·文献综述·

通过眼部结构协助诊断早期阿尔茨海默症的研究进展

韩 暄[1,2],王金燕[1],周 琦[3],宿晓娟[1],郭星雨[1],刘春梦[1],陈 婕[2],叶河江[2]

引用:韩暄,王金燕,周琦,等. 通过眼部结构协助诊断早期阿尔茨海默症的研究进展. 国际眼科杂志, 2024,24(1):77-81.

基金项目:四川省中医药管理局中医药科研专项课题(No.2023zd001);四川省中医药管理局中医药基础专项课题(No.2023MS580)

作者单位:[1](610072)中国四川省成都市,成都中医药大学;[2](610075)中国四川省成都市,成都中医药大学附属医院眼科;[3](646000)中国四川省泸州市,西南医科大学附属医院眼科

作者简介:韩暄,成都中医药大学在读硕士研究生,研究方向:中医药防治眼底疾病。

通讯作者:叶河江,博士,研究员,主任医师,博士研究生导师,成都中医药大学附属医院国家中医临床研究(糖尿病)基地办公室主任,研究方向:中西医结合防治眼底病. yehej@163.com

收稿日期:2023-07-10 修回日期:2023-11-24

摘要

阿尔茨海默症(AD)是常见的中枢神经系统退行性疾病,其神经病理学变化先于认知功能障碍和行为损害出现。目前,AD的早期诊断是基于有创性和价格昂贵的检测技术,难以在临床上广泛使用。因此,迫切需要新的标志物,以在早期阶段检测AD。眼睛作为大脑的延伸,研究发现,与大脑病理学变化相比,AD患者眼部病理学变化更早出现,如视网膜结构异常、视觉功能障碍、视网膜异常蛋白积聚、脉络膜厚度变化、角膜神经纤维密度降低、晶状体异常Aβ蛋白的沉积和瞳孔光反应敏感度下降等。本文针对近些年AD患者的眼部病理学变化进行综述,为临床早期诊断AD提供新思路。

关键词:阿尔茨海默症;视网膜;脉络膜;角膜;瞳孔;晶状体

DOI:10.3980/j.issn.1672-5123.2024.1.15

Research progress in assisting in the diagnosis of early Alzheimer's disease through eye structure

Han Xuan[1,2], Wang Jinyan[1], Zhou Qi[3], Su Xiaojuan[1], Guo Xingyu[1], Liu Chunmeng[1], Chen Jie[2], Ye Hejiang[2]

Foundation items: Specialized Project on Scientific Research of Traditional Chinese Medicine of Sichuan Provincial Administration of Traditional Chinese Medicine (No.2023zd001); Specialized Project on the Basis of Traditional Chinese Medicine of Sichuan Provincial Administration of Traditional Chinese Medicine (No.2023MS580)

[1]Chengdu University of Traditional Chinese Medicine, Chengdu 610072, Sichuan Province, China; [2]Department of Ophthalmology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610075, Sichuan Province, China; [3]Department of Ophthalmology, the Affiliated Hospital of Southwest Medical University, Luzhou 646000, Sichuan Province, China

Correspondence to: Ye Hejiang. Department of Ophthalmology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610075, Sichuan Province, China. yehej@163.com

Received:2023-07-10 Accepted:2023-11-24

Abstract

• Alzheimer's disease (AD) is a common degenerative disease of the central nervous system in which neuropathological changes precede cognitive dysfunction and behavioral impairment. Currently, early diagnosis of AD is based on invasive and expensive testing techniques that are difficult to use widely in the clinical setting. Therefore, there is an urgent need for new markers to detect AD at an early stage. The eye, as an extension of the brain, has been found to show earlier onset of ocular pathologic changes in patients with AD compared to brain pathologic changes, such as retinal structural abnormalities, visual dysfunction, retinal abnormal protein accumulation, choroidal thickness changes, decreased corneal nerve fiber density, deposition of abnormal Aβ proteins in the lens, and pupillary light decreased sensitivity of response, *etc*. This article reviews the ocular pathologic changes in AD patients in recent years to provide new ideas for the early clinical diagnosis of AD.

