Commentary: Viewing Alzheimer's disease from an ophthalmologist's eyes

In this issue of Indian Journal of Ophthalmology, Singh and Verma have compiled the results of the existing research on ocular biomarkers for the diagnosis of Alzheimer's disease (AD) into a detailed review article.[1]

AD Diagnosis

In 2011, the clinical diagnostic criteria for Alzheimer's disease dementia were revised, and research guidelines for initial stages of the disease were characterized to depict a deeper understanding of the disorder. Development of the new guidelines was led by the National Institute on Aging-Alzheimer's Association (NIA-AA) in the United States.[2] In their guidelines AD is defined by its underlying pathologic processes that can be documented by postmortem examination or *in vivo* by biomarkers. It recognizes three general groups of biomarkers based on the nature of the pathologic process that each measures. Biomarkers of Aβ plaques, biomarkers of fibrillar tau and biomarkers of neurodegeneration or neuronal injury. These biomarkers can be fluid biomarkers or imaging biomarkers. Cerebrospinal fluid (CSF) biomarkers are the only variety of fluid biomarkers utilized in the early diagnosis of AD. The imaging biomarkers utilize modalities like structural magnetic resonance imaging (MRI), functional MRI, 18F-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET), and amyloid-PET to identify AD.

AD Screening

Ocular fluid biomarkers

CSF biomarkers cannot be recommended for preventive screening due to their limited accessibility and the invasive nature of CSF collection. On the contrary, the biomarkers obtained from the blood oral, ocular, and olfactory fluids/tissues are easily accessible and less invasive to procure.[3] Anterior ocular fluid and CSF share many features, such as the similarity between blood–aqueous and blood–CSF barriers.[4] Despite that till date, aqueous biomarkers in the AD patients have not been studied as acquisition of the sample is an invasive procedure. Aqueous humor of individuals with AD may reveal higher levels of Ab42, the main biomarker found in neocortical deposits. One study has been done to evaluate the vitreous for the AD-related biomarkers utilizing the vitreous samples from the patients undergoing planned vitrectomy for other pathologies. These patients were evaluated for cognitive impairment using the mini mental status examination scores. The authors found that the patients with poor cognitive function have significantly lower vitreous humor levels of AD-related biomarkers Aβ40, Aβ42, and tTau. These biomarkers do not correlate with underlying eye conditions, suggesting their specificity in association with cognitive change.[5] At this point the correlations of AD with alternative biomarkers obtained from ocular fluids is uncertain and considered invasive as a screening tool.

Noninvasive ocular imaging biomarkers

Pupillometry is a low-cost, noninvasive technique that may be useful for monitoring cholinergic deficits which generally precedes the memory and cognitive disorders.[6] Kerbage *et al*. have described noninvasive methods to identify AD signatures in the human crystalline lens using *in vivo* technique of laser scanning along with a fluorescent ligand.[7] Retinal optical coherence tomography (OCT) has been used to measure the retinal thickness and retinal vascular measurements as the noninvasive screening biomarkers. A review article published in ophthalmology this year confirmed the associations between retinal measurements of spectral domain SD OCT and AD, highlighting the potential usefulness of SD OCT measurements as biomarkers of AD.[8] They assessed the associations between AD and measurements of ganglion cell-inner plexiform layer (GC-IPL), ganglion cell complex (GCC), macular volume, and choroidal thickness, in addition to retinal nerve fiber layer and macular thickness using SD OCT. Whereas another study published in the Alzheimers Dement (Amst), representing the largest optical coherence tomography cohort with amyloid-proven AD cases questions these claims. The authors show that retinal thickness does not discriminate AD from controls, despite evident changes on clinical, neuroimaging, and CSF measures, querying the use of retinal thickness measurements as an AD biomarker.[9] They recommended future studies, including longitudinal measurements of retinal layer thickness and specific molecular biomarkers such as amyloid, tau, and neuroinflammation, to assess the retina as a potential source of noninvasive AD biomarkers.[9] The same group has shown in another study that the retinal vasculature does not discriminate AD from control participants, despite evident changes on clinical, neuroimaging, and cerebrospinal fluid measures, querying the use of retinal vasculature measurements as AD biomarker.[10] Ongoing clinical trials using noninvasive ocular biomarkers like retinal thickness and vasculature measurements using OCT in proven AD cases can only answer these queries in the forthcoming years. We as ophthalmologists can study and present the indicators/biomarkers of the disease in the eye, but their validation, clinical application, or utilization as a research tool is up to the neurologists.

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