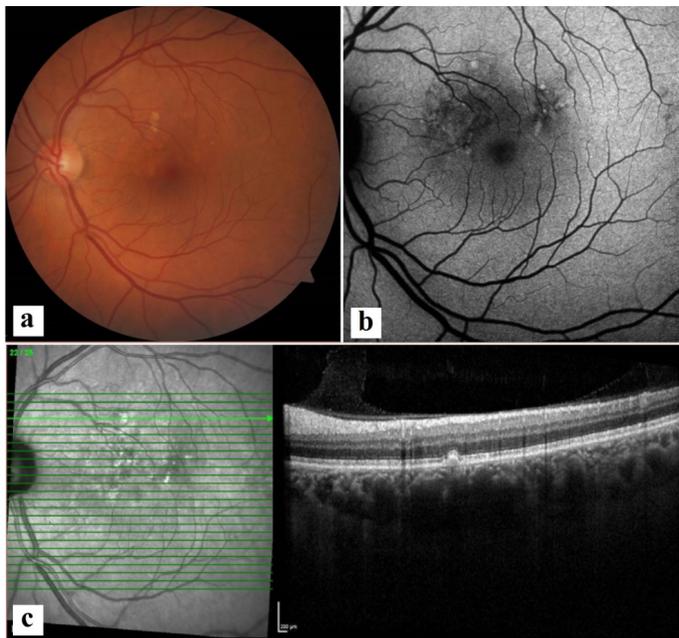


Fig. 3. Multimodal fundus images of a patient with pachydrusen: (a) Yellowish deposits with well-defined boundary at the supero-temporal region macula on color fundus photography (b) In fundus autofluorescence image, hyperfluorescent spots corresponding to yellowish drusen (c) Increased choroidal thickness, dilated Haller vessels, and a drusenoid deposit on enhanced depth imaging optical coherence tomography.

inflammatory eye diseases also must be excluded (Fig. 2a-b).

PACHYDRUSEN

The term “pachydrusen” was introduced by Spaide to de-

scribe pachychoroid-associated drusen to describe drusenoid lesions, large size of $>125\mu\text{m}$ and solitary, in the context of a thickened choroid and distinct from the typical soft drusen of AMD. Pachydrusen is confirmed to be located in the posterior pole, beneath the RPE, and described as isolated or scattered yellow-white deposits with well-defined boundary. Pachydrusen is found to be associated with increased central choroid thickness (CCT) (Fig. 3a-c).

The prevalence of pachydrusen is 41.67% in PPE, 60% in CSC, 61.1% in PNV, and 70% in the treatment-naive PCV. [4,26,27] Sheth et al. declared that pachydrusens give rise to long-standing damage to the RPE and underlying Bruch's membrane and the presence of pachydrusen is defined as a potential risk factor for the disease activity in PSD, namely leak in eyes with PPE and CSC, development of polyps/branching vascular network in PCV eye and type 1 CNV in PNV and PCV.[27]

Sato-akushichi et al. reported the prevalence of pachydrusen was 7.7% among the individuals aged 40 and over and 10% among the individuals aged 70 and over in the Japanese population. Pachydrusen was also reported more prevalent than soft drusen and pseudodrusen combined in the same population. The study indicated that 3.7% of pachydrusen progressed within 5 years, whereas 5.5% of pachydrusen regressed without photographically detectable signs of atrophy. Moreover, no RPE atrophy was observed after the regression of pachydrusen. In contrast to Sheth et al., Sato-akushichi et al. speculated that pachydrusen do not seem to affect RPE directly and may have little pathologic significance on macular diseases.[28]

FCE

FCE is an imaging finding that describes the localized excavation of choroidal tissue towards the sclera, observed in the absence of a disease-causing thinning of the sclera (posterior staphyloma).[29] Most cases are asymptomatic and fundus examination may reveal non-specific RPE changes or a yellow spot. OCT is the imaging method that best describes this situation. There are two subtypes according to OCT findings; in the conforming type of the photoreceptor tips are in direct contact with the RPE, in the non-conforming type, the photoreceptor ends are separated from the RPE below it with an intermittent hyporeflective cleft. Margolis et al. hypothesized that, initially, retinal elasticity facilitates the maintenance of the conforming FCE, but due to persistent stress on the outer retina, it transitions into the nonconforming type with enlarged choroidal excavation.[3] Nonconforming type FCE is like an inverse RPE detachment; it compresses the choriocapillaris and further

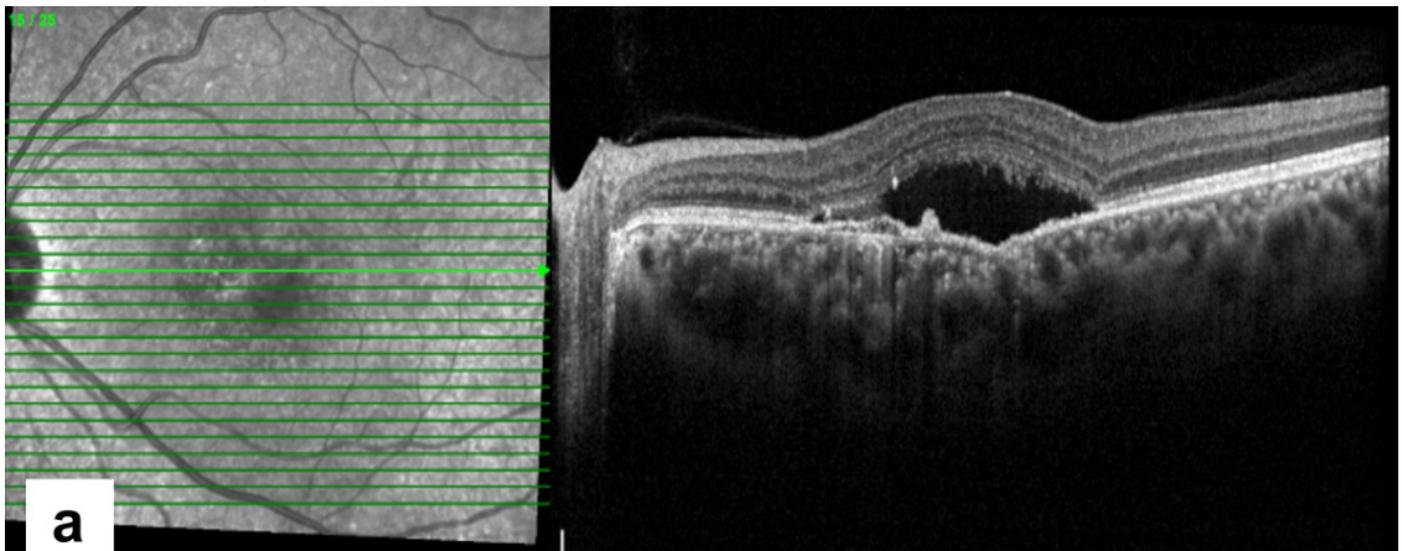


Fig. 4. Enhanced depth imaging optical coherence tomography of focal choroidal excavation (FCE) in the left eye of a patient with central serous chorioretinopathy who was using long-term systemic corticosteroid therapy for renal transplantation: (a) On optical coherence tomography subretinal fluid, FCE in subfoveal location, shallow pigment epithelium detachment localized nasally, and also thick choroid and dilated Haller veins.