• KEYWORDS: Alzheimer's disease; retina; choroid; cornea; pupil; lens

Citation: Han X, Wang JY, Zhou Q, et al. Research progress in assisting in the diagnosis of early Alzheimer's disease through eye structure. Guoji Yanke Zazhi(Int Eye Sci), 2024,24(1):77-81.

0 引言

阿尔茨海默症(Alzheimer's disease,AD)是由多种因素引起的、不可逆的慢性进行性中枢神经系统退行性疾病,是老年痴呆的常见病因。2020年一项全国调查研究显示,我国60岁及以上人群中痴呆患者约1507万,其中AD患者983万[1]。早期检测AD的主要方法是神经成像技术(如磁共振成像和正电子发射断层扫描成像)和脑脊液生物标志物分析[2]。然而,受限于神经成像技术成本高、分辨率有限[3]和脑脊液获取方式的有创性,使得这两种方法在临床上无法广泛使用[4]。眼睛作为大脑的延伸,

在一定程度上可以反映大脑的病理学变化,并且有研究表明 AD 患者眼部病理学变化先于大脑病理学变化出现[5]。本文总结了近些年 AD 患者的眼部病理学变化,为 AD 早期诊断提供新思路。

1 视网膜

1.1 视网膜厚度变化 临床和试验研究表明,AD 患者视网膜神经纤维层(retinal nerve fiber layer,RNFL)、神经节细胞层(ganglion cell layer,GCL)、内丛状层(internal plexiform layer,IPL)厚度降低,且 RNFL、GCL、IPL 厚度与大脑体积密切相关。RNFL 划分为上、下、鼻、颞四个象限,关于四个象限的 RNFL 厚度变化,有研究表明,与健康受试者相比,AD 患者 RNFL 上象限[6-7]、下象限[7-8]、鼻象限[9]、颞象限[10]厚度明显变薄。Mathew 等[11]发现 RNFL 厚度与大脑体积(包括大脑整体体积、颞叶、海马区、杏仁核、枕叶)呈正相关。Wang 等[12]通过光学相干断层扫描技术(optical coherence tomography,OCT)证实 AD 患者 GCL 厚度降低。此外,Casaletto 等[13]发现 GCL 厚度降低与内侧颞叶萎缩相关。研究者在观察到 AD 患者 IPL 厚度降低[14]的同时,还发现 IPL 厚度与枕、颞叶的灰质体积[15]和脑皮层体积[16]密切相关。

外核层(outer nuclear layer,ONL)与大脑额叶、颞叶关系密切[17],然而不同研究者对于 AD 患者 ONL 厚度变化持有不同意见。Salobrar-García 等[18]认为 ONL 变厚,而在另一项研究中未发现 ONL 厚度有显著差异[19]。目前针对视网膜外层厚度变化的研究较少,研究者尚未对该差异性结果做出合理解释。Asanad 等[14]发现 AD 患者视网膜 INL、外丛状层(outer plexiform layer,OPL)厚度降低,但是目前尚未有研究表明 INL、OPL 厚度与大脑体积之间存在密切联系。

总的来说,AD 患者 RNFL、GCL、IPL、INL、OPL 厚度降低。OPL、INL 厚度变化与大脑体积之间的联系尚未发现,而 RNFL、GCL、IPL 厚度与 AD 患者大脑体积密切相关,有望成为早期诊断 AD 的敏感指标。ONL 虽然与大脑额叶、颞叶关系密切,但是其厚度变化目前存在争议,未来需要进一步研究 ONL 在 AD 患者中的变化情况,以确定 ONL 对早期诊断 AD 的临床意义。

