Is OCT Angiography Useful in Neurodegenerative Diseases?

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There is expected to be a considerable increase in the incidence of neurodegenerative diseases such as mild cognitive impairment (MCI), Alzheimer's disease (AD), and Parkinson's disease (PD). It is estimated that one-third of all people born in recent years are expected to develop some form of dementia in their lifetime.[1] Alzheimer's clinical trials thus far have failed to reach primary endpoints, and the clinical and research community recognizes that a better understanding of the pathophysiology and treating at earlier stages of these diseases are the roads forward for effective therapeutic intervention. A robust, relatively low-cost, and patient-friendly biomarker for early diagnosis of neurodegenerative diseases, perhaps even before clinical symptomatology, is therefore currently a large unmet need.

AD is characterized by the progressive accumulation of extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles in the brain as well as altered levels of Aβ and tau in the cerebrospinal fluid. The retina is embryologically derived from the neural tube and is a uniquely accessible, noninvasive diagnostic target for neurodegenerative diseases. This led to considerable worldwide interest on the use of optical coherence tomography (OCT) for detection of retinal structural changes in AD, where thinning in the retinal nerve fiber layer (RNFL) formed by axons of the retinal ganglion cells has been demonstrated both histopathologically[2] and on OCT,[3] as has choroidal thinning.[4]

