The Role of New Imaging Methods in Managing Age-Related Macular Degeneration

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Abstract: The use of imaging for age-related macular degeneration (AMD) depends on how it benefits clinical management and on reimbursement. The latter should relate to the former. This review assesses how different forms of AMD can be imaged and what information this provides. For nonneovascular AMD high-resolution optical coherence tomography (OCT), autofluorescence, and near infrared imaging can identify the type of drusen, such as reticular pseudodrusen, which influences prognosis, and the amount of atrophy, for which phase 3 trials are underway. Clarifying the correct diagnosis for late-onset Stargardt and macular telangiectasia, if treatment becomes available, will be especially important. Choroidal thickness can be measured and changes with anti–vascular endothelial growth factor treatment, but how this influences management is less clear. The finding of a thick choroid may alter the diagnosis to pachychoroid neovasculopathy, which may have a different treatment response. Peripheral retinal changes are commonly found on ultrawide-field imaging but their importance is not yet determined. The mainstay of imaging is OCT, which can detect neovascular AMD by detecting thickening and be used for follow-up, as the presence or absence of thickening is the main determinant of treatment. Higher resolution systems and now OCT angiography are able to distinguish neovascular type, especially type 2 choroidal neovascularization but also polypoidal choroidal vasculopathy and retinal angiomatous proliferation. Fundus fluorescein and indocyanine green angiographies still have a role, although that partly depends on whether photodynamic therapy is being considered. Automated image analysis and machine learning will be increasingly important in supporting clinician decisions.

Key Words: age-related macular degeneration, imaging, optical coherence tomography, optical coherence tomography angiography, fundus autofluorescence

(Asia-Pac J Ophthalmol 2017;6:498–507)

Age-related macular degeneration (AMD) once diagnosed is a lifelong condition that requires accurate assessment and potentially long-term management. Newer imaging techniques can help better clarify diagnosis, refine treatment, and enable accurate monitoring. The best approach involves multimodal imaging but is probably only required in a subset of patients.

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Received for publication July 12, 2017; accepted August 15, 2017.
The authors have no funding or conflicts of interest to declare.
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ISSN: 2162-0989
DOI: 10.22608/APO.2017305

The main form of AMD requiring management is currently "wet" or neovascular AMD (nAMD) and the mainstay of treatment is anti–vascular endothelial growth factor (VEGF) injections. For this, the detection of active nAMD is required, which is largely dependent on finding sub- or intraretinal fluid and/or hemorrhage in a patient with some features of AMD, such as drusen. Treatment then involves monitoring the response by imaging for fluid. This can all be done with optical coherence tomography (OCT) and even more accurately as OCT technology has improved from time domain to Fourier domain systems, including spectral domain (SD-OCT) and swept source (SS-OCT), with higher resolution, better depth resolution, and eye tracking. The gold standard for detecting neovascularization and classifying it into subtypes, such as classic (type 2) and occult (type 1) choroidal neovascularization (CNV), is fundus fluorescein angiography (FFA). Sometimes, FFA can actually demonstrate a neovascular network but diagnosis is mainly based on patterns of leakage. Indocyanine green angiography (ICGA) does not leak as much as FFA and the infrared can penetrate the retinal pigment epithelium (RPE) pigment or hemorrhage to some extent. For these reasons, ICGA is better at distinguishing polypoidal choroidal vasculopathy (PCV), retinal angiomatous proliferation (RAP), and occult CNV. Additionally, OCT angiography (OCTA) can now be used to image the macular blood vessels and detect neovascular AMD, in some cases earlier than conventional imaging and increasingly, as technology advances, define lesion type. Its role to either complement FFA and ICGA or replace it will be reviewed.

As most treatment is dependent on detecting and monitoring fluid, it can be argued that only OCT is required and additional imaging should be reserved for those who respond suboptimally to anti-VEGF where an additional therapy might be required or the diagnosis should be reviewed. Thus far, OCT has shown good sensitivity and specificity with FFA at detecting AMD-related neovascularization, even with time domain OCT, and is more accurate with newer spectral domain or swept source OCT systems.[1–4]

In some cases, AMD can be "dry" with no evidence of neovascularization, rather drusen, RPE disturbance, geographic atrophy, and serous pigment epithelial detachments (PEDs). The risk of progression varies with lesion type and careful imaging is required for an accurate diagnosis. There is some evidence from the Age-Related Eye Disease Study (AREDS) for treating patients with vitamin supplements who have high-risk characteristics.[5] Dry AMD trials are underway, especially trying to slow down the progression of geographic atrophy (GA), and therefore imaging for dry AMD is becoming more important.[6,7] With the advent of OCTA, nonexudative CNV is being described, where there is no thickening or leakage apparent on OCT or FFA but a neovascular network is seen. The management of these lesions is currently being studied.[8]

A range of imaging techniques can help clarify the diagnosis either as the underlying cause for macular atrophy or for an alternative cause of CNV that can occur in the same age group as AMD. These include fundus autofluorescence (FAF), multicolor imaging, and wide-field imaging.

This review will look at the role of newer imaging techniques, in particular OCTA, higher resolution OCT, and multiwavelength imaging in relation to standard FFA, ICGA, and OCT imaging in managing AMD. Other less widely available technologies such as adaptive optics, hyperspectral imaging, and polarized OCT are not reviewed.