1.2 视网膜血管及血流量变化 AD 发生发展过程中存在大脑血管变化,但通过常规检测方法很难直接检测大脑血管的异常变化,而视网膜血管变化与 AD 患者大脑血管变化存在相似性[20]。诸多研究检测到 AD 患者视网膜血管变化,例如,血流量减少,静脉狭窄,血管密度降低。Kaufman 等[21]研究发现 AD 患者的视网膜血管狭窄和血流量减少,该试验结果同样被 Cunha 等[22]、Li 等[23]证实。关于 AD 患者视网膜血管密度变化,Robbins 等[24]发现,与健康受试者相比,AD 患者视网膜血管密度降低。Frost 等[25]分析 81 例 AD 患者的视网膜血管,临床结果提示视网膜中小动脉、视网膜静脉分形维数均降低。此外,Xie 等[26]经过研究发现 AD 患者血管分叉数明显低于健康人。动静脉分形维数和血管分叉数降低同样提示血管密度降低。因此未来可以通过视网膜血管异常预测大脑血管变化,进而为早期诊断 AD 提供有效依据。

1.3 视觉功能障碍 AD 患者会出现各种视觉功能障碍,包括视力、对比灵敏度、彩色视觉、以及运动感知异常等[27]。视网膜电图(electroretinogram,ERG)和视觉诱发电位(visual evoked potential,VEP)可以很好反应视觉功能。最近研究表明,ERG、VEP 异常波形与 AD 存在相关性。Gaber 等[27]发现 AD 模型大鼠 ERG a 波和 b 波振幅显著下降。Ngoo 等[28]通过图形 ERG 证实 AD 患者 P50 和 N95 波的振幅显著降低。此外,该研究还发现 AD 患者图形视觉诱发电位(pattern visual evoked potential,PVEP)的 P100 振幅下降,潜伏期增加[28]。AD 的主要发病机制是胆碱能神经元功能异常,闪光视觉诱发电位(flash visual evoked potential,FVEP)P2 与大脑中的胆碱能功能有关[29],研究表明 AD 患者出现 FVEP-P2 潜伏期延长[30]。异常视网膜电生理数据可能对早期诊断 AD 具有十分重要的意义。

1.4 视网膜异常蛋白积聚 大脑异常 Aβ 淀粉样蛋白(amyloid beta protein,Aβ)和 pTau 蛋白沉积是 AD 患者典型表现。近些年研究中,不少研究者在 AD 患者和 AD 模型大鼠的视网膜中同样发现了 Aβ 蛋白和 pTau 蛋白的沉积。有研究证实,AD 患者大脑和视网膜中的 Aβ 蛋白与 pTau 蛋白之间存在相似性[31]。Xu 等[32]研究发现,与对照组视网膜相比,AD 患者视网膜出现 Aβ 蛋白沉积。Lee 等[33]发现 AD 患者视网膜细胞内、外 Aβ 蛋白沉积明显多于对照组。Koronyo 等[34]采用基于姜黄素的淀粉样蛋白探针进行标记,并通过改进的激光扫描检眼镜观察视网膜 Aβ 蛋白,结果显示 AD 患者视网膜 Aβ 蛋白含量是健康对照组的 2.1 倍。另一项研究直接采用高光谱成像技术检测 AD 患者视网膜 Aβ 蛋白,研究发现视网膜 Aβ 蛋白含量可以成功预测大脑中 Aβ 蛋白的积累[35]。与临床研究一致,研究者在 3xTg-AD[36]、2xTg-ADp[37]、Tg2576[38]、PSAPP[38]、5xFAD[38]和 TgF9-AD[39]等 AD 模型小鼠中同样检测到视网膜中 Aβ 蛋白的沉积。除发现视网膜 Aβ 蛋白沉积外,AD 患者以及 3xTg-AD、APP/PS231、APP/PS1、Tg2576 等转基因 AD 模型小鼠还发现 Tau 蛋白沉积[40-43]。因此,视网膜中 Aβ 蛋白与 Tau 蛋白异常沉积可作为早期诊断 AD 的指标。

