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Retinal Microstructural and Microvascular Changes in Alzheimer Disease: A Review

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Abstract

"The eyes are a window to the brain," prompting the investigation of whether retinal biomarkers can indicate Alzheimer disease (AD) and cognitive impairment. AD is a neurodegenerative condition with a lengthy preclinical phase where pathologic changes in the central nervous system (CNS) occur before clinical symptoms. Mild cognitive impairment (MCI) often precedes AD. As part of the CNS, the retina exhibits similar pathologic changes related to AD as those seen in the brains of patients with MCI. Noninvasive imaging technologies such as optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) allow high-resolution visualization of the retina, providing an opportunity to screen and monitor AD noninvasively. In this review, we summarize the relationship between AD and retinal pathology detected by OCT and OCTA. The most common findings in patients with AD include peripapillary retinal nerve fiber layer thinning, decreased macular thickness, an enlarged foveal avascular zone, and decreased vascular densities in the superficial and deep capillary plexuses. These retinal changes correlate with magnetic resonance imaging (MRI) findings of cerebral atrophy, positron emission tomography (PET) findings of increased amyloid load, and neuropsychological testing results suggesting cognitive dysfunction. We conclude that retinal microstructural and microvascular abnormalities may serve as biomarkers for the early detection and clinical monitoring of AD and as tools for evaluating potential treatment effects. Future studies should focus on standardizing protocols for in vivo ophthalmic imaging to measure retinal pathology in AD and MCI.

Keywords

Alzheimer's disease; biomarkers; mild cognitive impairment; OCT; OCTA; retina

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INTRODUCTION

Alzheimer disease (AD) is the most common dementia, expected to affect 152 million people globally by 2050.[1,2] The global cost of dementia care was estimated to be $1.33 trillion in 2020 and is expected to increase to $9.12 trillion by 2050.[3] AD is primarily age-dependent; in people greater than age 65, 1 out of 9 has AD.[4] The hallmark pathology of AD includes amyloid-beta peptide (Aβ) plaques and neurofibrillary tangles in the brain, which are composed of hyperphosphorylated tau proteins. These abnormalities disrupt neural communication, leading to synaptic dysfunction and neuronal death[1] (Fig. 1). AD is characterized by progressive cognitive decline, memory loss, and impaired reasoning and judgment.[6] Neuropsychiatric symptoms include irritability, aggression, and apathy.[6] In severe AD, comorbid conditions include anxiety, depression, and immobility, which increases the risk of deep venous thrombosis and infection.[6] The visual variant of AD (vvAD), a form with dominant visual symptoms, typically presents before 65 years.[7] vvAD is a progressive neurodegenerative disease commonly preceded by posterior cortical atrophy (PCA) primarily affecting the parieto-occipital cortex, which is responsible for visual and cognitive tasks.[7] There are generally no abnormalities on routine ophthalmic examination. Visual field defects are frequently present and homonymous hemianopias or quadrantanopia are most common.[8] In PCA, most patients have trouble reading,[9] and examination findings of decreased visual acuity despite normal eye exam, visual field defects without brain structural changes on neuroimaging, poor color perception and depth perception, trouble recognizing objects and familiar faces, and impairment of eye movements.[7,10] Due to the early onset of vvAD and unusual visual symptoms, it is often misdiagnosed as functional vision loss, Lewy body dementia, and sometimes migraines.[6] Hence, vvAD diagnosis requires differentiation with a full neuro-ophthalmologic examination and frequently neuropsychological testing, magnetic resonance imaging (MRI) perfusion scans, and positron emission tomography (PET) imaging.[7,10] AD pathologic features occur before clinical symptoms.[11] Thus, early detection can lead to better disease management, helping to preserve memory, cognition, communication skills, and neuropsychiatric wellness.[12,13]