exacerbates choroidal ischemia. This leads to further focal RPE/Bruch's membrane complex injury, increasing the predisposition to CSC or CNV.^[30]

Hyperfluorescent window defects can be seen in FFA depending on the condition of the RPE on it. In ICGA, a hypofluorescent area may be observed showing choriocapillaris atrophy (Fig. 4). FCE has been reported in pachychoroid cases with increased subfoveal choroidal thickness and hyperpermeability in ICGA. The localization of choroidal hyperpermeability in or near the choroidal hyperpermeability area in ICGA, and the presence of this finding in both the patient eye and the other eye in the CSC and PCV case series suggested that FCE is a pachychoroid-related condition.^[6,31] FCE leads to atrophy of the overlying RPE and subsequent pump dysfunction, and CSC occurs as a complication.^[32] It has also been proposed that CNV and PCV are both the result of choroidal ischemia in areas of anatomic anomalies.^[33]

CSC

CSC is characterized by RPE changes, serous PEDs, and subretinal fluid and tends to occur unilaterally in young to middle-aged men. As age increases, gender predilection disappears, and the disease tends to show a more bilateral involvement. The acute and chronic form of the disease has been described. While the first attack regresses spontaneously 80% of the time, it can become chronic in the remaining cases. Even if the first attack regresses, the recurrence rate is around 50%. Acute CSC is the most common form of presentation and manifests as localized neurosen-

sory retinal detachment often regresses spontaneously and heals with minimal sequelae (Fig. 5), while the chronic form is often associated with long-term persistence of fluid (more than 6 months), cystoid macular degeneration, sec-

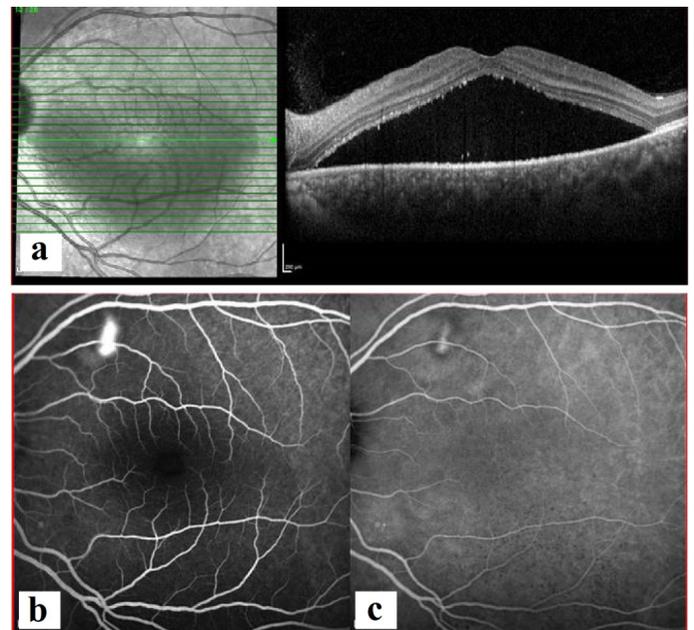


Fig. 5. Optical coherence tomography and angiography images of a case with acute central serous chorioretinopathy: (a) Large neurosensory detachment with subretinal fluid on enhanced depth imaging optical coherence tomography passing through fovea (b and c) Simultaneous fundus fluorescein angiography and indocyanine green angiography (ICGA) showing the smokestack configuration. The leak in ICGA is smaller in size as compared to fundus fluorescein angiography. Areas of choroidal hyperpermeability are seen in ICGA along the vascular arcades.

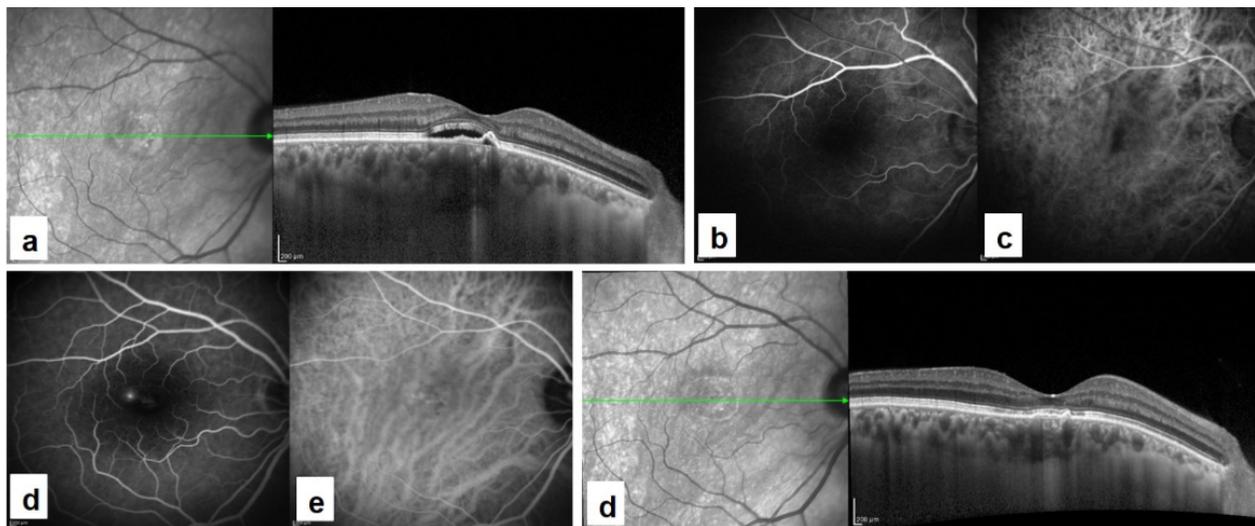


Fig. 6. Multimodal fundus images of a patient who underwent half-fluence photodynamic therapy in his right eye for chronic central serous chorioretinopathy. Before treatment: (a) Subretinal fluid, shallow irregular pigment epithelium detachment, increased choroidal thickness and dilated choroidal vessels on enhanced depth imaging (EDI) optical coherence tomography. (b) No leakage in early fundus fluorescein angiography. (c) Dilated choroidal vessels in early indocyanine green angiography (ICGA). (d) Point focus of leakage on late fundus fluorescein angiography. (e) Increased central permeability in late ICGA. After treatment: (f) Complete disappearance of subretinal fluid on EDI optical coherence tomography.