2 脉络膜

脉络膜位于视网膜和巩膜之间,由纤维组织、小血管和毛细血管组成,主要功能是向视网膜外层和玻璃体腔供氧[44]。有研究表明脉络膜直接或间接参与包括 AD 在内的多种视网膜退行性疾病的发生发展[23]。Gharbiya 等[45]将 21 例诊断为轻、中度 AD 患者(平均年龄 73.1±6.9 岁)和 21 名与其年龄匹配的健康受试者(平均年龄 70.3±7.3 岁)纳入研究,通过增强深度成像 OCT(enhanced depth imaging optical coherence tomography,EDI-OCT)分析脉络膜厚度,得出结论:AD 患者的脉络膜厚度低于健康受试者。Bayhan 等[46]、Bulut 等[47]同样做了类似的研究,结果表明,与健康对照组相比,AD 组脉络膜厚度较低。此外,Li 等[23]也指出 AD 患者脉络膜普遍呈变薄的趋势。AD 与脉络膜之间确实存在着密切联系,以上研究均证实 AD 患者的脉络膜厚度低于正常人。未来可以通过 OCT 检测脉络膜厚度变化以早期诊断 AD。

3 角膜

乙酰胆碱(acetylcholine,ACh)在周围和中枢神经系统中起着至关重要的作用。研究证实 AD 的发病过程中存在胆碱能神经元的丧失[48]。Dehghani 等[49]表明角膜上皮不仅存在高浓度的 ACh,角膜神经和上皮改变还可能与 AD 患者胆碱能神经元丧失密切相关。Marquez 等[50]通过角膜激光共聚焦显微镜证实,AD 模型大鼠的角膜神经纤维长度减少。Örnek 等[51]所在试验小组同样利用这一成像技术证实 AD 患者角膜敏感性降低。此外,轻度认知功能障碍(mild cognitive impairment,MCI)是 AD 发展的临床前阶段[52]。Ponirakis 等[53]发现 MCI 患者的角膜神经纤维密度、长度和角膜神经分支密度显著降低。角膜敏感性降低与角膜神经纤维长度、密度异常可用于早期 AD 诊断。

4 晶状体

伴随着人体衰老的过程,人类晶状体透明度逐渐丧失并出现蛋白质错误折叠以及不溶性蛋白质聚集和积累的增加[49]。AD 以大脑中 Aβ 蛋白沉积为主要病理特征,能否通过晶状体中是否存在 Aβ 蛋白协助诊断 AD 目前尚存在争议。Goldstein 等[7]解剖了 9 例已故 AD 患者的眼睛,在晶状体中检测到 Aβ 蛋白的沉积。Kerbage 等[54]使用荧光配体和激光扫描设备检测 5 例 AD 患者以及 5 名健康受试者晶状体中 Aβ 蛋白的含量,结果显示 AD 患者晶状体核上区域的 Aβ 蛋白含量大约是健康受试者的 2 倍,然而,这些研究并未发现晶状体中 Aβ 蛋白与 AD 患者大脑中 Aβ 蛋白的联系。在随后的 1a 时间里,Kerbage 等[55]又调查了 20 例 AD 患者和 20 名与其年龄匹配的健康受试者,通过 PET-CT 及荧光配体眼扫描技术检测大脑及晶状体中的 Aβ 蛋白,结果显示大脑和晶状体中 Aβ 蛋白存在显著相关性。然而,这与其它研究者发现的结果不一致。Michael 等[56]分析了 21 例 AD 患者和 15 名健康志愿者的晶状体,并未发现晶状体中的 Aβ 蛋白沉积和核上区域的 Aβ 蛋白含量增加。此外,在另一项研究中,Michael 等[57]用拉曼共聚焦显微镜未发现 7 例 AD 患者晶状体中存在 Aβ 蛋白。Ho 等[58]在试验过程中同样没有检测到晶状体中有 Aβ 沉积。Aβ 蛋白是否存在于 AD 患者的晶状体中,晶状体异常能否做为检测 AD 患者的敏感指标,尚待确定。

