Invited Commentary

Structural and Functional Retinal Changes in Preclinical Alzheimer Disease

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It has been more than 100 years since Alois Alzheimer identified Alzheimer disease (AD), and almost 40 years since the role of amyloid-β (Aβ) and tau proteins, 2 key molecular factors in the AD pathophysiologic patterns, were identified.[1] Alzheimer disease is now recognized as a multifaceted process that progresses along a continuum with a commonly defined starting point being the accumulation of the Aβ biomarker demonstrated on positron emission tomography (PET) or cerebrospinal fluid analysis. The epidemic of AD has already decreased the life expectancy in the US,[2] adding to the urgency to identify a noninvasive biomarker to easily detect not only those with symptomatic AD, but also those with preclinical AD for whom lifestyle modifications, such as diet, exercise, and cognitive engagement, may delay onset. The retina holds promise in being able to provide such a biomarker, yet challenges remain, ranging from our evolving understanding of underlying AD pathophysiologic characteristics to current limitations of retinal imaging.

Related article

In this issue of *JAMA Ophthalmology*, Byun and colleagues[3] report a single-center, cross-sectional study evaluating the association of retinal changes with AD neuroimaging biomarkers in 49 cognitively normal individuals. Participants underwent swept-source optical coherence tomography wherein macular thickness, retinal nerve fiber layer thickness, and ganglion cell–inner plexiform layer thickness were measured, and multifocal electroretinogram was performed. PET imaging using the 11 carbon-labeled Pittsburgh compound B ([^{11}C] PiB) ligand to detect Aβ and simultaneous 3-dimensional magnetic resonance imaging (MRI) were performed. The investigators observed delayed implicit time (reduction of 5.2% in ring 3 and 7.5% in ring 5) on multifocal electroretinogram as well as reduced regional thickness of the macula in the Early Treatment Diabetic Retinopathy Study inner ring (6.2% thinner) as well as inferior (22.4% thinner) and temporal (21.1% thinner) retinal nerve fiber layer thickness in the 16 individuals with Aβ deposition compared with the 33 individuals without Aβ deposition. The authors also found ganglion cell–inner plexiform layer thickness in the superior and superonasal subfields had a moderate correlation with cortical thickness of the AD signature regions on MRI, including the entorhinal, parahippocampal, middle temporal, angular gyrus, posterior cingulate cortex, and precuneus. There were low correlations with macular thickness and low to moderate correlations with multifocal electroretinogram amplitudes.

A logistic regression analysis was constructed to detect Aβ positivity as the outcome variable that included age, sex, *APOE*4 status, and vision as fixed variables. Years of education is known to affect the rate of cognitive decline and might also be an important factor to consider in future models.[4] *APOE*4 carrier status was noted in 27.3% of the Aβ-negative group compared with 43.8% in the Aβ-positive group. Individuals with *APOE*4 have a greater risk of developing AD and are more likely to have Aβ accumulation. It would be helpful to know whether the results differed in those with vs without *APOE*4 carrier status. While the model was sensitive at 93.75%, its specificity was relatively lower at 78.79%.

In the study, there were more individuals with hypertension (43.8% vs 33.3%) and individuals with diabetes (18.8% vs 6.1%) in the Aβ-positive group. Neurodegenerative functional changes noted on multifocal electroretinogram and structural changes observed on optical coherence tomography imaging are known to occur in individuals with diabetes, even in those without diabetic retinopathy; thus, it is important to recognize these changes as a potential confounder.[5] In addition, hypertension, smoking, diabetes, and obesity increase the risk for subsequent clinically diagnosed AD. Diagnostic biomarkers noted on PET and in cerebrospinal fluid are direct surrogates of brain AD lesions (amyloidosis or tauopathy) and therefore indicative of the presence of the disease, while progression markers identify later changes (eg, neuronal loss) indicative of disease progression but not necessarily specific to AD. The specificity of retinal findings compared with other diseases causing neurodegeneration, such as diabetes, hypertension, glaucoma, and others, remains a key challenge.

The differential association of neurodegenerative changes with specific regions of the retina also merits further investigation because ganglion cell–inner plexiform layer was similar while inner nasal macular thickness was thinner in Aβ-positive individuals. A layer-based analysis might be helpful to determine whether different layers of the retina are differentially affected, in addition to a topographic region-based analysis.

There continues to be controversy over whether Aβ accumulation alone indicates inevitable progression to AD. Standardization of Aβ positivity to define preclinical AD also remains an unmet need. Preclinical AD is currently defined using different biomarkers and criteria, and, although more invasive, cerebrospinal fluid–based approaches result in a higher Aβ-positive prevalence than PET-based ones.[6] As clinical trials move toward earlier intervention, Aβ-PET thresholds (defined as standardized uptake value ratio >1.4 in at least 1 of 4 regions of interest in this study) may need to be redefined.[7] These thresholds are levels of detection and not necessarily initial onset of amyloidosis. Consistency of PET tracers with the use of different amyloid tracers, such as [^{11}C] PiB, florbetapir (AV-45), 18 flutemetamol (^{18}F-PiB derivative), florbetaben (AV-1), and AZD4694 is another variable across studies and sites.

As we advance our knowledge, it is important to standardize the units and area of measurement of retinal structure and function across different studies so that results can be compared and potentially pooled across studies using

different biomarkers, such as PET/MRI only, PET/MRI with cerebrospinal fluid analysis, or those with genetic *APOE*4 status alone. Interoperability of measurements across different devices, use of 1 eye as in this study vs both eyes in others, and standardization of imaging protocols also merit discussion.

Owing to the inherent limitations in obtaining PET and MRI images in cognitively normal individuals, such data sets are valuable to determine biomarkers that could potentially be applied more broadly. Although these biomarkers are not yet ready for use in clinical practice, this study provides important data on both structural and functional retinal changes in preclinical AD. Although large, diverse population-based studies are needed to provide further insights into the long preclinical AD prodrome and further elucidate the role of retinal changes, these metrics bring us a step closer in our quest to developing retinal biomarkers in the detection of asymptomatic preclinical AD.

ARTICLE INFORMATION

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