ondary CNV and RPE atrophies and defined as the form in which permanent vision loss can develop.^[34]

Fundus examinations reveal serous macular detachment and diffuse RPE irregularities in chronic cases. OCT imaging can demonstrate attenuation of the outer retinal layers (related to chronic subretinal fluid) and defects in the external limiting membrane. Descending tract and mottled hyperautofluorescent areas are observed in FAF imaging. Delayed arterial filling and subsequent capillary and venous hyperemia manifest as capillary and venous congestion are frequently seen in eyes with CSC. These findings suggest that capillary or venous congestion after ischemia in one or more choroidal lobes may be the cause of CSC-related choroidal hyperpermeability. CSC is now proposed as a disease characterized by congestion in the distal vortex vein that developed in eyes with asymmetric vortex veins. Kishi and coworkers evaluated the correlation between the areas of filling delay in early-phase ICG angiography and the regions of dilated vortex veins in en-face OCT imaging and found there was a significant co-localization.^[35]

In FFA, hyperfluorescence in the form of window defect due to RPE atrophy, and in acute cases leaky foci from the RPE are observed. The enlargement of the leaky area in the later stages of angiography is a typical finding. In ICGA, dilated choroidal vessels in the macular region are observed and in mid phases, patchy areas of choroidal hyperpermeability are revealed. OCT angiography (OCTA) is especially important in detecting the development of secondary CNV.

The differential diagnosis of CSC includes vascular diseases of the choroid, inflammatory diseases (Vogt-Koyanagi-Harada, posterior scleritis), and anatomical anomalies such as an optic pit or dome-shaped maculopathy.

Although treatment options such as risk factor modifications, medical treatments, and anti-vascular endothelial growth factor (VEGF) injections are discussed, the strong benefits of these options have not been proven yet. Mineralocorticoid antagonists, which have been emphasized recently, are not found superior to placebo in a multicenter randomized study.^[36] Although applying laser photocoagulation to the focal points maintains its historical importance, the possibility of secondary CNV development in the laser field and its inability to apply it to leaky foci near the fovea makes it far from being an ideal treatment.

Two treatment modalities which are agreed on their efficacy in the treatment of chronic CSC are sub-threshold micropulse laser and half-dose or half-fluence photodynamic therapy (PDT). PDT increases the resorption of subretinal fluid by decreasing choroidal hyperpermeability.^[37-41] However, serious potential complications are reported such as choroidal ischemia, RPE atrophy, or development of iatrogenic CNV, hence new treatment protocols such as half dose or low fluence have been developed to prevent these complications.^[37,42-44] Modified photodynamic therapy (PDT) protocols are effective in the treatment and safe for complications (Fig. 6a-f).^[45-47] ICGA studies revealed that choroidal hyperpermeability decreased after PDT.

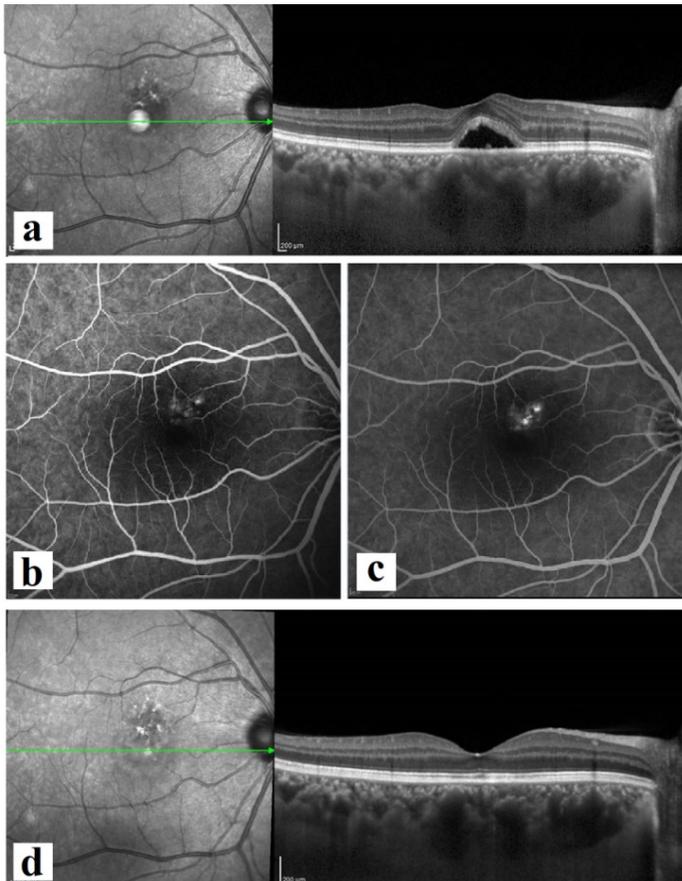


Fig. 7. Multimodal images of a patient with 4 months history of chronic central serous chorioretinopathy: (a) Subretinal fluid and large choroidal vessels on the enhanced depth imaging optical coherence tomography at baseline visit. (b and c) Two prominent leakage point located at the superionasal macular region is visible on the early and late phase of fundus fluorescein angiography. (d) Complete resolution of the subretinal fluid 2 months after subthreshold micropulse laser therapy.

Thus, the pressure on the choriocapillaris is removed and the areas with flow restriction can be corrected. In OCTA studies, although a decrease was observed in the flow of choriocapillaris in the first days of the treatment, the values return to normal around the 1st month and can even exceed the old values, while the choroidal thickness is effectively reduced.^[48-50]

Another effective method of treatment is sub-threshold micropulse laser treatment (Fig. 7a-d). The mechanism of action of sub-threshold micropulse laser treatment is photo stimulation, not photocoagulation, unlike argon laser, with the split laser pulses; the RPE is stimulated without increasing the temperature of the tissue. Since it does not cause burns, it can be safely applied to the macula and repeated treatments can be performed. The advantages are low cost of treatment, no side effects, and short application time. Subthreshold micropulse laser treatment was found

equally effective or superior compared to half-fluence PDT or half-dose PDT in retrospective studies.^[51-54] However, in one of the prospective randomized control studies; PLACE study, PDT showed superior efficacy with respect to complete resolution of SRF compared with micropulse laser at both short-term and long-term follow-up visits. Moreover, functional outcome was better with respect to both increased retinal sensitivity at the first and final evaluation visits and increased BCVA at the first evaluation visit in PDT group.^[55]

PNV

Choroidal neovascularizations are classified according to whether new vessels are located above or below the RPE on OCT. Type-1 CNV is located under the RPE and is typically characterized by the presence of PED. Although it is frequently seen in neovascular AMD, it can also be observed in pachychoroid diseases such as CSC, PCV, and PNV. Therefore, in cases without classical AMD findings, PNV should be considered in the presence of thick choroid and type-1 CNV.

