Assessment of Differences in Retinal Microvasculature Using OCT Angiography in Alzheimer's Disease: A Twin Discordance Report

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ABSTRACT: The authors report the optical coherence tomography angiography (OCTA)-based comparative assessment of the retinal microvasculature in a rare pair of 96-year-old female monozygotic twins discordant for Alzheimer's disease (AD). Using automated mapping of the superficial capillary plexus, the authors observed that the twin with advanced AD had a significantly reduced vessel density and a larger foveal avascular zone in the superficial capillary plexus as well as a thinner choroid compared to the twin who was cognitively normal. This unique twin discordance report adds to the evidence supporting the use of retinal microvasculature changes in the superficial capillary plexus on OCTA as a possible noninvasive biomarker for AD.

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INTRODUCTION

Alzheimer's disease (AD), the most common cause of dementia, is defined by both neuropathology and clinical symptoms. The neuropathology of AD consists of two hallmark elements: the deposition of plaques (amyloid) and tangles (tau protein). It is likely that these two biochemical conditions lead to the destruction or death of nerve cells and subsequently cause the clinical symptoms, suggesting that both amyloid and tau can be assessed as early AD markers.[1] However, measuring amyloid and tau through cerebrospinal fluid is not easily attainable for clinical diagnosis, and both may not be sensitive to disease progression.

Although increased age is the most important factor, genetic predisposition is also a risk factor for this disease. Twin studies are a classical method to address the effects of genes and the environment. Discordance for disease phenotype between genetically identical monozygotic twins has been used in AD research to understand the contribution of genetic versus environmental factors.[2,3,4] That the concordance rate for AD is higher in monozygotic than dizygotic pairs suggests a genetic component of disease.[5]

The most common vascular problems in AD include impairment of blood-brain barrier, decreased vascular density, decreased vascular diameter, and decreased blood flow.[6] The similarity between the cerebral and retinal vasculature has led recent efforts on investigating the retinal vasculature as a biomarker in AD.[7] In particular, microvascular or small vessel disease is now thought to be a major contributor to dementia, and studies have demonstrated that qualitative retinal vascular signs and quantitative retinal vascular measures, including retinal arteriolar narrowing, retinal venular widening, and suboptimal retinal vascular network, are associated with poorer cognitive performance.[8]

Quantitative measurement of retinal vascular caliber and its branching pattern has been performed previously in microvascular disease research using standardized photographic protocols, albeit with methodological and technical challenges.[8-11] Recent advances in retinal imaging, however, may provide new insights into cerebrovascular neurodegenerative processes in addition to what is currently possible with neuro-imaging.[8] In AD and other neurodegenerative diseases, retinal imaging with optical coherence tomography angiography (OCTA) has the potential to provide additional input toward understanding the vascular deficits in these diseases. Bulut et al. recently showed that there was a lower superficial capillary plexus (SCP)