The Retina as a Diagnostic Window to Brain Diseases

The retina is considered the terminus of the central nervous system (CNS).[14–17] The retina, optic nerve, and brain share an embryonic origin in the diencephalon and have a similar response to neuronal insult.[14,16,17] The retina is extremely metabolically active, receiving the highest ratio of blood flow to gram than any other organ, making it a useful marker for vascular changes in the CNS.[18] In addition, the retina mirrors pathologies occurring in the brain, and neurodegenerative diseases like AD.[19] Histologic studies first documented optic neuropathy in patients with late-onset Alzheimer disease (LOAD) in 1986.[20] Postmortem retinas in patients with confirmed early and advanced stage AD exhibit Aβ plaques deposits,[19,21] particularly in the superior and inferior quadrants of the retinal vasculature.[21,22] In addition, hyperphosphorylated tau protein aggregates occur in AD retinas.[23] Further studies have demonstrated histopathologic evidence of retinal nerve fiber layer (RNFL) degeneration and retinal ganglion cell (RGC) loss in AD.[24]

Optical Coherence Tomography and OCT Angiography in Evaluating AD Retinopathy

OCT was first introduced in 1991 and is a noninvasive imaging technique used to generate detailed cross-sectional images of the retina and the optic nerve head.[25,26] OCT is now considered the gold standard for retinal imaging.[27] It utilizes the concept of interferometry, sending light at specific wavelengths into a tissue and then analyzing and digitizing the reflected beam's interference with a reference beam to determine the tissue's components and create an image.[28] This is similar to how ultrasound uses sound to produce images.[26,29] Commercially available OCT technology produced over the years includes time-domain (TD), spectral-domain (SD), and swept-source (SS) OCT.[30] While OCT has high resolution, it distinguishes poorly between retinal microvascular and nonmicrovascular tissue.

Optical coherence tomography angiography (OCTA), approved by the US Food and Drug Administration in 2015, is a noninvasive imaging technique that visualizes retinal microvascular changes.[31,32] It utilizes the movement of red blood cells as diffractive particles to image choroidal and retinal vasculature.[28] Various OCTA methods have been developed, each with their advantages and limitations in ophthalmic research and clinical diagnostics. For example, split-spectrum amplitude decorrelation angiography (SSADA) algorithm calculates the blood flow by measuring the decorrelation of reflected light from the tissue.[33] A study compared the performance of 3 OCTA methods, speckle variance, amplitude-decorrelation, and phase variance, for imaging the human retina and choroid. It also evaluated 2 averaging methods, split spectrum, and volume averaging, to assess the quality of OCTA vascular images. No single universal method has been identified because each may have certain advantages for its application.[34] Volume averaging, aided by motion correction methods, is essential for improved clinical OCTA systems for comprehensive chorioretinal vascular mapping. One significant benefit of OCTA is that it does not require intravascular dye administration to achieve high-resolution visualization of vascular networks.[33]

Benefits of OCT/OCTA in Clinical Practice

OCT and OCTA are noninvasive and painless.[25,26,31,32,35] SS-OCT can improve patient comfort and compliance by using light outside of the visible light spectrum during the procedure.[30] As OCT technology has advanced, scanning rates and signal processing have both gotten faster, permitting real- time image visualization.[36] OCT can also generate detailed cross-sectional images of retinal layers with resolution comparable to histology,[26] lending it the ability to detect subtle and early changes in the retina.[25] These capabilities enable the use of retinal changes as biomarkers to identify early-stage neurodegenerative diseases like AD.[37] OCTA is an alternative to fluorescein angiography and indocyanine green angiography as it can produce 3D images of retinal vasculature in real time,[38] without using intravenous contrast.[39] Thus, patients with contrast dye contraindications such as renal failure, poor intravenous access, or pregnancy can undergo retinal microvasculature imaging.[39]

Retinal Microstructural Thinning as Biomarkers for AD Diagnosis

The retinal manifestations of AD as measured by OCT include thinning of the peripapillary RNFL (pRNFL) layer,[40] ganglion cell-inner plexiform layer (GC-IPL),[41] macula volume,[41–43] and choroid.[42] GC-IPL deterioration in AD patients occurs predominantly in the central, superior, and inferior retinal segments.[44] Macular volume reduction and thinning of the RNFL occurs within 3 mm of the fovea.[45] In patients with mild cognitive impairment (MCI), thinning of the RNFL and GC-IPL layers were also observed[41,42,46] (Table 1). Outer retinal thinning has also been reported in frontotemporal degeneration, Parkinson Disease, and white matter lesions in the brain.[48–51]

