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Clinical utility of OCTA

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INTRODUCTION

Optical coherence tomography angiography (OCTA) is a novel technology that can produce images of blood flow with unprecedented resolution of all the vascular layers of the retina and choroid in a rapid, non-invasive fashion. The technology dates back to 2005, when researchers demonstrated that blood flow could be visualized using swept-source OCT (SS-OCT) based on properties of the Doppler signal.[1] Since then, advancements have led to the technology becoming widely available for the clinical community, aiding in patient diagnosis and monitoring. This review article will highlight examples of ophthalmic diseases where OCTA has important clinical utility; specifically, diabetic retinopathy, age-related macular degeneration, retinal vein occlusions, white-dot syndromes, and early research into neurodegenerative diseases.

DIABETIC RETINOPATHY

In diabetic retinopathy (DR), OCTA allows for diagnosis, monitoring, and may even aid in the early detection of retinal changes in patients with diabetes.[2-4] A study from 2019 used OCTA to compare perfused capillary density (PCD) in diabetic patients with healthy controls. In this study, diabetic patients were further sub-categorized as having non-proliferative DR (NPDR), proliferative DR (PDR), or no DR.[2] Diabetic patients with no clinical signs of DR had a significantly higher PCD compared to the control group, providing objective measurement of preclinical retinal vascular changes. The researchers hypothesized that this increase in PCD may have been related to the increased recruitment of capillaries and capillary dilatation.[2] The NPDR and PDR groups demonstrated progressively decreasing PCD. OCTA also provides notable advantages over the current standard of fluorescein angiography (FA). PDR is characterized by retinal ischemia and the development of neovascularization (NV) at the vitreoretinal interface.[2] OCTA can measure these retinal NVs via observation of supra-retinal flow signals above the internal limiting membrane (ILM) or with outpouching of the ILM. A study in 2020 compared widefield OCTA to ultra-wide-field FA (UWF-FA) and ultra-wide-field colour fundus photography (UWF-CF) to detect retinal NV in eyes with PDR.[3] The study demonstrated that widefield OCTA can identify NV not yet evident on UWF-CF and represents a faster and safer alternative to UWF-FA for surveillance of PDR with comparable diagnostic accuracy. OCTA can also allow for differentiation of subtle NVs from microaneurysms, which may appear similar on FA.[4] Another study demonstrated the utility of widefield OCTA through flow overlay on cross-sectional B scans in the staging and prognostication of DR.[5] Intraretinal microvascular abnormalities (IRMA) are seen on OCTA as collateral vessels within the retina.[5] As the presence of IRMAs denotes the transition to severe NPDR, widefield OCTA can aid in identifying high-risk DR eyes (**Figure 1**).

