The Role of Optical Coherence Tomography (OCT) in the Diagnosis and Management of Retinal Angiomatous Proliferation (RAP) in Patients with Age-related Macular Degeneration

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Introduction

Retinal angiomatous proliferation (RAP), initially described as deep retinal vascular anomalous complex in 1992 by Hartnett et al., has been recently defined as a new, distinct form of exudative age-related macular degeneration (AMD). In choroidal neovascularisation (CNV), the choroidal new vessels may proliferate through the retinal pigment epithelium (RPE), infiltrate the retina, and eventually communicate with the retinal circulation, forming a retinal-choroidal anastomosis. In RAP, the neovascular process originates from the retinal vasculature. Yannuzzi et al. proposed 3 vasogenic stages: Stage 1 consists of the proliferation of intraretinal capillaries originating from the deep capillaryplexus in the paramacular area (intraretinal neovascularisation); Stage 2 is defined by the presence of retinal-retinal anastomoses, intraretinal oedema and may be associated with serous PED and/or subretinal neovascularisation; in Stage 3, retinochoroidal anastomoses and true choroidal new vessels are present.

The diagnosis of RAP is currently based on clinical slit-lamp biomicroscopic examination, fluorescein angiography and indocyanine green (ICG) angiography. Although the earliest fundus changes of RAP on biomicroscopy, such as extrafoveal intraretinal haemorrhages and some intraretinal oedema, are very peculiar and consistent, the diagnosis of RAP on biomicroscopy requires a high degree of experience and expertise. Moreover, as the severity of the disorder increases, the clinical picture becomes more complex and identifying the intraretinal neovascularisation may be very difficult. At the time of diagnosis, most of the RAP have already reached Stage 3 and appear as purely occult or minimally classic choroidal neovascularisation on fluorescein angiography, which is therefore inadequate in identifying the nature of the new vessels. At this stage, standard ICG angiography is more helpful in that it reveals a hot spot in late frames, corresponding to the neovascularisation. Moreover, high-speed ICG angiography usually allows an accurate identification of retinal feeding vessels.
arterioles, draining venules, and associated retinal-retinal or retinochoroidal anastomoses. However, these digital angiographic systems are strongly limited by the lack of stereopsis, which precludes precise localisation of the depth of the neovascular process.

Optical coherence tomography (OCT) is a non-invasive, non-contact, high-resolution imaging technique that is increasingly used to diagnose and manage a variety of retinal diseases and glaucoma. OCT produces a cross-sectional image of the retina with a resolution of 10 µm, thus enabling detailed evaluation of epi-, intra-, and sub-retinal morphology, which is not possible with other imaging modalities. OCT has been used to evaluate macular holes, epiretinal membrane, vitreomacular traction, macular oedema, central serous chorioretinopathy and choroidal neovascularisation. Given the peculiar neovascular sequence of RAP, which is initially confined within the retina and subsequently progresses posteriorly, beyond the photoreceptor layer into the subretinal space, OCT may prove particularly useful also in the diagnosis and management of RAP.

This preliminary report focuses on the role of OCT in the detection and management of RAP, first briefly reviewing the principle of operation and the interpretation of OCT images and then describing the changes occurring in the retina affected by RAP at different vasogenic stages. It also outlines the usefulness of OCT in monitoring the response of RAP to laser photocoagulation.

**Optical Coherence Tomography: Appearance of Normal Retina**

The tomogram of a normal fovea presents a series of characteristics that is important to recognise in order to correctly interpret pathologic findings. Bright colours (red and white) represent regions of high optical reflectivity and correspond to horizontally aligned retinal components (nerve fibre layer, plexiform layers, RPE). With the Stratus OCT, a thin highly reflective band above the RPE can also be observed and is currently attributed to the junction between photoreceptor inner and outer segments. Dark colours (blue and black) represent regions of minimal relative optical reflectivity and correspond to nuclear layers and photoreceptor inner and outer segments. At the foveola, the depression of the foveal pit reaches its maximum and only the hyporeflective photoreceptor layer (foveal cones) can be observed. Even when the fovea is thickened because of macular oedema, and the foveal profile is flattened or inverted, the foveola can be still recognised by the characteristic full thickness hyporeflectivity and this represents an important landmark during scan acquisition and analysis. In addition, in case of macular oedema or choroidal neovascularisation, 6 radial scans, centred on patient’s fixation and compressed into 1 scan, can be rapidly (1.92 s) acquired with the protocol “Fast Macular Thickness Map”, in order to image and map extrafoveal areas. Acquired images are then processed with the “Retinal Map” protocol, in order to obtain a retinal thickness map of the entire macular region. This map is displayed as a false colour image where bright colours (red and white) represent thick regions, dark colours (blue and black) represent thin areas, and green and yellow represent a region of intermediate thickness. However, while a single scan can be set at a transverse resolution of 512 A-scans per B-scan, yielding more detailed intraretinal information, the 6 radial lines of the “Fast macular thickness mapping protocol”, consisting of 128 A-scan per line, are best indicated for reconstructing a surface map and providing topographic information.