Increasing scientific evidence highlights the similarities between the structures of the eye and the brain, with the retina and optic nerve being considered part of the central nervous system (CNS). The retina reflects CNS injury through retrograde transsynaptic degeneration and abnormal protein aggregation.[47,52,53] The pathophysiology of AD, characterized by cerebral deposits of amyloid-beta (Aβ) and tau protein, is also present in the eyes of AD patients.[53] Therefore, this evidence suggests that ocular changes have the potential to be used as predictive markers for AD assessment or as diagnostic tools.

Retinal Microvascular Changes in AD at Diagnosis

Studies of AD using OCTA have identified a significant decrease in parafoveal superficial microvascular density and whole foveal vascular density.[54–56] Decreased retinal blood flow is thought to be related to Aβ plaque deposition in the retina compressing vasculature.[54,57] In addition, there is reduced blood vessel density in the deep capillary plexuses (DCP),[37,58] and a loss of superficial capillary plexus (SCP) complexity.[37] Wu et al[59] identified reduced density of the DCP in all quadrants and reduced density of the SCP in one quadrant. A study of OCTA in 16 people with either amnestic MCI (aMCI) or early AD (eAD) showed reduced superficial vascular complex (SVC) vascular density, and adjusted flow index compared with controls.[60] The observation of the association between the foveal avascular zone (FAZ) and AD is controversial[61] (Fig. 2). Bulut et al[62] found that FAZ was significantly enlarged, and choroidal thickness significantly decreased in AD patients when compared with healthy controls. O'Bryhim et al[63] also found FAZ enlargement in patients with biomarker-positive, preclinical AD in their initial study and in their 3-year follow-up study with the same patients.[64] However, Ashraf and colleagues found a weak association between increased FAZ area and AD in patients with Aβ+ status AD.[40] Vascular disease may synergize with changes in Aβ levels through a positive feedback system, where tissue damage caused by vascular factors exacerbates neurodegenerative damage, and vice versa.[65] The retinal circulation, sharing its origin and drainage with the intracranial circulation, is a potential marker of cerebral vascular disease.[66] More studies are needed to determine whether retinal microvascular changes are a cause or effect of brain degeneration in AD.

Monitoring Disease Progression With OCT/OCTA

In aMCI, there is progressive thinning in the ganglion cell complex (GCC) and RNFL as well as reduced vascular density and enlarged FAZ with increased disease duration.[46] Preclinical AD demonstrates stable retinal abnormalities from controls,[64] while advanced AD tends to be associated with progressive retinal change.[67] Another investigation found

that increased duration of AD was associated with decreased RNFL and GCL thicknesses.[67] This analysis also demonstrated that the RNFL, GCL, and IPL were thinner in AD patients with disease duration ≥ 3 years compared with < 3 years.[67] Despite this, cumulative changes related to disease duration were not observed in a study of preclinical AD.[63] In a cohort of 30 patients, preclinical AD subjects had increased FAZ, and reduced inner foveal thickness compared with controls,[63] yet a subsequent study 3 years later showed no progressive changes in FAZ area group over time.[64] However, there was a consistent difference in FAZ area between preclinical AD and normal subjects.[64]

In a cohort of 30 patients, preclinical AD subjects had increased FAZ, and reduced inner foveal thickness compared with controls.[63] However, a subsequent study 3 years later showed no progressive changes in the FAZ area group over time.[64] The consistent difference in FAZ area between preclinical AD and normal subjects suggests that OCT may be a good noninvasive biomarker for predicting future AD. In addition, this finding may indicate that the retina does not change significantly over a short period, and therefore, while the FAZ may be a good marker for diagnosing AD, it may not be useful for monitoring disease progression. the degree to which OCT changes correlate with AD severity, remains understudied.[68,69]

