Review Article

Choroidal biomarkers

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A structurally and functionally intact choroid tissue is vitally important for the retina function. Although central retinal artery is responsible to supply the inner retina, choroidal vein network is responsible for the remaining one-third of the external part. Abnormal choroidal blood flow leads to photoreceptor dysfunction and photoreceptor death in the retina, and the choroid has vital roles in the pathophysiology of many diseases such as central serous chorioretinopathy, age-related macular degeneration, pathologic myopia, Vogt–Koyanagi–Harada disease. Biomarkers of choroidal diseases can be identified in various imaging modalities that visualize the choroid. Indocyanine green angiography enables the visualization of choroid veins under the retinal pigment epithelium and choroidal blood flow. New insights into a precise structural and functional analysis of the choroid have been possible, thanks to recent progress in retinal imaging based on enhanced depth imaging (EDI) and swept-source optical coherence tomography (SS-OCT) technologies. Long-wavelength SS-OCT enables the choroid and the choroid–sclera interface to be imaged at greater depth and to quantify choroidal thickness profiles throughout a volume scan, thus exposing the morphology of intermediate and large choroidal vessels. Finally, OCT angiography allows a dye-free evaluation of the blood flow in the choriocapillaris and in the choroid. We hereby review different imaging findings of choroidal diseases that can be used as biomarkers of activity and response to the treatment.

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Biomarkers and Personalized Medicine

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.

Biomarkers are of increasingly high importance in medicine, particularly in the realm of "personalized medicine." They are valuable for predicting prognosis and treatment selection. Moreover, they may be helpful in detecting therapeutic responses. Thus, biomarkers are essential tools for the selection of appropriate patients for treatment with certain drugs and to enable personalized medicine, that is, "providing the right treatment to the right patient, at the right dose at the right time.". Diagnostic biomarkers are important in autoimmune diseases, and disease severity biomarkers are helpful tools in the treatment for inflammatory eye diseases.

The aim of this review is to identify, qualify, and implement the different kind of biomarkers of choroidal diseases.

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Anatomy of the Choroid

The choroid[1] is the vascular component that nourishes the outer portion of the retina.

The choroid is composed of various layers:

Bruch's membrane is a thin lamina resulting from the fusion of the basal laminae of the retinal pigment epithelium (RPE) and the choriocapillaris. Bruch's membrane is 2–4 μm thick and extends from the margin of the optic disc to the ora serrata. Ultrastructurally, it is composed of five sublayers: (i) the basement membrane of the RPE, (ii) the inner loose collagenous zone, (iii) a thicker, porous band of elastic fibers, (iv) the outer collagenous zone, and (v) the basal lamina of the endothelium of the choriocapillaris.[1]

The choriocapillaris is a continuous layer of large capillaries of 40–60 μm in diameter, lying in a single plane between Bruch's membrane and the Sattler's layer. The vessel walls are extremely thin and contain multiple fenestrations. These fenestrations are located mostly on the retinal side.[2] Furthermore, the fenestrae of the choriocapillaris (CC) are notable for their large size (approximately 800 Å) and the presence of an overlying

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diaphragm. The choriocapillaris are organized into a series of hexagonal-shaped lobules [Fig. 1a], which are smaller at the posterior pole (200–350 μm in diameter), and became progressively larger toward the periphery.[3] The lobule is supplied centrally by a precapillary arteriole that drains peripherally into the postcapillary venule. Arterial blood reaches the lobule at its center, circulates centripetally toward the edge of the lobule, and, subsequently, drains into the venous system. The choriocapillaris lobules are separated by many tiny intercapillary spaces that may grow with age (according to a power distribution) and disease (e.g., myopia, hypertension, age-related macular degeneration [AMD]). The main function of the choriocapillaris is to supplement the RPE and the outer retina with oxygen, micronutrients, ions, and water. When choriocapillaris does not provide a sufficient perfusion, RPE and the outer retina suffer a metabolic stress and hypoxemia.

The larger vessels of the choroid have an average diameter of 28.2 and 37.1 μm, for arteries and veins, respectively.[4] These vessels constitute two layers: the outer *Haller's layer* of large arteries and veins and the inner *Sattler's layer* of medium vessels that feed and drain the choriocapillaris (Krebs 1988) [Fig. 1b].

Finally, the suprachoroidal space is a zone of transition between choroid and sclera containing elements of both.[5]

The thickness of the choroid is variable depending on location, with a maximum of 0.22 mm at the posterior pole and with a thickness reduced to 0.1 mm at the ora serrata. Perfusion of the choroid comes from both the long and short posterior ciliary arteries and from the perforating anterior ciliary arteries [Fig. 2]. Venous blood drains through the vortex system. The physiological peculiarity of choroidal tissue is represented by its hemodynamic characteristics: this is vascular tissue with the highest blood flow in the whole body, and as a result, the venous blood is just slightly less saturated in oxygen than the arterial oxygen pressure.

Melanocytes, connective tissue, and cells of the immune system are interspersed in between the vessels of the choroidal stroma.

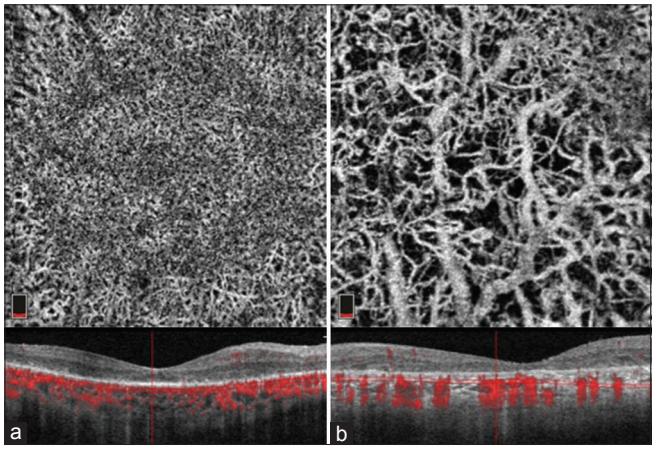

Figure 1: Atrophy of the outer retina bands and the RPE allows an "artifact-free" visualization of the choroid on optical coherence tomography angiography. Optical coherence tomography angiography illustrates that the choriocapillaris is characterized by a granular pattern of bright and dark (signal voids) areas (a), and visualizes the larger choroidal vessels and their anastomosis (b)