5 瞳孔

AD 的主要发病机制涉及 ACh 的匮乏。瞳孔光反应(pupillary light response,PLR)的收缩阶段由 ACh 驱动,因此对评估胆碱能神经元缺陷具有重要意义[59]。Fotiou 等[60]进一步证实瞳孔最大收缩速度(maximum velocity of constriction, MCV)和最大收缩加速度(maximum constriction acceleration,MCA)可能是胆碱能活性最敏感的测量指标,Fotiou 等[61]开展了为期 2 a 的试验研究,发现与健康受试者相比,MCV 和 MCA 是区分健康受试者与 AD 患者的最佳检测指标,且 AD 患者 MCV、MCA 均呈降低趋势。然而,其它研究尚未发现 AD 患者和健康受试者之间的这种显著差异[62]。MCV 和 MCA 作为反映胆碱能活性的指标,与 AD 发病过程中胆碱能神经元丧失存在相关性,但是,这种相关性目前存在争议。能否将 MCV 和 MCA 作为协助诊断 AD 的指标之一,未来需要进一步试验研究。

6 小结与展望

早期检测 AD 的技术手段在临床上不易普及,而眼科易成像、筛查成本低的检查特点使得其在临床上可广泛使用,对 AD 的早期诊断具有十分重要的临床意义。以上研究证实 AD 患者会出现视网膜内层厚度降低且内层视网膜厚度与大脑存在正相关性、视网膜异常蛋白积聚、视网膜血管密度、血流量降低及静脉狭窄,脉络膜厚度降低,角膜敏感性以及角膜神经纤维密度和长度降低,利用以上异常非侵入性指标为早期诊断 AD 提供理论依据。目前外层视网膜、MCV、MCA 以及晶状体异常作为早期诊断 AD 的敏感性指标存在较大争议,未来需要进一步研究,以评估其对 AD 早期诊断的阳性预测价值。

参考文献

[1] Jia LF, Du YF, Chu L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study. Lancet Public Health, 2020,5(12):e661-e671.

[2] Veitch DP, Weiner MW, Aisen PS, et al. Using the Alzheimer's Disease Neuroimaging Initiative to improve early detection, diagnosis, and treatment of Alzheimer's disease. Alzheimers Dement, 2022,18(4):824-857.

[3] Zhang J, Shi L, Shen Y. The retina: a window in which to view the pathogenesis of Alzheimer's disease. Ageing Res Rev, 2022,77:101590.

[4] Kenny A, Jiménez-Mateos EM, Zea-Sevilla MA, et al. Proteins and microRNAs are differentially expressed in tear fluid from patients with Alzheimer's disease. Sci Rep, 2019,9(1):15437.

[5] 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(1):44-53.

[6] Kesler A, Vakhapova V, Korczyn AD, et al. Retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Clin Neurol Neurosurg, 2011,113(7):523-526.

[7] Goldstein LE, Muffat JA, Cherny RA, et al. Cytosolic beta-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease. Lancet, 2003,361(9365):1258-1265.

[8] Lu Y, Li Z, Zhang XQ, et al. Retinal nerve fiber layer structure abnormalities in early Alzheimer's disease: evidence in optical coherence tomography. Neurosci Lett, 2010,480(1):69-72.

[9] Cunha JP, Proença R, Dias-Santos A, et al. OCT in Alzheimer's disease: thinning of the RNFL and superior hemiretina. Graefes Arch Clin Exp Ophthalmol, 2017,255(9):1827-1835.

[10] Gao LY, Liu Y, Li XH, et al. Abnormal retinal nerve fiber layer thickness and macula lutea in patients with mild cognitive impairment and Alzheimer's disease. Arch Gerontol Geriatr, 2015,60(1):162-167.

[11] Mathew S, WuDunn D, MacKay DD, et al. Association of brain volume and retinal thickness in the early stages of Alzheimer's disease. J Alzheimers Dis, 2023,91(2):743-752.

[12] Wang X, Jiao B, Liu H, et al. Machine learning based on Optical Coherence Tomography images as a diagnostic tool for Alzheimer's disease. CNS Neurosci Ther, 2022,28(12):2206-2217.