Correlation Between Retinal Changes and Cognitive Evaluation

Cognitive assessment such as the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), are ways to screen for AD clinically.[70,71] Decreased macular volume and whole macular vascular density, and enlarged FAZ has been reported in patients with impaired MMSE.[62,72] Thinner RNFL is associated with low MMSE and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores.[69] Decreased peripapillary capillary vessel density and parafoveal superficial vascular complex density are associated with low MoCA scores.[60] These all point to the possibility of using OCT and OCTA to diagnose and monitor clinical AD. In addition, Salobrar-García and colleagues demonstrated that patients with AD exhibited significant declines in visual acuity, contrast sensitivity, color perception, and visual integration compared with healthy controls. In mild AD patients, significant macular thinning was observed in the central region, while moderate AD patients showed macular thickening in the central region. In addition, AD patients showed significant thinning of the RNFL, GCL, and outer plexiform layer, but significant thickening of the outer nuclear layer. Mild AD was associated with significant thinning of the subfoveal and the nasal and inferior sectors of the choroid. In moderate AD, significant superonasal and inferotemporal peripapillary thinning was observed. These findings suggest early retinal changes in AD patients that alters with disease progression.[73]

Comparison and Correlation With Neuroimaging Modalities

Biomarkers from PET scans or cerebral spinal fluid (CSF) studies are necessary components of neuropathologic diagnosis of AD and disease staging. PET imaging measures the functional ability of the brain using contrast agents. It provides 2 additional biomarkers for AD-posterior cingulate and temporoparietal hypometabolism, and cortical Aβ deposition on 18FDG-PET and amyloid-PET, respectively.[74] CSF analysis of patients with AD presents with a decreased Aβ42 to Aβ40 ratio and decreased levels of Aβ42, indicating amyloid

plaque deposition in the brain.[75] Tau levels are also measured using CSF analysis; however, studies have shown that they correlate moderately with tau PET imaging.[75] Thus, PET aids in the accurate diagnosis of AD because it can image amyloid plaques and tau protein aggregation, which is characterized as neurofibrillary tangles in the brain.[75] MRI can directly visualize the structural components of the entire brain. Medial temporal lobe atrophy seen with MRI is a reliable finding in diagnosing AD.[74,76] Evaluating MRI images can be challenging as it requires expert opinion and interpretation using rating scales.[77] While MRI and PET biomarkers are considered analytically valid, the evidence is insufficient to determine their clinical validity and clinical utility.[78] The practical considerations for MRI and PET are that they are expensive, and necessitate intravenous contrast in the case of PET. Comparatively, OCT is inexpensive, quick, and noninvasive.[79]

In MRI and OCT studies of AD, there are significant correlations between parietal cortical atrophy and macular thickness,[80] fractional anisotropy of the optic tract and mean retinal thickness, IPL thickness, macular GCL thickness, and macular volume,[81] as well as primary visual cortex fractional amplitude of low-frequency fluctuations and pRNFL thickness.[81] In MRI and OCTA studies, the inferolateral ventricle volume correlates inversely with vessel and perfusion density of the retinal superficial capillary plexus.[82] A study of PET-related biomarkers revealed that Aβ binding potential is positively correlated with inner plexiform layer (IPL) thickness.[83]

OCT/OCTA in Animal Models

It can be difficult to gather longitudinal data from elderly populations[84]; thus, transgenic mice are a useful approximation of Alzheimer-related changes in the CNS and retina[85,86] and in evaluating drug efficacy.[87] Georgevsky et al[88] used OCT in APP/PS1 transgenic mice to identify significant thinning over 3 to 12 months in the inner and outer retina. Harper et al[89] corroborate these findings by noting the similar decline in retinal thickness with increased age. In a nonhuman primate model of AD, researchers targeted the entorhinal cortex (ERC) of rhesus monkeys with an adeno-associated virus expressing a double tau mutation. Within 3 months, they observed tau misfolding and propagation, accompanied by a robust neuroinflammatory response and biomarkers of inflammation and neuronal loss. This primate model highlights the early stages of tau seeding and propagation, offering a powerful translational approach for developing new AD therapies.[90] In addition, a study assessed age-related changes in the rhesus macaque eye, comparing them to human age-related eye diseases. Data from eye exams and imaging tests of 142 rhesus macaques revealed age-related increases in intraocular pressure, lens thickness, axial length, and macular measurements. Changes in retinal layer thicknesses were also observed, supporting the use of rhesus macaques for studying age-related eye diseases.[91]

