PERSPECTIVE
Retinal Biomarkers of Alzheimer Disease

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• PURPOSE: To address challenges associated with identifying retinal biomarkers for Alzheimer's disease (AD) and strategies for future investigation of novel ophthalmologic biomarkers.
• DESIGN: Perspective.
• METHODS: Summarization of the current understanding of retinal changes that have been identified using advances in imaging technology, analysis of current research into how these changes reflect neurodegenerative pathology, and recommendations for further research in this area that will allow for the identification of unique biomarkers for early AD.
• RESULTS: Some retinal changes detectable using various imaging modalities may reflect neurodegeneration or other AD-related pathology on a cellular level. Structural changes in both the peripapillary and macular retina and changes in vascular parameters have been identified. Some imaging findings correlate with known histopathologic findings, and some are associated with cognitive decline. However, multiple challenges exist, such as identifying retinal biomarkers that are specific to biomarker-positive AD, clinical syndrome of AD, and/or pathologic AD brain, finding features that are highly sensitive and specific to AD in patients with other eye diseases, and validating potential biomarkers in population-based longitudinal cohorts.
• CONCLUSIONS: Further research is needed to validate retinal biomarkers for AD, with accurate classification of patients according to diagnosis and cognitive symptoms. Advances in imaging technology, big data, and machine learning, as well as carefully designed studies, will help to identify and confirm potential biomarkers and may lead to novel treatment approaches. (Am J Ophthalmol 2020;218:337–341. © 2020 Elsevier Inc. All rights reserved.)

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OVER 46 MILLION OLDER ADULTS ARE AFFECTED BY dementia worldwide and more than 131 million cases are expected by 2050.[1] Alzheimer's disease (AD) is the most common type of dementia, but the complex molecular mechanisms underlying the pathogenesis of AD are poorly understood. There is a paucity of effective, noninvasive screening, prevention, or treatment modalities. Recent failures of highly anticipated clinical trials testing therapeutics for AD support the notion of a critical need for novel diagnostic approaches sensitive enough to detect patients at the early or preclinical stage of AD, who then can be recruited into trials. In addition, novel biomarkers may identify subgroups with higher risk as well as ones for whom targeted therapeutic pathways are relevant. The ideal screening approach for AD would need to be rapid, noninvasive, inexpensive, and scalable. Recent technological advances in imaging and data analysis may allow for the discovery of these types of specific screening biomarkers as well as further our understanding of AD pathophysiology.

As a direct extension of the central nervous system, the neurosensory retina provides substantial information on brain health and may facilitate noninvasive discovery of novel diagnostic or preventive measures.[2] Given their same origin during embryologic development, both the optic nerve and the retina share many similarities with the brain in anatomy, vasculature, immunology, and mechanisms of responding to injury. Owing to this strong connection between the retina and the brain, many have evaluated potential biomarkers involving the retina and the optic nerve. Indeed, the first description of the postmortem eyes of patients with AD in 1986, by Hinton and associates, revealed severe optic nerve degeneration, the loss of retinal ganglion cells (RGCs), and decreased retinal nerve fiber layer (RNFL) thickness.[3]

Since then, many potential retinal biomarkers of AD have been evaluated.[4] The reduction in the RNFL thickness is likely the most well-studied and consistent feature. Although the first in vivo observation of RNFL reduction associated with AD occurred less than 15 years ago,[5] subsequent evolution in imaging technology has led to greater characterization of the RNFL thinning associated with AD. The reduction in peripapillary and/or macular RNFL thickness in AD has been shown in multiple studies using various imaging modalities such as fundus photography, visual field, and optical coherence tomography (OCT).[6–8]

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However, not all studies have been conclusive, particularly in identifying the specific location where the RNFL thinning occurs.[4,9,10] Small sample size, strict inclusion criteria, and the variability between OCT types (eg, time-domain, spectral-domain, swept-source) that would affect eye tracking, speed of acquisition, and image resolution and segmentation methodologies are important factors that may have contributed to varying results.[11,12]

Unlike other diseases involving RNFL loss, such as glaucoma, that produce corresponding visual field defects, the thinning of RNFL in AD does not produce consistent, local visual function loss, possibly because the RNFL changes are scattered rather than sectoral. There is some evidence that the visual changes that do occur with AD may be a function of primary degenerative processes in the retinal neurons, specifically in the superior and inferior quadrants.[7,8] Other studies suggest that visual field defects may occur owing to changes in the visual cortex primarily in some patients.[13] Furthermore, RNFL thinning was not found to correlate with changes in cortical visual evoked response, and the relative sparing of the primary visual cortex in AD may explain the absence of some visual function loss despite the early RNFL loss.[14] Different types of RGCs have varying susceptibility to the amyloid pathology associated with AD, suggesting that a particular subpopulation of RGCs may be most affected in AD.[15] The larger magnocellular cells (M-cells), which contribute large-caliber fibers to the optic nerve, have been shown to be selectively affected in AD, and loss of these cells may lead to characteristic visual deficits.[16] In an AD mouse model, the inner retina was affected early before the onset of cognitive deficits[17]; thus the discrepancy in visual function and cognitive function may depend on what pathology occurred first and how the retinal and cortical pathologies are affecting each other. Additionally, visual field results in advanced AD may be confounded by other cognitive factors, rendering visual field testing a less reliable psychophysical assessment in this population.[18]