PNV is a relatively new clinical entity defined in 2014 by Pang and Freund. They reported a small case series of patients with type-1 CNV occurring over enlarged choroidal vessels with increased choroidal thickness and defined this entity as "PNV".^[2] Although by definition, it begins as a condition of no previous CSC attack, the distinction between complicated CSC and PNV has not yet been clarified.

There are gene studies in the literature to understand whether neovascular AMD and PNV are different pathologies. A study on the genetic basis of CSC and AMD, revealed that different polymorphisms in the CFH and VIPR2 genes play a role in the development of CSC or AMD, depending on the type of the polymorphism.^[56] In another study, in the CFH and ARMS2 genes, some alleles predispose to AMD development, while some alleles predispose to the development of PNV.^[11] In this study, they stated that PNV cases have a lower genetic predisposition to neovascular AMD (lower frequency of ARMS2A69 and CFH162V polymorphisms) and these data suggest that the genetic basis of PNV and neovascular AMD are different.

On OCT, CNV developing on a pachychoroid background typically presents as a flat irregular PED over the dilated Haller layer and according to the activity of the disease, subretinal fluid can be observed. Evaluation of type 1 CNV by dye angiography methods may be difficult due to leakage in FFA and increased choroidal permeability in ICGA. Whereas, OCTA can show the full size of the neovascular membrane and is not affected by leakage, staining, and

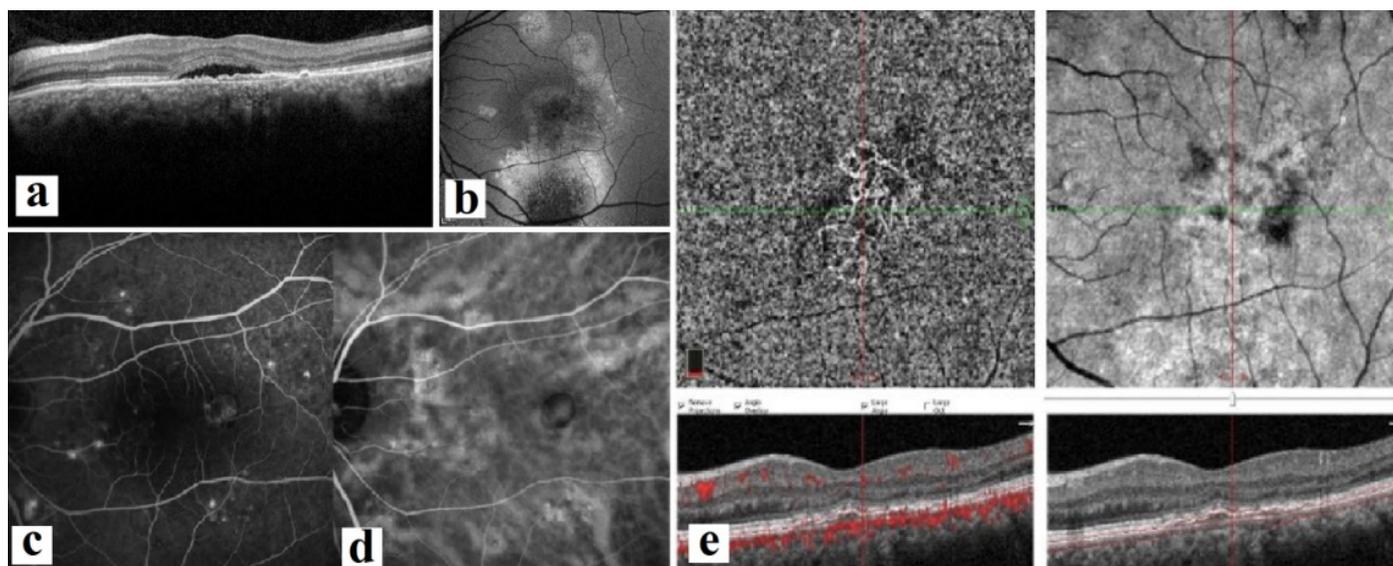


Fig. 8. Multimodal images of left eye of a patient with chronic central serous chorioretinopathy (CSC) complicated with secondary choroidal neovascularization: (a) Subretinal fluid with flat irregular pigment epithelial detachment and large choroidal vessels on enhanced depth imaging optical coherence tomography (b) Fundus autofluorescence image shows gravitational tracts due to persistent subretinal fluid. (c and d) Hyperfluorescent areas with multiple leaking points on fundus fluorescein angiography and choroidal hyperpermeability areas on indocyanine green angiography. (e) An aberrant flow signal of well-circumscribed choroidal neovascularization secondary to CSC on the choriocapillaris slab of en-face optical coherence tomography angiography.

increased choroidal permeability, unlike conventional dye angiograms (Figures 8a-e and 9a-d).^[57]

Intravitreal anti-VEGF injections and/or PDT are used in the treatment of PNV. In a study evaluating 18 unilateral PNV cases treated with anti-VEGF therapy (ranibizumab or aflibercept), they reported a significant decrease in mean CCT after 12 months of follow-up.^[58] The authors stated that the decrease in CCT may be due to the reduction in choroidal vascular permeability. In a retrospective study comparing the efficacy of intravitreal aflibercept applications performed according to the “Treat and Extend” regimen in PNV and neovascular AMD cases, similar anatomical and functional improvement was reported in both groups and it was shown that aflibercept injections can be administered with longer treatment intervals after the initial loading dose in the PNV group, unlike neovascular AMD.^[17] This may be due to the lower intraocular VEGF concentrations detected in PNV. A study supporting this hypothesis was performed by Hata et al. They measured VEGF concentration by enzyme-linked immunosorbent method in the aqueous humor of 9 PNV and 21 neovascular AMD cases who did not receive any treatment before and found that VEGF level was lower in the PNV group.^[59] Terao et al. reported that VEGF-A, bFGF, GM-CSF, and MCP-1 were significantly higher in the AMD group compared to the PNV group.^[60] A marked increase in inflammation and angiogenesis in neovascular AMD compared to PNV may be directly related to lesion enlargement.

In another published study, the results of ranibizumab and aflibercept treatment in PNV were compared, and it was reported that the rate of dry macula recovery at the 3rd month follow-up following after-loading doses was significantly higher in the aflibercept group (82.6% vs. 51.6%, $P=0.018$). While dry macula can be obtained with anti-VEGF therapy in almost 90% of the cases, adjuvant photodynamic therapy was required in 11.1% of the cases, and complete fluid resolution was achieved in all cases.^[61] In another study of the same group, adjuvant PDT was applied to PNV cases with persistent subretinal or intraretinal fluid despite at least 4 anti-VEGF injections, and dry macula was obtained in 85.7% of the cases at 3 months.^[62] PDT is an important treatment option, especially in cases where dry macula cannot be achieved with anti-VEGF therapy.