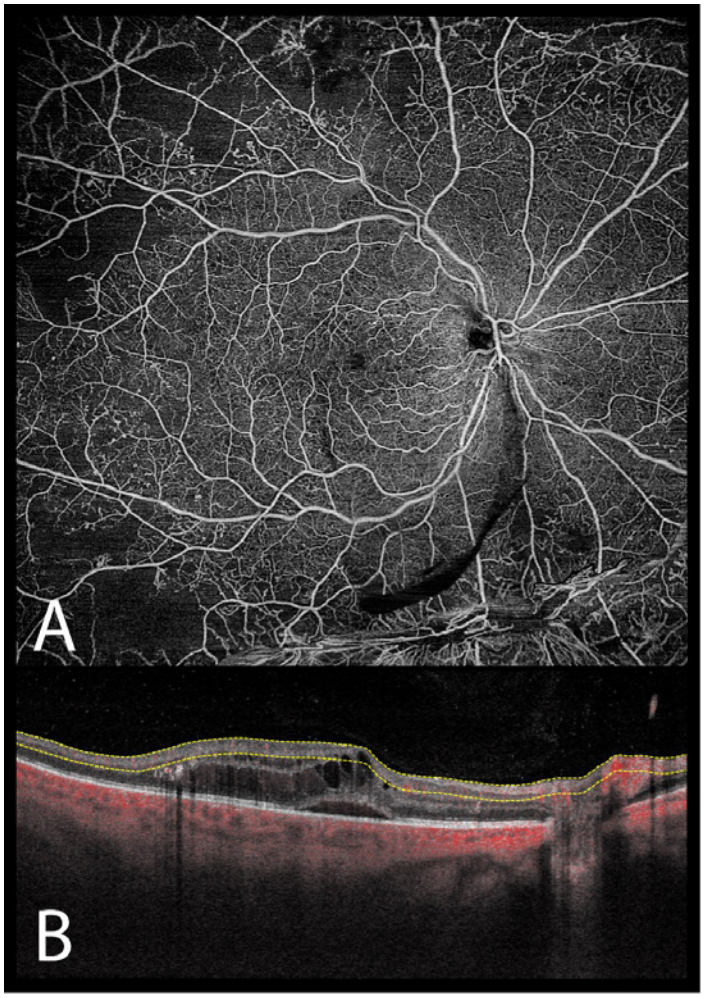

Figure 1: *Widefield OCTA imaging of diabetic retinopathy seen on OCTA (Zeiss Plex Elite 9000, Oberkochen, Germany). Widefield OCTA of the superior vascular plexus (A) showing areas of non-perfusion, vessel pruning, pre-retinal heme, and development of neovascularization. Corresponding flow B scan (B) showing subretinal and intraretinal fluid.*

NONEXUDATIVE NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

In recent years, widespread clinical use of OCTA has allowed further exploration into age-related macular degeneration (AMD) presenting with macular neovascularization (MNV) without macular fluid or leakage on FA (**Figure 2**).[6,7] This condition, originally described in the 1970s, is termed non-exudative neovascular AMD.[6,7] Using en-face OCTA correlated with B scan flow overlay, MNV can be reliably detected and monitored (**Figure 2**).[6] These eyes are at an increased risk of exudation compared to eyes with non-neovascular AMD.[6,8-10] The estimated incidence of new onset exudation where the fellow eye had exudative AMD was approximately 25% over different follow-up periods ranging from 6–20 months.[7] Growth of the MNV has been proposed as a possible biomarker to predict conversion to exudative AMD.[7] However, further longitudinal research is required, as this finding has not been consistently elucidated across all studies.[7] Although no randomized clinical trials have been conducted regarding the management of nonexudative neovascular AMD, the consensus is that it should not be treated, but rather monitored.[6,7] Some studies have proposed that this neovascularization may have a protective effect against geographic atrophy (GA), with results from some demonstrating a lower rate of GA lesion growth and surviving retinal pigment epithelium over areas of MNV with adjacent atrophy.[6,7,9] OCT and OCTA technology allows ophthalmologists to closely monitor these patients for the onset of exudation requiring early initiation of treatment.

RETINAL VEIN OCCLUSIONS

In retinal vein occlusions (RVO), OCTA has become particularly valuable in its ability to delineate specific microvascular details in the superficial and deep retinal plexuses and to provide depth-resolved measurements of the foveal avascular zone (FAZ). The size of FAZ measured separately in the superficial and deep vascular plexuses are significantly larger in eyes with RVO compared to fellow eyes, a measurement not possible with the clinical standard using FA.[11] Increased FAZ area in the superficial vascular plexus (SVP) has been shown to correlate with poorer visual acuity in RVO.[11] Both OCTA and FA can evaluate areas of central and peripheral non-perfusion. However, using OCTA to improve determination of the extent and severity of non-perfusion has important prognostic