[13] Casaletto KB, Ward ME, Baker NS, et al. Retinal thinning is uniquely associated with medial temporal lobe atrophy in neurologically normal older adults. Neurobiol Aging, 2017,51:141-147.

[14] Asanad S, Ross-Cisneros FN, Nassisi M, et al. The retina in Alzheimer's disease: histomorphometric analysis of an ophthalmologic

biomarker. Invest Ophthalmol Vis Sci, 2019,60(5):1491-1500.
[15] Ong YT, Hilal S, Cheung CY, et al. Retinal neurodegeneration on optical coherence tomography and cerebral atrophy. Neurosci Lett, 2015, 584:12-16.
[16] Jefferis JM, Mosimann UP, Clarke MP. Cataract and cognitive impairment: a review of the literature. Br J Ophthalmol, 2011,95(1): 17-23.
[17] Kim BJ, Lee V, Lee EB, et al. Retina tissue validation of optical coherence tomography determined outer nuclear layer loss in FTLD-tau. Acta Neuropathol Commun, 2021,9(1):184.
[18] Salobrar-García E, de Hoz R, Ramírez AI, et al. Changes in visual function and retinal structure in the progression of Alzheimer's disease. PLoS One, 2019,14(8):e0220535.
[19] Uchida A, Pillai JA, Bermel R, et al. Outer retinal assessment using spectral-domain optical coherence tomography in patients with Alzheimer's and Parkinson's disease. Invest Ophthalmol Vis Sci, 2018,59 (7):2768-2777.
[20] Cheung CYL, Ong YT, Ikram MK, et al. Microvascular network alterations in the retina of patients with Alzheimer's disease. Alzheimers Dement, 2014,10(2):135-142.
[21] Kaufman PL, Alm A. Adler Fisiología Del Ojo. Spain:Elservier; Madrid, 2004:747-786.
[22] Cunha JP, Proença R, Dias-Santos A, et al. Choroidal thinning: Alzheimer's disease and aging. Alzheimers Dement (Amst), 2017, 8: 11-17.
[23] Li M, Li RN, Lyu JH, et al. Relationship between Alzheimer's disease and retinal choroidal thickness: a cross-sectional study. J Alzheimers Dis, 2021,80(1):407-419
[24] Robbins CB, Grewal DS, Stinnett SS, et al. Assessing the retinal microvasculature in individuals with early and late-onset Alzheimer's disease. Ophthalmic Surg Lasers Imag Retina, 2021,52(6):336-344.
[25] Frost S, Kanagasingam Y, Sohrabi H, et al. Retinal vascular biomarkers for early detection and monitoring of Alzheimer's disease. Transl Psychiatry, 2013,3(2):e233.
[26] Xie JY, Yi QY, Wu YF, et al. Deep segmentation of OCTA for evaluation and association of changes of retinal microvasculature with Alzheimer's disease and mild cognitive impairment. Br J Ophthalmol, 2023 [Epub ahead of print].
[27] Gaber HA, Aly EM, Mohamed ES, et al. Prognosis of biomarker of Alzheimer's disease in the function of the retina and secondary molecular structure variation of the retina and brain. Int J Alzheimers Dis, 2023,2023:9775921.
[28] Ngoo QZ, Wan Hitam WH, Razak AA. Evaluation of retinal nerve fiber layer thickness, electroretinogram and visual evoked potential in patients with Alzheimer's disease. J Ophthalmol, 2019,2019:6248185.
[29] Wyatt-McElvain KE, Arruda JE, Rainey VR. Reliability of the flash visual evoked potential P2: double-stimulation study. Appl Psychophysiol Biofeedback, 2018,43(2):153-159.
[30] Strigaro G, Gori B, Zoccola C, et al. Impaired visual inhibition in amnestic mild cognitive impairment. Clin EEG Neurosci, 2022 [Epub ahead of print].
[31] Alber J, Goldfarb D, Thompson LI, et al. Developing retinal biomarkers for the earliest stages of Alzheimer's disease: what we know, what we don't, and how to move forward. Alzheimers Dement, 2020,16 (1):229-243.