Comparison of Currently Available Imaging Modalities for Choroidal Assessment

The alterations in the choroidal tissue are central to the pathogenesis of conditions, such as age-related choroidal atrophy, myopic chorioretinal atrophy, central serous chorioretinopathy (CSCR), chorioretinal inflammatory diseases, among others. Indocyanine green angiography (ICGA) is traditionally the gold standard for evaluation of the choroidal circulation. Newer imaging modalities, including enhanced-depth imaging optical coherence tomography (EDI-OCT), swept-source optical coherence tomography (SS-OCT), and optical coherence tomography angiography (OCTA) have greatly improved the visualization of the choroidal anatomy. Further, imaging analyses tools such as volumetric analysis, image averaging tools, and various third-party software have enhanced our capabilities of image interpretation and evaluation. The following section summarizes the currently available imaging modalities that aid in the assessment of various choroidal disorders.

Indocyanine green angiography

Indocyanine green (ICG) is a water-soluble and highly protein-bound (98%) dye, which has limited diffusion through the small fenestrations of the choriocapillaris. The retention of ICG in the choroidal circulation, and its low permeability, makes ICGA ideal for imaging choroidal circulation. ICG absorbs and reflects in the near-infrared portion of the spectrum (805 and 835 nm, respectively). It can be detected only with specialized infrared video angiography using modified fundus cameras, a digital imaging system, or a scanning laser ophthalmoscope (SLO). Due to its long operating wavelength, it fluoresces better through the RPE, lipid and hemorrhage facilitating the visualization of the choroid through subretinal hemorrhage or other pigmentary deposits in the retina or RPE. However, it is an invasive procedure with potential adverse reactions and contraindications.

Enhanced-depth imaging optical coherence tomography

On spectral-domain optical coherence tomography (SD-OCT), a broadband light source with a wavelength of 850 nm is split into a reference arm and a sample arm in order to reconstruct the microscopic structure of the chorioretinal tissue. Tomographic images obtained with SD-OCT devices generally exhibit better

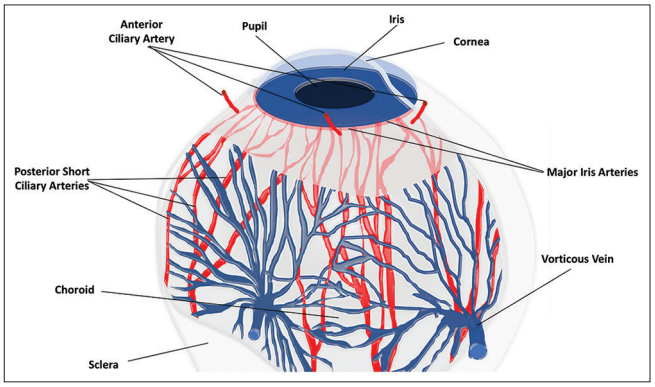

Figure 2: Schematic representation of the vascularization of the choroid. Perfusion of the choroid comes from the posterior ciliary arteries and from the perforating anterior ciliary arteries, while venous blood drains through the vortex system

quality if they are placed near the zero-delay line, which, in the conventional technique, is placed at the level of the posterior vitreous. The outer limit of the choroid and the sclera cannot usually be reliably identified using conventional SD-OCT due to scattering of light from pigmented RPE layer as well as decreasing sensitivity and resolution with increasing displacement from zero-delay line.

EDI-OCT is an acquisition technique in which the peak sensitivity is placed posteriorly, further toward the sclera, so the roll-off of sensitivity does not compromise the registration of deeper structures such as the choroid and choroidal–scleral interface. Therefore, in conditions such as pathological myopia where the choroid and sclera are thin, the complete depth of the sclera and the orbital fat may be visualized. Although EDI-OCT contributes to enhanced overall assessment of the choroid and choroidal–scleral interface, the technique does not contribute significantly to the visualization of the choriocapillaris and choroidal microvasculature due to their proximity to the RPE.

Swept-source optical coherence tomography

In comparison to SD-OCT, SS-OCT uses a different light source (wavelength-tunable laser) and a different detection method (dual balanced photo detector), which confer the advantages of higher imaging speed, higher detection efficiencies, improved imaging range, and reduced sensitivity roll-off with increasing depth. SS-OCT has the highest imaging speed of any commercially available OCT with 100,000 A-scans obtained per second. This improves scan quality by reducing the negative effect of patient's eye movement and allows for denser scan patterns and larger scan areas compared with SD-OCT scans for a given acquisition time. It has a high axial resolution of 5 μm and an improved signal-to-noise ratio which leads to better imaging of the internal structure of the choroid including the choriocapillaris and the choroidoscleral interface. Furthermore, the long wavelength of SS-OCT (1,050 nm) is less subject to light scatter by the RPE and lens opacities resulting in enhanced light penetration through the RPE, as well as better detection of signals from the deeper layers.

Optical coherence tomography angiography

OCTA is a novel imaging technique that provides noninvasive angiographic maps of the retinal and choroidal vasculature without the need for intravascular contrast agent. OCTA is able to detect endoluminal flow and allows detailed depth-resolved analysis of the microvascular network in each layer of the retina and choroid revealing subtle abnormalities that may not be detectable on routine fluorescein angiography (FA) and/or ICGA. While standard angiography provides two-dimensional images, OCTA offers three-dimensional optical reconstruction of the tissue, based on a volumetric dataset. OCTA has proven to be useful in documentation of *in vivo* choriocapillaris and choroidal vasculature in a reproducible manner and is an invaluable tool in the investigation of the choroid in physiological or pathological conditions such as choriocapillaris ischemia and choroidal neovascular membrane (CNV). Focal absence of choriocapillaris on OCTA or flow deficit areas may represent true choriocapillaris atrophy with complete loss of vessels, reduced blood flow, or simply an image artifact and needs to be carefully interpreted. Choriocapillaris ischemia detected on OCTA correlates very well with the hypocyanescent lesions seen on ICGA. Sometimes the flow deficit areas may be seen due to loss of signal transmission that needs to be ruled out using structural enface scans. Although OCTA is very useful for the evaluation of the choriocapillaris layer of the choroid, the medium and large choroidal vessels are not very well appreciated with this imaging technique.