Given rapid advances in OCT technology, many studies have explored various retinal layers and the choroid as potential biomarkers in addition to RNFL thinning. A meta-analysis of studies of retinal AD biomarkers using spectral-domain OCT found that thinning of the ganglion cell–inner plexiform layer and ganglion cell complex and decreased macular volume and thickness were associated with AD, in addition to the reduction in both macular and peripapillary RNFL thickness and choroidal thickness.[7] Because the macula contains a high proportion of the large RGC bodies and cell bodies are much greater in size than their axons present in the RNFL, ganglion cell–inner plexiform layer thinning at the macula may be more sensitive for early changes associated with AD and may also show less individual variation.[19,20] Using the enhanced-depth imaging capabilities of OCT, several studies have shown thinning of the choroid in AD patients compared to healthy controls.[21,22] However, the reliability of the segmentation, diurnal variation of the choroid, and other diseases that are associated with choroidal thinning such as aging, myopia, and glaucoma contribute to the challenges in evaluating the choroid as a biomarker.[4,23,24] Interestingly, a recent postmortem histopathologic study showed thinning in the superonasal choroid but unexpected thickening in the superotemporal choroid that corresponded to increased vascularity in severe AD.[25] The thickening was prominent in the macular region, and the authors discussed the different distribution of retinal Aβ deposit density, a compensatory vascular-inflammatory response specific to severe AD stage, and the limitations of in vivo OCT studies involving the choroid as potential hypotheses to explain this unexpected discrepancy.[25] Further ex vivo studies like this will be critical in understanding the validity and potential mechanisms of various in vivo biomarkers.

Change in the retinal vascular parameters is another source of potential biomarkers. Many have investigated associations between AD and various vascular parameters such as vessel caliber, fractal dimensions, branching patterns, and tortuosity using fundus photography, but the reported associations have been relatively weak and not consistent among studies.[26] However, with the advent of OCT angiography with much more sensitive detection of microvasculature, results have been more promising. Enlarged foveal avascular zone (FAZ), reduced vessel density, and perfusion have been reported in AD using OCT angiography.[22,27] One study identified altered central retinal thickness and FAZ in preclinical AD without any cognitive decline,[28] whereas another study found no significant difference in the FAZ but an unexpected, higher vessel density in preclinical AD.[29] Despite some conflicting results, these studies involving preclinical AD patients prior to the development of cognitive decline suggest the possibility of early diagnosis and therapy before symptomatic decline.

Targets of other imaging modalities include retinal amyloid detection via curcumin[30] or hyperspectral imaging.[31] Hyperspectral imaging detects the level of soluble Aβ aggregates that are specific to AD pathology and thus may be less affected by other age-related neurodegeneration.[32] In the first in vivo study, the hyperspectral imaging signature was most significant during the early disease state, presumably because it identifies the soluble Aβ deposits instead of insoluble plaques that accumulate in late AD.[31,32] In addition, the study claimed that mild-to-moderate cataract or glaucoma did not seem to affect the quality of the data; however, additional studies are needed because patients with advanced retinopathies, glaucoma, or severe cataract were excluded from the study. If validated in larger studies, hyperspectral imaging may become a useful biomarker of early disease state. A recent study using adaptive-optics scanning laser ophthalmoscopy found hyperreflective granular membranes surrounding the optic nerve in patients with mild clinical impairment (MCI)

and early AD compared to controls.[10] The authors hypothesized that these membranes may be manifestations of inner retinal gliosis occurring in the early stage of disease. Although these membranes may obscure RNFL thinning on OCT in early AD, they may also be a potential biomarker for the early AD pathology.[10] Recent studies showed significantly different retinal fluorophore distribution between AD and healthy controls via fluorescent lifetime imaging ophthalmoscopy.[33,34] The molecules responsible for the AD signature on fluorescent lifetime imaging ophthalmoscopy are not known; thus, investigation of these metabolites may lead to novel hypotheses and/or new therapeutic targets. There are many important and unanswered questions, including (1) how these imaging biomarkers compare to known neuroimaging or cerebrospinal fluid (CSF) biomarkers such as tau protein and beta-amyloid, and (2) which biomarker(s) are predictive of early onset of dementia or rapid disease progression. Substantial research will be required to obtain systemic biomarker data on large, well-characterized cohorts.