[32] Xu QA, Boerkoel P, Hirsch-Reinshagen V, et al. Müller cell degeneration and microglial dysfunction in the Alzheimer's retina. Acta Neuropathol Commun, 2022,10(1):145.
[33] Lee S, Jiang KL, McIlmoyle B, et al. Amyloid beta immunoreactivity in the retinal ganglion cell layer of the Alzheimer's eye. Front Neurosci, 2020,14:758.
[34] Koronyo Y, Biggs D, Barron E, et al. Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer's disease. JCI Insight, 2017,2(16):e93621.
[35] Hadoux X, Hui F, Lim JKH, et al. Non-invasive *in vivo* hyperspectral imaging of the retina for potential biomarker use in Alzheimer's disease. Nat Commun, 2019,10:4227.
[36] Grimaldi A, Brighi C, Peruzzi G, et al. Inflammation, neurodegeneration and protein aggregation in the retina as ocular biomarkers for Alzheimer's disease in the 3xTg-AD mouse model. Cell Death Dis, 2018,9(6):685.
[37] Shi HS, Koronyo Y, Rentsendorj A, et al. Identification of early pericyte loss and vascular amyloidosis in Alzheimer's disease retina. Acta Neuropathol, 2020,139(5):813-836.
[38] Alexandrov PN, Pogue A, Bhattacharjee S, et al. Retinal amyloid peptides and complement factor H in transgenic models of Alzheimer's disease. Neuro Report, 2011,22(12):623-627.
[39] Tsai Y, Lu B, Ljubimov AV, et al. Ocular changes in TgF344-AD rat model of Alzheimer's disease. Invest Ophthalmol Vis Sci, 2014,55 (1):523.
[40] Gupta VB, Chitranshi N, den Haan J, et al. Retinal changes in Alzheimer's disease-integrated prospects of imaging, functional and molecular advances. Prog Retin Eye Res, 2021,82:100899.
[41] Chiasseu M, Alarcon-Martinez L, Belforte N, et al. Tau accumulation in the retina promotes early neuronal dysfunction and precedes brain pathology in a mouse model of Alzheimer's disease. Mol Neurodegener, 2017,12(1):58.
[42] Zhao HK, Chang R, Che HJ, et al. Hyperphosphorylation of tau protein by calpain regulation in retina of Alzheimer's disease transgenic mouse. Neurosci Lett, 2013,551:12-16.
[43] Latina V, Giacovazzo G, Cordella F, et al. Systemic delivery of a specific antibody targeting the pathological N-terminal truncated tau peptide reduces retinal degeneration in a mouse model of Alzheimer's Disease. Acta Neuropathol Commun, 2021,9(1):38.
[44] Laviers H, Zambarakji H. Enhanced depth imaging-OCT of the choroid: a review of the current literature. Graefes Arch Clin Exp Ophthalmol, 2014,252(12):1871-1883.
[45] Gharbiya M, Trebbastoni A, Parisi F, et al. Choroidal thinning as a new finding in Alzheimer's disease: evidence from enhanced depth imaging spectral domain optical coherence tomography. J Alzheimers Dis, 2014,40(4):907-917.
[46] Bayhan HA, Aslan BS, Celikbilek A, et al. Evaluation of the chorioretinal thickness changes in Alzheimer's disease using spectral-domain optical coherence tomography. Clin Exp Ophthalmol 2015, 43 (2): 145-151.
[47] Bulut M, Yaman A, Erol MK, et al. Choroidal thickness in patients with mild cognitive impairment and Alzheimer's type dementia. J Ophthalmol, 2016,2016:7291257.
[48] Ferreira-Vieira TH, Guimaraes IM, Silva FR, et al. Alzheimer's disease: targeting the cholinergic system. Curr Neuropharmacol, 2016,14 (1):101-115.
[49] Dehghani C, Frost S, Jayasena R, et al. Ocular biomarkers of Alzheimer's disease: the role of anterior eye and potential future directions. Invest Ophthalmol Vis Sci, 2018,59(8):3554.
[50] Marquez A, Guernsey LS, Frizzi KE, et al. Tau associated

