sciendo

Retinal examination modalities in the early detection of Alzheimer's disease: Seeing brain through the eye

Xiaoxi Ma[1,2], Xi Wang[3], Yiqin Xiao[3], Qianhua Zhao[1,2,4]

[1]Department of Neurology, Huashan Hospital, Fudan University, Shanghai 200040, China;
[2]National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, Shanghai 200040, China;
[3]Department of Ophthalmology, Huashan Hospital, Fudan University, Shanghai 200040, China;
[4]MOE Frontiers Center for Brain Science, Fudan University, Shanghai 200040, China

Alzheimer's disease (AD), the most common type of dementia, is a chronic, progressive degenerative disease, with the main clinical features being progressive impairment in cognition, behavior, and ability to do activities of daily living. Although the neuropathological changes in AD can be assessed by histopathologic examination, cerebrospinal fluid (CSF) or blood assays, and through positron emission tomography (PET) imaging, clinical application of these biomarkers is limited due to the cost, invasiveness, and availability.[1]

The retina is a part of the central nervous system (CNS) and shares common features with the brain in many aspects, including its embryonic origin, structure, and physiological function. The retina originates from the diencephalon and maintains its connection with the brain via the optic nerve anatomically. Vasculature, blood barriers, and populations of neurons and glial cells of the retina and cerebrum are also homologous, which provides a basis for the secretion and transportation of AD-related proteins, namely, amyloid β (Aβ), phosphor-Tau (p-Tau), *etc*. The presence of Aβ and p-Tau is observed in postmortem retinas in AD patients, though they do not morphologically resemble neuritic plaques and neurofibrillary tangles in the brain. As the only extension of the CNS outside the skull, and with the accessibility for noninvasive imaging, the retina has been considered an ideal "window" to detect and monitor AD-related pathology.[2]

Different retinal examination modalities including electrophysiological examinations, optical coherence tomography (OCT), OCT-angiography (OCT-A), retinal fundus photography, and retinal hyperspectral imaging (rHSI) have been developed over the past decades and used in AD-related studies. Rapidly advancing retinal imaging technologies can provide tremendous amounts of information regarding the structural, functional, and molecular changes of retinal tissue in vivo.

RETINAL ELECTROPHYSIOLOGICAL CHANGES IN AD

Visual impairment, such as dysfunction or deterioration in visual acuity, contrast sensitivity, color, depth, and motion perception, is common in AD. Electrophysiological examinations can objectively reveal a decline in these features. Commonly used methods include electroretinogram (ERG), visual evoked potential (VEP), *etc*. Pattern-ERG (p-ERG) parameters change significantly in the early stages of AD and can distinguish mild cognitive impairment (MCI) due to AD from MCI due to vascular etiology.[3] The latency of flash visual evoked potentials-P2 (FVEP-P2) is also significantly delayed in AD and MCI patients compared with that in healthy controls.[4]

Address for Correspondence:
Qianhua Zhao , Department of Neurology, Huashan Hospital , Fudan University, 12 Wulumuqi Rd.(M), Shanghai 200040, China.
E-mail: qianhuazhao@fudan.edu.cn

Yiqin Xiao, Department of Ophthalmology, Huashan Hospital, Fudan University, 12 Wulumuqi Rd.(M), Shanghai 200040, China. E-mail: xiaoyiqin1028@163.com

Access this article online

Website: www.intern-med.com

DOI: 10.2478/jtim-2021-0053

RETINAL STRUCTRAL CHANGES IN AD

Structural changes in retinal tissue can be detected via OCT, which can provide high-resolution two-dimensional cross-sectional imaging and three-dimensional volumetric measurements of the retina. It is a diagnostic technique widely used in ophthalmology and has recently been used for the analysis of retinal changes in neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), Parkinson disease (PD), and AD. The mean total macular thickness in the peripapillary retinal nerve fiber layer (pRNFL), the inner plexiform layer (INL), and the outer nuclear layer (ONL) was found reduced in ALS patients, and there is evidence that pRNFL is diminished during PD progression.[5] Currently, spectral domain OCT and swept source OCT are commonly used for retinal structure detection in AD patients.

Though still controversial, many studies have shown that the thinning of pRNFL and total macular in OCT are promising indicators for AD and MCI and are correlated with the cognitive function.[6] Significant correlations were found between retinal measures and brain volume, neuropsychological test scores, Aβ or tau levels in the CSF, and Aβ or tau deposition detected by PET imaging.[7-9] The average RNFL thickness may reflect early AD pathology, as indicated by CSF $A\beta_{42}$/Tau level.[8] The inner perifovea retinal thickness was found to be related to the hippocampal and entorhinal cortex volume in structural MR scan in our previous study.[10] A Rotterdam study found that thinning of the ganglion cell layer–inner plexiform layer (GC–INL) was associated with the prevalence of dementia, while a thinner baseline RNFL was associated with incident dementia.[11] Moreover, MCI patients who eventually converted to AD had significantly thinner baseline RNFL and GC-IPL than stable MCI,[12] suggesting the potential predictive value of the RNFL and GC-IPL thickness for AD progression. However, retinal structure characteristics in AD patients overlap with those in other neurodegenerative diseases mentioned above, indicating the relatively low specificity of OCT.

