Editorial

Optical coherence tomography angiography of non-exudative choroidal neovascularization

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Age-related macular degeneration (AMD) has been classified in two groups, neovascular and non-neovascular, which historically has been synonymous with exudative and non-exudative, respectively. Neovascular AMD occurs when pathologic blood vessels, choroidal neovascularization (CNV), arise from the choroid and extend above Bruch's membrane toward the outer retina. Often these vessels are exudative in nature, resulting in leakage of fluid, lipid exudate, or blood causing vision loss. The exudation from CNV allows detection as leakage with dye based angiography and as fluid with structural optical coherence tomography (OCT). In 2013, Querques *et al*. used multi-model imaging to detect treatment naïve quiescent CNV (1). This diagnosis requires presence of (I) moderate reflective material between an elevated retinal pigment epithelium and Bruch's membrane on spectral domain OCT; (II) absence of fluid on OCT; (III) staining with fluorescein angiography; and (IV) a plaque identified with indocyanine green angiography. This study confirmed the existence of non-exudative neovascular AMD, and that exudation is not required for the presence of CNV. OCT angiography (OCTA), which can detect CNV as moving blood cells in the outer retinal slab (2) rather than relying on the presence of leakage on FA or fluid on OCT, is an ideal imaging modality to further study non-exudative CNV.

In 2015, Palejwala *et al*. first described the use of OCTA to detect non-exudative CNV (3). In this study, 32 fellow eyes of patients with neovascular AMD were scanned using OCTA. Two cases of clinically silent non-exudative CNV were found as flow in the outer retinal slab without exudation on structural OCT and without leakage on fluorescein angiography. One case was followed longitudinally and over 8 months, the CNV vessel area enlarged by 20%, however, exudation never developed. Several other studies have subsequently further characterized non-exudative CNV using OCT angiography (4-7).

The recent study by Carnevali *et al*. aimed to describe features of treatment naïve quiescent CNV (TNQ-CNV) and estimate the detection rate by OCTA (7). This was an observational case series comparing TNQ-CNV diagnosed by traditional imaging methods to those which could be imaged on commercially available OCTA, AngioPlex and AngioVue. A group of 22 eyes of 22 patients with drusenoid pigment epithelial detachment (PED) without vascular network on ICGA were used as negative controls. OCTA detected CNV in 18/22 study eyes and there were no false positive eyes. They concluded there was sensitivity of 81.8% (18/22 patients) and 100% specificity. The most common morphology was irregular, foveal sparing, with a nonvisible core and well-defined margin.

While OCT angiography is a powerful tool, it is important to be aware of confounding projection artifact to avoid falsely identifying CNV. As light passes through moving red blood cells in the superficial retina, a flickering shadow is cast onto the deeper structures and is misinterpreted as moving red blood cells by OCT angiogram algorithms (8-11). One must

thus be cognizant of this principle during evaluation for CNV with OCTA. An excellent illustration is provided by Zheng *et al*. (11), who compare slabs containing segments of RPE (RPE-fit) versus slabs which follow the RPE contour; the apparent vessels in the former are in fact projection artifact from retinal vessels. The authors suggest projection artifact may have been interpreted as vascularized drusen in a separate study (5). The use of new algorithms to suppress projection artifact and appropriate sectioning is therefore critical to minimizing false positives in CNV detection (9). Carnevali *et al*. are to be commended for their consideration of potential projection artifacts. To avoid falsely identifying drusenoid PEDs as CNV, they applied algorithms to suppress projection artifact and manually adjusted automatic segmentation software to separate the capillary plexus, outer retinal layers and the choriocapillaris. They then analyzed only the choriocapillaris slab.

CNV is typically diagnosed by FA and ICG which is invasive, time consuming and carries the risk of an adverse reaction. OCTA has the advantage of imaging faster at higher resolution, in 3 dimensions, and in different layers. Surveillance of non-exudative quiescent CNV in this noninvasive way is appropriate because monitoring can be frequent without need for invasive procedures, given no required treatment.

Findings reported by Carnevali *et al*. and others provide useful information on non-exudative CNV, but the real utility will be to observe over time to learn its natural history which may remain quiescent for long periods of time, regress or wax and wane. It is likely that some quiescent CNV is a precursor to exudative CNV, but it could potentially also represent more mature vessels with competent endothelial cell junctions, or be a separate entity from exudative CNV. Only when features of non-exudative quiescent CNV are understood that can be used to predict development of exudative CNV will the technology be useful to influence prognosis and treatment. Further longitudinal studies are needed to establish what constitute high risk features. These studies could also shed light on other questions such as the effect of anti-VEGF on non-exudative CNV in the fellow eye.

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Footnote

Conflicts of Interest: D Huang and Y Jia have a significant financial interest in Optovue, Inc., a company that may have a commercial interest in the results of this research. D Huang received royalties on an optical coherence tomography patent licensed to Carl Zeiss Meditec, Inc. These potential conflicts of interest have been reviewed and managed by Oregon Health and Science University (OHSU). The other authors have no conflicts of interest to declare.

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