Choroidal Biomarkers in Age-Related Macular Degeneration

Historically, ICGA was extremely useful in AMD when the treatment for CNVs was laser photocoagulation, and ICGA could help localize an extrafoveal vessel making it accessible to treatment. With the advent of anti-vascular endothelial growth factor (VEGF) treatment, and high-quality noninvasive imaging like SD-OCT, and with an increased volume of patients in busy clinical setting, the use of invasive imaging modalities such as FA and ICGA has drastically decreased.

However, the gold standard for CNV detection is currently still FA.[6,7] Nevertheless, many studies have reported that ICGA can improve the ability to detect CNV in patients with neovascular AMD compared with FA alone,[8] particularly when type 1 CNV is present. In these studies, ICG angiograms obtained using both SLO and digital video-angiography enabled visualization of 55% and 61% of CNV, respectively, in cases where the CNV could not be determined with FA alone.[9,10] Detection of classic CNV on ICG angiography reportedly approaches 100% in patients with neovascular AMD, thanks to the longer wavelength of ICGA that allows detailed visualization of deeper retinal structures and choroidal circulation through sero-sanguineous pigment epithelium detachments, which are a common biomarkers of neovascular activity in CNV and often hinder OCT view as they can attenuate the signal.[11]

Rush *et al*.[12] have shown that ICGA size of CNV measured at baseline and after 2 months of intravitreal treatment holds a prognostic value, irrespective of CNV type. In particular, a decrease in size ≥33% is associated with significant decrease in size or complete disappearance of CNV at 12 months and is significantly more likely to gain over three lines of visual acuity. This CNV size evaluation through ICGA can be used to identify the subset of patients that may not require regular anti-VEGF therapy beyond 12 months 14.

At present, the possibility of accurately assessing the size of the CNV by OCTA[13] is possible but limited by the technology itself: different size of acquisition field as well as different software used to elaborate the size, in addition to the known projection artifact and motion artifact, make it difficult to properly compare studies. It appears that the size of CNV assessed on OCTA is smaller than the ICGA assessment,[14] but significant variability has been described depending on the use of SS-OCT or SD-OCT.

IGCA also holds a place in cases of inflammatory diseases of the elderlies where CNVs occur in the absence of choroiditis and vitreous inflammation. Invernizzi *et al*.[15] have recently published a case series in which CNV was the presenting feature of intraocular tuberculosis in elderly patients living in nonendemic areas. These cases were initially misdiagnosed as AMD, with poor response to anti-VEGF treatment. ICGA was able to detect choroidal involvement (tubercular granulomas/choroiditis) in the absence of any apparent signs of intraocular inflammation

detectable by funduscopic examination or by routine ocular imaging techniques such as OCT and FA.

ICGA is also still the only imaging modality that can help identifying feeder vessels that may be accessible to direct photocoagulation, particularly in patients with high cardiovascular risk and comorbidities or social constraints preventing them from repeated intravitreal injections.

Choroidal Biomarkers in Pachychoroid Disease

Pachychoroid diseases started to be discussed in 2013 when Freund *et al*. described pachychoroid pigment epitheliopathy (PPE). The pachychoroid disease spectrum includes PPE, CSCR, pachychoroid neovasculopathy (PNV), and aneurysmal type 1 neovascularization (polypoidal choroidal vasculopathy).[16,17] Focal choroidal excavation and peripapillary pachychoroid syndrome were recently added to this spectrum.[18,19] Features of the pachychoroid phenotype are choroidal hyperpermeability, dilated choroidal vessels (pachyvessels), and focal or diffuse increase in choroidal thickness, best seen with EDI-OCT or SS-OCT. Pachychoroid vascular changes co-localize with focal disruptions in the RPE and Bruch's membrane, leading eventually to the various clinical manifestations. ICGA shows choroidal hyperpermeability in these regions.[17] En face OCT imaging demonstrates that pachyvessels are often attributable to pathologically dilated veins of Haller's layer that cause a secondary, corresponding attenuation of the overlying inner choroidal layers.[20] Using OCTA, Gal-Or *et al*.[21] identified and quantified areas of signal voids in the choriocapillaris and demonstrated that inner choroidal flow signal attenuation is topographically associated with pachyvessels.

Choroidal Biomarkers in Central Serous Chorioretinopathy

CSCR is a major cause of central vision loss in young adults, with an incidence of approximately 1/10,000 and a male: female ratio between 72% and 88%.[22] CSCR can occur in an acute form or relapse in a chronic form, defined as such if it persists for at least 6 months. Although acute episodes usually resolve spontaneously within 2–3 months, relapses, and/or chronic evolution occur in 30%–50% of cases, resulting in visual loss secondary to retinal thinning and foveal cysts, without an approved treatment available at the time.[23] It is referred as a "chorioretinopathy" since it appears to involve the retina, with a variable area of detachment of the neuroepithelium, but starting from an alteration of the barrier and channel pump in the choriocapillaris.[22] CSCR primarily occurs because of disturbance in choroidal circulation with hyperpermeability and dilatation of choroidal vessels.[24] This choroidal hyperpermeability can be documented in CSCR with ICGA [Fig. 3a] and is thought to contribute to the development of serous pigment epithelial detachments (PEDs) and accumulation of subretinal fluid.[25] The role of the choroid in the pathogenesis of CSCR has been further confirmed by SD-OCT studies, which have demonstrated an overall increase in choroidal thickness in affected eyes [Fig. 3c].[26,27]

OCTA measurements of the choriocapillaris flow in chronic CSCR has demonstrated regions of hypoperfusion surrounded by a hyperperfused area [Fig. 3b][28] that have a moderate correspondence with late staining on ICGA. A similar study by Xu *et al*.[29] has confirmed these OCTA findings and demonstrated their disappearance as soon as 3 months after half-dose photodynamic therapy (PDT). The hyperperfusion demonstrated on OCTA of the choriocapillaris in chronic CSCR may be reactive and may cause an increased hydrostatic pressure within the fenestrated vessels of the choriocapillaris.