IMAGING NONNEOVASCULAR AMD

Drusen

The main early feature of AMD is drusen that may be associated with progression to late AMD, either GA or neovascularization. Higher resolution imaging and using different wavelengths has helped subclassify drusen.

Drusen can be described as soft drusen, refractile drusen, basal laminar or cuticular drusen, and subretinal reticular pseudodrusen. This classification is based on their appearance using multimodal imaging including color photographs, MultiColor, FAF, near infrared reflectance imaging, SD-OCT, and FFA.

Soft drusen appear as yellow-white slightly elevated lesions, typically 63 μm to more than 1000 μm in diameter, and may have a central paler area. On FAF, the outer edges of soft drusen may show slight hyperautofluorescence compared with the central portion. Near infrared reflectance images can show a slight difference in greyscale tones in areas of soft drusen. High-resolution SD-OCT cross-sections show low mounds, which may be attached by basal linear deposits. They are found under the RPE (Fig. 1). On FFA, soft drusen may be hyperfluorescent in the late stages, though not always.[9,10]

Cuticular drusen are punctate and round in appearance, measuring 50 μm to 75 μm in size. They are hyperfluorescent on FFA, giving a starry sky appearance. They appear hypofluorescent on FAF imaging. By SD-OCT they are imaged under the RPE. Reticular pseudodrusen (RPD) have a wavy or saw-tooth pattern and are triangular in shape (Fig. 1).[9,11,12] Refractile drusen may represent resolving drusen and are associated with atrophy. The glistening appearance seems to come from calcium deposits.

Refractile drusen are relatively common in intermediate AMD and are associated with the development of GA. However, not all such drusen develop late AMD and regression can occur.[13]

Drusen are focal deposits of extracellular material between the RPE and the Bruch membrane. Reticular pseudodrusen seem to be drusenoid material in the subretinal layer rather than sub-RPE layers.[14] On SD-OCT, RPD are seen as triangular hyperreflective deposits internal to the RPE located between the RPE and the ellipsoid zone (Fig. 1). On color fundus photographs, they appear slightly paler than soft drusen and are better visualized using infrared or the red channel on MultiColor imaging. Indeed, using the combined blue, green, and red channels and looking at them together and separately gives the best imaging of drusen compared with white light flash imaging. The blue light mainly comes from more superficial retina, green intermediate, and red deeper layers. Combing the findings with a cross-section at the same point on SD-OCT then can help confirm the presence of drusen and type.[10] On infrared reflectance RPD may appear as "dots," "targets," or ribbon-shaped hyporeflective lesions at the macula.[15,16] The least sensitive method of detecting RPD is FFA, whereas ICGA may show some subtle signs, such as hypofluorescent dots, in the mid to late phase of the angiogram, associated with impaired filling of the choroidal vasculature.[14]

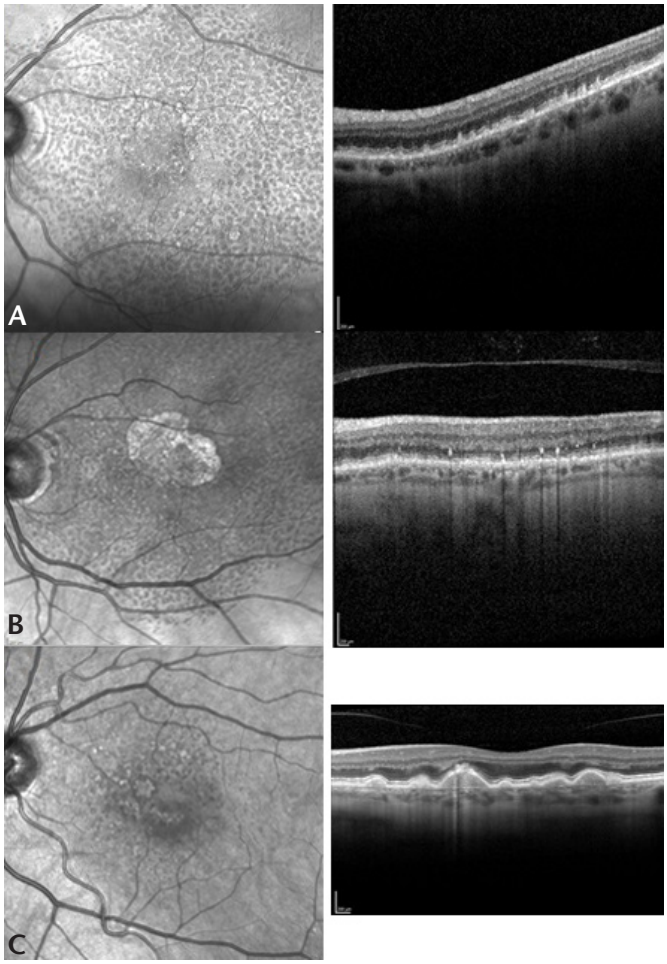

FIGURE 1. A, Reticular psuedodrusen. B, Reticular psuedodrusen with geographic atrophy. C, Soft drusen.

