Ophthalmologica

Review Article

Ophthalmologica 2023;246:278–294
DOI: 10.1159/000533910

Received: May 30, 2023
Accepted: August 27, 2023
Published online: September 13, 2023

Pushing Retinal Imaging Forward: Innovations and Their Clinical Meaning – The 2022 Ophthalmologica Lecture

Enrico Borrelli[a, b] Alessandro Berni[a, b] Leonardo Mastropasqua[c] Giuseppe Querques[a, b] Srinivas R. Sadda[d, e] David Sarraf[d, f] Francesco Bandello[a, b]

[a]Vita-Salute San Raffaele University Milan, Milan, Italy; [b]IRCCS San Raffaele Scientific Institute, Milan, Italy; [c]Department of Medicine and Science of Ageing, Ophthalmology Clinic, University G. D'Annunzio Chieti-Pescara, Chieti, Italy; [d]Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [e]Doheny Image Reading Center, Doheny Eye Institute, Los Angeles, CA, USA; [f]Department of Ophthalmology, David Geffen School of Medicine at UCLA, Stein Eye Institute, Los Angeles, CA, USA

Keywords
Retinal imaging · Ophthalmologica Lecture · Optical coherence tomography · Optical coherence tomography angiography · Macula

Abstract
Retinal imaging has greatly expanded our understanding of various pathological conditions. This article presents a summary of the key points covered during the 2022 Ophthalmologica Lecture held at the Euretina Congress in Hamburg. The first part of the article focuses on the use of optical coherence tomography angiography to examine and comprehend the choroid in age-related macular degeneration (AMD). Subsequently, we delve into the discussion of the "postreceptor neuronal loss" theory in AMD, which was studied using en face structural optical coherence tomography (OCT). Following that, we explore pertinent findings obtained through cross-sectional OCT in retinal and optic nerve diseases, such as AMD, diabetic macular edema, pathologic myopia, central serous chorioretinopathy, and Leber's hereditary optic neuropathy.

Introduction

Retinal imaging is an essential modality for the assessment of patients with different retinal disorders as it provides high-resolution morphological information about the retinal and choroidal layers. Imaging techniques that include structural optical coherence tomography (OCT) and OCT angiography (OCTA) are now key technological tools for the evaluation of macular and retinal diseases and offer new and important insights into the pathogenesis of many retinal and choroidal disorders, including age-related macular degeneration (AMD), diabetic macular edema (DME), myopic macular neovascularization (MNV), central serous chorioretinopathy (CSC). Also, retinal imaging has been employed to study optic nerve disorders, including Leber's hereditary optic neuropathy (LHON). Importantly, these imaging systems can illustrate important findings that may be associated with disease progression and visual prognosis (i.e., imaging biomarkers).

In this review, we will summarize the findings on structural OCT and OCTA studies of the retina and

karger@karger.com
www.karger.com/oph

Correspondence to:
Enrico Borrelli, borrelli.enrico@yahoo.com

choroid in AMD. Moreover, we will highlight the potential clinical benefit of employing imaging techniques to define biomarkers associated with disease progression.

OCTA to Improve Our Understanding in AMD

Intermediate AMD

AMD is the leading cause of severe visual impairment in adults older than 50 years [1]. With the growing aging population, the global burden of AMD is expected to rise to around 288 million people [1].

AMD may be classified into different stages including the advanced forms that may be characterized by the presence of a MNV and/or retinal pigment epithelium (RPE) atrophy. These sequelae are usually preceded by early and intermediate stages which are characterized by the presence of drusen and/or pigmentary abnormalities [2]. Although many factors are implicated in the pathogenesis of AMD, robust evidence suggests that choroidal ischemia plays a major role in the development and progression of AMD [3, 4].

The choriocapillaris (CC) is a highly anastomosed network of capillaries located between Bruch's membrane and the medium-sized choroidal vessels. The homeostasis of the outer retina relies on the CC's critical functions. Specifically, the CC provides nutrients and oxygen to the RPE and photoreceptors and removes the metabolic waste material produced by the RPE. Similarly, the CC's health is strongly dependent on the outer retinal structures. As an example, the physiological regulation of the CC is based on vascular endothelial growth factor (VEGF) levels, whose production is dependent on the RPE. Therefore, the CC can be considered as an integral component of a tightly knit and symbiotic unit with the photoreceptors and RPE. The dysfunction of this unit may lead to the development of drusen between the RPE and Bruch's membrane and progressive photoreceptor, RPE, and CC loss.

Different approaches have been used to demonstrate that microvascular choroidal changes are associated with AMD. CC dropout has been shown by histopathologic studies to be present and progressive throughout the different AMD stages [5]. Mullins et al. [6] found that the density of drusen and other sub-RPE deposits is inversely correlated with the density of CC vessels. In addition, the number of nonfunctional capillary segments (i.e., "ghost" vessels) is increased in the presence of drusen, which may impair trophic signaling between the RPE and CC, eventually leading to endothelial cell loss.

OCTA has significantly improved our ability to visualize and assess the CC as this imaging modality has overcome significant limitations of previous dye-based imaging techniques for evaluation of the CC [7]. On en face OCTA imaging of the CC, we may visualize small dark regions, referred to as flow (or signal) voids, which alternate with granular bright areas representing CC flow. Advanced image processing has facilitated quantification of the total number and average size of CC signal voids in healthy and AMD eyes [8–12].

Using OCTA, the CC has been extensively studied in intermediate AMD eyes [13–16]. In an initial study, 42 patients (42 eyes) with intermediate AMD were compared with 20 healthy controls (20 eyes) [13]. The non-detectable perfused CC area, which is a measure reflecting the total CC vascular dropout, and the average CC signal void size were quantified using a spectral domain OCTA device. In order to mitigate shadowing and projection artifacts from confounding the analysis, the CC directly beneath drusen and major retinal vessels was excluded. Moreover, intermediate AMD patients were divided according to the fellow eye status, yielding a group of bilateral intermediate AMD patients and a group with unilateral intermediate AMD and neovascular AMD in the fellow eye. This spectral domain study showed no differences in the non-detectable perfused CC area among the three groups. However, the average CC signal void size was significantly increased in patients with unilateral intermediate AMD, as compared with both bilateral intermediate AMD and healthy individuals. We speculate that this apparent discrepancy between non-detectable perfused CC area and signal void size could be secondary to a compensatory VEGF-driven CC hypervascularity under the hypoxic RPE. Since fellow intermediate AMD eyes of patients with unilateral neovascular AMD are known to be at higher risk of progressing to late AMD [17], these results would seem to corroborate the presence of an ischemic choroidopathy that may predispose to the development of neovascularization. Therefore, CC alterations appear to play a relevant role in the pathogenesis of neovascular AMD. A major limitation of the latter study was the inability to evaluate the CC beneath drusen as a spectral domain device was employed to analyze images. However, previous histopathological studies have suggested that drusen may preferentially develop over areas of vascular depletion [6]; therefore, it was hypothesized that OCTA may show zonal differences in CC perfusion in patients with intermediate AMD.

To clarify whether the CC perfusion may have topographical differences in patients with intermediate AMD, in a follow-up study [14], we employed a swept-

source OCTA device which facilitated a more precise assessment of the CC under drusen owing to a longer wavelength that improves RPE penetration [18]. In this swept-source study, 30 eyes with intermediate AMD and 30 healthy controls were prospectively enrolled. Importantly, CC images were investigated in three different regions in order to provide a topographical analysis, as follows: (i) drusen region, (ii) 150-μm-wide ring around the drusen margin, and (iii) drusen-free region. Compared with controls, intermediate AMD eyes showed an overall lower number of signal voids, a greater signal void average size, and a greater signal void total area. Of note, changes in these metrics were greater in regions beneath and near drusen, corroborating previous findings that drusen may preferentially develop over areas of vascular depletion [6].

Retinal imaging has been also employed to investigate the outer retinal dysfunction that results as a consequence of CC impairment in intermediate AMD eyes. Data from several studies using different approaches reported that photoreceptors may be affected in AMD eyes [19, 20]. An histopathological report by Curcio and colleagues [19] showed that eyes with drusen are characterized by a significant reduction in photoreceptor number. Moreover, using adaptive optics scanning laser ophthalmoscopy, Boretsky et al. [20] demonstrated a progressive reduction in photoreceptor density throughout progressive AMD stages. Since CC flow appears to be crucial for proper sustenance of photoreceptors, the reduction in CC perfusion in AMD eyes might provide a potential rationale for damage to photoreceptors via an ischemic mechanism [5]. Therefore, multimodal imaging was employed to explore associations between CC alterations and photoreceptor damage in intermediate AMD eyes [21]. The latter damage was quantitatively assessed by analyzing the reflectivity of the en face OCT images segmented at the ellipsoid zone (EZ) level. The reflectivity signal arising from the EZ seems to originate from the photoreceptor inner segment ellipsoids, which are densely packed with mitochondria (Fig. 1, 2) [22]. Assuming that both damage and dysfunction of photoreceptors may be visualized as hyporeflective areas on the en face image, several reports have analyzed the reflectivity of the EZ as a surrogate for photoreceptor damage [23, 24]. A major challenge in using en face structural OCT to assess photoreceptor reflectivity is the presence of ancillary patient-dependent factors (e.g., cataract) that may significantly influence structure brightness and confound comparisons across a cohort. To solve the latter problem, several reports have successfully "normalized" the images [25–28].

In a study of 35 patients (35 eyes) with intermediate AMD and 35 healthy individuals (35 eyes), swept-source OCT and OCTA imaging were employed to topographically correlate photoreceptor and CC impairment, respectively [21]. In the latter study, the "normalized" EZ reflectivity was significantly reduced in intermediate AMD eyes, even after considering only regions without drusen. The latter results suggested a significant and diffuse impairment of photoreceptors in these eyes. More importantly, the "normalized" EZ reflectivity was positively associated with CC perfusion in the drusen-free region, while no relationship between these two parameters was seen in regions with drusen, as well as in healthy eyes. Therefore, these results suggested that in AMD, there appears to be some pathological dependence between CC perfusion and photoreceptor impairment, at least in regions without drusen.

In intermediate AMD, the relationship between photoreceptor damage and CC perfusion was also investigated using multifocal electroretinogram (mfERG) and OCTA, respectively [16]. In the latter study, 17 eyes from 17 patients with intermediate AMD were prospectively enrolled. In order to provide a topographical analysis, the amplitude and implicit time of mfERG amplitudes and implicit times of N1 (first negative component) and P1 (first positive component) of the first-order kernel recorded in the two central rings (i.e., R1 and R2) were included in the analysis. The latter strategy was based on the assumption that the two central rings overlay a 2.8-mm-diameter circle area centered on the fovea, similar to the region covered by the OCTA scan. Overall, the latter study demonstrated that both the total area covered by signal voids and average signal void size had a significant direct relationship with N1 implicit time. As the N1 wave is thought to originate from the postreceptoral signals after cones, whereas the P1 wave is known to be more influenced by the inner retina, we assumed that the CC changes may mainly affect post-photoreceptor function. In addition, the association between CC changes and mfERG implicit time, but not response amplitude, may suggest the presence of an association with neuroretinal functional abnormalities rather than actual cell loss [29].