Herein, we discuss the utility of OCT angiography, which has very recently shown promise to detect microvasculature changes in the retina in neurodegenerative diseases, as well as the current limitations of OCTA technology as a diagnostic tool in these diseases.

Using OCTA, Bulut et al. showed that the superficial capillary plexus (SCP) vessel density (VD) was lower in AD compared
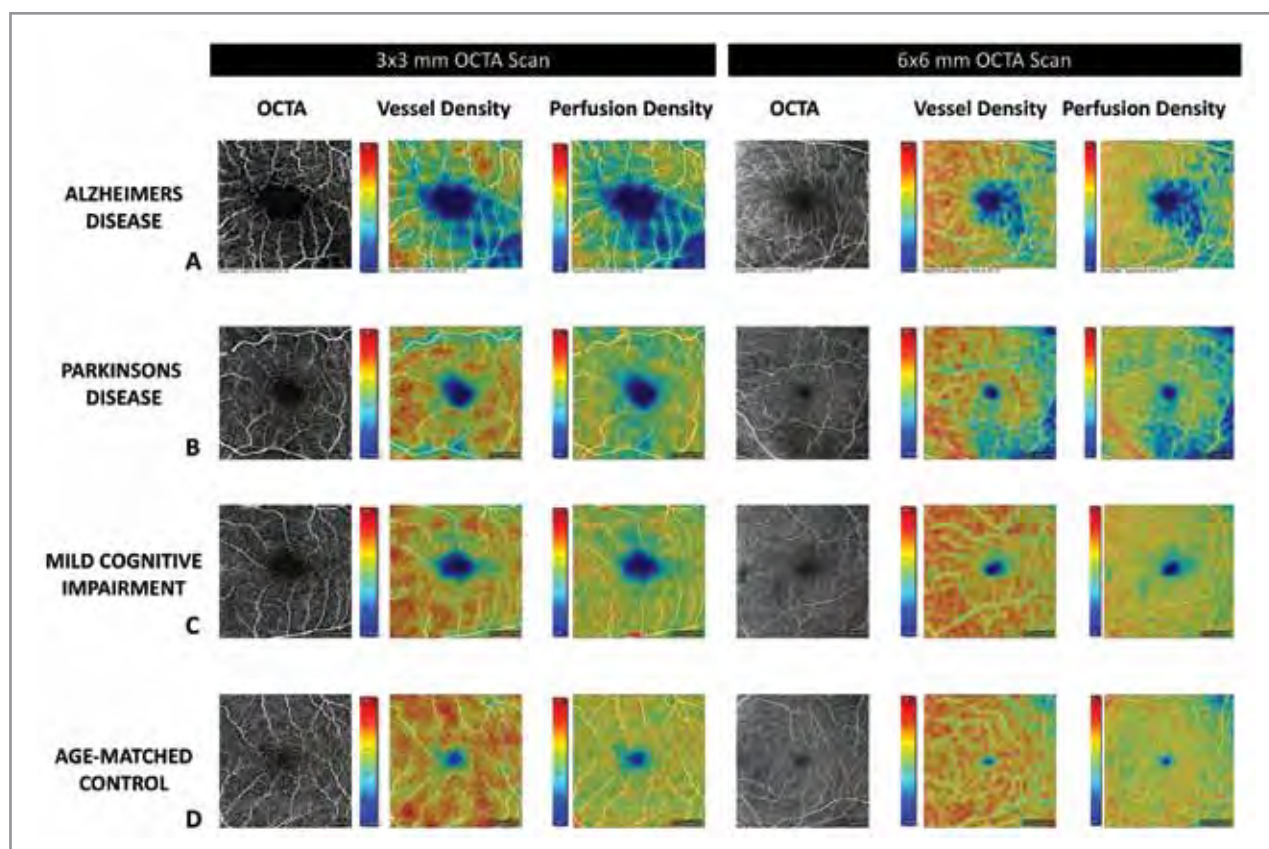
Figure 1. 3 mm × 3 mm and 6 mm × 6 mm optical coherence tomography angiography (OCTA) images of the superficial capillary plexus in Alzheimer's disease (AD) (A), Parkinson's disease (PD) (B), mild cognitive impairment (MCI), (C) and an age-matched control subject (D). The color-coded maps (Cirrus Angioplex, Carl Zeiss Meditec, Dublin, CA) represent the vessel density (total length of perfused vasculature per unit area) and perfusion density (total area of perfused vasculature per unit area) with the corresponding color-coded scales to the left of the image. The age-matched control maps represent normal vessel density and perfusion density values, which are reduced to different extents in AD, PD, and MCI. There is also enlargement of the foveal avascular zone in AD, PD, and MCI.