Drusen volume has been measured with serial OCTs and found to increase over time, but spontaneous regression can occur and may proceed the development of late AMD, both nAMD and GA.[17]

Eyes with RPD have a 4- to 6-fold higher risk of progression to late AMD within 5 years, both GA and CNV.[18,19] Additionally, RPD have been linked as an independent risk factor to the development of GA in fellow eyes of eyes being treated with anti-VEGF for CNV.[19,20] In the Comparison of Age-Related Macular Degeneration Treatment Trial (CATT), RPD were independently associated with a higher incidence of both nAMD and GA in the fellow eye. Dot RPD were associated with nAMD, whereas confluent RDP were associated with GA. The CATT researchers concluded that RDP should be considered along with the AREDS severity score for predicting late AMD.[21]

Geographic Atrophy

Trials are currently underway to try to slow down the progression of GA. The lampalizumab CHROMA and SPECTRI studies by Roche were phase 3, double-masked, multicenter, randomized, sham injection–controlled studies evaluating the

efficacy and safety of lampalizumab administered by intravitreal injections in participants with GA secondary to AMD. In these studies, eyes with GA that were most likely to progress were recruited, defined by having increased FAF on the edge of the GA area, further refined by a particular genetic change in complement factor D. Unfortunately, these trials did not meet their primary endpoint but have led to a greater understanding of how to image and monitor GA.

A review by Sadda et al[22] in 2016 discussed the benefits of combining the information from color fundus imaging with FAF, near infrared reflectance, and SD-OCT to measure and monitor change in GA and to select groups most likely to progress over the course of a trial. The use of FFA and ICGA was advocated in selected cases.

The rate of GA progression varies depending on FAF patterns in the junctional zone between normal and atrophic retina. These can be classified as none, focal, banded, or diffuse trickling. The Geographic Atrophy Progression Study demonstrated multifocal atrophic spots and extrafoveal atrophic lesions as more likely to progress in size over 12 months. Diffuse and banded patterns of FAF compared with none and focal patterns were also more likely to progress.[23,24] Geographic atrophy also progressed more frequently in areas with RPD. Images obtained using FAF can be affected by media opacities, floaters, the size of the pupil, and the proximity to the foveal center, as foveal pigment masks the underlying RPE and so the autofluorescence signal. Ambiguity in such circumstances can be resolved by the use of near infrared reflectance imaging and SD-OCT. Green FAF can offer a better assessment of center-involving GA compared with blue FAF.[25,26]

En face SD-OCT imaging, along with FAF and near infrared reflectance, can be used to measure the growth of GA and to identify anatomic changes in the outer retinal layers at the edges of the affected area that are likely to change next, and thus be useful for treatment trials.[27,28] Automated prediction and measurement of areas of GA has shown encouraging results in various study models.[29]

Recently, the definition and best methods for imaging GA have been revised by the Classification of Atrophy Meeting. They decided that the most reliable method for measuring and accurate grading of the size and nature of an area of macular atrophy is by SD-OCT and have developed the term complete retinal pigment epithelium and outer retinal atrophy of which GA is a subset. In this there are 4 grades depending on how the RPE and outer retina are affected. Geographic atrophy previously was defined as occurring in the absence of CNV but now can be diagnosed in the presence or absence of CNV.[30]

Imaging the Choroid

High-resolution SD-OCT with enhanced depth imaging and SS-OCT have enabled better visualization of the choroid. One theory for the development of AMD is that decreased choroidal perfusion and choroidal thinning lead to ischemia, dry AMD, and then a rise in VEGF and thus the development of CNV.[31]

Choroidal thickness measurements in AMD, however, are variable and further work has found some overlap between apparent nAMD and PCV with a thickened choroid in a subset now being classified as part of a diagnosis of neovascular pachychoroid.[32]

One study, looking at a sample of patients with wet and dry AMD, found a wide range of thicknesses, from 77.5 μm to 399.5 μm with a standard deviation of 90.2. Eyes with wet AMD had a mean subfoveal choroidal thickness of 194.6 μm (SD, 88.4; n = 40) compared with 213.4 μm (SD, 92.2; n = 17) in the dry AMD group. The choroidal thickness in eyes with dry AMD was correlated inversely with age; however, the number of anti-VEGF injections, number of years of disease, and visual acuity did not significantly correlate with choroidal thickness.[33]

In another study following patients treated with anti-VEGF for CNV and PCV, the baseline subfoveal choroidal thickness was not significantly different between PCV and typical AMD eyes but it reduced with treatment.[34] In typical AMD the mean thickness changed from 213.7 μm to 190.3 μm and in PCV from 240.8 μm to 213.4 μm. The choroidal thickness of the untreated eye did not change. There was no statistical difference in the reduction between AMD and PCV. The number or type of anti-VEGF injections, photodynamic therapy (PDT), or baseline choroidal thickness also did not seem to influence the change.