**Optical Coherence Tomographic (OCT) Appearance of Retinal Angiomatous Proliferation (RAP)**

The highly detailed information regarding high-resolution (512 A-scan per B-scan) cross-sectional macular anatomy provided by OCT is extremely useful for the identification of RAP and its associated manifestations. Although the earliest stages of RAP are barely visible on both contact lens slit-lamp biomicroscopy and angiographic exams due to the small size of the initial lesions, typical intraretinal features can be observed if the scan line is slowly moved across the macula near the foveal centre, over the area of fundus anomaly suggestive of RAP. For these reasons, all the scans of eyes undergoing OCT for detection of RAP consisted of high-resolution single-line scans, 2 perpendicularly crossing at patient’s fixation and 1 angled in order to image simultaneously the foveal centre and retinal pathology. Retinal maps were not considered an adequate acquisition protocol to image RAP because the spacing between scan lines and the lower resolution of each line (128 A-scans per B-scan) may have precluded proper imaging of small intra-subretinal abnormalities, particularly in the early stages. Patients with significant media opacities impairing a clear visualisation of the fundus (i.e., dense cataract, posterior capsular haze, vitreous haemorrhage) were excluded from our study. All OCT scans were performed by the same experienced examiner (AP), who was familiar with the biomicroscopic and angiographic appearance of the examined lesion.

The earliest OCT sign, corresponding to Stage 1 (intraretinal neovascularisation), consists of a focal area of increased intraretinal reflectivity, usually extrafoveal and not associated with other epi-, intra- or sub-retinal changes or retinal thickening. This area corresponds to the focal area of intraretinal staining on FA and to the focal area of intense hyperfluorescence, the so-called “hot spot”, on ICG angiogram. If intraretinal haemorrhages are also present, they may not be distinguishable from the intraretinal
vascular lesion in that they are both hyper-reflective on OCT. The signs of progression of RAP on OCT are represented by the presence of intraretinal and subretinal fluid (Fig. 1). The first (i.e., macular oedema) is characterised by well-defined, confluent, intraretinal hyporeflective spaces which are confined to the outer retina in the extrafoveal area and involve the entire retinal thickness in the foveal centre, where they are clearly separated by reflective septae. The second (i.e., neurosensory detachment) is characterised by a well-defined hypo-

**Fig. 1.** The red-free photograph shows a localised area of intraretinal haemorrhages (A). The arrow indicates the location and direction of the OCT scan. The early and late frames of the fluorescein angiograms show cascading layers of retinal and subretinal leakage interpreted as occult choroidal neovascularisation (B, C). The early and mid-frames of ICG angiograms reveal a focal “hot spot” (D,E), whereas the late frame shows leakage into the retina, presumably from fibrin accumulation (F). Vertical OCT (G) taken through the “hot spot” seen on ICG angiography demonstrates a localised area of increased intraretinal reflectivity (arrowhead) associated with foveal cystoid spaces (small arrows), extrafoveal hyporeflective confluent spaces at the level of the outer retinal layers (large arrows) and subfoveal optically empty areas corresponding to serous retinal detachment (small arrowheads).

**Fig. 2.** The red-free photograph shows multiple soft drusen and a localised area of intraretinal haemorrhages (A). The arrow indicates the location and direction of the OCT scan. The early fluorescein angiogram reveals a continuous retinal-retinal anastomosis and the well-defined hyperfluorescence of the intraretinal angiomatous proliferation (B). The late fluorescein angiogram shows pooling of dye due to a serous pigment epithelial detachment (C). The ICG angiogram shows the intraretinal neovascularisation (D, E) and a larger area of hyperfluorescence presumably due to subretinal neovascularisation in the late phase (F). The OCT taken through the hot spot seen on ICG (G) reveals multiple foveal cystoid spaces (small arrow), and increased juxtafoveal intraretinal reflectivity (large arrowhead) overlying a dome-shaped elevation of an irregularly thickened outer highly reflective band (PED with “presumed” subretinal CNV, large arrows); under the fovea a well-defined hyporeflective space corresponding to subretinal fluid is also present (small arrowheads).