Type 3 MNV in Neovascular AMD

Type 3 MNV was first described by Hartnett et al. [30] in 1992 to refer to a distinct form of intraretinal MNV associated with AMD. This lesion was described as a "deep retinal vascular anomalous complex" located in the outer retina that may be associated with a pigment epithelium detachment (PED). Subsequently, Yannuzzi et al. [31] coined the term retinal angiomatous proliferation (RAP) to

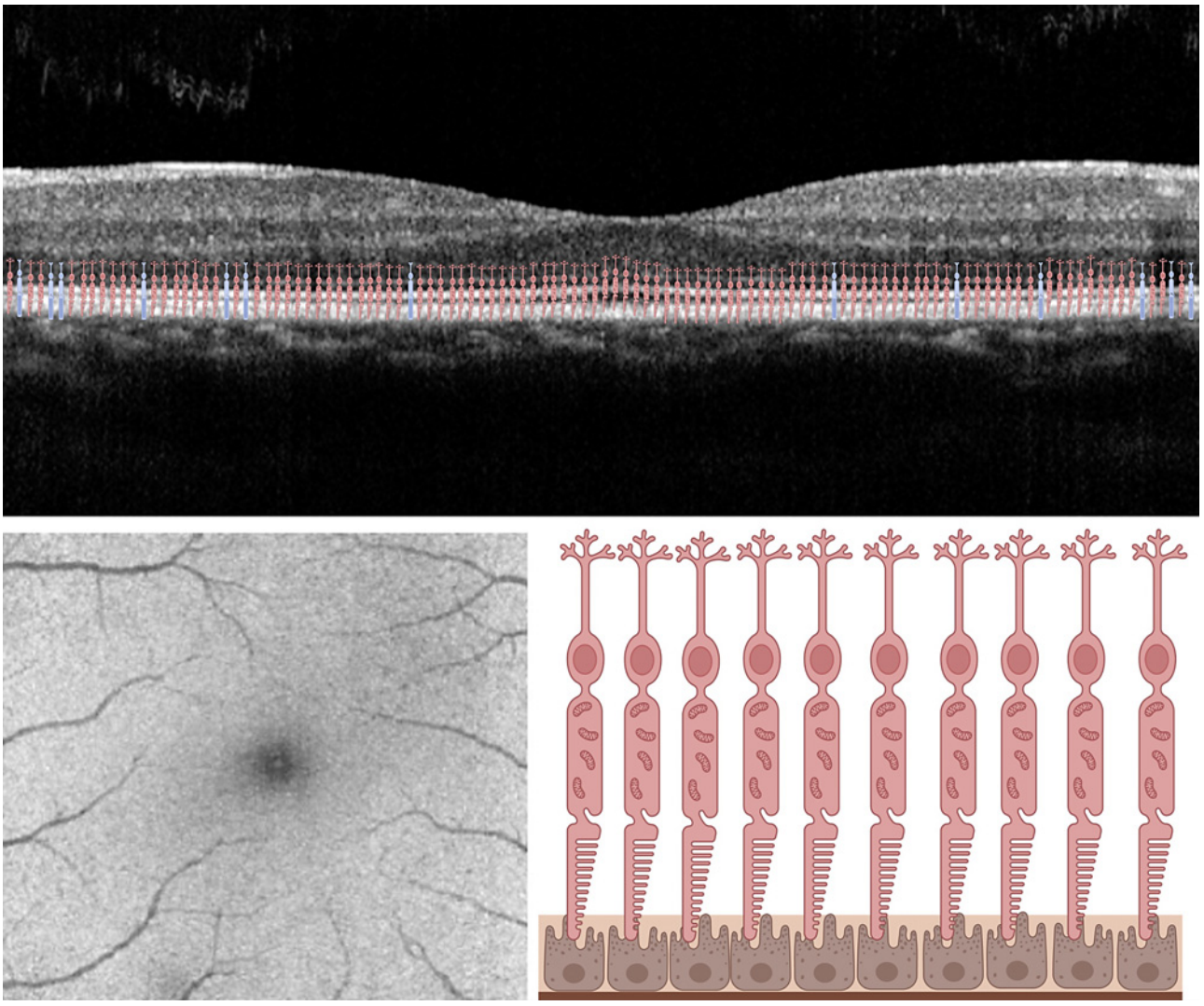

Fig. 1. Representative image of photoreceptor status in a healthy individual. The OCT B-scan image (top) showing the integrity of the outer retina is overlaid by a cartoon render of healthy photoreceptors. The corresponding EZ en face image (bottom left) displays a high and uniform reflectivity representative of preserved photoreceptor structure. A magnification of the cartoon render of healthy photoreceptors (bottom right) displays densely packed mitochondria at the inner segment level.

refer to this peculiar type of MNV. Finally, the term type 3 MNV was employed in order to expand Gass' anatomical classification for AMD-associated MNVs [32].

Over recent years, various authors have sought to elucidate the actual origin of type 3 MNV using both histologic and advanced structural OCT and OCTA imaging analysis. Histopathological studies demonstrated that these lesions contain vascular elements of retinal derivation, including collagenous material and Müller cell processes, which implant into the sub-RPE space without evidence of connections with the CC [33, 34]. Furthermore, imaging studies clearly showed that type 3 MNV originates from the deep retinal capillary plexus and descends toward the RPE which is usually detached because of the presence of an associated fibrovascular, drusenoid, or serous PED [35–39].

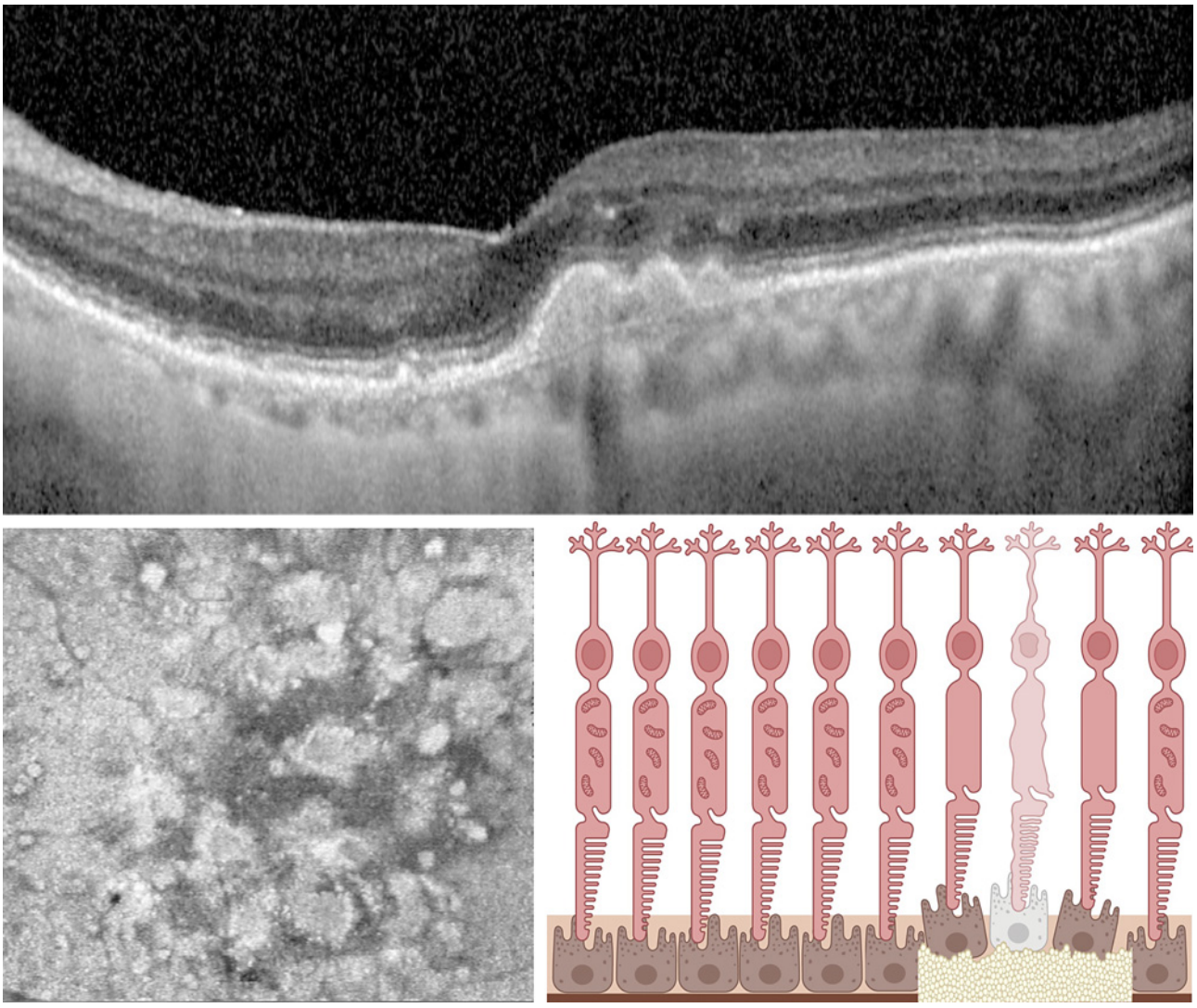

Fig. 2. Representative image of photoreceptor status in a patient with intermediate AMD. The OCT B-scan image (top) demonstrates the presence of large drusen with associated disruption of the EZ layer. The corresponding EZ en face image (bottom left) demonstrates areas of reduced reflectivity indicating photoreceptor impairment mainly co-localized with presence of drusen. In the cartoon render image (bottom right), photoreceptors in patients with AMD are characterized by loss of mitochondria secondary to RPE impairment, presence of drusen and CC hypoperfusion.

The development of type 3 MNV appears to be associated with an imbalance between VEGF and other RPE-derived cytokines [40]. It was indeed demonstrated that in eyes with untreated neovascular AMD, the aqueous humor levels of VEGF were significantly higher in eyes with type 3 MNV versus eyes with type 1 or type 2 MNV, which originate from the choroid rather than the retina [40]. Therefore, outer retinal ischemia was proposed as a driving mechanism, eventually leading to the development of this form of MNV. The latter theory was further corroborated by structural OCT studies showing a reduced choroidal thickness in subjects with AMD and type 3 MNV [41, 42].