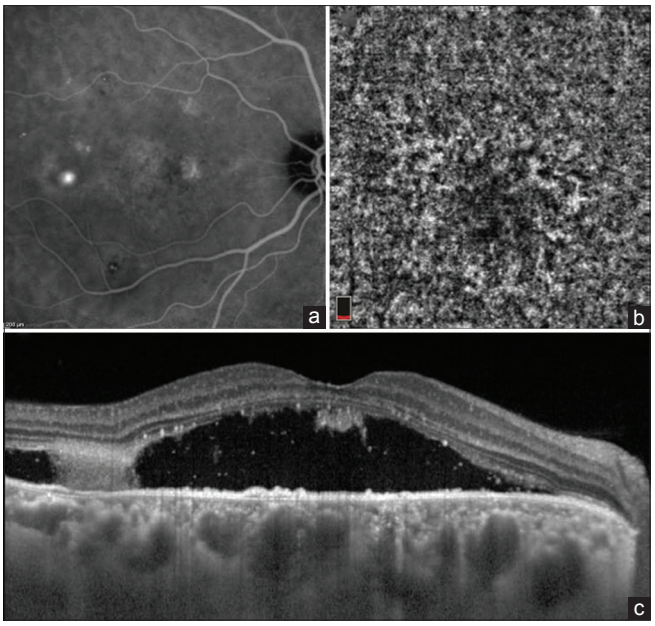

Figure 3: The gold standard to assess choroidal hyperpermeability in central serous chorioretinopathy remains indocyanine green angiography (a). A less invasive method is represented by optical coherence tomography angiography of the choriocapillaris that shows (with a moderate correspondence with the indocyanine green angiography leak) areas of flow void surrounded by hyperintense areas of increase flow (b): There seems to be a reactive hyperperfusion that could cause an increased hydrostatic pressure within the fenestrated vessels of the choriocapillaris. Enhanced-depth imaging optical coherence tomography (c) shows an increased thickness of the whole choroid

Choroidal Biomarkers in Polypoidal Choroidal Vasculopaty/Aneurysmal Type 1

ICGA has been the gold standard imaging modality to diagnose PCV/AT1.[30] Characteristic ICGA features include branching vascular network and aneurysms [Fig. 4a-c].[30] In addition, markedly dilated and hyperpermeable choroidal vessels have been observed in the mid- and late-phases of ICGA in eye with PCV.[31-34] These abnormally dilated large choroidal vessels typically appear as a cluster of relatively straight and dilated vessels. Compared with normal choroidal vessels, these "pachyvessels" do not taper toward the posterior pole but retain their large caliber and terminate abruptly. By studying cross-sectional OCT with ICGA [Fig. 4d], these vessels have increased diameter and appear as large hyporeflective lumen on OCT and can be seen to arise predominantly from Haller's layer.[18,35,36]

More recently, studies based on SD-OCT further suggest that the abnormally dilated choroidal vessels (pachyvessels) may result in compression and ischemia of the overlying

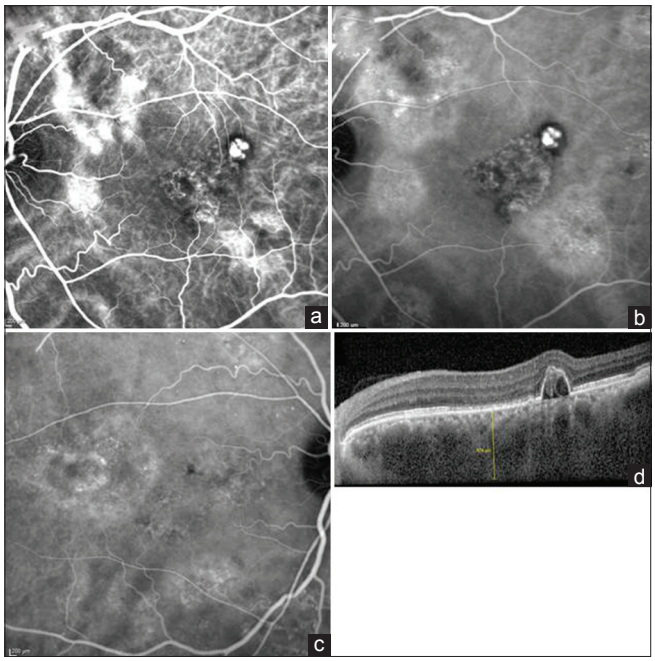

Figure 4: Choroidal hyperpermeability demonstrated on indocyanine green angiography in the both eyes of a patient presenting with polypoidal choroidal vasculopathy in the left eye. (a) Early phase (1 min) indocyanine green angiography in which branching vascular network and polyps are seen. In addition, dilated large choroidal vessels can be seen temporal to the optic disc. (b) Mid-phase (5 min) indocyanine green angiography in which diffuse hyperfl uoresecence can be seen in areas with pachyvessels. (c) Choroidal hyperpermeability was also evident from the mid phase indocyanine green angiography of the fellow eye in this patient. (d) Markedly thickened choroid (>500 μm) can be detected in the left eye using spectral-domain optical coherence tomography

choriocapillaris and may contribute to the pathogenesis of PCV.[20] Ischemia of the choriocapillaris is believed to result in increased extravasation of fluid from the choriocapillaris or larger choroidal vessels, leading to the observation of choroidal hyperpermeability. Choroidal hyperpermeability is characterized by multifocal areas of hyperfluorescence with blurred margins which are best observed in late phase (10–15 minutes) ICGA.[37] Other features commonly observed on ICGA in eyes with PCV/AT1 include choroidal venous dilatation, choroidal filling defects, delayed arterial filling in the early phase, and focal or punctate hyperfluorescence.[16,17,38-40] Both diffuse and punctate hyperfluorescence on ICGA have been frequently observed also in the contralateral eyes of patients with PCV/AT1.[17]

Although eyes with choroidal hyperpermeability often have increased choroidal thickness, not all eyes with thick choroids exhibit choroidal hyperpermeability.[38] Recent imaging studies combining ICGA and SD-OCT findings have suggested that choroidal vascular hyperpermeability may be followed by choriocapillaris atrophy[20] and subsequent clinical manifestation in the form of retinal pigment epitheliopathy and PED.[17,39] It has been further hypothesized that the choriocapillaris attenuation may produce an ischemic microenvironment which promotes VEGF expression and development of type 1 neovascularization.[16,40,41] Development of aneurysms in chronic type 1 NV eventually leads to the clinical manifestation of PCV/AT1.[41,42]