PCV

PCV is a type 1 CNV with aneurysmal dilatations at its edges that develops at the base of pachychoroid vessels.^[63] In an enucleated PNV case, CNV was shown to be accompanied by aneurysmal enlargements located between the RPE and Bruch’s membrane.^[64] Therefore, some authors argue that it should be named aneurysmal type-1 CNV instead of PCV.^[65]

Aneurysmal dilation of type 1 CNV might develop over time and might be complicated by lipid leakage and hemorrhage. Fundus examination reveals orange nodules, serous or hemorrhagic PED, subretinal hemorrhage, subretinal

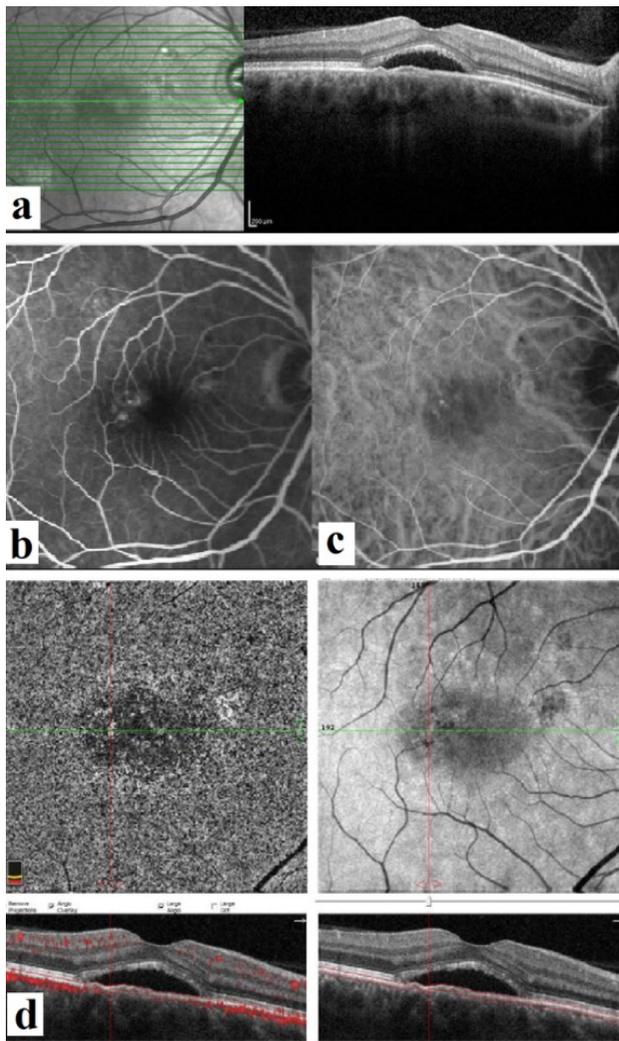


Fig. 9. Multimodal fundus images of the right eye of a pachychoroid neovascularopathy case: **(a)** Flat irregular pigment epithelial detachment and subretinal fluid with elongated photoreceptors on enhanced depth imaging optical coherence tomography (OCT) **(b)** Leaking point at the temporal macula in fundus fluorescein angiography. **(c)** Hyperfluorescent plaque appearance of choroidal neovascularization in indocyanine green angiography. **(d)** En face choriocapillaris slab and b scan OCT superimposed with flow data prove choroidal neovascularization existence on OCT angiography.

fluid, fibrosis, and scarring. The most feared complication and the cause of poor visual prognosis is massive subretinal hemorrhage. On OCT, inverted V-shaped, sharply peaked PED appearance, multilobular PEDs, ring-like lesion inside the PED, and flat irregular PED and double layer sign can be seen in the area where the branching vascular network and polyps are located.^[66] ICGA is the gold standard for definitive diagnosis. In ICGA, choroidal hyperpermeability, hyperfluorescent plaque appearance due to branching vascular network, and polyp structures that appear as grape bunches are striking. Polyps show early filling and are observed as a bright hyperfluorescent interior and hypofluorescent wall structure in the early stages (Fig. 10a-c). In the later stages, the center of the polyps is hypo, and the wall structure is hyperfluorescent due to staining.^[67] Although OCTA is also useful in imaging PCV lesions, it may be insufficient to visualize polyp structures in cases with high-speed turbulent flow or thrombosis within the polyp.^[68]

Photodynamic therapy, anti-VEGF therapy, or a combination of these can be used in the treatment. In the EVEREST II study, the PDT and ranibizumab combination group compared to the ranibizumab therapy and accordingly the rate of final letter gain (8.8 letters; 5.1 letters respectively) and polyp regression (69.3%;34.7% respectively) were higher, while the mean number of injections was lower (5.2; 7.3 respectively) in the combined group.^[69] In the PLANET study, the groups receiving aflibercept monotherapy and aflibercept combined with rescue PDT were compared, and at the end of 52 weeks, similar visual acuity gain (10.7 letters;10.9 letters respectively) and polyp regression rate (38.9%; 44.8% respectively) are reported.^[70] In the recently published 96-week results of the PLANET study; among the groups; visual acuity gain (10.7 letters; 9.1 letters, respectively), complete polyp regression rate (33.1%; 29.1%, respectively), and the percentage of cases without active polyps (82.1%; 85.6%, respectively) were found to be similar between the groups. It was reported that aflibercept

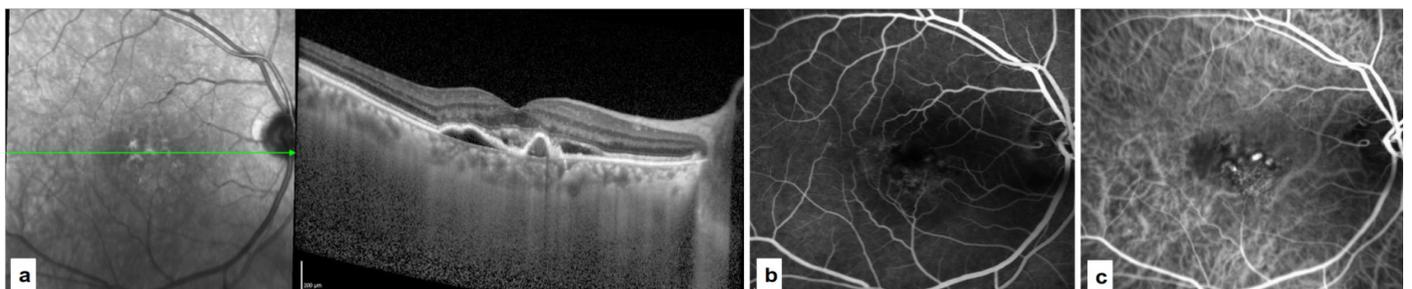


Fig. 10. Multimodal fundus images of the right eye of a polypoidal choroidal vasculopathy case: **(a)** On enhanced depth imaging optical coherence tomography, shallow serous pigment epithelium detachment with a hyperreflective inverted V-shaped pigment epithelium detachment and subretinal fluid. **(b)** Leakage of the inferior macula in fundus fluorescein angiography **(c)** Bright hyperfluorescent polyps surrounded by hypofluorescent wall and branching vascular network in indocyanine green angiography.