Considering the central role of the CC in the nourishment of the outer retina and RPE, several OCTA reports have investigated the CC in eyes with

type 3 MNV. In a spectral domain OCTA study, we quantitatively evaluated the CC in eyes affected by type 3 MNV and in the fellow unaffected eyes (i.e., without evidence of MNV) [43]. In addition, the latter eyes were compared with the fellow unaffected eyes of patients with unilateral type 1 or 2 MNV. Specifically, 21 patients with unilateral type 3 MNV and 20 individuals with unilateral type 1 or 2 MNV were analyzed. In the OCTA analysis, both the total area occupied by signal voids and the average CC signal void size (i.e., both variables reflecting the CC hypoperfusion) were significantly higher in eyes with type 3 MNV as compared with the fellow unaffected eyes. These findings suggest that CC hypoperfusion may cause ischemic abnormalities of the RPE, eventually leading to the development of type 3 MNV. Notably, the fellow unaffected eyes of patients with unilateral type 3 MNV showed a greater CC impairment as compared with the fellow unaffected eyes with unilateral type 1/2 MNV. The latter results appear to suggest that CC hypoperfusion affects both eyes in patients with unilateral type 3 MNV, which may partially explain the increased risk of these unaffected eyes to develop type 3 MNV over time.

A subsequent study employing swept-source technology and image compensation with structural information confirmed previous findings of CC hypoperfusion in eyes with type 3 MNV [44]. In this study, 26 type 3 MNV eyes from 21 patients and 26 intermediate AMD eyes from 17 patients were analyzed. As compared with intermediate AMD eyes, both the total area occupied by signal voids and the average CC signal void size were increased in eyes with type 3 MNV. Taken together, results from OCTA studies appear to corroborate the hypothesis that the CC impairment may play a relevant role in the development of type 3 MNV, perhaps even greater than in eyes with type 1/2 MNV.

OCTA has provided a reliable and detailed illustration of the microvascular morphology of type 3 MNV. These lesions appear to be characterized by a distinct high-flow, tuft-like capillary network which is localized in the outer retina and appears to develop from the deep retinal capillary plexus with downgrowth to the sub-RPE space [7]. Notably, precursor lesions without exudation (i.e., nascent type 3 MNV) may precede more mature type 3 lesions associated with significant exudation and may also be visualized on OCTA images with the presence of flow confined to the outer retina and associated with the existence of hyper-reflective foci (HRFs) on structural OCT images [7].

OCTA data are commonly visualized using two-dimensional (2D) B-scan or en face images [45]. However, a 2D visualization may be inadequate to describe vascular entities that span multiple retinal layers and extend vertically (e.g., type 3 MNV) to the RPE. Moreover, 2D images may be limited by overlapping anatomy and vessel foreshortening [45]. Therefore, several reports have employed a three-dimensional (3D) volume-rendered visualization of OCTA data with projection artifact removal to describe intraretinal lesions, including type 3 MNV [46–52].

In two previous reports, 3D OCTA visualization was employed to fully characterize type 3 MNV in vivo (Fig. 3) [53, 54]. In an initial study, 13 patients (15 eyes) with AMD and treatment-naïve type 3 MNV were prospectively enrolled [53]. In order to obtain 3D visualization of type 3 lesions, a previously validated algorithm [52] was applied to OCTA volume data that were first processed with a volume projection removal algorithm. The latter analysis showed that treatment-naïve type 3 lesions appear as vascular branches originating from the deep retinal capillary plexus. Of note, a number of these vascular branches may suddenly terminate within the outer retinal layers, as they may constitute immature (or nascent) lesions. In contrast, other branches appear to reach the sub-RPE space and may eventually connect and merge with other branches to form a glomerular lesion. Furthermore, 3D visualization can enhance the recognition of type 3 lesions as a higher number of branches emerging from the deep retinal capillary plexus may be distinguished with 3D versus 2D visualization (35 vs. 22 lesions identified, respectively). Taken together, these findings seem to suggest that a volume-rendered 3D visualization may be more appropriate to characterize type 3 lesions by resolving the limitations of anatomic overlap.

In a subsequent study, a volume-rendered 3D visualization was employed to provide a longitudinal description of changes in MNV features occurring after anti-VEGF intravitreal therapy [54]. Histologically, type 3 lesions do not completely regress after anti-VEGF treatment [55, 56]. This was speculated to be related to their intrinsic structure, as type 3 lesions have a complex organization [55]. Therefore, using volume-rendered 3D OCTA, we studied the modifications occurring to 14 treatment-naïve eyes with type 3 MNV undergoing a loading dose of anti-VEGF therapy [54]. At the follow-up visit (i.e., 30 days after the third anti-VEGF injection), all the analyzed eyes were still characterized by the presence of a type 3 MNV complex, although a number of eyes showed absence of exudation after treatment. Our analysis also revealed that the number of branches

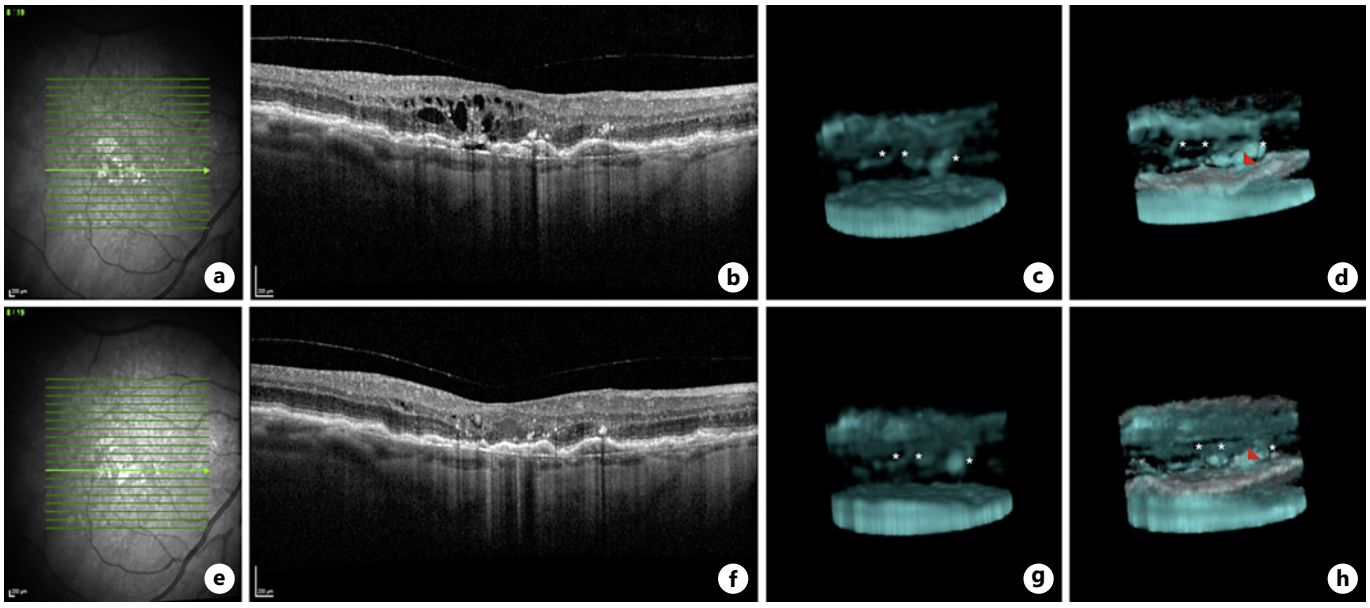

Fig. 3. Multimodal imaging of the left eye of an 80-year-old woman diagnosed with type 3 MNV. Before therapy (**a–d**); after therapy (**e–h**). The green arrow in the near-infrared reflectance image (**a**, **e**) illustrates the location and direction of the structural OCT B-scan (**b**, **f**) demonstrating presence of a type 3 MNV with associated intraretinal fluid. The 3D volume rendering visualization of flow within the region with the type 3 MNV complex (**c**, **g**) demonstrates the presence of several branches (highlighted with white asterisks) originating from the deep vascular complex and moving downward obliquely. These neighboring branches seem to converge into various adjacent glomerular-like lesions (red arrowheads). The 3D volume rendering visualization combining both flow (cyan) and structural (white) data (**d**, **h**) of the same region reveals that glomerular lesions (red arrowheads) extend to the RPE/sub-RPE space. After three intravitreal aflibercept injections, the structural OCT (**b**, **f**) displays absence of signs of exudation. The 3D volume rendering visualization of flow (**c**, **g**) shows the presence of two residual intraretinal vascular branches (white asterisks) that do not appear to reach the RPE/sub-RPE space in the 3D visualization of combined flow and structural information (**d**, **h**). (Reproduced with permission from Borrelli et al. [54], 2021 © Elsevier.)

significantly decreased after treatment (mean number of 2.5 ± 0.7 vascular branches at baseline and 1.4 ± 0.6 at the follow-up visit). More importantly, the extent of decrease in type 3 MNV branching was directly correlated with reduction in central macular thickness and improvement in visual acuity. The latter finding may suggest that a volume-rendered 3D OCTA visualization of vessel branching may provide an imaging biomarker of treatment response.

En face Structural OCT to Investigate the Postreceptor Functional Loss in AMD

Although AMD is primarily considered to be an outer retinal disease, increasing evidence suggests that the inner retinal layers are also affected from the early stages of this disease [57, 58]. The involvement of the innermost retinal layers in AMD may be explained by at least 3 potential hypotheses: (i) postreceptoral ischemia, (ii) mechanical compression from underlying drusen, and (iii) postreceptor functional loss [15]. According to the latter theory, the neuronal damage occurring in the inner retina is caused by disorganized synaptic architecture and transneuronal degeneration over time, due to chronically reduced input to the inner retina secondary to photoreceptor damage [15, 58, 59]. In a structural OCT study [15], 68 eyes from 68 patients with intermediate AMD and 50 eyes from 50 healthy subjects were retrospectively analyzed to better understand the relationship between inner neuronal loss and photoreceptor damage in intermediate AMD. While the latter was assessed by analyzing the EZ reflectivity, the inner neuronal loss was quantified by measuring the ganglion cell complex (GCC) thickness. In the intermediate AMD cohort, the average or minimum GCC thickness was thinner, as compared with healthy controls. Notably, the EZ "normalized" reflectivity appeared to have a strong significant direct relationship with GCC thickness in AMD patients, while no relationship between these two parameters was seen in healthy eyes. Furthermore, those eyes exhibiting a greater outer retinal damage after the transition from