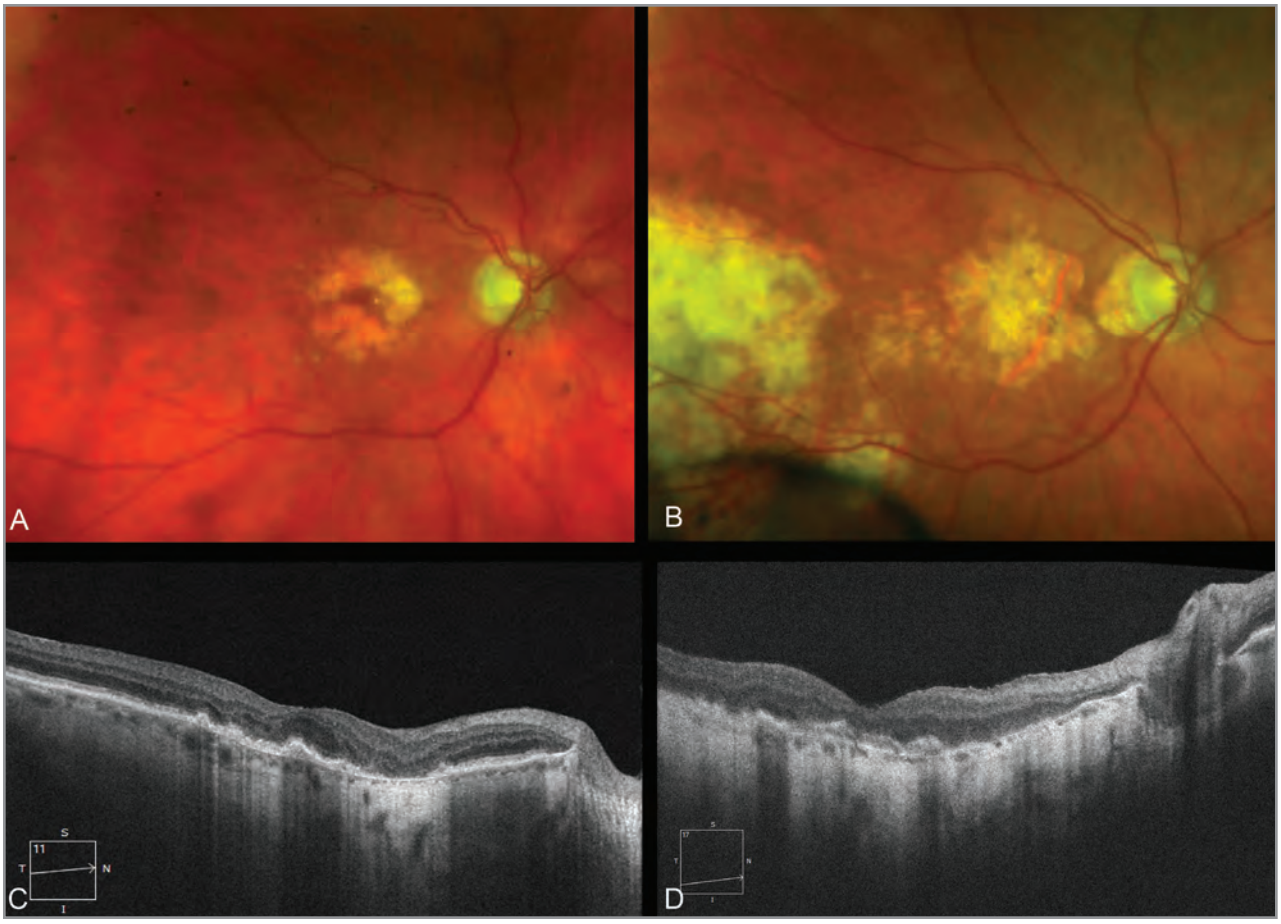

Figure 1. Color fundus photographs of the right eye of the monozygotic identical 96-year-old twin sisters discordant for Alzheimer's disease (AD) (cognitively normal sister is A and the twin with Alzheimer's dementia is B). There is geographic atrophy in both twins that involves the fovea in B and barely spares the fovea in A. In B, there is also chorioretinal scarring temporally from a prior retinal detachment repair. C and D show the corresponding cross-sectional optical coherence tomography B-scans. The subfoveal choroidal thickness was 114 µm in the cognitively normal twin (C) and 75 µm in the twin with AD (D).

retinal vascular density, a larger foveal avascular zone (FAZ) area, and a thinner subfoveal choroid in patients with AD compared to age-matched controls.[12,13] They also observed a correlation between the Mini Mental State Examination (MMSE) and vascular density parameters.

Herein, we report a rare pair of monozygotic identical twins discordant for AD and illustrate the differences in retinal microvasculature among them assessed using OCTA.

CASE REPORT

A pair of 96-year-old female identical monozygotic twins, severely discordant for AD, underwent OCTA imaging using the Cirrus 5000 Spectral-Domain OCT with Zeiss AngioPlex (Carl Zeiss Meditec, Dublin, CA).

Both twins were pseudophakic in both eyes. The cognitively normal twin had Fuchs' dystrophy and non-neovascular age-related macular degeneration (AMD) with parafoveal geographic atrophy (GA) in the right eye and foveal GA in the left eye (Figure 1A). At the time of imaging, her vision was 20/40 in the right eye and 20/200 in the left. She had not had any prior neuroimaging. Her medical history was significant for osteoarthritis, hyperlipidemia, and hypothyroidism. Her MMSE score was 28/30, which is considered normal. She was a former occasional smoker who stopped smoking 70 years ago.

The twin with AD had Fuchs' dystrophy, history of a retinal detachment repaired by vitrectomy and scleral buckling in the right eye, and non-neovascular AMD with foveal GA in both eyes (Figure 1B). We were unable to obtain a subjective Snellen vision due to her advanced cognitive impairment. Her medical history was significant for hypertension, hyperlipidemia, decreased hearing, and smoking, which she had stopped 35 years ago. Her last neuroimaging was