As well as having a potential role in the pathogenesis of PCV/AT1, choroidal hyperpermeability may also have a prognostic role. Choroidal hyperpermeability has been reported in 10%–50% of eyes with PCV.[37,43] Several studies have reported poorer response and persistent fluid after anti-VEGF therapy in eyes with choroidal hyperpermeability.[43-46] In a recent study, choroidal hyperpermeability, but not choroidal thickness, was associated with better visual outcome in eyes with PCV treated with combination therapy (PDT combined with anti-VEGF).[37] Furthermore, eyes with CVH required lower injection number in combination therapy. The authors suggested that PDT may benefit eyes with choroidal hyperpermeability by modulating or occluding the abnormal hyperpermeable choroidal vessels and lead to reduction in the hydrostatic pressure of the choroid.[37] Therefore, choroidal hyperpermeability may be a potential prognostic biomarker for selecting patients for combination therapy.

The constellation of morphological changes commonly seen in eyes with PCV/AT1, including increased choroidal thickness (on OCT) and hyperpermeability (on ICGA), attenuation of choriocapillaris, and presence of pachyvessels is also seen in many eyes with CSCR, PPE, PNV, focal choroidal excavation, and peripapillary pachychoroid syndrome. Together, these clinical entities are now recognized as clinical manifestations within the pachychoroid spectrum. Central to the concept of "pachychoroid disease" is that the choroidal alterations have key functional implications which have pathogenic importance. The fact that these different manifestations share a common underlying pathogenic process further help explain the overlapping features observed, as well as progression from one form to another.[47,48] For example, neovascularization with or without aneurysmal changes may arise from eyes with a background of chronic CSC.[48-50] These patients tended to be younger and have absent or minimal soft drusen compared with patients with neovascular AMD. It has been postulated that this type of neovascularization may have a different etiology compared with neovascular AMD.

Despite the compelling imaging findings that demonstrate alterations within the choroid in PCV/AT1, there remain areas which need further clarification. The mechanisms which lead to the characteristic choroidal changes described remain to be elucidated. Congestion of choroidal blood flow and increased hydrostatic pressure have been proposed as possible mechanisms.[41] To answer this question, future imaging studies that enable *in vivo* determination of direction and velocity of blood flow within the choroid will be needed. Novel therapies targeting at "decongesting" the choroid and prevention of choriocapillaris may offer new therapeutic approaches to treating PCV/AT1.

Choroidal Biomarkers in Myopic Eyes

Progressive atrophy of the RPE has been observed in myopic eyes and can be clinically detected as increasing severity of myopic macular degeneration.[51] The International meta-analysis for pathologic myopia (META-PM) classification system categorizes MMD with increasing severity into category 1 (no change), category 2 (tessellated fundus), category 3 (diffuse atrophy), category 4 (patchy atrophy), and

category 5(macular atrophy).[52] The risk of visual loss as well as complications such as myopic choroidal neovascularization increases with increasing MMD severity.[51,52] However, the underlying mechanism that leads to progression in MMD remains poorly understood.

Pronounced choriocapillary obstruction in a lobular fashion has been observed in histological examination of highly myopic eyes.[53] In these areas, choriocapillaris loss is seen, leaving behind choroidal arterioles. Using OCT, decreased choroidal thickness has been observed non-invasively in myopic eyes *in vivo*.[54,55] The significance of choroidal thinning or atrophy in the development of MMD has been studied by several groups. For example, reduction in choroidal thickness was found to be more strongly associated with severity of myopic macular degeneration than scleral thickness, suggesting that progressive loss of choroidal vasculature may have a significant pathogenic role in the development of MMD.[56]

However, studying the choriocapillaris using traditional modalities such as fluorescein or ICGA has yielded limited information, due to the lack of depth resolution and leakage of dye within the choriocapillaris. With the advent of OCTA, the choriocapillaris may be assessed in a depth-resolved manner.[57] This can be achieved by direct visualization using a slab 0–10 μm deep to the RPE–Bruch's membrane complex. However, projection artifacts from overlying retinal vasculature often interfere with interpretation. Hence, a second, "indirect" method has been proposed, in which the interrogation slab is placed 34–44 μm deep to the RPE–Bruch's membrane complex.[58] Using this method, the choriocapillaris network can be seen as a sheet of hyperreflectivity interspersed with circular areas with low or no signal, which represent the lobular pattern of the choriocapillaris meshwork. This method has the advantage of reducing projection artifacts from retinal vasculature. The deeper choroidal vessels appear hyporeflective in the presence of intact RPE and choriocapillaris network but become hyperreflective if there is loss of the overlying RPE and choriocapillaris.

OCTA changes in eyes with lacquer cracks were evaluated in one study.[59] Choriocapillaris defects observed on OCTA were shorter than the full extent of the lacquer crack measured using ICGA. These findings suggest that the choriocapillaris impairment in lacquer cracks is likely secondary to Bruch's membrane and RPE changes.[59]

In contrast, choriocapillaris flow impairment may precede the development of significant RPE changes. In eyes with patchy atrophy, it is not surprising to find that complete loss of choriocapillaris can be seen.[59] In eyes with diffuse atrophy, low flow density within the choriocapillaris was observed in 78%–81%.[60] In highly myopic eyes with even milder fundus changes, such as tessellated fundus without clinically evident RPE atrophy, low-density choriocapillaris can be observed in up to 18%.[60] The pattern of choriocapillaris flow impairment changed from predominantly localized to extensive with increasing severity of MMD.[60] This observation suggests that disturbance in choriocapillaris flow may occur early in the pathogenesis of MMD development and progression. To further investigate this, longitudinal studies will be necessary to evaluate whether eyes with CC flow impairment are likely to develop severe MMD in future.

Several groups have attempted to quantify choriocapillaris flow.[61,62] However, the repeatability and reproducibility of these parameters have not been demonstrated and normative values have not been established. Other specific challenges related to OCTA in highly myopic eyes include difficulty in accurate segmentation due to irregular choroid–scleral interface and extreme thinning of the choroid, as well as aberrant increase in signal transmission which may result from RPE loss. In addition, it is important to be mindful that lack of flow signal may not necessarily mean absence of flow, but merely that flow is below the detectable threshold. Conversely, eyes with detectable flow signals on OCTA may also still have decreased flow speed.