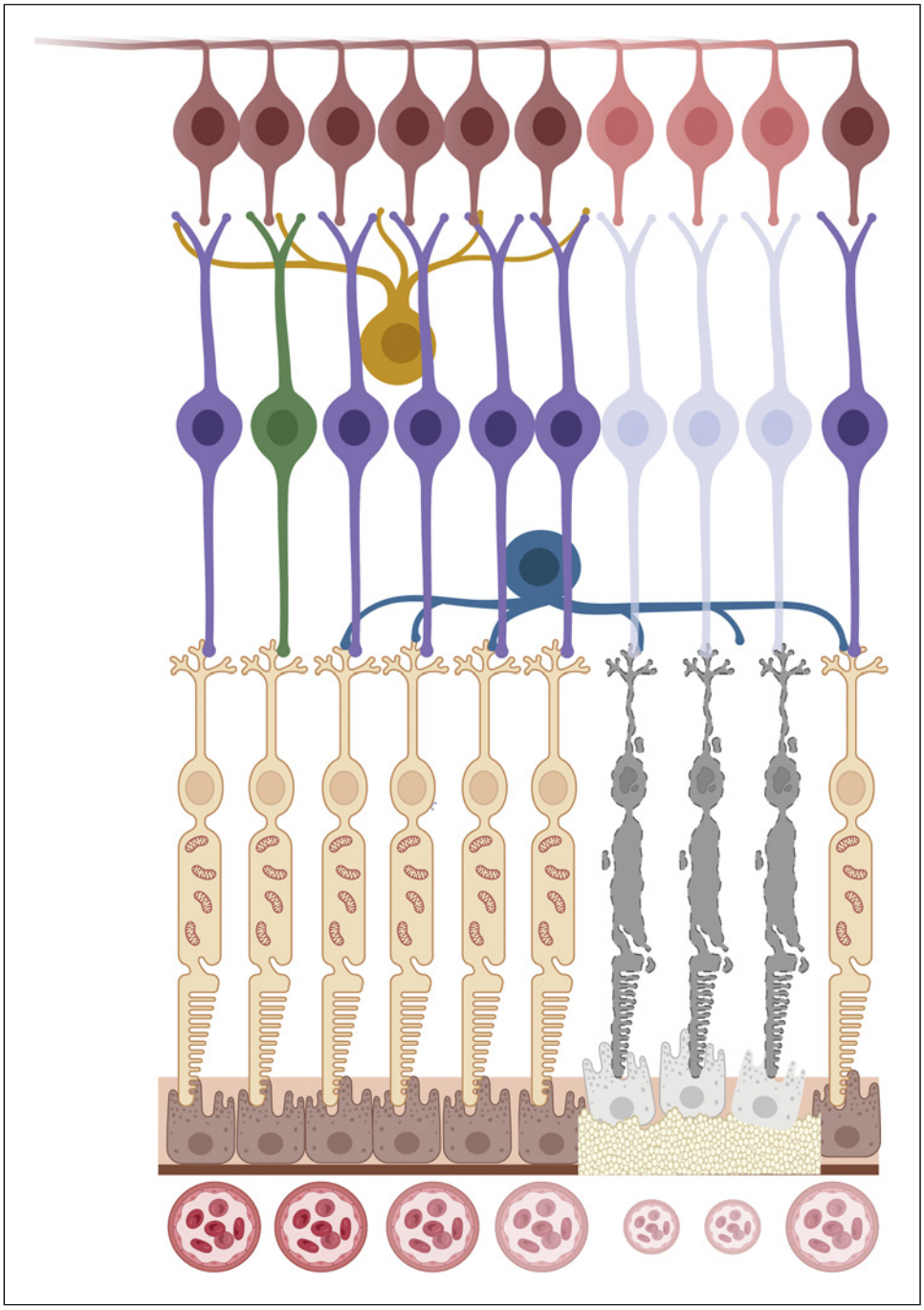

Fig. 4. Cartoon rendered representation of the inner retinal involvement in AMD. According to the postreceptor functional loss theory, subsequent damage to photoreceptors is responsible for a chronically reduced input to the inner retina, resulting in transneuronal degeneration over time.

intermediate to neovascular AMD were features by a larger GCC longitudinal thinning [60]. Thus, these results may suggest that in AMD there is some pathologic dependence between these two neuroretinal structures and would seem to corroborate the postreceptoral theory for the explanation of the inner retina damage occurring in intermediate AMD (Fig. 4).

Identification of Biomarkers Using Cross-Sectional Structural OCT

Structural OCT has become an essential tool for the assessment of individuals with retinal and optic nerve disorders as it provides high-resolution morphological information about the retinal and choroidal layers.

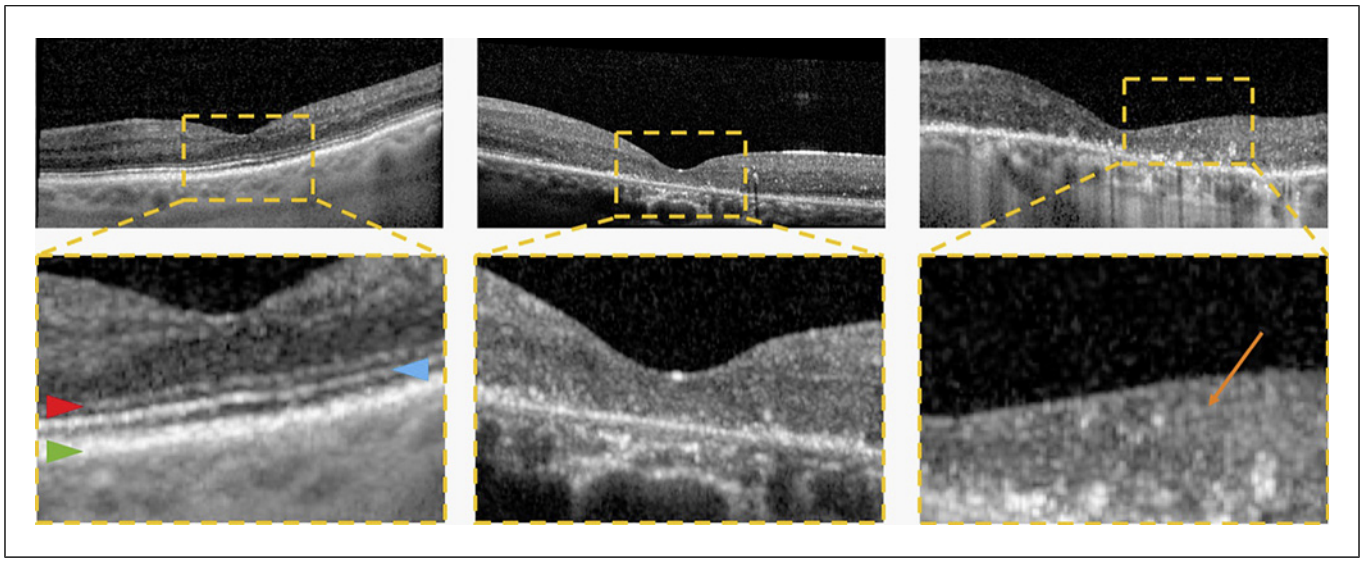

Fig. 5. OCT images showing findings associated with worse visual outcomes in patients with DME. Representative horizontal optical coherence tomography (OCT) B-scan images through the fovea from three eyes with resolved DME (above). A magnified visualization of the foveal region is reported in the bottom row. OCT images were graded for qualitative features previously proposed as signs of neuroretina damage. In details, the appearances of the external limiting membrane (ELM – red arrowhead), ellipsoid zone (EZ – blue arrowhead), and retinal pigment epithelium (RPE – green arrowhead) were graded for integrity. These three OCT bands were intact in the first case (left) and absent in the second case (middle). The presence of disorganization of the retinal inner layers (DRIL – highlighted with the orange arrow) was also graded (right). Presence of interruption of the ELM or DRIL was associated with worse visual outcomes in patients with DME. (Reproduced with permission from Borrelli et al. [62], 2022 © Elsevier.)

OCT can also be extremely useful to predict and evaluate treatment response and guide therapeutic strategies.

OCT has facilitated the identification of specific features associated with disease progression, which may play a role in a patient-based decision-making process and may be thus defined as biomarkers [61]. Of note, biomarkers can be either *prognostic* or *predictive:* while prognostic biomarkers represent clinical or biological characteristics providing information on patients' outcomes regardless of the treatment [61], a predictive biomarker may indicate the potential benefit from treatment for a specific patient, as compared to the baseline condition [61]. Several prognostic and predictive OCT biomarkers have been described as structural qualitative or quantitative features associated with different retinal disorders [62–71].

Age-Related Macular Degeneration

Structural OCT is an essential diagnostic tool for the evaluation of individuals with AMD as provides anatomic details regarding the neuroretina and RPE. Previous reports have identified several OCT biomarkers associated with late AMD (i.e., exudative and neovascular AMD) occurrence and progression. These biomarkers include the size, volume, and subtype of drusen, the presence of HRFs, thin double-layer sign, and subretinal drusenoid deposits (i.e., also known as reticular pseudodrusen), thinning of the outer retina, photoreceptor degradation, choroidal thinning, and CC loss [72–79].

Diabetic Macular Edema

Diabetic retinopathy is a leading cause of visual impairment [80]. DME is a common complication as this may occur in approximately 12% of diabetic retinopathy patients [81]. Structural OCT is commonly employed in the management of patients with DME. Furthermore, this imaging modality grants a qualitative and quantitative assessment of structural parameters of the macula with good precision and reproducibility. Although DME is defined by an accumulation of intraretinal and/or subretinal fluid with concomitant retinal thickening, this disease may also be associated with a progressive structural loss of the neuroretina which may impact visual outcome for these patients [82–86].

Significantly, the utilization of OCT in evaluating the retina of DME eyes has yielded both qualitative and