RETINAL VASCULAR CHANGES IN AD

Retinal vascular dysfunction has been reported in AD patients, including narrowing retinal vessel diameter, reduction of venular fractal dimensions, increased tortuosity, decreased blood flow, microvascular changes, changes in choroidal thickness, etc.[13-16] There are currently many methods available for retinal vascular parameters measurement, but a unified conclusion has not yet been reached.

In some studies, OCT-A showed increased size of the foveal avascular zone and reduced density of superficial capillary plexus in AD patients,[14, 15] while another research reported no significant difference in foveal avascular zone, but significantly reduced density of superficial capillary plexus in AD patients compared to the control group.[17] Quantitative retinal vasculature analysis with retinal fundus photography showed a reduction of venular fractal dimensions in cognitive impairment (CI) individuals.[16] rHSI showed higher retinal vein tortuosity and larger diameter of arteries near the optic head in CI patients with Aβ-positive PET.

AD-RELATED PATHOLOGY IN THE RETINA

Several emerging retinal imaging technologies such as curcumin imaging, imaging of cellular apoptotic changes, and rHSI are also being explored which might provide additional value in retinal AD-related pathology detection. Among them, rHSI is the most applicable tool.

As an inexpensive, noninvasive retinal imaging modality, rHSI can detect the light scattering changes to reflect the structure and chemical composition of each retinal quadrant. Soluble Aβ oligomers form the most characteristic optical signal of AD.[18] In a study involving 19 patients with CI, whose MMSE scores ranged from 10 to 26, covering mild, moderate, and severe AD, rHSI was found to have higher sensitivity in early AD (MMSE 22–26), which was not affected by comorbid ophthalmologic pathologies such as glaucoma and cataract.[19] Significant difference was found between retinal reflectance spectra of Aβ-positive MCI patients and age-matched Aβ-negative controls. rHSI feature scores are also significantly correlated with cerebral Aβ load, suggesting that rHSI can predict the Aβ load in the brain.[20] rHSI could be a potential early screening tool for AD, but only a few studies have reported its preliminary application in small samples of AD patients. Based on the current evidence, more validation studies covering different stages of AD patients are warranted.

In summary, retina is a promising window for visualizing cerebral pathology, especially in patients with AD biomarkers. With retinal imaging technology being increasingly incorporated into general practices of ophthalmology, it becomes more available in clinical practice. Besides, retinal imaging avoids invasive procedures and is far less expensive than PET imaging. Features such as low cost, noninvasiveness, and easy accessibility make retina imaging suitable for large-scale population screening for AD.

Despite its beneficial potentials, there are still some limitations that need to be addressed. Some measures, for example, retinal nerve fiber thinning and vascular changes,

might not be specific for AD, which are highly variable in the normal population and are also affected by other age-related neurodegenerative diseases. In addition, since the prospective studies covering the whole spectrum of the disease were limited, the sequence of the pathological events including retinal degeneration, Aβ/Tau-related change, and cognitive deterioration remains to be elucidated. Studies to date suggest a range of retinal imaging technologies can be used for the clinical research of AD. However, it is time for the research focus to shift from establishment of the method to validation in the real-world clinical practice. It is crucial to assess the sensitivity, specificity, diagnostic accuracy, and cut-off values before the retina-related measurement can be utilized as a routine clinical examination. In search of new retinal biomarkers for AD, it is also extremely important to test its diagnostic power in comparison with the gold standard biomarkers such as Aβ-PET, tau-PET, CSF $A\beta_{42}$, p-Tau, etc. Clinical study design involving parallel comparisons of retinal measures and other AD biomarkers is also required for future research. Retinal biomarkers, as shown in a few cohort studies to date, undergo significant changes as the AD progresses. To confirm the current findings and validate their prognostic value, further studies with longitudinal designs and large sample sizes are needed. Moreover, as single imaging methods only reflect one specific retinal pathology, comprehensive measures integrating multiple imaging modalities are warranted to further improve its diagnostic accuracy in the times to come.

Source of Funding

This work was supported by grants of the Clinical Research Plan of SHDC (grant no. SHDC2020CR4007), the National Natural Science Foundation of China (82071200), Shanghai Science and Technology Committee (19411961700), the MOE Frontiers Center for Brain Science (JIH2642001/028), the National Project of Chronic Disease (2016YFC1306402), the Shanghai Municipal Science and Technology Major Project (2018SHZDZX01), and ZJLab.

Conflict of Interest

The authors have no conflicts of interest to disclose.