If choriocapillaris flow impairment is indeed an integral part of the pathogenesis and progression of MMD, strategies to protect the choriocapillaris before the development of permanent loss may provide a way to prevent or slow down MMD progression. Long-term longitudinal studies will be required to further investigate this hypothesis. Before that, further refinements in OCTA technology to improve segmentation accuracy, reduce artifacts, and quantify choriocapillaris flow will be needed. Finally, longitudinal studies will further clarify whether choriocapillaris loss may be a biomarker for individuals at risk of MMD progression.

Choroidal Biomarkers in Uveitic Entities

Acute posterior multifocal placoid pigment epitheliopathy

APMPPE is a rare disorder of uncertain etiology characterized by acute onset of multiple yellowish-white placoid lesions at the level of the RPE mainly affecting the posterior pole and rarely extending beyond suggested to be the most likely pathological event resulting in development of the characteristic placoid lesions.[63]

In the acute stage, ICGA reveals hypocyanescence in areas of yellowish white placoid lesions in the early phase, which persists in the late phase of the angiogram indicating choroidal capillary non-perfusion. As the remission of placoid lesions progresses, the areas of hypocyanescence gradually become less hypocyanescent in the late phase and ultimately isocyanescent in the inactive stage of the disease.[64] ICGA is able to detect several additional hypocyanescent lesions compared with those detected on FA, autofluorescence, and OCT. It also picks up choroidal perfusion defects much after the clinical and OCT resolution of the lesions.

In the acute stage, EDI-OCT reveals focal areas of choriocapillaris thickening and hyporeflectivity beneath the placoid lesions and an overall increase in the subfoveal choroidal thickness. In the inactive stage, along with resolution of outer retinal hyperreflectivity, EDI-OCT shows regression of focal areas of choriocapillaris thickening and hyporeflectivity along with a reduction in the full choroidal thickness.[65] These changes precede the recovery of choriocapillaris hypoperfusion on ICGA.

In the acute stage, OCTA images at the level of the choriocapillaris show areas of hypoperfusion corresponding to areas of outer retinal hyperreflectivity and choriocapillaris thickening on EDI-OCT. OCTA choroidal flow attenuation has been shown to extend beyond the visible retinal involvement in some studies.[65-67] It is important to differentiate between