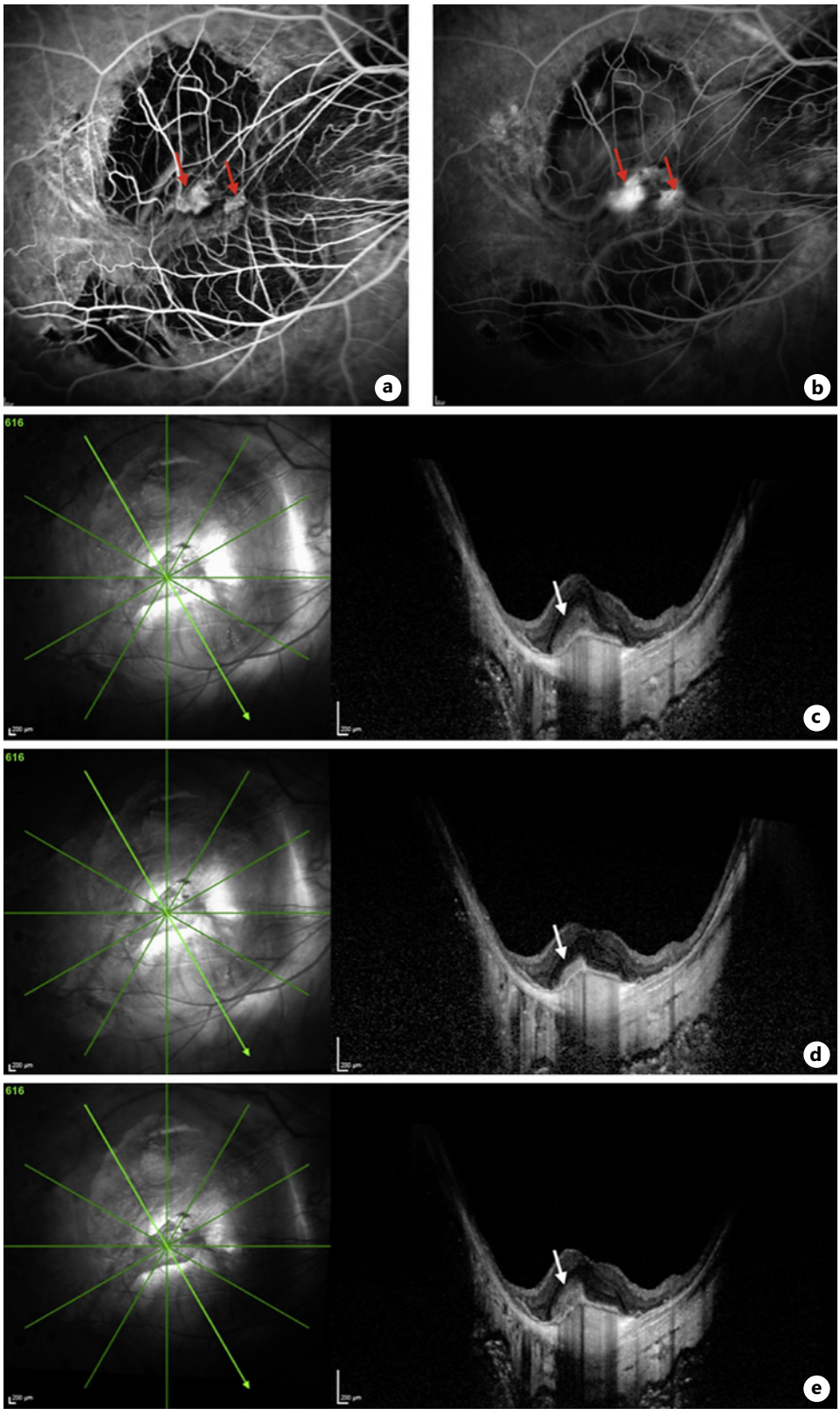

Fig. 6. Multimodal imaging of a patient with successfully treated myopic MNV and developing disease recurrence. **a**, **b** Early and late-phase fluorescein angiography (FA) reveals a hyperfluorescent region (red arrow) with leakage corresponding to myopic MNV. **c** Structural optical coherence tomography (OCT) B-scan confirms the presence of an active type 2 myopic MNV (white arrow) with fuzzy margin (visual acuity of 20/80 Snellen) in the subretinal space. **d** After 2 anti-VEGF injections, structural OCT shows resolution of exudation (baseline visit in our study) and reduction of the subretinal hyper-reflective material (SHRM) (visual acuity of 20/32 Snellen). Furthermore, baseline risk factors for disease recurrence are visualized, including a large region of patchy atrophy and a wide inactive lesion. At the 14-month follow-up visit, structural OCT (**e**) confirms the presence of disease recurrence with the type 2 MNV lesion that is characterized by increased thickness and a fuzzy margin (visual acuity of 20/63 Snellen) (Reproduced with permission from Borrelli et al. [64], 2022 © British Medical Journal.)

quantitative evaluations, resulting in several biomarkers linked to the advancement of diseases and visual outcomes. These biomarkers include thinning of the inner and outer retinal layers [62], the presence of HRFs within the retina [87], and disorganization of the inner retinal layers [88].

In a previous study using structural OCT, specific qualitative and quantitative modifications of the outer retina appeared to be correlated with worse long-term visual acuity in DME eyes undergoing anti-VEGF treatment (Fig. 5) [62]. Specifically, the latter study enrolled patients with an extended follow-up (i.e., >5 years) and confirmation of DME resolution in at least one assessment (study visit) after 5 years of visits following the initiation of anti-VEGF intravitreal treatment. Fifty patients (61 eyes) were analyzed and two subgroups (i.e., 24 eyes with a visual acuity lower than 20/40 constituting a "poor/intermediate vision" group and 37 eyes with a visual acuity higher than 20/40 constituting a "good vision" group). In the latter study, the neuroretina was qualitatively and quantitatively assessed with a topographic analysis in order to detect changes occurring at the level of the inner and outer retina. In addition to previous studies using structural OCT that have demonstrated that eyes with resolved DME may manifest a thinning of the outer retinal layers [83–86], results from this study [62] demonstrated that the thicknesses of the foveal and parafoveal outer retina are significantly lower in subjects with worse long-term visual outcomes. Notably, damage of the external limiting membrane in the foveal region was also demonstrated to be associated with worse visual outcomes in these patients.

Myopic MNV

MNV represents a common sight-threatening complication in pathologic myopia as it may affect up to 5–11% of these individuals [89]. Although anti-VEGF therapy is efficacious for treatment of myopic MNV and these lesions typically show a rapid therapeutic response, patients may experience recurrences that significantly impact long-term visual outcomes [90, 91]. However, early diagnosis and timely treatment of active myopia-associated MNV can improve visual outcomes in these patients [92].

A recent study [64] investigated the presence of OCT biomarkers associated with a higher likelihood for development of exudative recurrence in eyes with newly diagnosed myopic MNV that were successfully treated with anti-VEGF therapy (Fig. 6). In this study, 64 treatment-naïve eyes with myopic MNV were analyzed once the exudation was resolved after anti-VEGF therapy. Potential factors which could correlate with disease recurrence within 36 months after resolution of exudation were assessed, including demographics, clinical characteristics, and structural OCT findings. Among the demographic and clinical factors, age, gender, and the number of anti-VEGF injections to resolve exudation at the first occurrence did not significantly impact the 3-year incidence of recurrence. However, the maximum MNV width measured on structural OCT images at baseline was associated with a greater risk for disease recurrence. The latter finding was in agreement with previous fluorescein angiography studies showing that baseline MNV size was a significant risk factor for recurrence of exudation [93]. Of note, the MNV size may indirectly reflect the extent of choroidal flow abnormalities, which may play an important pathogenic role driving MNV growth.

In addition, the same study also demonstrated that a larger region of patchy atrophy was also associated with a greater risk of disease recurrence. The latter finding further confirms that similar mechanisms related to choroidal ischemia may drive either development of MNV or atrophy. These findings may help in the identification of patients at higher risk of recurrence and inform the best strategy for follow-up.

Central Serous Chorioretinopathy

CSC is a common disease usually affecting the working-age population and typically characterized by idiopathic accumulation of sub-RPE and subretinal fluid [94–96]. While the acute form of CSC is notable for a self-limited course with spontaneous resolution of fluid and an excellent prognosis [97], the chronic form of CSC can be complicated by persistent fluid and the development of MNV [98], cystoid macular degeneration [99], and large regions of RPE atrophy [100, 101]. These factors may portend a worse visual prognosis and can occur even after the resolution of subretinal fluid ("resolved" CSC) [102]. Given that effective therapies are available for CSC-associated exudative MNV [103–106] and treatments may become available in the near future for cystoid macular degeneration and macular RPE atrophy, it would be of great importance to detect these complications at the earliest stage possible.

A previous longitudinal study over 3 years was designed to explore the relationships in the demographics, clinical characteristics, structural OCT findings, and development of macular complications in a cohort of eyes with "resolved" chronic (resolution lasting at least 6

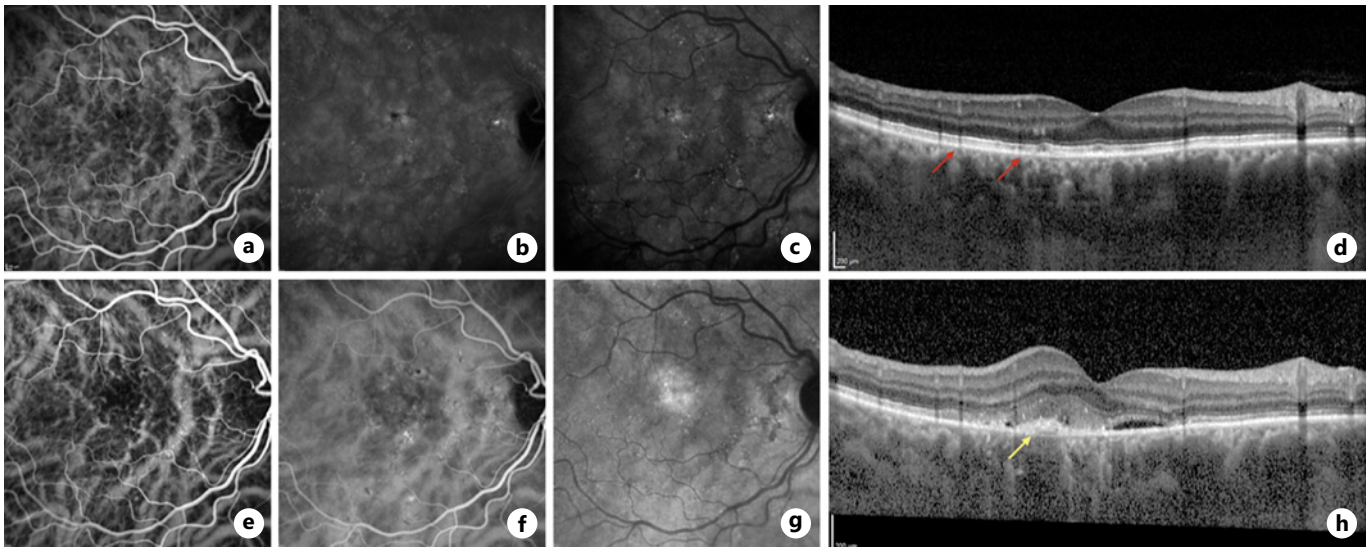

Fig. 7. Multimodal imaging of a patient with "resolved" chronic CSC and development of type 1 choroidal neovascularization. Top panel: baseline; bottom panel: 18-month follow-up visit. Early (**a**), mid- (**b**), and late-phase (**c**) indocyanine green angiography (ICGA) reveals choroidal hyperpermeability and absence of CNV. **d** Structural optical coherence tomography (OCT) image reveals the presence of baseline risk factors for CNV development, including inner choroidal attenuation (red arrows). At the 18-month follow-up visit, early (**e**), mid- (**f**), and late-phase (**g**) ICGA displays a hyperfluorescent macular lesion. **h** Structural OCT confirms the presence of a type 1 CNV (yellow arrow) with subretinal hyper-reflective material and fluid. The location of the neovascularization on the structural OCT corresponds with the hyperfluorescent area on ICGA. (Reproduced with permission from Borrelli et al. [63], 2021 © Elsevier.)

months) CSC at the study baseline (Fig. 7) [63]. Among the demographic and clinical factors, age, sex, and previous photodynamic therapy exposure did not significantly impact the 3-year progression to macular complications. On the contrary, the presence of inner choroidal attenuation on structural OCT images was associated with a greater risk for progression to MNV. A thinning of the inner choroid was hypothesized to be the result of primary atrophy of the CC or, alternatively, to occur because of mechanical compression from underlying enlarged vessels [107]. The association between inner choroidal thinning and progression to MNV confirmed previous findings that choroidal ischemia may drive the emergence and growth of choroidal neovascularization in these eyes through an increase in VEGF levels. Similarly, the presence of intraretinal HRFs on OCT images, which may represent intraretinal migrated RPE cells producing VEGF [63] and which may be the result of CC ischemia, was an additional baseline risk factor for the development of MNV.