Another study suggests that a decrease in subfoveal choroidal thickness with anti-VEGF treatment does correlate with an eye being more likely to become dry. In this study 144 eyes were treated with three 4-week injections then 8 weekly for a year with aflibercept. Fifty-eight had typical nAMD and 86 PCV. The mean subfoveal choroidal thickness decreased by 13.3% at 12 months, from 268.1 ± 101.3 μm at baseline to 233.0 ± 99.7 μm at 3 months and remained unchanged at 232.4 ± 99.6 μm at 12 months, although this did fluctuate between treatments. The decrease in subfoveal choroidal thickness was associated significantly with gain in visual acuity for PCV eyes but not for eyes with typical nAMD. Eyes without persistent or recurrent retinal fluid after the loading phase showed a greater decrease in subfoveal choroidal thickness compared with those with fluid, in both typical neovascular AMD and PCV eyes.[35]

Examining 25 eyes in a study of nonexudative AMD, both average choroidal thickness and choroidal vessel density were significantly lower in eyes with RPD.[36]

The choroidal features of 156 eyes with AMD and PCV in patients recruited from the Asian AMD Phenotyping Study analyzed with SD-OCT revealed 2 subtypes of PCV: typical PCV with increased choroidal vascularity and another group with low vascularity. The significance of this for clinical management is as yet uncertain.[37]

There is variability in the ability of OCT machines to measure choroidal thickness and some fluctuation in thickness. In a sample of 40 eyes using the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), a change of greater than 35 μm in subfoveal choroidal thickness was found necessary to detect true clinical change associated with disease progression or improvement in nAMD.[38]

The role of measuring choroidal thickness in clinical management is uncertain, as this information does not alter treatment regimens. It does, however, have a role in clarifying the diagnosis, as some cases diagnosed as AMD may in fact be pachychoroidopathy. This is characterized by a thick choroid, RPE abnormalities, and/or choroidal vascular hyperpermeability. These changes can involve widespread thickening of the choroid or focal thickening, or possibly just areas where there is loss of the inner choroid and dilated veins of Halle. The term pachydrusen has been coined for drusen-like deposits that can occur over such areas. These are usually larger than 125 μm and are single, or there may be a few, and can lead to focal disruptions of the overlying elipsoid layer. It is hypothesized that there is a spectrum of disease that includes

pachychoroid pigment epitheliopathy, chronic central serous retinopathy, and PCV. In this context the term pachychoroid neovasculopathy is being used. In a study of 200 patients in Japan aged over 50 with possible neovascular AMD, 20% were classified as pachychoroid neovasculopathy. However, PCV lesions were detected in similar proportions in both groups. Although a relatively small sample, it was found that the pachychoroid patients had a longer treatment-free interval when using ranibizumab.[32–34,39,40]

It has been reported that OCTA finds changes in the choroid during all stages of AMD. The accuracy of these findings is less certain due to the difficulty of measuring choroidal vessels with OCTA.[39] One report found that the earlier stages are associated with patchy thinning of the choriocapillaris, whereas GA is associated with loss of the choriocapillaris lying under the area of GA and asymmetric alteration of the choriocapillaris at the margins of the geographic atrophy.[41]

A small case series using OCTA also found that the superficial and deep retinal plexuses are altered in AMD at the intermediate AMD stage, along with a choroidal thickness reduction.[42]

Ultrawide-Field Imaging in AMD

The significance of peripheral changes in AMD is still a matter of debate. The OPERA study research group, using ultrawide-field imaging comparing AMD eyes with control subjects, found a higher incidence of peripheral neovascularization, GA, peripheral drusen, reticular pseudodrusen, and RPE hyper- and hypopigmentation in AMD eyes.[43] Using ultrawide-field FAF imaging, various patterns of fluorescence have been observed in eyes with early and advanced AMD. The most common peripheral patterns were granular hyper- or hypofluorescence along with focal pinpoint hyperfluorescence and patchy or reticular hypofluorescence. Normal FAF patterns were also seen in about a third of cases.[44,45] The value of these findings for further management is yet to be clarified.

AMD Differential Diagnoses

If treatment becomes available for GA, it is likely that it will become more important that the diagnosis is clear, as currently possible treatments are being developed as a consequence of the genetic understanding of the complement pathway. Patterns similar to GA associated with AMD can occur with late-onset Stargardt disease, late-onset retinal degeneration, and bull's eye maculopathy, as can CNV (Fig. 2).[46] Typical Stargardt flecks are shown on FAF and wide-field FAF is most likely not to miss this finding. Late-onset retinal degeneration is rare but also causes a particular pattern of atrophy and rarely associated CNV, where wide-field color and FAF can be helpful. Bull's eye maculopathy has a characteristic appearance that should not be confused with AMD but as it advances can look similar to GA. Angioid streaks are also best shown on FAF and such patients need careful assessment to make sure associated systemic conditions, such as pseudoxanthoma elasticum, are not missed.

Juxtafoveal telengectasia type 2 (MacTEL) can be confused with dry or wet AMD. It causes patches of atrophy and cystic spaces but not thickening unless complicated by a CNV. There may be dark RPE patches and crystals. Standard FFA imaging shows an oval late staining that can be confused with leakage. A lack of the normal dark fovea due to low macular pigment is seen on FAF, but the most diagnostic finding is an increased blue reflectance on multicolor imaging.[47,48] This is enhanced by a short period of dark adaptation and reduced by photo bleaching.[49] Additionally, OCTA shows a characteristic capillary pattern temporal to the fovea, with reduced vessel density in both the superficial and deep plexus.[50,51] Therefore, FFA is probably no longer needed to be confident of this diagnosis (Fig. 3).