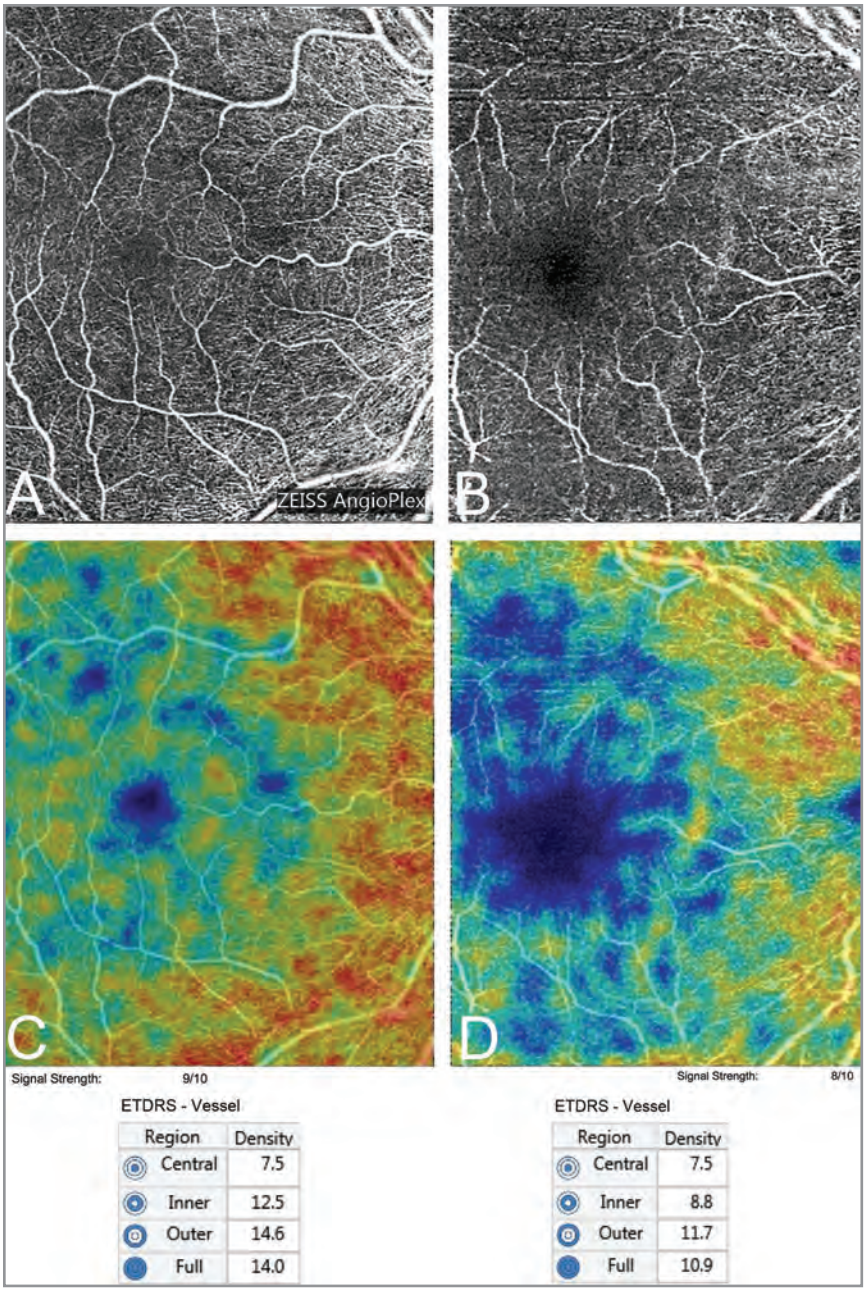

Figure 2. Optical coherence tomography angiography images of the superficial capillary plexus (SCP) of the twin sisters. Panel A (signal strength 9/10) shows the SCP of the cognitively normal twin with a relatively well-preserved foveal avascular zone (FAZ) and SCP, whereas B (signal strength 8/10) shows the twin with Alzheimer's disease (AD) where there is a marked decrease in the SCP vessel density and an enlarged FAZ. C and D show the corresponding quantitative color-coded vessel density maps in the SCP (Angioplex Vessel Map, SW 10.0.0.12787; Carl Zeiss Meditec, Dublin, CA; investigational use software in the U.S., commercially available in some markets outside of the U.S.) The color map shows a marked decrease in the SCP vessel density in the twin with AD (middle left) compared to the cognitively normal twin (middle right). The corresponding vessel density numerical values shown in the various Early Treatment Diabetic Retinopathy Study grid regions shown on the bottom are significantly lower in the twin with AD.

performed 7 years prior to the OCTA imaging and showed diffuse volume loss with temporal lobe predominance mostly in the hippocampal region, asymmetrically worse on the right. Per the last neurology examination, the twin with AD has significant cognitive impairment, no insight regarding her deficits, and required assistance for activities of daily living. She was unable to perform the MMSE due to lack of focus, concentration, and severe dementia.