monotherapy is not inferior to aflibercept combined with rescue PDT.^[71]

Conclusion

There is still no consensus on etiopathogenesis of pachychoroid spectrum diseases and whether they are different progressive stages of the same disease. If these diseases are different stages of the same disease, the factors leading to the development of CNV, aneurysmal dilation, recurrent subretinal fluid, or PED are currently unknown. Prospective studies with a large number of patients with long-term follow-ups are needed to explain these differences between pachychoroid spectrum diseases.

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References

1. Warrow DJ, Hoang QV, Freund KB. Pachychoroid pigment epitheliopathy. *Retina* 2013;33:1659–72. [\[CrossRef\]](#)
2. Pang CE, Freund KB. Pachychoroid neovasculopathy. *Retina* 2015;35:1–9. [\[CrossRef\]](#)
3. Margolis R, Mukkamala SK, Jampol LM, Spaide RF, Ober MD, Sorenson JA, et al. The expanded spectrum of focal choroidal excavation. *Arch Ophthalmol* 2011;129:1320–5. [\[CrossRef\]](#)
4. Lee J, Byeon SH. Prevalence and clinical characteristics of pachydrusen in polypoidal choroidal vasculopathy: Multimodal image study. *Retina* 2019;39:670–8. [\[CrossRef\]](#)
5. Phasukkijwatana N, Freund KB, Dolz-Marco R, Al-Sheikh M, Keane PA, Egan CA, et al. Peripapillary pachychoroid syndrome. *Retina* 2018;38:1652–67. [\[CrossRef\]](#)
6. Cheung CM, Lee WK, Koizumi H, Dansingani K, Lai TY, Freund KB. Pachychoroid disease. *Eye (Lond)* 2019;33:14–33. [\[CrossRef\]](#)
7. Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Ho A, Orlock D. Digital indocyanine green videoangiography of central serous chorioretinopathy. *Arch Ophthalmol* 1994;112:1057–62.
8. Saito M, Saito W, Hashimoto Y, Yoshizawa C, Fujiya A, Noda K, et al. Macular choroidal blood flow velocity decreases with regression of acute central serous chorioretinopathy. *Br J Ophthalmol* 2013;97:775–80. [\[CrossRef\]](#)
9. Saito M, Saito W, Hirooka K, Hashimoto Y, Mori S, Noda K, et al. Pulse waveform changes in macular choroidal hemodynamics with regression of acute central serous chorioretinopathy. *Invest Ophthalmol Vis Sci* 2015;56:6515–22. [\[CrossRef\]](#)
10. Dansingani KK, Perlee LT, Hamon S, Lee M, Shah VP, Spaide RF, et al. Risk alleles associated with neovascularization in a pachychoroid phenotype. *Ophthalmology* 2016;123:2628–30. [\[CrossRef\]](#)
11. Miyake M, Ooto S, Yamashiro K, Takahashi A, Yoshikawa M, Akagi-Kurashige Y, et al. Pachychoroid neovasculopathy and age-related macular degeneration. *Sci Rep* 2015;5:16204.
12. Agrawal R, Seen S, Vaishnavi S, Vupparaboina KK, Goud A, Rasheed MA, et al. Choroidal vascularity index using swept-source and spectral-domain optical coherence tomography: A comparative study. *Ophthalmic Surg Lasers Imaging Retina* 2019;50:e26–32. [\[CrossRef\]](#)
13. Demirel S, Özcan G, Yanık Ö, Batioğlu F, Özmert E. A comparative study of the choroidal vascularity indexes in the fellow eyes of patients with pachychoroid neovasculopathy and central serous chorioretinopathy by binarization method. *Graefes Arch Clin Exp Ophthalmol* 2020;258:1649–54. [\[CrossRef\]](#)
14. Demirel S, Yanık Ö, Özcan G, Batioğlu F, Özmert E. A comparative study on the choroidal vascularity index and the determination of cut-off values in the pachychoroid spectrum diseases. *Jpn J Ophthalmol* 2021;65:482–91. [\[CrossRef\]](#)
15. Spaide RF, Ledesma-Gil G, Cheung CM. Intervortex venous anastomosis in pachychoroid-related disorders. *Retina* 2021;41:997–1004. [\[CrossRef\]](#)
16. Hogan MJ, Alvarado JA, Weddell JE. *Histology of the Human Eye: An Atlas and Textbook*. Philadelphia: Saunders; 1971.
17. Matsumoto H, Hoshino J, Mukai R, Nakamura K, Kikuchi Y, Kishi S, et al. Vortex vein anastomosis at the watershed in pachychoroid spectrum diseases. *Ophthalmol Retina* 2020;4:938–45. [\[CrossRef\]](#)
18. Ersoz MG, Karacorlu M, Arf S, Hocaoglu M, Muslubas IS. Pachychoroid pigment epitheliopathy in fellow eyes of patients with unilateral central serous chorioretinopathy. *Br J Ophthalmol* 2018;102:473–8. [\[CrossRef\]](#)
19. Ersoz MG, Arf S, Hocaoglu M, Muslubas IS, Karacorlu M. Indocyanine green angiography of pachychoroid pigment epitheliopathy. *Retina* 2018;38:1668–74. [\[CrossRef\]](#)
20. Ersoz MG, Karacorlu M, Arf S, Hocaoglu M, Muslubas IS. Outer nuclear layer thinning in pachychoroid pigment epitheliopathy. *Retina* 2018;38:957–61. [\[CrossRef\]](#)
21. Sakurada Y, Fragiotta S, Leong BC, Parikh R, Hussnain SA, Freund KB. Relationship between choroidal vascular hyperpermeability, choriocapillaris flow density, and choroidal thickness in eyes with pachychoroid pigment epitheliopathy. *Retina* 2020;40:657–62. [\[CrossRef\]](#)
22. Karacorlu M, Ersoz MG, Arf S, Hocaoglu M, Muslubas IS. Long-term follow-up of pachychoroid pigment epitheliopathy and lesion characteristics. *Graefes Arch Clin Exp Ophthalmol* 2018;256:2319–26. [\[CrossRef\]](#)
23. Demirel S, Değirmenci MF, Batioğlu F, Özmert E. Evaluation of the choroidal features in pachychoroid spectrum diseases by optical coherence tomography and optical coherence tomography angiography. *Eur J Ophthalmol* 2019;31:184–93. [\[CrossRef\]](#)
24. Kumar V, Azad SV, Verma S, Surve A, Vohra R, Venkatesh P.