Some associations with CNV may need treatment in their own right, such as bird shot chorioretinopathy, which causes

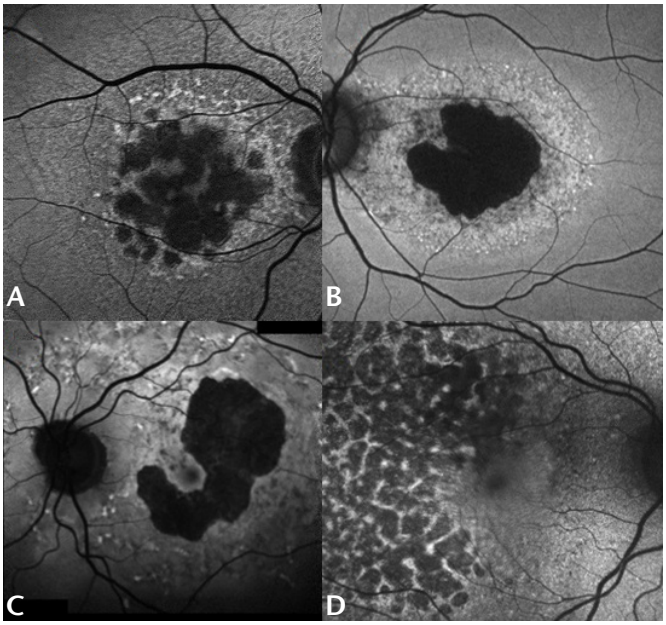

FIGURE 2. Autofluorescence images showing geographic atrophy differential diagnosis. A, GA secondary to AMD and reticular pseudodrusen; age 75. B, GA secondary to bull's eye maculopathy, PROM1 mutation p.R373C; diagnosed at age 58. C, GA secondary to late onset Stargardt disease; age 71. D, GA secondary to late-onset retinal degeneration; age 70.

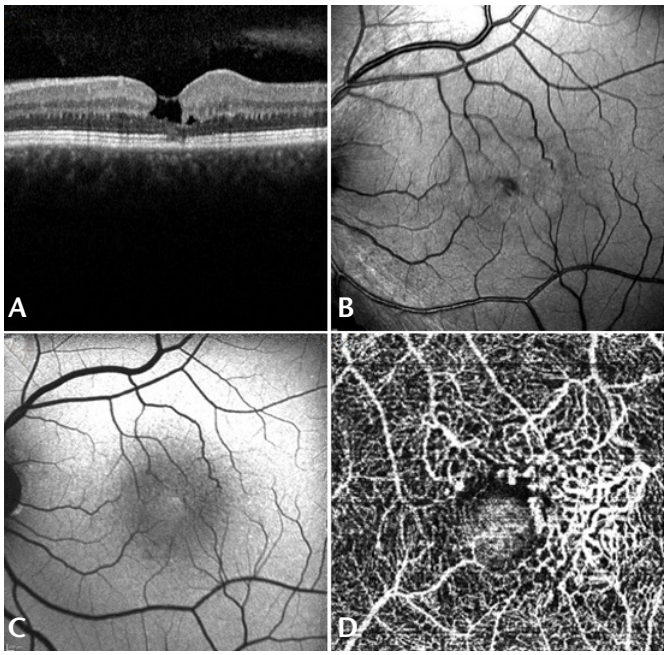

FIGURE 3. Type 2 juxtafoveal telengectasia (MacTel). A, OCT showing some loss of the RPE and nerve fibers, not swelling. B, Increased blue reflectance. C, Blue autofluorescence showing loss of normal fovea pigment. D, OCTA.

pale choroidal spots and vasculitis and can occur in the same age range as AMD. Wide-field color imaging, with its ability to be viewed as color or infrared, can be helpful to make sure this is not missed, along with FFA and ICGA, in addition to a careful clinical examination.

IMAGING NEOVASCULAR AMD

OCTA in Relation to OCT/FFA/ICG

Optical coherence tomography angiography is a fast, new imaging modality, which uses the principles of OCT to define the retinal vascular structure, using sequential B-scans to detect blood flow.[52] En face images can then be generated showing the superficial and deep retinal capillary plexus and the choroid. Cross-sectional OCT combined with depiction of flow can help demonstrate the location of a vascular abnormality. Although OCTA detects neovascular AMD by detecting flow in a vascular complex, it does not show leakage.[52,53]

Currently, FFA is the gold standard for diagnosing CNV in AMD and defines CNV through evidence of angiographic leakage.[54] It can show a clear vascular network in some cases. However, ICGA is able to more clearly define vascular networks, particularly with sub-RPE lesions, as it leaks less and by using infrared can partly penetrate the RPE.[55] Both FFA and ICGA have known limitations, as they require invasive procedures with the possibility of dye-related anaphylaxis.

As it can accurately define macular fluid and response to treatment, OCT is used to manage CNV.[54] However, it cannot delineate the retinal vascular structure and therefore cannot always clearly define CNV.

At present, OCTA does have limitations, partly due to motion and projection artefacts, along with reduced penetration into the choroid creating difficulty in determining whether neovascularization is accurately visualized; however, this is a rapidly changing field with newer, faster machines becoming available.