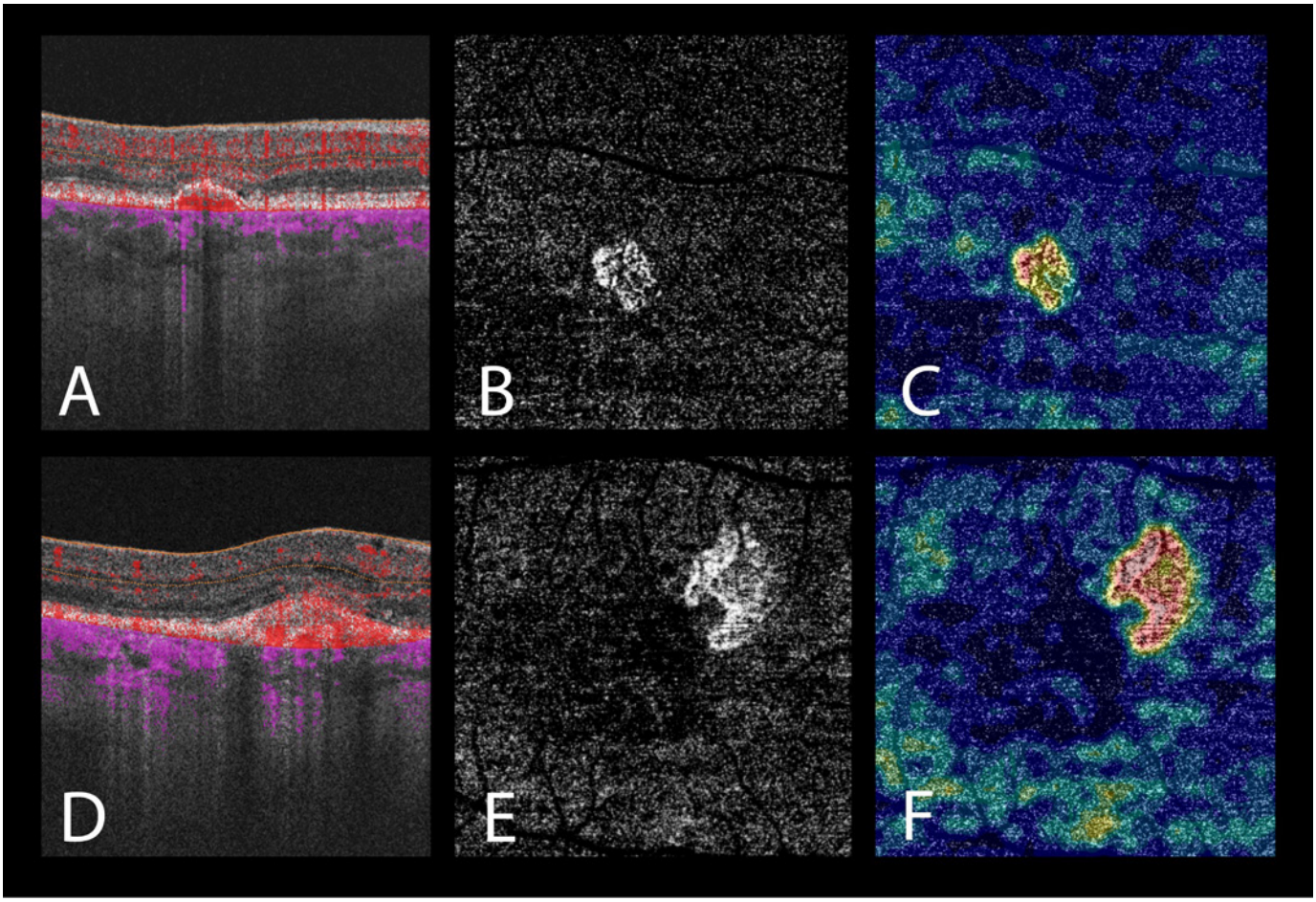

Figure 2: *Nonexudative neovascular age-related macular degeneration seen on OCTA (Topcon DRI Triton, Tokyo, Japan). Cross-sectional B scan with flow overlay (A) showing pigment epithelial detachment without subretinal or intraretinal fluid. OCTA of the outer retina (B) reveals choroidal neovascularization. Perfusion density mapping of the outer retina (C) highlights area of neovascularization. Follow up images after development of exudation and treatment, including B scan with flow overlay (D), OCTA of outer retina (E), and perfusion density map (F).*

implications. Although macular edema is often responsible for vision loss in RVO, photoreceptor damage from non-perfusion can cause persistently poor vision.[12] Specifically, grade 4 macular ischemia, according to the Bradley classification, is correlated with poor visual outcomes.[12] However, grades 2 and 3 macular ischemia show no such significant correlation.[12] OCTA also allows for visualization of microvascular changes including vascular tortuosity, telangiectasia, and collateral vessel development.[13]