Challenges and Limitations

One of the challenges in ascertaining biomarkers for AD is working with a disease entity that is significantly heterogeneous both clinically and genetically.[84] Some studies indicate progressive structural and vascular changes in the retina reflecting increased disease severity when analyzing the correlation between these biomarkers and the retina,[46,63,92] yet other studies suggest that at certain disease states, no changes may occur.[64,83]

OCT and OCTA have minimal variability in measurements over time in healthy eyes and therefore, they can theoretically reliably detecting subtle changes in the retina.[93] However, measurement variability was found in older patient populations and measurements around the central circle of the macula.[94] In addition, interpretation of data must be cautious when using OCT and OCTA devices from different manufacturers, as significant inter-device variability has been observed.[95–98]

The OCT protocols are relatively standardized, and further standardizing the definitions of the inner and outer boundaries of the choroid can improve choroidal thickness measurement accuracy and reliability.[99] The OCT protocols are relatively standardized, and further standardizing the definitions of the inner and outer boundaries of the choroid can improve the accuracy and reliability of choroidal thickness measurements. To assess the reliability of manual choroidal thickness measurements, different posterior boundary definitions of the choroidal-scleral junction (CSJ) on enhanced depth imaging optical coherence tomography (EDI-OCT) were compared. It was found that choroidal thickness measurements are more reproducible when measured to the border of the choroid stroma than to the vascular lumen or sclera.[100] In addition, pigmented uveal melanocytes affect choroidal morphology on EDI-OCT in rhesus macaque and human eyes. Racial differences in pigmentation may impact the visibility of the choriocapillaris and CSJ, influencing the accuracy of choroidal thickness measurements.[101]

On the other hand, lack of uniform guidelines for OCTA procedures make interpretation of results across studies difficult.[102] A proposed standardized protocol involves consistently dark room for imaging; scripted patient instruction, recruiting a trained OCTA operator,[103] and using the same machine across exams.[39] En face OCTA images may produce different measurements depending on the unique algorithm or process used to analyze the images, including vessel enhancement filters,[104] binarization,[105,106] segmentation method,[107] and the OCTA device used.[108] To achieve standardization, Tan et al[109] encourage researchers to understand the different processing tools available and to investigate optimal methodologies for clinical use. Thus, the standardization of OCT and OCTA protocols improves reliability of results, ensures consistency, and would enable the building of large image databases for healthy controls and patients with disease.[102,103]

Future Directions

Pathologic retinal changes at each stage of AD highlight the idea of tailored interventions based on the disease stage.[110] As of April 2024, there are 124 drugs being assessed by 164 clinical trials with the most common drug targets being neurotransmitter receptors, inflammation amyloid, and synaptic plasticity.[111] For MCI, preclinical, mild, moderate, and severe AD, interventions vary[112]; thus, retinal imaging may assist in choosing treatment strategies. Combining OCT with other neuroimaging techniques, such as MRI, could enhance diagnostic accuracy. Multimodal deep learning is a diagnostic approach by utilizing images (eg, MRI, PET), clinical data, and genetic information to predict disease stages,[113] which is a future avenue of AD disease assessment using comprehensive patient data. In addition, adding biomarkers such as Aβ-42 and t-Tau/p-Tau and account for differences in

the lifestyle, genetics, and environment of AD patients suggests another way to personalize treatment and disease monitoring.[114]

CONCLUSION

OCT and OCTA are rapidly advancing, noninvasive imaging techniques that can help with early diagnosis of AD and clinical monitoring by detecting retinal changes. For this to become a reality, continued innovation in imaging technology and the development of standardized methodologies is critical. This highlights the importance of ongoing research and funding support for OCT/OCTA for AD diagnosis and monitoring. We believe there is already substantial evidence for adopting routine AD screening in the geriatric and geriatric populations using these imaging modalities. Finally, developing standardized guidelines and policies is crucial for the widespread use of OCT and OCTA in AD diagnosis. This should be prioritized as these imaging techniques continue to improve.