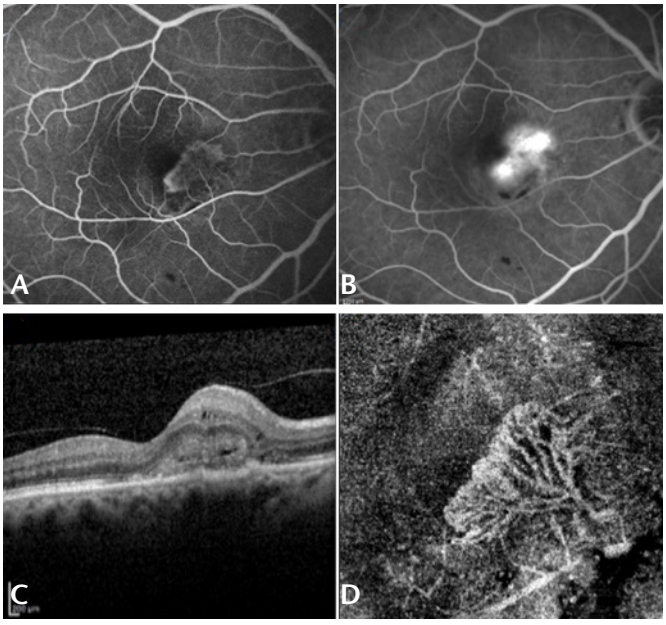

FIGURE 4. Imaging of type 2 classic CNV. A–B, Early and late FFA. C, OCT showing typical features of a type 2 CNV. D, OCTA showing CNV network.

Several studies have highlighted the use of OCTA in diagnosing neovascular AMD as compared with FFA.[56–59] Promisingly, Coscas et al[59] were able to show more than 90% concordance between traditional multimodal imaging (FFA, ICGA, and OCT) and OCTA. There are now various commercial devices available using SD-OCTA and SS-OCTA.[60–62] Swept source OCTA has the benefit of better choroidal penetration and therefore can better define a CNV.[63]

Compared with FFA/ICGA, OCTA can be more readily repeated, allowing sequential measurements of CNV size. This has been shown to vary with treatment by anti-VEGFs. Remodelling of the vascular network can be seen with pruning of smaller branching vessels, but the main trunk of the CNV remains patent.[64,65] Costanzo et al[55] found that OCTA defined a smaller CNV size compared with ICGA for type 1 CNV. Possibly, OCTA is showing the true CNV size, as it is not affected by leakage; however, if the flow is slow this would be missed by OCTA. Serial measurements of CNV with OCTA may become useful for monitoring and deciding treatment intensity.

Defining the Type of Neovascular AMD

As all neovascular AMD can be treated with anti-VEGF, the exact subtype of neovascularization may not be important, although certain features may influence the likely prognosis. In some cases, such as peripapillary PCV, photodynamic therapy with visudyne alone maybe the best option. In other PCV cases, PDT with anti-VEGF, as suggested in the EVEREST study, may work best, although the PLANET study showed that in 90%

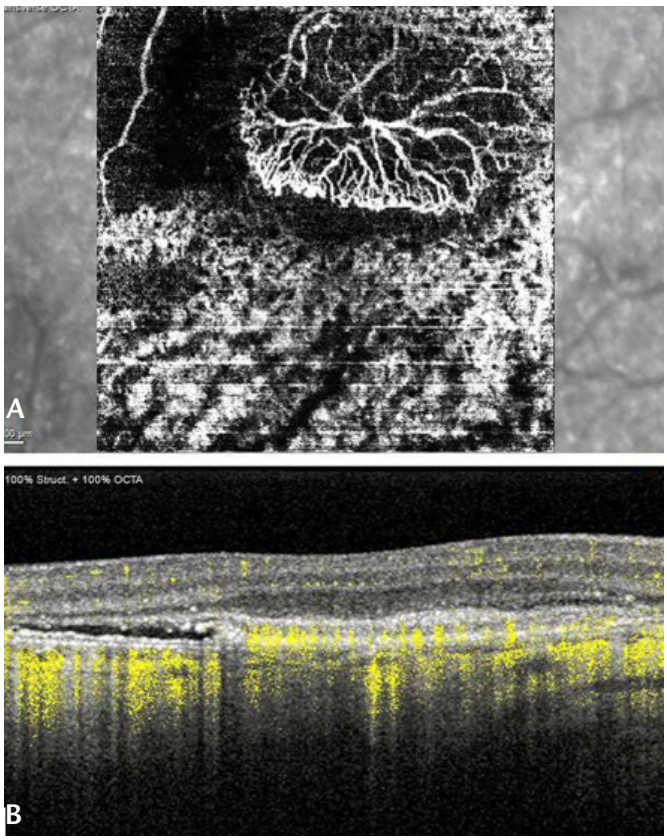

FIGURE 5. A, OCTA shows flow in the area of thickening in the cross-section and a well-defined neovascular membrane on en-face imaging. B, Structural OCT cross-section shows slight thickening in front of the RPE and subretinal fluid. This is consistent with a CNV but not clear.

additional PDT did not add any benefit in terms of visual acuity. This was a continuous treatment regimen for a year, so there may still be a role for PDT to try to stabilize the situation and reduce the risk of sudden hemorrhage.