- Peripapillary pachychoroid syndrome: New insights. *Retina* 2022;42:80–7. [\[CrossRef\]](#)
25. Pautler SE, Browning DJ. Isolated posterior uveal effusion: Expanding the spectrum of the uveal effusion syndrome. *Clin Ophthalmol* 2015;9:43–9.
26. Kang HG, Han JY, Kim M, Byeon SH, Kim SS, Koh HJ, et al. Pachydrusen, choroidal vascular hyperpermeability, and punctate hyperfluorescent spots. *Graefes Arch Clin Exp Ophthalmol* 2021;259:2391–400. [\[CrossRef\]](#)
27. Sheth J, Anantharaman G, Kumar N, Parachuri N, Bandello F, Kuppermann BD, et al. Pachydrusen: The epidemiology of pachydrusen and its relevance to progression of pachychoroid disease spectrum. *Eye (Lond)* 2020;34:1501–3. [\[CrossRef\]](#)
28. Sato-akushichi M, Kinouchi R, Ishiko S, Hanada K, Hayashi H, Mikami D, et al. Population-based prevalence and 5-year change of soft drusen, pseudodrusen, and pachydrusen in a Japanese population. *Ophthalmol Sci* 2021;1:100081. [\[CrossRef\]](#)
29. Lim FP, Wong CW, Loh BK, Chan CM, Yeo I, Lee SY, et al. Prevalence and clinical correlates of focal choroidal excavation in eyes with age-related macular degeneration, polypoidal choroidal vasculopathy and central serous chorioretinopathy. *Br J Ophthalmol* 2016;100:918–23. [\[CrossRef\]](#)
30. Chung H, Byeon SH, Freund KB. Focal choroidal excavation and its association with pachychoroid spectrum disorders: A review of the literature and multimodal imaging findings. *Retina* 2017;37:199–221. [\[CrossRef\]](#)
31. Ellabban AA, Tsujikawa A, Ooto S, Yamashiro K, Oishi A, Nakata I, et al. Focal choroidal excavation in eyes with central serous chorioretinopathy. *Am J Ophthalmol* 2013;156:673–83. [\[CrossRef\]](#)
32. Suzuki M, Gomi F, Hara C, Sawa M, Nishida K. Characteristics of central serous chorioretinopathy complicated by focal choroidal excavation. *Retina* 2014;34:1216–22. [\[CrossRef\]](#)
33. Lee CS, Woo SJ, Kim YK, Hwang DJ, Kang HM, Kim H, et al. Clinical and spectral-domain optical coherence tomography findings in patients with focal choroidal excavation. *Ophthalmology* 2014;121:1029–35. [\[CrossRef\]](#)
34. Pauleikhoff L, Agostini H, Lange C. Central serous chorioretinopathy. *Ophthalmologie* 2021;118:967–80. [\[CrossRef\]](#)
35. Kishi S, Matsumoto H, Sonoda S, Hiroe T, Sakamoto T, Akiyama H. Geographic filling delay of the choriocapillaris in the region of dilated asymmetric vortex veins in central serous chorioretinopathy. *PLoS One* 2018;13:e0206646. [\[CrossRef\]](#)
36. Lotery A, Sivaprasad S, O'Connell A, Harris RA, Culliford L, Ellis L, et al. Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI): A randomised, double-blind, placebo-controlled trial. *Lancet* 2020;395:294–303. [\[CrossRef\]](#)
37. Piccolino FC, Eandi CM, Ventre L, de la Longrais RC, Grignolo FM. Photodynamic therapy for chronic central serous chorioretinopathy. *Retina* 2003;23:752–63. [\[CrossRef\]](#)
38. Chan WM, Lam DS, Lai TY, Tam BS, Liu DT, Chan CK. Choroidal vascular remodelling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: A novel treatment at the primary disease level. *Br J Ophthalmol* 2003;87:1453–8. [\[CrossRef\]](#)
39. Yannuzzi LA, Slakter JS, Gross NE, Spaide RF, Costa DL, Huang SJ, et al. Indocyanine green angiography-guided photodynamic therapy for treatment of chronic central serous chorioretinopathy: A pilot study. *Retina* 2003;23:288–98. [\[CrossRef\]](#)
40. Silva RM, Ruiz-Moreno JM, Gomez-Ulla F, Montero JA, Gregório T, Cachulo ML, et al. Photodynamic therapy for chronic central serous chorioretinopathy: A 4-year follow-up study. *Retina* 2013;33:309–15. [\[CrossRef\]](#)
41. Alkin Z, Perente I, Ozkaya A, Alp D, Agca A, Aygit ED, et al. Comparison of efficacy between low-fluence and half-dose verteporfin photodynamic therapy for chronic central serous chorioretinopathy. *Clin Ophthalmol* 2014;8:685–90. [\[CrossRef\]](#)
42. Colucciello M. Choroidal neovascularization complicating photodynamic therapy for central serous retinopathy. *Retina* 2006;26:239–42. [\[CrossRef\]](#)
43. Chan WM, Lai TY, Lai RY, Liu DT, Lam DS. Half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy: One-year results of a randomized controlled trial. *Ophthalmology* 2008;115:1756–65. [\[CrossRef\]](#)
44. Reibaldi M, Boscia F, Avitabile T, Russo A, Cannemi V, Uva MG, et al. Low-fluence photodynamic therapy in longstanding chronic central serous chorioretinopathy with foveal and gravitational atrophy. *Eur J Ophthalmol* 2009;19:154–8. [\[CrossRef\]](#)
45. Chan WM, Lai TY, Lai RY, Tang EW, Liu DT, Lam DS. Safety enhanced photodynamic therapy for chronic central serous chorioretinopathy: One-year results of a prospective study. *Retina* 2008;28:85–93. [\[CrossRef\]](#)
46. Reibaldi M, Cardascia N, Longo A, Furino C, Avitabile T, Faro S, et al. Standard-fluence versus low-fluence photodynamic therapy in chronic central serous chorioretinopathy: A non-randomized clinical trial. *Am J Ophthalmol* 2010;149:307–15. e2. [\[CrossRef\]](#)
47. Cheng CK, Chang CK, Peng CH. Comparison of photodynamic therapy using half-dose of verteporfin or half-fluence of laser light for the treatment of chronic central serous chorioretinopathy. *Retina* 2017;37:325–33. [\[CrossRef\]](#)
48. Demirel S, Özcan G, Yanık Ö, Batioğlu F, Özmert E. Vascular and structural alterations of the choroid evaluated by optical coherence tomography angiography and optical coherence tomography after half-fluence photodynamic therapy in chronic central serous chorioretinopathy. *Graefes Arch Clin Exp Ophthalmol* 2019;257:905–12. [\[CrossRef\]](#)
49. Nassisi M, Lavia C, Alovise C, Musso L, Eandi CM. Short-term choriocapillaris changes in patients with central serous chorioretinopathy after half-dose photodynamic therapy. *Int J Mol Sci* 2017;18:2468. [\[CrossRef\]](#)
50. Demircan A, Yesilkaya C, Alkin Z. Early choriocapillaris changes after half-fluence photodynamic therapy in chronic central serous chorioretinopathy evaluated by optical coherence tomography angiography: Preliminary results. *Photodiagnosis Photodyn Ther* 2018;21:375–8. [\[CrossRef\]](#)
51. Özmert E, Demirel S, Yanık Ö, Batioğlu F. Low-fluence photodynamic therapy versus subthreshold micropulse yellow