peripheral and central neurodegeneration: identification of an early imaging marker for tauopathy. Neurobiol Dis, 2021,151:105273.
[51] Örnek N, Dağ E, Örnek K. Corneal sensitivity and tear function in neurodegenerative diseases. Curr Eye Res, 2015,40(4):423-428.
[52] Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol, 1999, 56(3):303-308.
[53] Ponirakis G, Al Hamad H, Sankaranarayanan A, et al. Association of corneal nerve fiber measures with cognitive function in dementia. Ann Clin Transl Neurol, 2019,6(4):689-697.
[54] Kerbage C, Sadowsky CH, Jennings D, et al. Alzheimer's disease diagnosis by detecting exogenous fluorescent signal of ligand bound to Beta amyloid in the lens of human eye: an exploratory study. Front Neurol, 2013,4:62.
[55] Kerbage C, Sadowsky CH, Tariot PN, et al. Detection of amyloid β signature in the lens and its correlation in the brain to aid in the diagnosis of Alzheimer's disease. Am J Alzheimers Dis Other Demen, 2015,30(8):738-745.
[56] Michael R, Rosandić J, Montenegro GA, et al. Absence of beta-amyloid in cortical cataracts of donors with and without Alzheimer's disease. Exp Eye Res, 2013,106:5-13.
[57] Michael R, Otto C, Lenferink A, et al. Absence of amyloid-beta in lenses of Alzheimer patients: a confocal Raman microspectroscopic study. Exp Eye Res, 2014,119:44-53.
[58] Ho CY, Troncoso JC, Knox D, et al. Beta-amyloid, phospho-tau and alpha-synuclein deposits similar to those in the brain are not identified in the eyes of Alzheimer's and Parkinson's disease patients. Brain Pathol, 2014,24(1):25-32.
[59] El Haj M, Chapelet G, Moustafa AA, et al. Pupil size as an indicator of cognitive activity in mild Alzheimer's disease. EXCLI J, 2022,21:307-316.
[60] Fotiou DF, Stergiou V, Tsiptsios D, et al. Cholinergic deficiency in Alzheimer's and Parkinson's disease: evaluation with pupillometry. Int J Psychophysiol, 2009,73(2):143-149.
[61] Fotiou DF, Brozou CG, Haidich AB, et al. Pupil reaction to light in Alzheimer's disease: evaluation of pupil size changes and mobility. Aging Clin Exp Res, 2007,19(5):364-371.
[62] Van Stavern GP, Bei L, Shui YB, et al. Pupillary light reaction in preclinical Alzheimer's disease subjects compared with normal ageing controls. Br J Ophthalmol, 2019,103(7):971-975.

2023《中国科技期刊引证报告》核心版眼科期刊主要指标及排名

(以综合评价总分为序)

期刊名称	核心总被引频次		核心影响因子		综合评价总分	
	数值	排名	数值	排名	数值	排名
中华眼科杂志	2068	2	1.881	1	76.2	1
眼科新进展	1189	3	0.766	2	56.9	2
国际眼科杂志	**2095**	**1**	**0.728**	**4**	**55.2**	**3**
中华实验眼科杂志	1114	4	0.760	3	37.6	4
中华眼科医学杂志电子版	167	10	0.458	8	37.4	5
中华眼底病杂志	719	6	0.564	6	34.6	6
临床眼科杂志	341	8	0.302	9	32.3	7
眼科	355	7	0.302	9	21.7	8
中华眼视光学与视觉科学杂志	753	5	0.591	5	19.4	9
中国斜视与小儿眼科杂志	239	9	0.500	7	15.7	10

摘编自 2023 版《中国科技期刊引证报告》核心版