The subtype may also inform the risk for the other eye and so influence the monitoring strategy. The risk over 5 years for a RAP lesion developing in the other eye is said to be 100%.[66]

Type 2 CNV (Classic)/Type 1 CNV (Occult)

Several studies have characterized the OCTA definitions of occult nAMD/type 1 CNV and classic nAMD/type 2 CNV, which either have well-circumscribed, high-flow networks (described as lacy wheel, sea fan, or Medusa head shaped) or poorly circumscribed, irregular vascular networks (filamentous).[57,58,61,67] These lesions are found in the corresponding subretinal (type 2/classic) and sub-RPE (type 1/occult) location as per the Gass classification. Sensitivity and specificity has been highest for type 2 CNV, as it is front of the RPE and so easier to image. In a study of 115 eyes with type 1 CNV, en face OCTA and structural OCT showed better detection of type 1 CNV than either FFA alone or en face OCTA alone. Combining en face OCTA and structural OCT information may therefore be a useful way to noninvasively diagnose and monitor the treatment of type 1 CNV (Figs. 4, 5).[59]

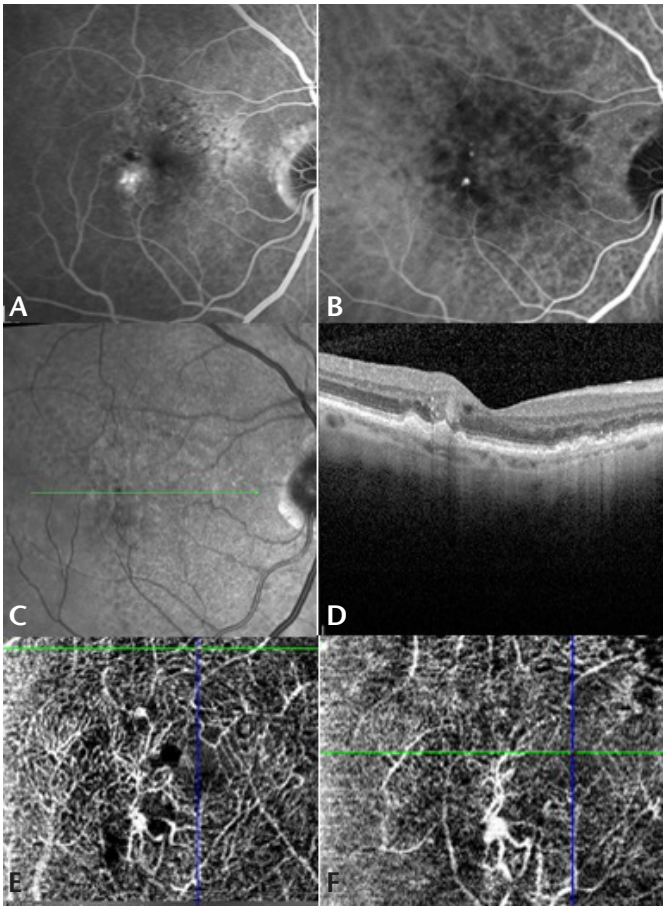

FIGURE 6. Retinal angiomatous proliferation. A, Fluorescein showing a dark spot from hemorrhage and a small leak. B, ICGA showing 3 small bright dots, which could be RAP, PCV, or micronaneurysms. C, Infrared showing OCT cut through the dot of hemorrhage. D, OCT shows reticular psuedodrusen and an intraretinal disturbance in front of the RPE. E–F, OCTA shows intraretinal vascular connections consistent with a stage 1 RAP.

Retinal Angiomatous Proliferation (Type 3 CNV)

The different RAP lesions have been classified into 3 stages. In stage 1 there is intraretinal anastomosis, forming a neovascular complex. In stage 2 the vascularization connects to the subretinal space and in stage 3 the RAP is associated with a serous PED, then CNV and retinal choroidal anastamosis. According to 1 study, RAP accounts for 12–15% of newly diagnosed nAMD.[68] Bilateral involvement is often found, with 100% rates seen at 3 years in a Korean study. Some of the proposed risk factors for RAP include female sex, advancing age, hypertension, and reticular pseudodrusen.[69]

Features of FFA suggesting RAP include a small bright area of intraretinal leakage in a patient with drusen, reticular pseudodrusen being commonly associated, or a spot of leakage associated with a serous PED. Stereoscopic images may be able to define the intraretinal level of the lesion and show retinal to subretinal connections as characterized by a 90-degree diving vessel. These changes are often best seen with ICGA, as it leaks less in the early stages but leaks late in RAP.[70]

In RAP lesions, SD-OCT imaging shows a hyperreflective lesion in the neuroretinal layers, intraretinal cysts, serous PED, and RPE interruptions in the affected area.[70] In eyes with RAP the subfoveal choroidal thickness is reduced compared with normal age-matched subjects.[71,72]

In the CATT study, RAP made up 10.7% of patients treated. At 1 year and 2 years of follow-up, these lesions were more likely to be dry, have GA, and not have fibrosis compared with other nAMD subtypes. The mean visual acuity improvement was similar to other types.[73]

On OCTA, RAP lesions can be seen but the images need careful assessment, as the RAP connections may be missed if only the en face image is examined.[57] This does require a greater degree of skill in confirming a lesion with the use of OCTA (Fig. 6). The lesions have been defined as tufts in the outer retinal segment seen arising from the deep retinal plexus, which may be associated with evolving sub-RPE neovascularization.[74]

Polypoidal Choroidal Vasculopathy

Although ICGA remains the gold standard for diagnosing PCV,[75] OCT plus OCTA can also have a role. The ICG molecule is stimulated by the absorption of infrared light in the range from 790 nm to 805 nm. The RPE and the choroid absorb up to 75% of the blue-green light used for fluorescein angiography but only up to 38% of the near infrared light used for ICGA. This plus the ICG molecule leaking less and remaining intravascular allows better resolution of the choroidal vasculature than seen with fluorescein angiography. Stereo ICGA, and/or combining the imaging findings with those seen on OCT, is important to determine the depth of the lesion and so the differentials of a macroaneurysm or large microaneurysms or retinal angiomatous proliferation. In the early phase of ICGA, pulsation of polypoidal vessels may sometimes be observed if a 30-second video is run.