- wavelength laser in the treatment of chronic central serous chorioretinopathy. *J Ophthalmol* 2016;2016:3513794. [CrossRef]
52. Sun Z, Huang Y, Nie C, Wang Z, Pei J, Lin B, et al. Efficacy and safety of subthreshold micropulse laser compared with threshold conventional laser in central serous chorioretinopathy. *Eye (Lond)* 2020;34:1592–9. [CrossRef]
 53. Scholz P, Altay L, Fauser S. Comparison of subthreshold micropulse laser (577 nm) treatment and half-dose photodynamic therapy in patients with chronic central serous chorioretinopathy. *Eye (Lond)* 2016;30:1371–7. [CrossRef]
 54. Roca JA, Wu L, Fromow-Guerra J, Rodríguez FJ, Berrocal MH, Rojas S, et al. Yellow (577 nm) micropulse laser versus half-dose verteporfin photodynamic therapy in eyes with chronic central serous chorioretinopathy: Results of the Pan-American Collaborative Retina Study (PACORES) Group. *Br J Ophthalmol* 2018;102:1696–700. [CrossRef]
 55. Van Dijk EH, Fauser S, Breukink MB, Blanco-Garavito R, Groenewoud JM, Keunen JE, et al. Half-dose photodynamic therapy versus high-density subthreshold micropulse laser treatment in patients with chronic central serous chorioretinopathy: The PLACE trial. *Ophthalmology* 2018;125:1547–55. [CrossRef]
 56. Hosoda Y, Yoshikawa M, Miyake M, Tabara Y, Ahn J, Woo SJ, et al. CFH and VIPR2 as susceptibility loci in choroidal thickness and pachychoroid disease central serous chorioretinopathy. *Proc Natl Acad Sci U S A* 2018;115:6261–6. [CrossRef]
 57. Demirel S, Yanik Ö, Nalçı H, Batioğlu F, Özmert E. The use of optical coherence tomography angiography in pachychoroid spectrum diseases: A concurrent comparison with dye angiography. *Graefes Arch Clin Exp Ophthalmol* 2017;255:2317–24. [CrossRef]
 58. Padrón-Pérez N, Arias L, Rubio M, Lorenzo D, García-Bru P, Català-Mora J, et al. Changes in choroidal thickness after intravitreal injection of anti-vascular endothelial growth factor in pachychoroid neovascularopathy. *Invest Ophthalmol Vis Sci* 2018;59:1119–24. [CrossRef]
 59. Hata M, Yamashiro K, Ooto S, Oishi A, Tamura H, Miyata M, et al. Intraocular vascular endothelial growth factor levels in pachychoroid neovascularopathy and neovascular age-related macular degeneration. *Investig Ophthalmol Vis Sci* 2017;58:292–8.
 60. Terao N, Koizumi H, Kojima K, Yamagishi T, Yamamoto Y, Yoshii K, et al. Distinct aqueous humour cytokine profiles of patients with pachychoroid neovascularopathy and neovascular age-related macular degeneration. *Sci Rep* 2018;8:10520. [CrossRef]
 61. Jung BJ, Kim JY, Lee JH, Baek J, Lee K, Lee WK. Intravitreal aflibercept and ranibizumab for pachychoroid neovascularopathy. *Sci Rep* 2019;9:2055. [CrossRef]
 62. Lee WJ, Lee JH, Lee BR. Fundus autofluorescence imaging patterns in central serous chorioretinopathy according to chronicity. *Eye (Lond)* 2016;30:1336–42. [CrossRef]
 63. Kokame GT. Prospective evaluation of subretinal vessel location in polypoidal choroidal vasculopathy (PCV) and response of hemorrhagic and exudative PCV to high-dose antiangiogenic therapy (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc* 2014;112:74–93. [CrossRef]
 64. Li M, Dolz-Marco R, Messinger JD, Sloan KR, Ferrara D, Curcio CA, et al. Clinicopathologic correlation of aneurysmal Type 1 neovascularization in age-related macular degeneration. *Ophthalmol Retina* 2019;3:99–111. [CrossRef]
 65. Dansingani KK, Gal-Or O, Sadda SR, Yannuzzi LA, Freund KB. Understanding aneurysmal Type 1 neovascularization (polypoidal choroidal vasculopathy): A lesson in the taxonomy of 'expanded spectra'-a review. *Clin Exp Ophthalmol* 2018;46:189–200. [CrossRef]
 66. Cheung CM, Lai TY, Teo K, Ruamviboonsuk P, Chen SJ, Kim JE, et al. Polypoidal choroidal vasculopathy: Consensus nomenclature and non-indocyanine green angiograph diagnostic criteria from the Asia-Pacific ocular imaging society PCV workgroup. *Ophthalmology* 2021;128:443–52. [CrossRef]
 67. Destro M, Puliafito C. Indocyanine green videoangiography of choroidal neovascularization. *Ophthalmology* 1989;96:846–53. [CrossRef]
 68. Wang M, Zhou Y, Gao SS, Liu W, Huang Y, Huang D, et al. Evaluating polypoidal choroidal vasculopathy with optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 2016;57:OCT526–32. [CrossRef]
 69. Koh A, Lai TY, Takahashi K, Wong TY, Chen LJ, Ruamviboonsuk P, et al. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: A randomized clinical trial. *JAMA Ophthalmol* 2017;135:1206–13. [CrossRef]
 70. Lee WK, Iida T, Ogura Y, Chen SJ, Wong TY, Mitchell P, et al. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy in the PLANET study: A randomized clinical trial. *JAMA Ophthalmol* 2018;136:786–93. [CrossRef]
 71. Wong TY, Ogura Y, Lee WK, Iida T, Chen SJ, Mitchell P, et al. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy: Two-year results of the aflibercept in polypoidal choroidal vasculopathy study. *Am J Ophthalmol* 2019;204:80–9. [CrossRef]