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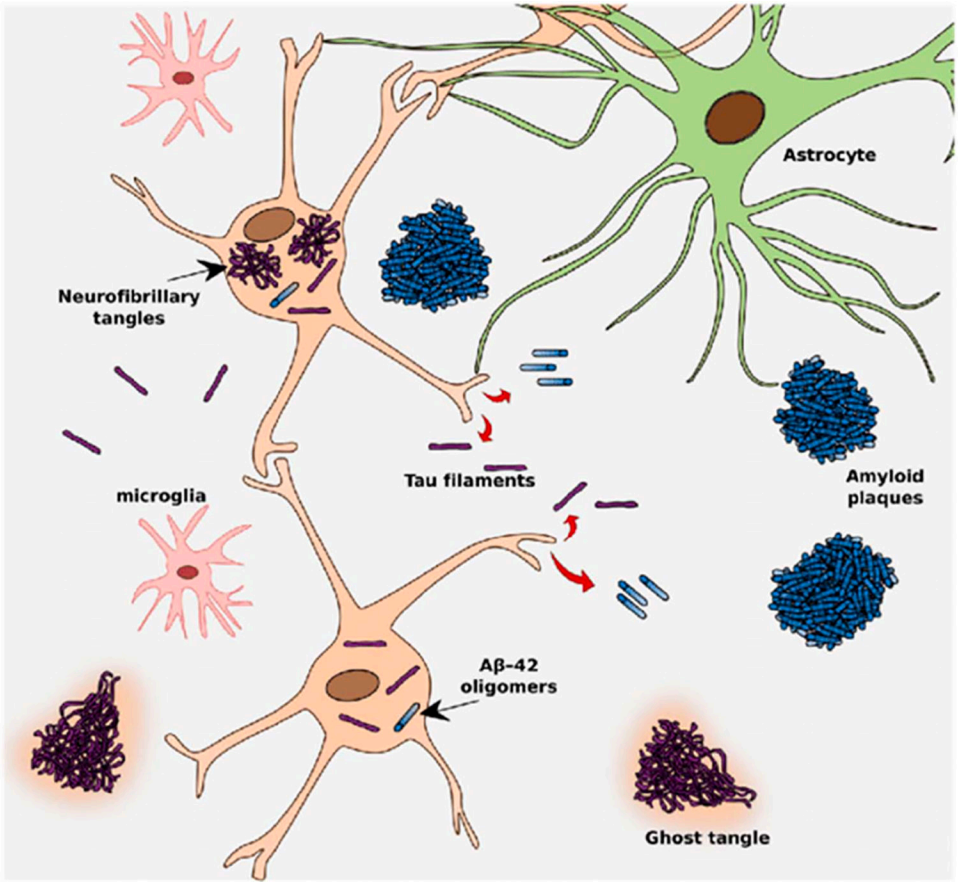

FIGURE 1.
Tau and amyloid pathology in Alzheimer disease.[5]