The image grading protocol for the EVEREST study, which compared ranibizumab with or without photodynamic therapy for PCV, used 6 diagnostic features: a nodular appearance of the polyp on stereoscopic viewing; a hypofluorescent halo around the nodule; abnormal vascular channel(s) supplying the polyps, now called branching vascular networks (BVNs); pulsatile filling of polyps; orange subretinal nodules corresponding to the hyperfluorescent area on ICGA; massive submacular hemorrhage.

Nodular hyperfluorescence on stereoscopic ICGA was seen in 91.8%, a hypofluorescent halo around the nodule in 68.9%, and pulsation during dynamic ICGA in 6.6%.[76]

The SD-OCT findings representing PCV were sharp PED notch and a rounded hyporeflective area representing the polyp lumen within the hyperreflective lesions adherent to the underside of the retinal pigment epithelium. A further larger prospective study of 188 eyes in 156 patients had a sensitivity of 89.4% and specificity of 87.5% using SD-OCT as a screening tool to distinguish PCV from nAMD. They found 2 of 3 positive signs from the following—dome-shaped PED, double-layer sign (subtle thickening between the Bruch membrane and the RPE), and thumb-like polyps—were diagnostic.[77]

Although OCTA can detect PCV and the associated BVNs, the sensitivity varies. It has been hypothesized that turbulent flow inside the polyp might not generate a decorrelation signal inside the threshold range of commercially available OCTAs.[78]

In 1 study OCTA was able to detect the BVN in all cases. Using cross-sectional OCTA, BVN locations were shown to be in the space between the RPE and the Bruch membrane. Using en face OCTA, the BVN vascular pattern could be shown more clearly than by ICGA. Using cross-sectional OCTA, the polyps were shown to be just below the top of the PED. In 1 case, the polypoidal lesion was not detectable at the outer retinal slab.[79]

Recently, PCV has been classified into 2 angiographic subtypes: polypoidal CNV (type 1), which is beneath the RPE, and typical PCV (type 2), with the latter being more common in the Chinese population. The 2 subtypes are identified by the presence or absence of feeder vessels usually noticeable in type 1, which have vascular networks resembling rake-like or umbrella-like configurations. Type 1 may be a variant of AMD and type 2 a distinct disease.[80]

With OCTA finding more BVN and the finding that the BVN is usually between the Bruch membrane and the RPE rather than in the choroid, there is a proposal that really PCV is just a variant of CNV and a new term has been coined, anuerysmal type 1 CNV, to be used instead of PCV.

Cheung et al[81] showed the sensitivity of OCTA versus FFA for detecting a polyp to be 40.5%. For now, a multimodal imaging approach seems the most reliable using ICGA as a gold standard to confirm these lesions, although OCTA and OCT could be used as a tool for screening for recurrence.

Nonexudative Neovascular nAMD

Optical coherence tomography angiography has helped to identify the existence of a subtype of neovascular nAMD, described as nonexudative nAMD.[53] In a small series, 3 cases in which a plaque was found on ICGA in asymptomatic patients with intermediate AMD, OCTA found type 1 neovascularization corresponding to the plaques.[8]

This may help identify at-risk patients who warrant sooner review with regard to monitoring their AMD.

Auto Reading of OCT for AMD

There has been significant investment into automating the review of color fundus and OCT imaging. The aim is to aid in managing the increasing burden of ophthalmological conditions, such as nAMD and diabetic retinopathy, presenting to the ophthalmology department. Using the UK Biobank, researchers in the United Kingdom and the United States have been able to create a rapid automated analysis of retinal thickness on OCT images. The group were able to acquire, store, and remotely analyze these images. This proof of concept study highlights the future direction of automated big data analysis of ophthalmological imaging for clinical trials, epidemiological studies, and screening.[82] Recently, Google Deep Mind has partnered with Moorfield's Eye Hospital to create an algorithm for automated assessment of OCT and digital fundal images, aiming to classify pathological images with the use of neural networks, with a large data set.[83] Bogunovic et al[84] have been able to show that a machine learning–based model reviewing patient OCTs was good at predicting whether nAMD patients would be in high or low as-needed treatment groups after the initial loading phase for ranibizumab therapy. Using artificial intelligence and deep learning in predicting treatment decisions based on automated segmentation of retinal layers, measurement of retinal fluid, and correspondence with functional outcomes may represent the future of management of conditions such as nAMD.[84–87]

CONCLUSIONS

Selective use of multimodal imaging can produce the most accurate diagnostic information and management information for AMD. Although rare, the possible differential diagnoses for AMD should not be forgotten. The increasing resolution and capability of OCT, including SS-OCT and OCTA along with the potential of machine learning, mean this is likely to be the main imaging modality in the future for AMD.

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