to controls, and there was an association between the Mini Mental State Examination score and both SCP VD and foveal avascular zone (FAZ) area.[5] Kwapong et al. showed similar changes in the early stages of PD compared to controls.[6] This suggests that retinal capillary impairment may occur early in the PD cascade before clinically apparent motor disorders manifest.

Our clinical research team has imaged 70 AD eyes, 72 MCI eyes, and 254 control eyes (all aged ≥ 50 years) and found that subjects with AD had a decreased SCP vessel density as well as perfusion density in the 3 mm area as well as the perifoveal 3 mm ring compared to those with MCI and cognitively intact controls (Figures 1 and 2). There was, however, no difference in SCP vessel or perfusion density between patients with MCI and controls.[7]

There is good evidence from the last 10 years that vascular dysfunction in MCI and AD leads to cerebral hypoperfusion.[8,9] It is also possible that some of the observed microvascular changes in the inner retina may be due to Aβ accumulation.[10-12] In fact, genetic biomarker-positive individuals with preclinical AD have retinal vascular and architectural alterations even when cognitively intact. With clinical trial emphasis on the evaluation of pharmacologics to prevent neuronal loss, it is necessary to be able to noninvasively identify which individuals with preclinical AD may benefit from intervention. Biomarker testing for asymptomatic, preclinical AD is currently invasive and expensive. There is now some initial evidence on the potential ability of OCTA to detect preclinical biomarker positive AD. In a series of 14 participants with biomarkers (PET Scan and/or Aβ 42 protein) positive for AD (preclinical AD), but cognitively healthy based on neuropsychometric testing, O'Bryhim et al. concluded that the FAZ was larger and the inner fovea was thinner compared to controls.[13,14]
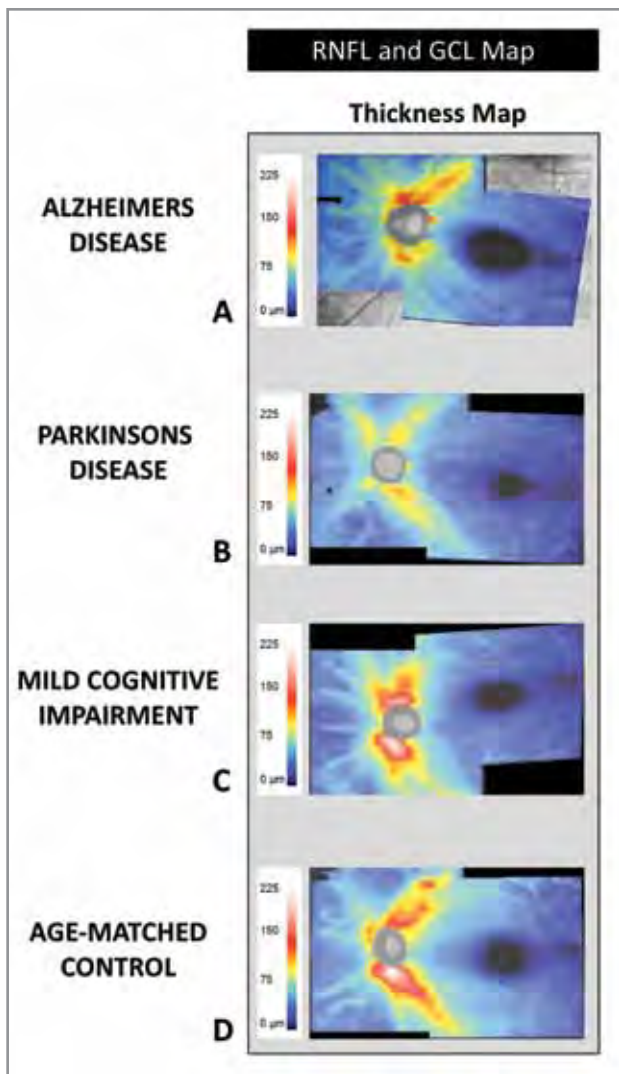
Figure 2. Combined color-coded retinal nerve fiber layer and ganglion cell layer thickness maps (with scale on left) in Alzheimer's disease (AD) (A), Parkinson's disease (PD) (B), mild cognitive impairment (MCI) (C), and an age-matched control (D) showing retinal nerve fiber layer and ganglion cell layer thinning to varying extents in AD, PD, and MCI compared to an age-matched control subject.

DO CHANGES ON OCTA CORRELATE WITH CHANGES IN THE BRAIN?

Cortical atrophy on magnetic resonance imaging (MRI), as a biomarker for neurodegeneration, can be assessed by quantifying global cortical atrophy, medial temporal lobe atrophy, and parietal cortical atrophy.[15,16] Only a few prior studies have evaluated the correlation of OCT parameters with brain MRI, such as association between macular thickness, ganglion cell layer, and RNFL thinning with decreased temporal lobe and occipital lobe volumes and parietal cortical atrophy.[17-19] Using OCTA, we looked at 30 eyes of 16 patients (six MCI, 10 AD) and found that the infero-lateral ventricle volume inversely correlated with the 6-mm circle and 3-mm circle vessel density in the 6 mm × 6 mm OCTA images. The lateral ventricle and hippocampal volumes did not correlate with vessel or perfusion density in our patient population. Although these are initial results limited by a small sample size, they do suggest a relationship between the retinal microvasculature as assessed by OCTA and cerebral volume. It is, however, still unknown whether retinal degeneration occurs after neurodegeneration or is an unrelated phenomenon that could either precede or occur simultaneously with brain degeneration.

LIMITATIONS OF CURRENT OCTA ANALYSIS IN NEURODEGENERATIVE DISEASES

Several unanswered questions remain before OCTA can be routinely used in clinical practice or even in clinical trials. Although it may be expected that retinal microvascular abnormalities may be linked to progression of the neurodegenerative disease, there is as yet no direct relationship of disease duration or severity with retinal microvascular densities or retinal layer thickness.