In the same study, the presence of inner choroidal attenuation, outer nuclear layer thinning, and dome-shaped PED were independent risk factors for the development of RPE atrophy within 3 years. Interestingly, the presence of a dome-shaped PED was the most predictive of the three parameters. The development of dome-shaped PEDs is thought to be secondary to a sustained elevation of the hydrostatic pressure below the RPE [108]. This may eventually result in the PED's collapse and consequent RPE atrophy. Greater RPE displacement from the inner choroid may increase the risk of RPE ischemia and atrophy, especially at the apex [66].

Leber's Hereditary Optic Neuropathy

In addition to retinal disorders, imaging biomarkers can also be useful in the assessment of patients with optic nerve disorders. Structural OCT has been indeed employed to describe both cross-sectional values and longitudinal alterations in RNFL and ganglion cell-inner plexiform layer (GC-IPL) thicknesses in different optic nerve disorders, including LHON [109–111].

LHON is a mitochondrial disease which selectively affects retinal ganglion cells and their axons converging in the optic nerve [112, 113]. Idebenone may be an efficacious and safe therapy in patients with LHON, as it is associated with a better visual prognosis in these patients [114].

In order to define baseline biomarkers associated with a better visual outcome in LHON patients treated with idebenone, a recent study on 17 patients (34 eyes)

aimed to determine whether an association exists among the baseline anatomic characteristics detected with structural OCT, the clinical features of this disease, and long-term visual outcomes in patients with LHON treated with idebenone within 1 year after disease onset [115].

Among the demographic and clinical factors, age, gender, and time elapsed between symptoms' onset and initiation of therapy did not significantly impact the 2-year visual outcome [115]. Conversely, the multivariable analysis demonstrated that the superior, supero-temporal, and infero-temporal macular GC-IPL thicknesses were significantly associated with the 2-year visual outcome in these patients. In contrast, there were no significant associations between RNFL thicknesses and visual outcome, which is consistent with previous reports showing that the peripapillary RNFL thickness may fail to provide OCT biomarkers of visual outcomes in patients with LHON. Specifically, the RNFL thickness does not appropriately reflect optic nerve atrophy at the earliest stages of LHON since a preserved RNFL thickness on OCT may be the result of a combination of both swelling of fibers and loss or atrophy, rather than a pure indicator of actual preservation of NFL anatomy [110].

Conversely, the status of the GC-IPL in the macular region may better reflect the number of preserved ganglion cells in patients with LHON, and the GC-IPL thickness was significantly associated with improvement in visual acuity in patients with LHON treated with idebenone within 1 year after disease onset. Interestingly, results of the above-mentioned study [115] demonstrated that this association was significant in the superior and temporal parafoveal sectors of the macula, while this association was not significant in the inferior and nasal regions. The former corresponds to the upstream portion of the papillomacular bundle where mitochondrial dysfunction affects ganglion cells early on [109]. Therefore, the assessment of the GC-IPL thickness in the superior and temporal regions may better reflect the extent of ganglion cell preservation; therefore, this may appear to be a better strategy to select those patients that might gain benefit from idebenone therapy.

Conclusions

This review highlights new insights regarding the retina and choroid in subjects with AMD and other retinal and optic nerve disorders as revealed by structural OCT and OCTA imaging. Most of these findings have been discussed during the Ophthalmologica Lecture discussed by Dr. Enrico Borrelli during the 2022 Euretina meeting.

Although retinal imaging has improved our understanding in several retinal and optic nerve disorders, this remains in a state of rapid evolution and development and future advances in imaging technologies will further elucidate whether these insights are confirmed and clinically relevant. However, remarkable insights in AMD have been achieved with retinal imaging, and these findings have been corroborated by prior histological studies. Importantly, OCTA systems have provided incredible in vivo representations of the CC and highlighted that the inner choroid may play an integral role in the pathophysiology of AMD. Also, novel algorithms applied to OCTA data have allowed a 3D visualization of type 3 MNV that, for the first time, resemble the histopathological representations. Finally, the employment of structural OCT to characterize patients with macular and optic nerve disorders (i.e., AMD, DME, pathologic myopia, CSC, and LHON) cannot be underestimated. Structural OCT provides a simple, fast, and noninvasive tool to detect clinical biomarkers of disease progression that may guide time of follow-ups and treatment strategies. In summary, retinal imaging has offered important insights into retinal and optic nerve disorders and represents a potential and powerful tool to evaluate and characterize many important ocular diseases.

Acknowledgments

Figures 1, 2, and 4 were created with BioRender.com.

Conflict of Interest Statement

The authors have no disclosures.

Funding Sources

No funds were received for this study.

Author Contributions

E.B. and A.B.: drafting, revision, and final approval of the manuscript. L.M., G.Q., S.S., D.S., and F.B.: revision and final approval of the manuscript.

References

1 Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(2):e106–116.
2 Ferris FL, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, et al. Clinical classification of age-related macular degeneration. Ophthalmology. 2013;120(4):844–51.
3 Zarbin MA, Rosenfeld PJ. Pathway-based therapies for age-related macular degeneration: an integrated survey of emerging treatment alternatives. Retina. 2010;30(9):1350–67.
4 Querques G, Rosenfeld PJ, Cavallero E, Borrelli E, Corvi F, Querques L, et al. Treatment of dry age-related macular degeneration. Ophthalmic Res. 2014;52(3):107–15.
5 Seddon JM, McLeod DS, Bhutto IA, Villalonga MB, Silver RE, Wenick AS, et al. Histopathological insights into choroidal vascular loss in clinically documented cases of age-related macular degeneration. JAMA Ophthalmol. 2016;134(11):1272–80.
6 Mullins RF, Johnson MN, Faidley EA, Skeie JM, Huang J. Choriocapillaris vascular dropout related to density of drusen in human eyes with early age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52(3):1606–12.
7 Borrelli E, Sarraf D, Freund KB, Sadda SR. OCT angiography and evaluation of the choroid and choroidal vascular disorders. Prog Retin Eye Res. 2018;67:30–55.
8 Nassisi M, Baghdasaryan E, Tepelus T, Asanad S, Borrelli E, Sadda SR. Topographic distribution of choriocapillaris flow deficits in healthy eyes. PLoS One. 2018;13(11):e0207638.
9 Al-Sheikh M, Phasukkijwatana N, Dolz-Marco R, Rahimi M, Iafe NA, Freund KB, et al. Quantitative OCT angiography of the retinal microvasculature and the choriocapillaris in myopic eyes. Invest Ophthalmol Vis Sci. 2017;58(4):2063–9.
10 Al-Sheikh M, Falavarjani KG, Pfau M, Uji A, Le PP, Sadda SR. Quantitative features of the choriocapillaris in healthy individuals using swept-source optical coherence tomography angiography. Ophthalmic Surg Lasers Imaging Retina. 2017;48(8):623–31.
11 Borrelli E, Gabela MC, Sacconi R, Querques L, Vella G, Zuccaro B, et al. Choroidal luminal and stromal areas and choriocapillaris perfusion are characterised by a non-linear quadratic relation in healthy eyes. Br J Ophthalmol. 2021;105(4):567–72.
12 Sacconi R, Borrelli E, Corbelli E, Capone L, Rabiolo A, Carnevali A, et al. Quantitative changes in the ageing choriocapillaris as measured by swept source optical coherence tomography angiography. Br J Ophthalmol. 2019;103(9):1320–6.
13 Borrelli E, Uji A, Sarraf D, Sadda SR. Alterations in the choriocapillaris in intermediate age-related macular degeneration. Invest Ophthalmol Vis Sci. 2017;58(11):4792–8.
14 Borrelli E, Shi Y, Uji A, Balasubramanian S, Nassisi M, Sarraf D, et al. Topographic analysis of the choriocapillaris in intermediate age-related macular degeneration. Am J Ophthalmol. 2018;196:34–43.
15 Borrelli E, Abdelfattah NS, Uji A, Nittala MG, Boyer DS, Sadda SR. Postreceptor neuronal loss in intermediate age-related macular degeneration. Am J Ophthalmol. 2017;181:1–11.
16 Borrelli E, Mastropasqua R, Senatore A, Palmieri M, Toto L, Sadda SR, et al. Impact of choriocapillaris flow on multifocal electroretinography in intermediate age-related macular degeneration eyes. Invest Ophthalmol Vis Sci. 2018;59(4):AMD25–30.
17 Gangnon RE, Lee KE, Klein BEK, Iyengar SK, Sivakumaran TA, Klein R. Severity of age-related macular degeneration in 1 eye and the incidence and progression of age-related macular degeneration in the fellow eye: the Beaver Dam Eye Study. JAMA Ophthalmol. 2015;133(2):125–32.
18 Lane M, Moult EM, Novais EA, Louzada RN, Cole ED, Lee B, et al. Visualizing the choriocapillaris under drusen: comparing 1,050 nm swept-source versus 840 nm spectral-domain optical coherence tomography angiography. Invest Ophthalmol Vis Sci. 2016;57(9):OCT585–590.
19 Curcio CA, Medeiros NE, Millican CL. Photoreceptor loss in age-related macular degeneration. Invest Ophthalmol Vis Sci. 1996;37(7):1236–49.
20 Boretsky A, Khan F, Burnett G, Hammer DX, Ferguson RD, van Kuijk F, et al. In vivo imaging of photoreceptor disruption associated with age-related macular degeneration: a pilot study. Lasers Surg Med. 2012;44(8):603–10.
21 Borrelli E, Sacconi R, Zuccaro B, Cavalleri M, Bordato A, Zucchiatti I, et al. Photoreceptor alteration in intermediate age-related macular degeneration. Sci Rep. 2020;10(1):21036.
22 Staurenghi G, Sadda S, Chakravarthy U, Spaide RF; International Nomenclature for Optical Coherence Tomography IN·OCT Panel. Proposed lexicon for anatomic landmarks in normal posterior segment spectral-domain optical coherence tomography: the IN·OCT consensus. Ophthalmology. 2014;121(8):1572–8.
23 Hood DC, Zhang X, Ramachandran R, Talamini CL, Raza A, Greenberg JP, et al. The inner segment/outer segment border seen on optical coherence tomography is less intense in patients with diminished cone function. Invest Ophthalmol Vis Sci. 2011;52(13):9703–9.
24 Pappuru RR, Ouyang Y, Nittala MG, Hemmati HD, Keane PA, Walsh AC, et al. Relationship between outer retinal thickness substructures and visual acuity in eyes with dry age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52(9):6743–8.
25 Charafeddin W, Nittala MG, Oregon A, Sadda SR. Relationship between subretinal hyperreflective material reflectivity and volume in patients with neovascular age-related macular degeneration following anti-vascular endothelial growth factor treatment. Ophthalmic Surg Lasers Imaging Retina. 2015;46(5):523–30.
26 Hu Z, Nittala MG, Sadda SR. Comparison of retinal layer intensity profiles from different OCT devices. Ophthalmic Surg Lasers Imaging Retina. 2013;44(6 Suppl):S5–10.
27 Lee SY, Stetson PF, Ruiz-Garcia H, Heussen FM, Sadda SR. Automated characterization of pigment epithelial detachment by optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53(1):164–70.
28 Borrelli E, Palmieri M, Viggiano P, Ferro G, Mastropasqua R. Photoreceptor damage in diabetic choroidopathy. Retina. 2020;40(6):1062–9.
29 Hood DC. Assessing retinal function with the multifocal technique. Prog Retin Eye Res. 2000;19(5):607–46.
30 Hartnett ME, Weiter JJ, Staurenghi G, Elsner AE. Deep retinal vascular anomalous complexes in advanced age-related macular degeneration. Ophthalmology. 1996;103(12):2042–53.
31 Yannuzzi LA, Negrão S, Iida T, Carvalho C, Rodriguez-Coleman H, Slakter J, et al. Retinal angiomatous proliferation in age-related macular degeneration. Retina. 2001;21(5):416–34.
32 Freund KB, Ho IV, Barbazetto IA, Koizumi H, Laud K, Ferrara D, et al. Type 3 neovascularization: the expanded spectrum of retinal angiomatous proliferation. Retina. 2008;28(2):201–11.
33 Monson DM, Smith JR, Klein ML, Wilson DJ. Clinicopathologic correlation of retinal angiomatous proliferation. Arch Ophthalmol. 2008;126(12):1664–8.
34 Shimada H, Kawamura A, Mori R, Yuzawa M. Clinicopathological findings of retinal angiomatous proliferation. Graefes Arch Clin Exp Ophthalmol. 2007;245(2):295–300.
35 Nagiel A, Sarraf D, Sadda SR, Spaide RF, Jung JJ, Bhavsar KV, et al. Type 3 neovascularization: evolution, association with pigment epithelial detachment, and treatment response as revealed by spectral domain optical coherence tomography. Retina. 2015;35(4):638–47.