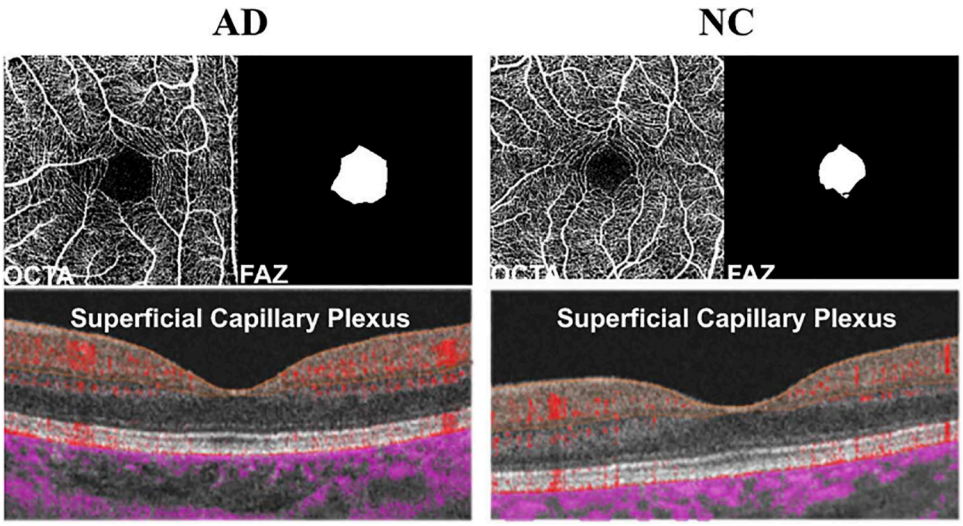

FIGURE 2.

OCTA images of the superficial capillary plexus layer comparing the FAZ of a patient with AD to the FAZ of normal control. FAZ enlargement is present in the AD patient.61 AD indicates Alzheimer disease; FAZ, foveal avascular zone; OCTA, optical coherence tomography angiography.

TABLE 1.

Summary of Reported Retinal OCT and OCTA Findings in Patients With Alzheimer Disease

				OCT					OCTA				
References	**Diagnosis**	**Cases/ studies**	**Controls**	**RNFL thinning**	**Macular thinning**	**GCC thinning**	**↓Macular volume**	**Choroid thinning**	**↓DPVD**	**↓SPVD**	**↓Choroidal thickness**	**↓ppVD**	**Enlarged FAZ**
Berisha et al[115]	AD	9	8	Yes	_	_	_	_	_	_	_	_	_
Garcia-Martin et al[45]	Mild AD	20	28	Yes	—	—	Yes	—	—	—	—	—	—
Cunha et al[44]	Mild AD	50	172	Yes	Yes	—	—	—	—	—	—	—	—
Den Haan et al[43]	AD, MCI	887, 216	864	Yes *	Yes *	—	—	—	—	—	—	—	—
Bulut et al[62]	ATD	26	26	—	—	—	—	—	—	Yes	Yes	—	Yes
Lahme et al[56]	AD	36	38	—	—	—	—	—	—	—	—	Yes	—
O'Bryhim et al[63]	Preclinical AD	14	16	—	—	—	—	—	—	—	—	—	Yes
Chan et al[42]	AD, MCI	1257, 305	1460	Yes	Yes	Yes	Yes	Yes	—	—	—	—	—
Zhang et al[60]	aMCI/ eAD	16	16	—	—	—	—	—	—	Yes *	—	Yes *	—
Chua et al[37]	AD, MCI	24, 37	29	—	—	—	—	—	Yes	Yes *	—	—	—
Wu et al[59]	AD, MCI	18, 21	21	—	—	—	—	—	Yes *	Yes	—	—	—
Ge et al[41]	AD, MCI	126 studies	—	Yes *	Yes	—	—	Yes *	—	—	—	—	—
Jin et al[54]	AD	9 studies	—	—	—	—	—	—	Yes	Yes	—	—	—
O'Bryhim et al[64]	Preclinical AD	9	11	—	—	—	—	—	—	—	—	—	Yes
Rifai et al[55]	Preclinical AD, MCI, AD	14 studies	—	—	—	—	—	—	—	Yes	—	—	Yes
Katsimpris et al[57]	AD	10 studies	—	—	—	—	—	—	—	Yes	—	—	—
Yeh et al[58]	AD, MCI	444, 391	770	—	—	—	—	—	Yes *	Yes *	—	—	Yes

*Statistically significant in MCI patients.

ATD indicates Alzheimer's type dementia; DPVD, deep plexus vessel density; FAZ, foveal avascular zone; GCC, ganglion cell complex; ppVD, peripapillary vessel density; RNFL, retinal nerve fiber layer; SPVD, superficial plexus vessel density.