While we pursue the investigation of retinal biomarkers, several challenges should be acknowledged. First, how the cognitive diagnosis (eg, MCI, AD) is made in the study population should be assessed to understand potential misclassification. Significant efforts have taken place to clarify the distinctions between the clinical syndrome of AD and the histopathologic findings in the brain diagnostic of pathologic AD, which often correlate poorly.[35] Before the CSF or positron emission tomography biomarkers of amyloid or tau became available for research, only clinical and autopsy data existed. Therefore, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria distinguished the following 3: (1) a clinical syndrome thought to be AD but with other conditions that could play a role in dementia ("Possible AD"), (2) a clinical syndrome thought to be AD without other conditions ("Probable AD"), and (3) an AD clinical syndrome during life with confirmed AD pathology at autopsy ("Definite AD").[36] Since that time, amyloid and more recently tau positron emission tomography scans, and the possibility of obtaining CSF biomarkers, have led to more complicated nomenclatures to capture the notion that people may have AD neuropathology in the absence of dementia, and even without any evidence of cognitive decline. In several frameworks including those recently adopted by the National Institute on Aging (NIA) and the Alzheimer's Association, this led to descriptions of "preclinical AD," envisioned as inevitably progressing to clinical AD with sufficient time.[37] Others have looked at the same phenomena in older adults who die with substantial neuropathologic AD findings but no clinical symptoms and refer to that as "resilience" instead of "preclinical AD."[38] The prevalence of this unique resilient subgroup has been reported as high as 25% in some community-based cohorts.[39] Thus, evaluations of potential retinal biomarkers will need to be very clear as to whether the investigation is addressing the clinical dementia syndrome of AD, the pathologic findings of AD, or both, and also with a caveat that the resilient group may be misclassified.

Second, another challenge is in identifying the retinal biomarkers that are specific to AD. A recent study using swept-source OCT compared macular thickness, inner retinal layer thickness, and peripapillary RNFL thickness in patients with amnestic MCI and found preferential thinning of the inner retinal layers around the fovea when compared to healthy controls, and that the macular changes correlated with cognitive scores particularly when comparing MCI patients to normal patients, suggesting that the retinal changes may correlate with any form of cognitive decline and not with a specific neurodegenerative disease such as AD.[12] Another example is macular pigment optical density based on the level of retinal carotenoids, which has been shown to correlate with cognitive function.[40] Thus, any retinal biomarkers should be validated as to whether or not they are specific for AD in larger cohorts that include various neurodegenerative diseases.

Third, the majority of studies on retinal biomarkers of AD exclude patients who have significant eye conditions such as age-related macular degeneration, glaucoma, diabetic retinopathy, or cataract owing to the confounding effect of these diseases on the retinal neurovascular unit. However, the prevalence of these eye conditions is extremely high in the aging population. As such, the ideal screening tool will need to detect ophthalmic biomarkers even in the presence of common aging eye diseases,[41] which will require the identification of highly sensitive and specific features associated with AD, even in patients with established eye conditions. Fourth, replication of the results in a longitudinal, population-based cohort will be critical. There is such clinical, genetic, and pathologic heterogeneity in AD that the variability of biomarker results in small convenience sampling studies may be considerable. Furthermore, we do not know the duration of preclinical AD. Therefore, our ability to test biomarkers multiple times until the development of clinical manifestations of AD will be important to increase our chance of detecting the earliest changes. Fifth, several possibilities exist regarding what information the retinal biomarkers may provide. Retinal biomarkers may correlate with brain biomarkers and become preferable owing to low cost and noninvasiveness; they may associate with the symptoms at a certain stage of AD (ie, prodromal, preclinical, early) and become useful as a screening tool for clinical trial recruitment; and/or they may identify a subset of people who are brain biomarker positive and will develop clinical dementia, differentiating them from the resilient subgroups and therefore providing different research strategies for different subgroups. Thus, careful attention to the sequence of biomarkers, clinical onset, and ophthalmic biomarker

changes will be needed to understand the potential role of ophthalmic biomarkers in a strategy to characterize people with respect to AD risk.

Lastly, development of widely available, scalable ophthalmic biomarker screening tools will require a substantial amount of data. Recent advances in computing vision and applications of deep learning in many ophthalmic imaging analyses show promise for analyzing similar eye imaging data related to AD and generating novel hypotheses. For example, a recent study used supervised machine learning to evaluate texture metrics in order to differentiate between the structural characteristics of the retinal tissue in AD, Parkinson disease, and healthy patients.[42] The UK Biobank data from 32,038 subjects found that RNFL thinning was predictive for decreased cognitive function over time.[43] Significant collaborative efforts on a large scale must occur in order to agree on the minimal set of scanning protocols and/or to design similar protocols whose results can be calibrated across these kinds of studies. Collaboration is needed to ensure that data across multiple studies can be combined to build data-sharing platforms in order to overcome the potential for confounding variables associated with cross-sectional or smaller cohort studies and to increase the size of the combined dataset to enable machine learning approaches.

The eye provides a unique opportunity to learn about the aging brain and AD pathology. With the rise of noninvasive imaging techniques of unprecedented resolution and the opportunity to combine the data interpretation with machine learning approaches, the potential for finding ophthalmic biomarkers of AD is brighter than ever. This exciting area of research will continue to accelerate with collaborations among investigators across different subspecialties in medicine. These studies may also provide a roadmap for other neurodegenerative diseases where the eye can be a window into disease pathogenesis.

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