On OCTA (6 mm × 6 mm scan), we observed a significant difference in the SCP between the twins (Figure 2), with the twin with AD showing significant loss of vessels in the SCP and a larger FAZ area. The automated quantitative color-coded vessels density maps (Angioplex Vessel Map, SW 10.0.0.12787; Carl Zeiss Meditec, Dublin, CA; investigational use software in the U.S., commercially available in some markets outside of the U.S.) showed differences in the inner, outer, and full Early Treatment Diabetic Retinopathy Study grids among the twins with the differences ranging from a 24.7% to 42% reduction for the twin with AD. The subfoveal choroidal thickness was also reduced in the twin with AD (75 µm) compared to the cognitively normal twin (114 µm).

DISCUSSION

The retina and brain are associated over a range of neurological and neurovascular conditions of varying etiologies because they respond similarly to disease.[1] Microglial activation has been reported in AD (as well as in other neurodegenerative diseases, such as Parkinson's disease and glaucoma) in relation to protein aggregates and degenerated neurons. The activated microglia can release proinflammatory cytokines, which can aggravate and propagate neuroinflammation, thereby degenerating neurons and impairing brain as well as retinal function.

A reduced retinal vascular density or enlarged FAZ could be associated with decreased angiogenesis due to the binding of vascular endothelial growth factor to Abeta and its confinement in the plaques and also the accumulation of Abeta deposits in the internal vessel walls, leading to occlusion of the vascular structures and decreased blood flow.[7,14] Both Abeta accumulation and neurofibrillary tangles are found in many parts of the visual system in patients with AD, including the retina. The link between retinal ganglion cell neuronal and optic nerve axonal loss with AD has been demonstrated, and ganglion cell layer loss and peripapillary retinal nerve fiber layer reduction, assessed by OCT, has been associated with AD.[15] Choroidal thinning has also been reported in AD.[12,16]

Previous studies of monozygotic twin pairs concordant or discordant for AD with adequate family history data indicate that both genetic and non-genetic factors influence disease onset and expression.[17,18,19] Well-established risk factors include diabetes, hypertension, smoking, depression, cognitive or physical inactivity, and obesity.[20] These were not markedly different among the twins in our report. In monozygotic twins discordant for AD, amyloid precursor protein, sirtuin-1, and peptidyl prolyl isomerase 1 gene expressions have been shown to be up-regulated in the twin with AD compared to the healthy twin.[21] Due to cost constraints however, we were unable to perform genetic testing on this set of twins.

Finding biomarkers that are better linked to early consequences of AD pathology and sensitive to disease progression are crucial to diagnostic advances and better therapeutic evaluations. Although this report does provide data that substantiates recent reports on the decline in vessel density and enlargement of FAZ in AD, the results need to be considered carefully. There are limitations of twin studies and alternative causes of discordance that also need to be taken into consideration. The twins in our report had other comorbidities including non-neovascular AMD with GA. Histopathologic studies have shown that in eyes with GA, the nuclei of the outer nuclear layer are markedly attenuated (76.9% loss), whereas the nuclei of the inner nuclear layer were relatively preserved (9.5% loss). There was also a reduction in ganglion cells (30.9%) in eyes with GA, but considerable numbers remained even in the areas of complete retinal pigment epithelium atrophy.[22] In this report, we only evaluated the differences in the SCP, which is defined from the internal limiting membrane to the inner plexiform layer per the machine algorithm used. We manually confirmed that the segmentation of the inner retinal layers was accurate and that the layers were well preserved with no disorganization of the retinal inner layers. Therefore, the impact of the outer nuclear layer loss, the most significantly affected layer in GA, is mitigated. In addition, both twins had GA although it was more advanced in the twin with AD. It is important, however, to recognize that GA is a confounder in the vessel density analysis in this report. Nonetheless, we believe that the difference in the vessel density in the SCP between the twins is unlikely to be explained by the difference in GA alone; the true impact of this confounding effect remains to be better elucidated in future studies.

There are several challenges in obtaining high quality OCTA images, especially in patients with advanced AD who are easily fatigued; this was also encountered by Bulut et al.[13] This can be compounded if the patients have poor vision. Obtaining good quality OCTA imaging that is free of segmentation errors in such patients may be difficult during a routine clinic but OCTA engines with faster scan speeds might help overcome this limitation. These limitations notwithstanding, it may be possible that OCTA changes in the retinal microvasculature could precede, not only cerebral small vessel disease, but also structural changes such as nerve fiber layer and ganglion cell layer thinning.[23,24]

In conclusion, this report on a rare set of 96-year-old monozygotic identical twins, severely discordant for AD, provides a unique opportunity to illustrate the differences in retinal microvasculature using OCTA in advanced AD and adds to the evidence that there is a reduction in the SCP vessel density and enlargement of FAZ in AD. This report also adds support to the use of retinal microvasculature as a potential biomarker for AD. Further investigation including discordant twin studies with larger samples may potentially help correlate retinal microvasculature changes with epigenetic differences, environmental factors, and phenotypic differences in monozygotic twins.

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