WHITE DOT SYNDROMES

The use of OCTA in white dot syndromes has provided insight into disease pathophysiology, diagnosis, and management.[14-17] Although these syndromes are rare and can be clinically similar, OCTA has allowed further characterization and differentiation of these pathologies. Lesions in multiple evanescent white dot syndrome (MEWDS) and acute posterior multifocal placoid pigment epitheliopathy (APMPPE) have clinically similar features.[14-18] Use of OCT and OCTA technology demonstrates distinct pathophysiologic processes for these conditions. Normal OCTA of the choriocapillaris in MEWDS has shown that this is likely not a choriocapillaris pathology, but rather a primary photoreceptor inflammatory process.[15] In APMPPE, OCTA reveals patchy flow deficits in the choriocapillaris (**Figure 3**) co-localized with inflammatory lesions, suggesting primary choriocapillaris ischemia with a secondary effect on the outer retinal layers and the retinal pigment epithelium.[16] Although both MEWDS and APMPPE are generally self-limiting, it is important to distinguish between these conditions. MEWDS can be a masquerade for multifocal choroiditis, syphilis, and vitreoretinal lymphoma.[14] Rarely, APMPPE can be complicated by central nervous system vasculitis.[14] The utility of OCTA in detecting choroidal neovascularization is well known.[17] This is useful in white dot syndromes such as birdshot chorioretinopathy and idiopathic multifocal chorditis (iMFC) with panuveitis, which can develop neovascularization secondary to ischemia, requiring treatment.[14,17] Choriocapillaris flow deficits or reduced flow are seen on OCTA in other white dot syndromes, such as acute idiopathic maculopathy (AIM) and serpiginous or serpiginous-like chorditis.[14,17] Conversely, acute macular neuroretinopathy (AMN) is associated with deep capillary plexus ischemia.[14]