36 Kuehlewein L, Dansingani KK, de Carlo TE, Bonini Filho MA, Iafe NA, Lenis TL, et al. Optical coherence tomography angiography of type 3 neovascularization secondary to age-related macular degeneration. Retina. 2015;35(11):2229–35.
37 Querques G, Souied EH, Freund KB. Multimodal imaging of early stage 1 type 3 neovascularization with simultaneous eye-tracked spectral-domain optical coherence tomography and high-speed real-time angiography. Retina. 2013;33(9):1881–7.
38 Phasukkijwatana N, Tan ACS, Chen X, Freund KB, Sarraf D. Optical coherence tomography angiography of type 3 neovascularisation in age-related macular degeneration after antiangiogenic therapy. Br J Ophthalmol. 2017;101(5):597–602.
39 Su D, Lin S, Phasukkijwatana N, Chen X, Tan A, Freund KB, et al. An updated staging system of type 3 neovascularization using spectral domain optical coherence tomography. Retina. 2016;36(Suppl 1):S40–9.
40 Dell'Omo R, Cassetta M, Dell'Omo E, di Salvatore A, Hughes JM, Aceto F, et al. Aqueous humor levels of vascular endothelial growth factor before and after intravitreal bevacizumab in type 3 versus type 1 and 2 neovascularization. A prospective, case-control study. Am J Ophthalmol. 2012;153(1):155–61.e2.
41 Kim JH, Kim JR, Kang SW, Kim SJ, Ha HS. Thinner choroid and greater drusen extent in retinal angiomatous proliferation than in typical exudative age-related macular degeneration. Am J Ophthalmol. 2013;155(4):743–9.
42 Koizumi H, Iida T, Saito M, Nagayama D, Maruko I. Choroidal circulatory disturbances associated with retinal angiomatous proliferation on indocyanine green angiography. Graefes Arch Clin Exp Ophthalmol. 2008;246(4):515–20.
43 Borrelli E, Souied EH, Freund KB, Querques G, Miere A, Gal-Or O, et al. Reduced choriocapillaris flow in eyes with type 3 neovascularization and age-related macular degeneration. Retina. 2018;38(10):1968–76.
44 Le HM, Souied EH, Querques G, Colantuono D, Borrelli E, Sacconi R, et al. Choriocapillaris flow impairment in type 3 macular neovascularization: a quantitative analysis using swept-source optical coherence tomography angiography. Retina. 2021;41(9):1819–27.
45 Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. Prog Retin Eye Res. 2018;64:1–55.
46 Spaide RF. Volume rendering of optical coherence tomography angiography reveals extensive retinal vascular contributions to neovascularization in ocular toxoplasmosis. Retina. 2015;35(11):2421–2.
47 Spaide RF, Suzuki M, Yannuzzi LA, Matet A, Behar-Cohen F. Volume-rendered angiographic and structural optical coherence tomography angiography of macular telangiectasia type 2. Retina. 2017;37(3):424–35.
48 Cabral D, Ramtohul P, Fradinho AC, Freund KB. Volume rendering of deep retinal age-related microvascular anomalies. Ophthalmol Retina. 2022;6(12):1185–93.
49 Cabral D, Pereira T, Ledesma-Gil G, Rodrigues C, Coscas F, Sarraf D, et al. Volume rendering of dense B-scan optical coherence tomography angiography to evaluate the connectivity of macular blood flow. Invest Ophthalmol Vis Sci. 2020;61(6):44.
50 Breazzano MP, Bacci T, Curcio CA, Freund KB. Novel multimodal imaging and volume rendering of type 3 macular neovascularization. Retina. 2020;40(10):e55–7.
51 Nesper PL, Soetikno BT, Treister AD, Fawzi AA. Volume-rendered projection-resolved OCT angiography: 3D lesion complexity is associated with therapy response in wet age-related macular degeneration. Invest Ophthalmol Vis Sci. 2018;59(5):1944–52.
52 Borrelli E, Sacconi R, Brambati M, Bandello F, Querques G. In vivo rotational three-dimensional OCTA analysis of microaneurysms in the human diabetic retina. Sci Rep. 2019;9(1):16789.
53 Borrelli E, Sacconi R, Klose G, de Sisternes L, Bandello F, Querques G. Rotational three-dimensional OCTA: a notable new imaging tool to characterize type 3 macular neovascularization. Sci Rep. 2019;9(1):17053.
54 Borrelli E, Mastropasqua L, Souied E, Sadda S, Vella G, Toto L, et al. Longitudinal assessment of type 3 macular neovascularization using 3D volume-rendering OCTA. Can J Ophthalmol. 2022;57(4):228–35.
55 Skalet AH, Miller AK, Klein ML, Lauer AK, Wilson DJ. Clinicopathologic correlation of retinal angiomatous proliferation treated with ranibizumab. Retina. 2017;37(8):1620–4.
56 Li M, Dolz-Marco R, Messinger JD, Wang L, Feist RM, Girkin CA, et al. Clinicopathologic correlation of anti–vascular endothelial growth factor–treated type 3 neovascularization in age-related macular degeneration. Ophthalmology. 2018;125(2):276–87.
57 Lee EK, Yu HG. Ganglion cell–inner plexiform layer and peripapillary retinal nerve fiber layer thicknesses in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2015;56(6):3976–83.
58 Hendrickson A, Warner CE, Possin D, Huang J, Kwan WC, Bourne JA. Retrograde transneuronal degeneration in the retina and lateral geniculate nucleus of the V1-lesioned marmoset monkey. Brain Struct Funct. 2015;220(1):351–60.
59 Sullivan R, Penfold P, Pow DV. Neuronal migration and glial remodeling in degenerating retinas of aged rats and in non-neovascular AMD. Invest Ophthalmol Vis Sci. 2003;44(2):856–65.
60 Borrelli E, Barresi C, Lari G, Berni A, Battista M, Reibaldi M, et al. Capturing the transition from intermediate to neovascular AMD: longitudinal inner retinal thinning and factors associated with neuronal loss. Invest Ophthalmol Vis Sci. 2023;64(4):21.
61 Barresi C, Chhablani J, Dolz-Marco R, Gallego-Pinazo R, Berni A, Bandello F, et al. Retinal neurodegeneration in age-related macular degeneration. Eur J Ophthalmol. 2023 Jul 2:11206721231186166.
62 Borrelli E, Grosso D, Barresi C, Lari G, Sacconi R, Senni C, et al. Long-term visual outcomes and morphologic biomarkers of vision loss in eyes with diabetic macular edema treated with anti-VEGF therapy. Am J Ophthalmol. 2022;235:80–9.
63 Borrelli E, Battista M, Sacconi R, Gelormini F, Querques L, Grosso D, et al. OCT risk factors for 3-year development of macular complications in eyes with "resolved" chronic central serous chorioretinopathy. Am J Ophthalmol. 2021;223:129–39.
64 Borrelli E, Battista M, Vella G, Sacconi R, Querques L, Grosso D, et al. Three-year OCT predictive factors of disease recurrence in eyes with successfully treated myopic choroidal neovascularisation. Br J Ophthalmol. 2022;106(8):1132–8.
65 Vujosevic S, Torresin T, Bini S, Convento E, Pilotto E, Parrozzani R, et al. Imaging retinal inflammatory biomarkers after intravitreal steroid and anti-VEGF treatment in diabetic macular oedema. Acta Ophthalmol. 2017;95(5):464–71.
66 Au A, Santina A, Abraham N, Levin MF, Corradetti G, Sadda S, et al. Relationship between drusen height and OCT biomarkers of atrophy in non-neovascular AMD. Invest Ophthalmol Vis Sci. 2022;63(11):24.
67 Wakatsuki Y, Hirabayashi K, Yu HJ, Marion KM, Corradetti G, Wykoff CC, et al. Optical coherence tomography biomarkers for conversion to exudative neovascular age-related macular degeneration. Am J Ophthalmol. 2023;247:137–44.
68 Hirabayashi K, Yu HJ, Wakatsuki Y, Marion KM, Wykoff CC, Sadda SR. OCT risk factors for development of atrophy in eyes with intermediate age-related macular degeneration. Ophthalmol Retina. 2023;7(3):253–60.
69 Corvi F, Corradetti G, Tiosano L, McLaughlin JA, Lee TK, Sadda SR. Topography of choriocapillaris flow deficit predicts development of neovascularization or atrophy in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2021;259(10):2887–95.
70 Corradetti G, Tiosano L, Nassisi M, Alagorie AR, Corvi F, Nittala MG, et al. Scotopic microperimetric sensitivity and inner choroid flow deficits as predictors of progression to nascent geographic atrophy. Br J Ophthalmol. 2021;105(11):1584–90.

