Viewing the Brain Through Retina: A New Avenue for Early Diagnosis of Alzheimer's Disease

Annals of Neurosciences
30(4) 219–221, 2023

DOI: 10.1177/09727531231190992
journals.sagepub.com/home/aon

Varisha Zuhair[1], Hussain Sohail Rangwala[1], Zaib Un Nisa Mughal[1], Hareer Fatima[1], Areeba Tufail Shaikh[2] and Abdullah Mussarat[1]

Introduction

Alzheimer's disease (AD) is a leading cause of dementia, affecting 55 million people worldwide.[1] The neurodegenerative process begins around 60–65 years with the formation of amyloid β-protein plaques and neurofibrillary tangles in the brain. The disease remains subclinical for decades, during which cellular changes occur without noticeable symptoms. Memory loss, cognitive decline, confusion, and mood abnormalities appear in advanced stages at which point extensive neuronal damage has occurred.[2] There is an urgent need for early detection methods for AD to identify candidates for antidementia treatments before significant neuronal damage occurs.[3] Early detection is crucial for identifying candidates for antidementia treatments like Lecanemab, which can delay clinical symptoms and slow down disease progression.[4]

Diagnostic Guidelines and Its Limitations

The National Institute on Aging and Alzheimer's Association recognised the preclinical stage of AD in 2011 and stressed the need for intervention during this phase for better treatment outcomes. However, current diagnostic methods for the preclinical stage are limited. Brain scans, memory, and cognitive tests are recommended[5] but are applicable only for symptomatic AD. Several neuroimaging techniques, blood, and CSF biomarkers such as Aβ, pTau, and neurofilament light chains have been proposed as early indicators.[6] The reliability of these biomarkers and neuroimaging techniques in the preclinical phase is uncertain. Additionally, their invasiveness and high costs, such as lumbar puncture, PET scans, and MRI, make them impractical for population-level use. Therefore, there is still a critical need for accurate and cost-effective indicators to diagnose AD in its non-symptomatic stage.

Main Text

Recent findings linking retinal changes with early-stage AD have opened up intriguing possibilities for utilising ophthalmological examinations and retinal biomarkers in the early detection of the disease. The retina, an extension of the brain, provides a unique and accessible window to analyse brain pathology directly, offering a cost-effective, and non-invasive approach.[7]

Research has found significant retinal degeneration, neuroretinal thinning, and other structural and functional changes in the retina of AD patients.[8] The studies revealed the occurrence of characteristic AD lesions such as Aβ40, Aβ42, and pTau inclusions in the retina, similar to the lesions found in the brain of AD patients.[9] A study of retinal and brain samples from 86 human donors found significantly increased levels of Aβ42 in the retinas of patients with Mild Cognitive Impairment (MCI), particularly in the entorhinal and temporal cortices of the brain; a hub for memory and perception. Higher levels of retinal Aβ42 were observed in AD dementia patients compared to those with MCI, indicating continued accumulation as the disease progresses.[10] PET scans have demonstrated that the retinal amyloid load has a direct quantitative relationship with amyloid load in the brain which strongly implies that amyloid deposition in the retina and the brain are the results of the

[1]Department of Medicine, Jinnah Sindh Medical University, Karachi, Pakistan
[2]Department of Medicine, Ziauddin University, Karachi, Pakistan

Corresponding author:
Abdullah Mussarat | Department of Medicine, Jinnah Sindh Medical University, Iqbal Shaheed Rd, Karachi, Pakistan.
E-mail: ab.mussarat@gmail.com

same pathological process.[11] Disruption of retinal microvasculature and accumulation of Aβ40 and Aβ42 in capillaries, similar to that in the brain, further supports that the brain and retina follow a parallel trajectory in the development of AD. These changes were associated with a reduction in the retinal vascular platelet-derived growth factor receptor-beta and progressive loss of pericytes, which are integral components of the blood-retina and blood-brain barriers.[12] Therefore, assessment of retinal microvasculature through ophthalmic investigations like Optical Coherence Tomography (OCT) and Retinal amyloid-fluorescence imaging can provide valuable information for prompt diagnosis of AD. Additionally, astrocytes and muller glial cells were found to be hyperreactive in the retina of patients with MCI and early-stage AD. These astrocytes and muller glial cells expressed high levels of glial fibrillary acidic protein and S100β, which are important inflammatory markers in the retina of patients with MCI. The neuroinflammatory process is a driving factor in the pathogenesis of AD, and identifying these inflammatory markers can be key to early diagnosis of AD.[13]

Conclusion

OCT, retinal amyloid-fluorescence imaging, and retinal hyperspectral imaging are valuable ophthalmological investigations for neurological diagnosis. These widely available and non-invasive modalities are suitable for population-level use due to their lower cost. However, concerns persist among neurologists regarding their accuracy in AD diagnosis. Some observed changes in OCT, like retinal nerve fibre thinning and vasculopathy, are nonspecific and can be found in other retinopathies[14] or normal aging. To address these discrepancies, more precise and sensitive imaging techniques are needed to differentiate AD-related retinal changes, quantify pathology, determine the stage, and predict prognosis. Expanding research in this field is crucial to enable early and optimal treatment, delay dementia onset[15] and empower patients to plan for their future while reducing the disease's financial burden.

Authors' Contributions

The conceptualisation was done by VZ and AM. The literature and drafting of the manuscript were conducted by VZ, AM, HSR, ATS, ZM, and HF. The editing and supervision were performed by VZ and AM. All authors have read and agreed to the final version of the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Zaib Un Nisa Mughal https://orcid.org/0009-0004-0855-8479
Abdullah Mussarat https://orcid.org/0000-0002-5979-5835
Hareer Fatima https://orcid.org/0009-0002-3823-0349

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