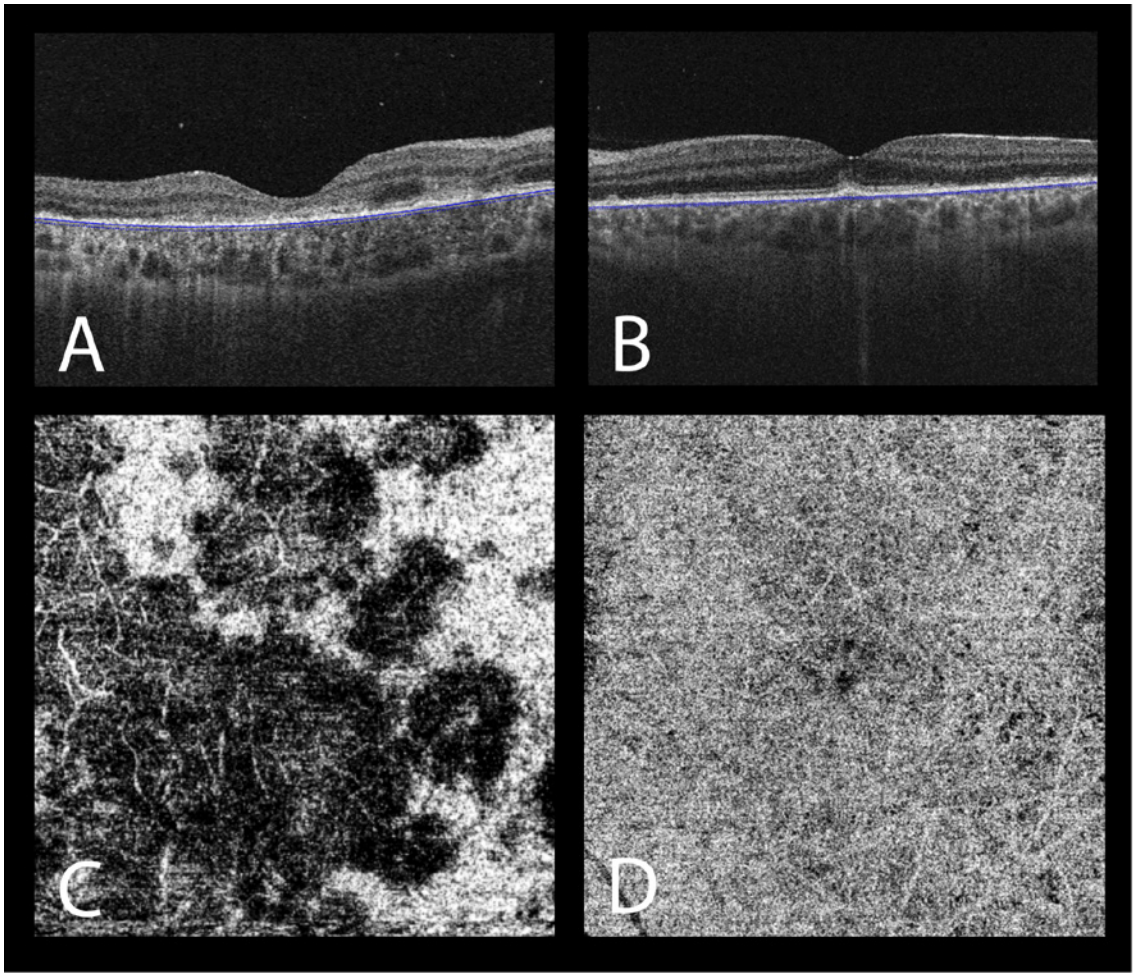

Figure 3: *Acute posterior multifocal placoid pigment epitheliopathy and multiple evanescent white dot syndrome seen on OCTA (Topcon DRI Triton, Tokyo, Japan). APMPPE: Single cross-sectional B scan through the fovea (A) demonstrates increased hyperreflectivity in the outer nuclear layer and RPE mottling. 6x6 OCTA of the choriocapillaris (C) shows patchy areas of non-perfusion. MEWDS: Single cross-sectional B scan through the fovea (B) shows focal areas with disruption of the ellipsoid zone. 6x6 OCTA of the choriocapillaris (D) shows normal vasculature with no patchy areas of non-perfusion.*

NEURODEGENERATIVE DISEASES

The use of OCTA in patients with neurodegenerative conditions such as Alzheimer's dementia (AD) is an evolving area of research.[19-23] Given the similarities between the microvasculature in the retina and brain, retinal vascular findings on OCTA may provide diagnostic or predictive value for neurodegenerative conditions.[19] In patients with AD, some studies have reported statistically significant OCTA findings compared with control groups and others have found correlations between OCTA measurements and cognitive scores measured by tests such as the Montreal Cognitive Assessment (MoCA).[20,22,24,25] In the eyes of these patients, significantly decreased vessel density in the SVP has been reported.[20] Some studies have also reported a significant decrease in the deep vascular plexus (DVP) density and radial peripapillary capillary level as well, although this has not been reliably replicated.[20-22] A machine learning algorithm used multimodal retinal imaging and patient information to detect AD with reasonable success (AUC of 0.841 in the best-performing model).[25] The algorithm paid particular attention to FAZ size along with SVP density to help make the differentiation.[25] In patients with no diagnosis of cognitive impairment or dementia, density in the SVP was found to correlate with cognitive test scores.[19] These findings could play a role in early detection of cognitive changes.[19] Further research with standardized OCTA acquisition and longitudinal approaches is required to elucidate the full potential of OCTA in the field of cognitive decline.[20,22]

CONCLUSION

OCTA is establishing itself as a valuable tool which provides clinicians with useful diagnostic information in many retinal diseases alongside information that can aid disease management. Furthermore, its use extends beyond the retina and provides potential insights into other ocular conditions and even systemic disease. The evidence for OCTA in clinical practice is growing, with new studies published each year, revealing important insights into the nature and treatment of disease. OCTA provides advantages over the current standard of ophthalmic vascular imaging, allowing for rapid acquisition of non-invasive and reproducible images. Despite these advantages, OCTA-based clinical evidence is still in the early stages of development and further clinical trials are needed to allow for the implementation of this imaging modality into guidelines for various ophthalmic diseases. The standardization of imaging protocols and artifact management will be central to a more widespread adoption of this emerging technology.

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