71 Corvi F, Tiosano L, Corradetti G, Nittala MG, Lindenberg S, Alagorie AR, et al. Choriocapillaris flow deficits as a risk factor for progression of age-related macular degeneration. Retina. 2021;41(4):686–93.
72 Chu Z, Shi Y, Zhou X, Wang L, Zhou H, Laiginhas R, et al. Optical coherence tomography measurements of the retinal pigment epithelium to Bruch membrane thickness around geographic atrophy correlate with growth. Am J Ophthalmol. 2022;236:249–60.
73 Dolz-Marco R, Balaratnasingam C, Messinger JD, Li M, Ferrara D, Freund KB, et al. The border of macular atrophy in age-related macular degeneration: a clinicopathologic correlation. Am J Ophthalmol. 2018;193:166–77.
74 Marsiglia M, Boddu S, Bearelly S, Xu L, Breaux BE Jr, Freund KB, et al. Association between geographic atrophy progression and reticular pseudodrusen in eyes with dry age-related macular degeneration. Invest Ophthalmol Vis Sci. 2013;54(12):7362–9.
75 Niu S, de Sisternes L, Chen Q, Rubin DL, Leng T. Fully automated prediction of geographic atrophy growth using quantitative spectral-domain optical coherence tomography biomarkers. Ophthalmology. 2016;123(8):1737–50.
76 Veerappan M, El-Hage-Sleiman AKM, Tai V, Chiu SJ, Winter KP, Stinnett SS, et al. Optical coherence tomography reflective drusen substructures predict progression to geographic atrophy in age-related macular degeneration. Ophthalmology. 2016;123(12):2554–70.
77 Shi Y, Zhang Q, Zhou H, Wang L, Chu Z, Jiang X, et al. Correlations between choriocapillaris and choroidal measurements and the growth of geographic atrophy using swept source OCT imaging. Am J Ophthalmol. 2021;224:321–31.
78 Zhang Q, Shi Y, Shen M, Cheng Y, Zhou H, Feuer W, et al. Does the outer retinal thickness around geographic atrophy represent another clinical biomarker for predicting growth? Am J Ophthalmol. 2022;244:79–87.
79 Hirabayashi K, Yu HJ, Wakatsuki Y, Marion KM, Wykoff CC, Sadda SR. OCT risk factors for development of atrophy in eyes with intermediate age-related macular degeneration. Ophthalmol Retina. 2023;7(3):253–60.
80 Lechner J, O'Leary OE, Stitt AW. The pathology associated with diabetic retinopathy. Vision Res. 2017;139:7–14.
81 Paulus YM, Gariano RF. Diabetic retinopathy: a growing concern in an aging population. Geriatrics. 2009;64(2):16–20.
82 Bonnin S, Tadayoni R, Erginay A, Massin P, Dupas B. Correlation between ganglion cell layer thinning and poor visual function after resolution of diabetic macular edema. Invest Ophthalmol Vis Sci. 2015;56(2):978–82.
83 Uji A, Murakami T, Nishijima K, Akagi T, Horii T, Arakawa N, et al. Association between hyperreflective foci in the outer retina, status of photoreceptor layer, and visual acuity in diabetic macular edema. Am J Ophthalmol. 2012;153(4):710–7.
84 Ito SI, Miyamoto N, Ishida K, Kurimoto Y. Association between external limiting membrane status and visual acuity in diabetic macular oedema. Br J Ophthalmol. 2013;97(2):228–32.
85 Maheshwary AS, Oster SF, Yuson RMS, Cheng L, Mojana F, Freeman WR. The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in diabetic macular edema. Am J Ophthalmol. 2010;150(1):63–7.e1.
86 Shin HJ, Lee SH, Chung H, Kim HC. Association between photoreceptor integrity and visualoutcome in diabetic macular edema. Graefes Arch Clin Exp Ophthalmol. 2012;250(1):61–70.
87 Vujosevic S, Bini S, Torresin T, Berton M, Midena G, Parrozzani R, et al. Hyperreflective retinal spots in normal and diabetic eyes: B-scan and en face spectral domain optical coherence tomography evaluation. Retina. 2017;37(6):1092–103.
88 Sun JK, Lin MM, Lammer J, Prager S, Sarangi R, Silva PS, et al. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol. 2014;132(11):1309–16.
89 Wong TY, Ferreira A, Hughes R, Carter G, Mitchell P. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. Am J Ophthalmol. 2014;157(1):9–25.e12.
90 Yang HS, Kim JG, Kim JT, Joe SG. Prognostic factors of eyes with naïve subfoveal myopic choroidal neovascularization after intravitreal bevacizumab. Am J Ophthalmol. 2013;156(6):1201–10.e2.
91 Kang HM, Koh HJ. Ocular risk factors for recurrence of myopic choroidal neovascularization: long-term follow-up study. Retina. 2013;33(8):1613–22.
92 Ikuno Y, Ohno-Matsui K, Wong TY, Korobelnik JF, Vitti R, Li T, et al. Intravitreal aflibercept injection in patients with myopic choroidal neovascularization: the MYRROR study. Ophthalmology. 2015;122(6):1220–7.
93 Yang HS, Kim JG, Kim JT, Joe SG. Prognostic factors of eyes with naïve subfoveal myopic choroidal neovascularization after intravitreal bevacizumab. Am J Ophthalmol. 2013;156(6):1201–10.e2.
94 Spaide RF, Campeas L, Haas A, Yannuzzi LA, Fisher YL, Guyer DR, et al. Central serous chorioretinopathy in younger and older adults. Ophthalmology. 1996;103(12):2070–9; discussion 2079-80.
95 Kaye R, Chandra S, Sheth J, Boon CJF, Sivaprasad S, Lotery A. Central serous chorioretinopathy: an update on risk factors, pathophysiology and imaging modalities. Prog Retin Eye Res. 2020;79:100865.
96 Donald J, Gass M. Pathogenesis of disciform detachment of the neuroepithelium: VI. Disciform detachment secondary to heredodegenerative, neoplastic and traumatic lesions of the choroid. Am J Ophthalmol. 1967;63(3):1–139.
97 Borrelli E, Barresi C, Battista M, Berni A, Ricardi F, Cascavilla ML, et al. Prevalence and morphologic biomarkers of metamorphopsia in eyes with "resolved" chronic central serous chorioretinopathy. Retina. 2023;43(9):1563–72.
98 Fung AT, Yannuzzi LA, Freund KB. Type 1 (Sub-retinal pigment epithelial) neovascularization in central serous chorioretinopathy masquerading as neovascular age-related macular degeneration. Retina. 2012;32(9):1829–37.
99 Iida T, Yannuzzi LA, Spaide RF, Borodoker N, Carvalho CA, Negrao S. Cystoid macular degeneration in chronic central serous chorioretinopathy. Retina. 2003;23(1):1–7; quiz 137-8.
100 Takahashi A, Ooto S, Yamashiro K, Tamura H, Oishi A, Miyata M, et al. Pachychoroid geographic atrophy: clinical and genetic characteristics. Ophthalmol Retina. 2018;2(4):295–305.
101 Imamura Y, Fujiwara T, Spaide RF. Fundus autofluorescence and visual acuity in central serous chorioretinopathy. Ophthalmology. 2011;118(4):700–5.
102 Mrejen S, Balaratnasingam C, Kaden TR, Bottini A, Dansingani K, Bhavsar KV, et al. Long-term visual outcomes and causes of vision loss in chronic central serous chorioretinopathy. Ophthalmology. 2019;126(4):576–88.
103 Peiretti E, Caminiti G, Serra R, Querques L, Pertile R, Querques G. Anti-vascular endothelial growth factor therapy versus photodynamic therapy in the treatment of choroidal neovascularization secondary to central serous chorioretinopathy. Retina. 2018;38(8):1526–32.
104 Lai TYY, Staurenghi G, Lanzetta P, Holz FG, Melissa Liew SH, Desset-Brethes S, et al. Efficacy and safety of ranibizumab for the treatment of choroidal neovascularization due to uncommon cause: twelve-month results of the MINERVA study. Retina. 2018;38(8):1464–77.
105 Chhablani J, Kozak I, Pichi F, Chenworth M, Berrocal MH, Bedi R, et al. Outcomes of treatment of choroidal neovascularization associated with central serous chorioretinopathy with intravitreal antiangiogenic agents. Retina. 2015;35(12):2489–97.
106 Chhablani J, Pichi F, Silva R, Casella AM, Murthy H, Banker A, et al. Antiangiogenics in choroidal neovascularization associated with laser in central serous chorioretinopathy. Retina. 2016;36(5):901–8.

107 Sakurada Y, Fragiotta S, Leong BCS, 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(4):657–62.
108 Daruich A, Matet A, Dirani A, Bousquet E, Zhao M, Farman N, et al. Central serous chorioretinopathy: recent findings and new physiopathology hypothesis. Prog Retin Eye Res. 2015;48:82–118.
109 Balducci N, Savini G, Cascavilla ML, La Morgia C, Triolo G, Giglio R, et al. Macular nerve fibre and ganglion cell layer changes in acute Leber's hereditary optic neuropathy. Br J Ophthalmol. 2016;100(9):1232–7.
110 Barboni P, Carbonelli M, Savini G, Ramos CVF, Carta A, Berezovsky A, et al. Natural history of Leber's hereditary optic neuropathy: longitudinal analysis of the retinal nerve fiber layer by optical coherence tomography. Ophthalmology. 2010;117(3):623–7.
111 Barboni P, Savini G, Valentino ML, Montagna P, Cortelli P, De Negri AM, et al. Retinal nerve fiber layer evaluation by optical coherence tomography in Leber's hereditary optic neuropathy. Ophthalmology. 2005;112(1):120–6.
112 Newman NJ. Hereditary optic neuropathies: from the mitochondria to the optic nerve. Am J Ophthalmol. 2005;140(3):517–23.
113 Carelli V, Ross-Cisneros FN, Sadun AA. Mitochondrial dysfunction as a cause of optic neuropathies. Prog Retin Eye Res. 2004;23(1):53–89.
114 Klopstock T, Yu-Wai-Man P, Dimitriadis K, Rouleau J, Heck S, Bailie M, et al. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. Brain. 2011;134(Pt 9):2677–86.
115 Borrelli E, Berni A, Cascavilla ML, Barresi, C, Battista, M, Lari, G, et al. Visual outcomes and optical coherence tomography biomarkers of vision improvement in patients with leber hereditary optic neuropathy treated with idebenone. Am J Ophthalmol. 2023;247(22):35–41.