**Fig. 3.** The clinical photograph (A), ICG angiogram (B) and OCT (D) show the retinal angiomatous proliferation presented on Figure 1 and treated with focal direct laser photocoagulation. An OCT scan obtained immediately after ICG-guided laser photocoagulation reveals a diffuse increase in intraretinal reflectivity precluding the visualisation of the previously observed intraretinal lesion (D, arrowhead). This feature is secondary to the increased backscattering of all retinal layers due to the oedema induced by the laser treatment. The fundus photograph and ICG angiogram at 1 month disclose a persistence of intraretinal haemorrhage “hot spot” (E, F), and therefore a second laser treatment was performed. The OCT over the treated area shows increased reflectivity due to the scarring process, reduction of the intraretinal hyporeflective spaces and some residual subretinal fluid. The fundus photograph and ICG angiogram at 2 months reveal a significant reduction of the intraretinal haemorrhages and disappearance of the hot spot (H, I). The OCT shows flattening of the retinal pigment epithelium elevation, further reduction of retinal thickening and resolution of the subretinal fluid (I). The fundus photograph at 6 months shows focal atrophy. No hot spot can be noticed on the ICG angiogram and the OCT shows restoration of normal macular profile and internal retinal structure (O).
2. In addition to intraretinal and subretinal fluid, in the presence of a serous PED, OCT also reveals a dome-shaped elevation of the outer highly reflective band. By simultaneous imaging of the extrafoveal intraretinal neovascularisation and the foveola on the same optical cross-section, we can determine the lateral extension of the new vessels and their distance from the fovea. This is particularly relevant for planning and monitoring laser treatment. As the RAP further progresses and choroidal neovascularisation develops (Stage 3), the lateral extent and height of the RPE elevation, as well as the hyporeflective spaces corresponding to IRF and SRF, may become more severe. Due to the impossibility of distinguishing between actively proliferating new vessels and scar tissue, and to clearly image structures under the RPE, since most of the OCT signal is reflected and backscattered by the RPE, OCT is limited in identifying the choroidal extent of the neovascularisation. It is thus impossible to clearly differentiate Stage 2, or subretinal neovascularisation, from Stage 3, or choroidal neovascularisation.

Finally, OCT is particularly useful in measuring the neuroretinal foveal thickness and the RPE elevation. These measurements can be both used to objectively and quantitatively assess and monitor retinal oedema and PED. They are best acquired by manually positioning the callipers between the inner high reflectivity band and the outer margin of the outer retinal layers, in order to determine the neuroretinal foveal thickness and between the inner margin of the elevated outer high reflectivity band (i.e., RPE) and the sub-RPE extension of the normal, “undetached”, RPE plane (i.e., “presumed” Bruch’s membrane) in order to measure the height of the PED, using the retinal thickness quantitative analysis protocol offered by Stratus OCT.

**Tomographic Assessment of Therapeutic Response**

In addition to significantly improving our ability to recognise and accurately locate RAP, particularly in the early stages, OCT is extremely helpful in documenting retinal morphological changes following treatment. In particular, we have extensively used OCT to monitor the anatomic outcome after conventional thermal laser treatment of RAP stages 1 and 2.

A favourable response to laser treatment is generally associated with the following temporal sequence of OCT structural changes (Fig. 3):

1. Immediately after laser: Increased homogeneous intraretinal reflectivity involving all retinal layers at the level of the laser treatment and including the intraretinal lesion; this appearance is presumably due to the retinal oedema and whitening secondary to laser photocoagulation.
2. Between 2 weeks and 1 month: Resolution of the CME and serous retinal detachment, persistence of a focal area of hyper-reflectivity on top of the elevated RPE.
3. Within 3 months: Flattening and resolution of the RPE detachment, initial thinning of the neurosensory retina over the treated area.
4. After 3 months: Complete thinning of the neurosensory retina and marked backscattering from the choroid due to atrophy and central shadowing of the RPE due to pigment.

**Limits**

The reliability of both quantitative and qualitative information provided by OCT is strongly dependent on image quality. Operator skill and patient’s characteristics are the 2 main factors influencing the outcome of the examination. The most important factor dependent on operator in patients affected by RAP is the correct placement of the scan over the neovascular lesion and the foveola for simultaneous imaging of these 2 structures. A pre-OCT red-free photograph and ICG angiogram available during the OCT exam provide a useful indication on where to place the OCT scan line. The most relevant factor dependent on patient is stability of fixation, because an unstable or poor fixation due to a central scotoma or low vision (<20/100) may impair a correct scan positioning and preclude reliable repeat scans at follow-up visits.

**Discussion**

OCT is a promising investigative tool to image and measure retinal morphological changes induced by RAP. This form of neovascular AMD is not uncommon and it may have a peculiar natural history and prognostic parameters. Although later stages are not likely to respond to any form of currently available treatment, earlier stages may benefit from conventional thermal laser treatment. Current diagnostic methods are not always sufficient to document the nature of the neovascular lesion with certainty due to the difficulties in interpreting the multiple fundus changes and the indistinct leakage secondary to RAP. The preliminary results of our case series indicate that OCT provides valuable information complementary to that available by fundus exam and fluorescein and ICG angiography. In particular, it allows objective demonstration and confirmation of the findings of the biomicroscopic and angiographic examination in a fast, non-invasive and well-tolerated manner. Moreover, we have found it particularly useful in monitoring the response to laser photocoagulation treatment.

However, additional clinical experience and longitudinal studies in patients with choroidal neovascularisation and RAP are needed to determine its exact place and utility in research and clinical practice.
REFERENCES