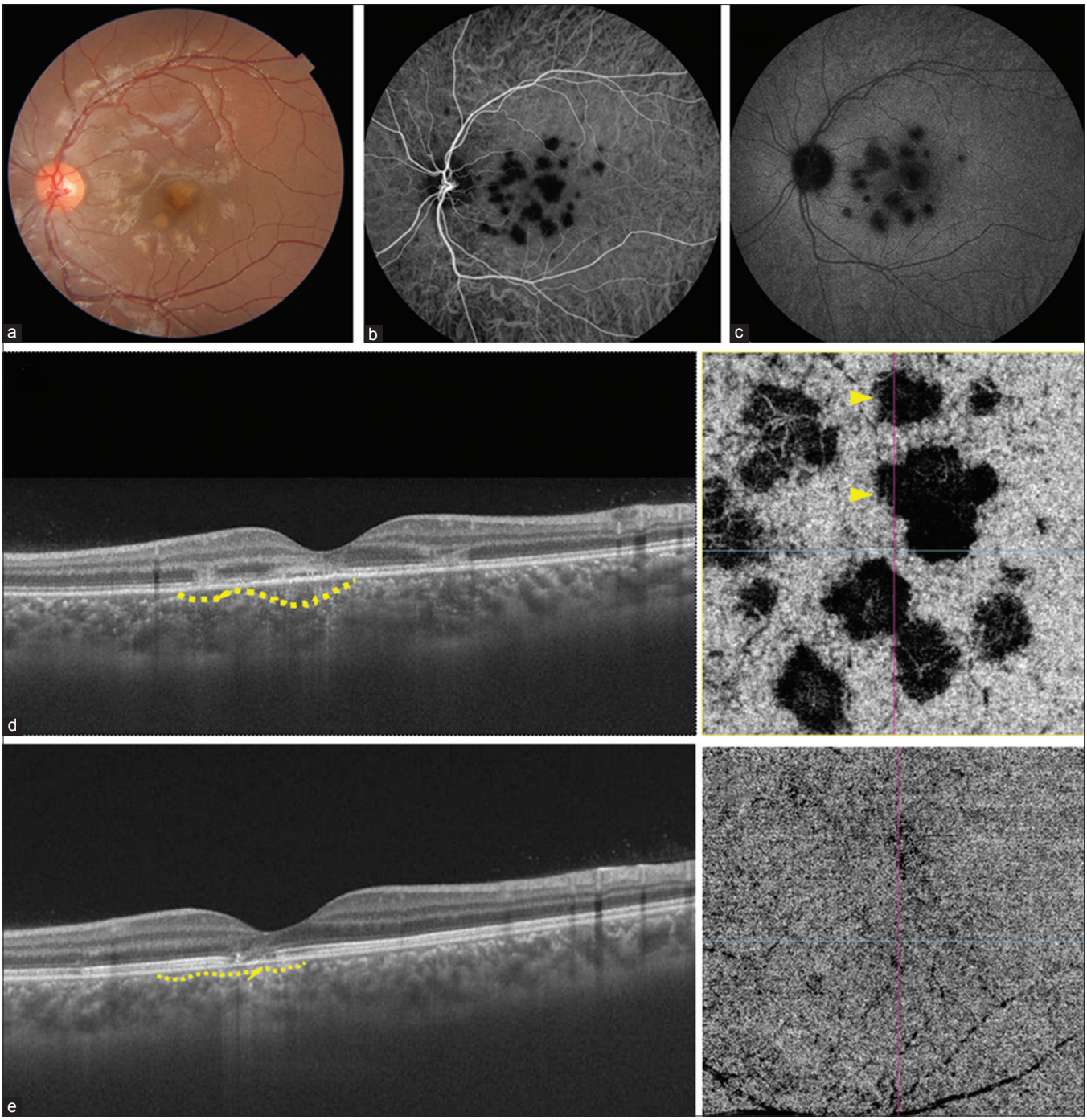

Figure 5: Multimodal imaging of a young female patient with tubercular serpiginous like choroiditis. Fundus photograph shows yellowish serpiginous like choroiditis lesions in the macula (a). Indocyanine green angiography shows early (b) and late (c) hypocyanescence suggestive of choriocapillaris ischemia. Enhanced-depth imaging optical coherence tomography shows choriocapillaris thickening and hypo-reflectivity corresponding to the serpiginous-like choroiditis lesions (yellow dotted line) (d). Optical coherence tomography angiography *en face* image at the level of choriocapillaris shows dark flow deficit areas (yellow arrowheads), which correspond to the hypocyanescent lesions on indocyanine green angiography and choriocapillaris thickening on enhanced-depth imaging optical coherence tomography (e). In the healed stage, enhanced-depth imaging optical coherence tomography shows choriocapillaris thinning (yellow dotted line) and increased choroidal reflectance (f). Optical coherence tomography angiography shows resolution of the dark areas of flow deficit

signal attenuation artifacts and true flow deficits on OCTA. There is recovery of choroidal flow, with appearance of distinct small-sized vascular channels with healing of the APMPPE lesions.

Serpiginous choroiditis and serpiginous-like choroiditis

Serpiginous choroiditis (SC) is a descriptive term for a progressive, recurrent, usually bilateral posterior uveitis characterized by a geographic pattern of choroiditis that typically

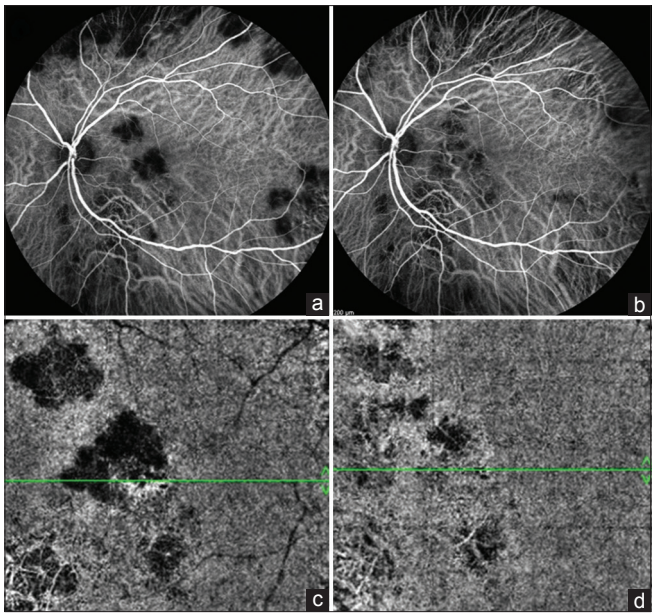

Figure 6: Differentiation between choriocapillaris ischemia and choriocapillaris atrophy in a patient of serpiginous like choroiditis on indocyanine green angiography and optical coherence tomography angiography imaging. In active serpiginous-like choroiditis, early phase indocyanine green angiography shows dark hypocyanescent lesions with fuzzy margins suggestive of choriocapillaris ischemia (a). In the healed stage of serpiginous like choroiditis, indocyanine green angiography shows hypocyanescent lesions with less fuzzy borders and visibility of ill-defined underlying choroidal vessels suggestive of choriocapillaris atrophy (b). Optical coherence tomography angiography image of the acute stage lesions shows dark areas of flow deficit corresponding to the areas of choriocapillaris ischemia on indocyanine green angiography (c). In the healed stage, there is resolution of areas of flow deficit with visibility of underlying medium sized choroidal vessels in areas of choriocapillaris atrophy (d)

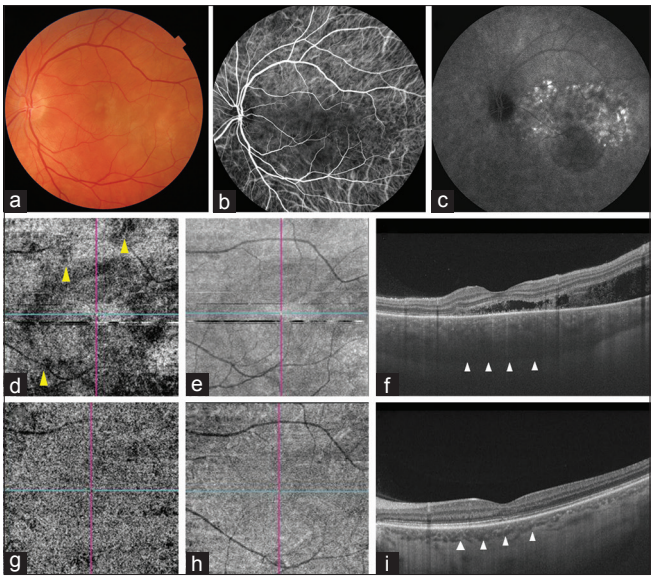

Figure 7: Multimodal imaging in a 29-year-old male patient of Vogt–Koyanagi–Harada disease. Fundus photograph of the left eye shows presence of exudative retinal detachment involving the macula with underlying creamy yellowish-white choroiditis lesions (a). Indocyanine green angiography shows multiple hypocyanescent lesions in the early phase (b) which remain hypocyanescent or isocyanescent in the late phase (c). Optical coherence tomography angiography *en face* image at the level of the choriocapillaris shows multiple dark areas of flow deficit (yellow arrowheads) suggestive of choriocapillaris ischemia (d). The structural *en face* scan does not show loss of signal transmission (e). Swept-source optical coherence tomography shows increase in total choroidal thickness and clear demarcation of the choroidoscleral interface (white arrowheads) (f). Optical coherence tomography angiography at 3-month follow-up shows resolution of most areas of flow deficit indicating resolution of choriocapillaris ischemia with minimal choriocapillaris atrophy (g). The corresponding structural *en face* scan shows no loss of signal transmission (h). Swept-source optical coherence tomography at 3-month follow-up visit shows marked reduction in the total choroidal thickness (i)

extends centrifugally from the peripapillary area with an active advancing edge and affects the overlying RPE and the outer retina. Serpiginous-like choroiditis (SLC) is a distinct form of the disease, which has been particularly described in tuberculosis endemic countries to differentiate it from classic autoimmune SC. This entity is characterized by choroidal lesions that grow in a serpentine manner with an active advancing edge and healing center. Various clinical, imaging, and histopathological studies have shown that eyes with both SC and SLC have choriocapillaris hypoperfusion due to inflammation involving the inner choroidal layers (choriocapillaris).[68-71]