Current studies are limited by small sample sizes since a significant number of these patients having poor-quality scans due to motion artifact and inability to fixate. For OCTA to be a useful clinical biomarker, image quality must be adequate to accurately segment and analyze the retinal microvasculature. Obtaining good-quality images is particularly a challenge in those with severe cognitive impairment due to the inability to follow instruction, easy fatigability, and poor concentration.

Confounding diseases such as glaucoma and age-related macular degeneration (AMD) have to be carefully accounted for. For example, glaucoma is also a neurodegenerative disease with progressive loss of neuronal tissue and results in reduced vessel density.[20] Macular pathology such as an epiretinal membrane or AMD, which are not uncommon in an older adult population also impact segmentation of the OCTA and, thus, affect vessel and perfusion density measurements. Another limitation is that current studies have excluded patients with known vascular diseases, so it is not yet known whether these results can translate to patients with concurrent retinal microvasculature changes from other etiologies such as diabetes and hypertension, which are prevalent in the aging population at risk of neurodegenerative diseases. The impact of medications such as levodopa on OCTA measurements is also yet unknown.

Retinal capillary diameters (5 µm to 10 µm) are at the lower limit of the transverse resolution of the

OCT beam, potentially making the vessel density changes inaccurate. Another important limitation is that the field of view from currently available OCTA systems is relatively small, which restricts imaging to the posterior pole. There are significant changes in the retinal periphery, both in terms of changes in retinal blood vessels as measured by the fractal dimension as well as presence of peripheral drusen, which are beyond the field of view of current OCTA systems.[21] Koronyo et al. reported that retinal Aβ plaque mirrored brain pathology, and retinal deposits often occurred in the peripheral retina.[10] They demonstrated the ability to image retinal amyloid deposits with a modified scanning laser ophthalmoscope and were able to construct a retinal amyloid index, which was about two-fold higher in patients with AD versus controls. In the future, widefield OCTA systems may allow evaluation of these peripheral areas. Eventually, it is important to obtain not only imaging but also histopathology from the same regions in both the retinal periphery and macula for confirmation of retinal biomarkers in AD.[12]

It is important to recognize that there are certain differences in the measurements of vessel density (total length of perfused vasculature per unit area) and perfusion density (total area of perfused vasculature per unit area) across different instrument platforms. Measurements of vessel density, perfusion density, and FAZ dimensions are not interchangeable across different OCTA platforms.[22] The reproducibility of measurements could be lower in eyes with retinal microvasculature abnormalities and are also impacted by the OCTA scan size.[23,24] Geometric features of vessels visible on retinal imaging such as width and tortuosity are considered to infer the health of the retinal microvasculature. Another approach to quantify retinal microvasculature is through fractal analysis, a contemporary method of applying non-traditional mathematics to patterns that defy understanding with traditional Euclidean concepts. Jiang et al. have reported differences using fractal analysis on OCTA superficial and deep capillary plexus between patients with AD and control subjects.[25]

CONCLUSIONS

Although current studies do support that retinal microvasculature deficits can be recognized early by OCTA in persons with AD, MCI, and PD, prospective, longitudinal studies with larger sample sizes are needed to obtain statistically reliable associations in order to determine the clinical specificity of OCTA measures as useful retinal biomarkers for the early detection of these neurodegenerative diseases. Whether these retinal microvasculature changes are progressive over time and whether they have the potential for reversal also remains to be determined.

With advances in OCTA technology, we anticipate further advances in the resolution and field of view as well as improvement in reproducibility indices that are necessary to accurately detect small changes over time. There are currently several prospective studies underway including at our institution to detect these changes over time. OCTA is likely to continue to have an increasing role in the diagnosis and monitoring of neurodegenerative diseases.

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