REFERENCE

1. 2021 Alzheimer's disease facts and figures. Alzheimers Dement 2021;17:327-406.
2. London A, Benhar I, Schwartz M. The retina as a window to the brain-from eye research to CNS disorders. Nat Rev Neurol 2013;9:44-53.
3. Mavilio A, Sisto D, Prete F, Guadalupi V, Dammacco R,Alessio G. RE-PERG in early-onset Alzheimer's disease: A double-blind, electrophysiological pilot study. PLoS One 2020;15:e0236568.
4. Fix ST, Arruda JE, Andrasik F, Beach J,Groom K. Using visual evoked potentials for the early detection of amnestic mild cognitive impairment: a pilot investigation. Int J Geriatr Psychiatry 2015;30:72-9.
5. Maldonado RS, Mettu P, El-Dairi M,Bhatti MT. The application of optical coherence tomography in neurologic diseases. Neurol Clin Pract 2015;5:460-9.
6. Ge YJ, Xu W, Ou YN, Qu Y, Ma YH, Huang YY, *et al.* Retinal biomarkers in Alzheimer's disease and mild cognitive impairment: A systematic review and meta-analysis. Ageing Res Rev 2021;69:101361.
7. Shi Z, Cao X, Hu J, Jiang L, Mei X, Zheng H, *et al.* Retinal nerve fiber layer thickness is associated with hippocampus and lingual gyrus volumes in nondemented older adults. Prog Neuropsychopharmacol Biol Psychiatry 2020;99:109824.
8. Asanad S, Fantini M, Sultan W, Nassisi M, Felix CM, Wu J, *et al.* Retinal nerve fiber layer thickness predicts CSF amyloid/tau before cognitive decline. PLoS One 2020;15:e0232785.
9. van de Kreeke JA, Nguyen HT, Konijnenberg E, Tomassen J, den Braber A, Ten Kate M, *et al.* Longitudinal retinal layer changes in preclinical Alzheimer's disease. Acta Ophthalmol 2021;99:538-44.
10. Tao R, Lu Z, Ding D, Fu S, Hong Z, Liang X, et al. Perifovea retinal thickness as an ophthalmic biomarker for mild cognitive impairment and early Alzheimer's disease. Alzheimers Dement (Amst) 2019;11:405-14.
11. Mutlu U, Colijn JM, Ikram MA, Bonnemaijer PWM, Licher S, Wolters FJ, *et al.* Association of Retinal Neurodegeneration on Optical Coherence Tomography With Dementia: A Population-Based Study. JAMA Neurol 2018;75:1256-63.
12. Choi SH, Park SJ, Kim NR. Macular Ganglion Cell -Inner Plexiform Layer Thickness Is Associated with Clinical Progression in Mild Cognitive Impairment and Alzheimers Disease. PLoS One 2016;11:e0162202.
13. Salobrar-Garcia E, Méndez-Hernández C, Hoz R, Ramírez AI, López-Cuenca I, Fernández-Albarral JA, *et al.* Ocular Vascular Changes in Mild Alzheimer's Disease Patients: Foveal Avascular Zone, Choroidal Thickness, and ONH Hemoglobin Analysis. J Pers Med 2020;10:231.
14. Grewal DS, Polascik BW, Hoffmeyer GC,Fekrat S. Assessment of Differences in Retinal Microvasculature Using OCT Angiography in Alzheimer's Disease: A Twin Discordance Report. Ophthalmic Surg Lasers Imaging Retina 2018;49:440-4.
15. Bulut M, Kurtuluş F, Gözkaya O, Erol MK, Cengiz A, Akıdan M, *et al.* Evaluation of optical coherence tomography angiographic findings in Alzheimer's type dementia. Br J Ophthalmol 2018;102:233-7.
16. Cabrera DeBuc D, Somfai GM, Arthur E, Kostic M, Oropesa S,Mendoza Santiesteban C. Investigating Multimodal Diagnostic Eye Biomarkers of Cognitive Impairment by Measuring Vascular and Neurogenic Changes in the Retina. Front Physiol 2018;9:1721.
17. Wang X, Zhao Q, Tao R, Lu H, Xiao Z, Zheng L, *et al.* Decreased Retinal Vascular Density in Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI): An Optical Coherence Tomography Angiography (OCTA) Study. Front Aging Neurosci 2020;12:572484.
18. More SS, Vince R. Hyperspectral imaging signatures detect amyloidopathy in Alzheimer's mouse retina well before onset of cognitive decline. ACS Chem Neurosci 2015;6:306-15.
19. More SS, Beach JM, McClelland C, Mokhtarzadeh A, Vince R. In Vivo Assessment of Retinal Biomarkers by Hyperspectral Imaging: Early Detection of Alzheimer's Disease. ACS Chem Neurosci 2019;0:4492-501.
20. Hadoux X, Hui F, Lim JKH, Masters CL, Pébay A, Chevalier S, et al. Non-invasive in vivo hyperspectral imaging of the retina for potential biomarker use in Alzheimer's disease. Nat Commun 2019;10:4227.

How to cite this article: Ma X, Wang X, Xiao Y, Zhao Q. Retinal examination modalities in the early detection of Alzheimer's disease: Seeing brain through the eye. J Transl Intern Med 2021; 10: 185-187.