ICGA shows multiple areas of hypocyanescence in the early phase (for both active and healed lesions) with fuzzy margins (active lesions). In the active stage, the lesions continue to appear hypocyanescent with ill-defined fuzzy edges in the late phase. However, in the healing stages, the borders of these hypocyanescent lesions become more discrete and well defined in the early phase of ICGA, whereas the late phase ICGA shows hypofluorescence with the islands of preserved choriocapillaris and medium-sized underlying choroidal vessels appearing as ill-defined late central isofluorescence [Fig. 5].[68-70] The hypofluorescent areas seen in the active stage represent choriocapillaris nonperfusion and correlate well with the areas of choriocapillaris thickening and hyporeflectance on EDI-OCT and areas of flow deficit on *en face* OCTA scans.

In the active stage of the disease, the EDI-OCT findings include decrease in choroidal reflectance and choriocapillaris hypoperfusion seen as increased choriocapillaris thickness and hyporeflectance in the area of the lesion. In the healing stages, EDI-OCT shows increased choroidal reflectance, choroidal thinning, and focal areas of choriocapillaris thinning and atrophy.[72,73]

In the active stage of disease, segmentation just beneath the RPE–Bruch's membrane complex shows well-demarcated "dark areas" corresponding to the choroiditis lesions. These "dark areas" represent either capillary loss/hypoperfusion or sluggish flow that may be below the limits of detection. Some of these areas may result from decreased signal transmission (due to overlying outer retinal deposits or RPE hyperplasia) rather than true loss of blood flow. Therefore, it is imperative to analyze the en face OCTA images along with the structural *en face* and cross-sectional B scan images for proper interpretation of the areas of apparent flow deficit. The hypocyanescent areas on ICGA, which represent choriocapillaris hypoperfusion or atrophy, correlate well with the areas of flow deficit on enface OCTA maps. Moreover, OCTA enables better distinction between choriocapillaris

atrophy and choriocapillaris hypoperfusion – both of which appear hypocyanescent on ICGA [Fig. 6]. This is due to demonstration of islands of preserved choriocapillaris and underlying medium to large choroidal vessels on OCTA in the healed stage which appear as mainly hypocyanescence with ill-defined late central isocyanescence on ICGA.[74]

OCTA is also an immensely valuable tool in early detection of Type 1 and Type 2 choroidal neovascularization in patients of SLC which may otherwise be difficult to detect due to the masking effect of adjacent active and healed choroiditis lesions and pigmentary changes.[75]

Vogt–Koyanagi–Harada disease

Vogt–Koyanagi–Harada (VKH) is defined as a bilateral, chronic granulomatous panuveitis, which may or may not be associated with central nervous system, auditory, and integumentary manifestations. It has been classified according to the revised diagnostic criteria.[76] Exudative retinal detachment was found to be the most common and specific clinical feature diagnostic for acute VKH disease.

The inflammation primarily involves the choroidal stroma with subsequent involvement of the RPE and outer retina. ICGA has been shown to be very sensitive, not only in revealing the presence of small choroidal inflammatory foci but also in providing information on the choriocapillaris circulation and on inflammation of the choroidal stromal vessels.

Fig. 7 illustrates the changes on ICGA and other imaging modalities in a young male patient diagnosed with VKH disease.

1. Early choroidal stromal vessel hyperfluorescence along with disturbance/delay in early choriocapillaris circulation
2. Hypocyanescent dark dots that represent choroidal stromal inflammatory foci or granulomas. They can be further subclassified into two types:
   a. Dark dots that become isofluorescent in the late phase indicate partial thickness inflammatory granulomas
   b. Dark dots that persist in the late phase indicate full thickness choroidal granulomas with overlying choriocapillaris nonperfusion.

This is the most useful sign for diagnosing subclinical disease activity and for monitoring the effect of therapy and is the last angiographic sign to resolve.

3. Fuzzy vascular patterns of large choroidal stromal vessels is seen in the intermediate phase that progresses to diffuse stromal hyperfluorescence in the late phase.[77]

EDI-OCT and SS-OCT show markedly increased choroidal thickness in acute VKH disease and are able to quantify the changes in the subfoveal choroidal thickness following steroidal treatment.[78-80] It has been shown that SS-OCT provides much better resolution images of the choroid than EDI-OCT, resulting in more measurable images especially in the acute stage of the disease when the choroid is severely swollen [Fig. 7]. Where both SS-OCT and EDI-OCT images are measurable, the measurements are comparable. In addition, choroidal granulomas in VKH may be visualized on EDI-OCT as hypo-reflective, homogeneous, and round lesions with well-defined margins with increased choroidal transmission effect visible beneath the granulomas.[81]

The OCTA images at the level of the choriocapillaris layer show multiple dark foci of variable shapes and sizes with clearly demarcated edges that represent choriocapillaris hypoperfusion. It is important to rule out loss of signal transmission on structural *en face* and cross-sectional B scan images while interpreting the dark areas as flow deficit [Fig. 7].

On comparison with ICGA, the areas of flow deficit on OCTA show consistent correlation with the hypocyanescent spots indicating true choriocapillaris ischemia. Even in the clinical absence of choroiditis lesions or exudative retinal detachment, OCTA helps in picking up foci of choriocapillaris hypoperfusion/flow deficit, which correlates well with the hypocyanescent spots on ICGA thereby helping in the detection of subclinical active disease and instituting appropriate therapy. The dark foci on OCTA correspond to thickening and hyporeflectivity of the choriocapillaris layer on EDI-OCT. The resolution of flow deficit areas on OCTA correlates well with overall decrease in the subfoveal choroidal thickness and normalization of choriocapillaris thickness and pattern on EDI-OCT.[82] Thus, OCTA is an effective adjunct that may be sensitive in monitoring disease activity in VKH and is a useful non-invasive too in the diagnosis and management of this condition.

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Conflicts of interest

There are no conflicts of interest.

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