Review

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Ocular Biomarkers in Alzheimer's Disease: Insights into Early Detection Through Eye-Based Diagnostics – A Literature Review

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Abstract

Alzheimer's Disease (AD) is a significant challenge in neurodegenerative disorders, characterized by a gradual decline in cognitive functions. Diagnosis typically occurs at advanced stages when therapeutic options are less effective, underscoring the importance of early detection. Traditional diagnostic methods are often invasive and costly, spurring interest in more accessible and economical alternatives.

The eye, as a direct link to the brain through the optic nerve, suggests that ocular changes could serve as early indicators of AD. This has led to the exploration of non-invasive ocular diagnostic tools. Technologies such as Optical Coherence Tomography (OCT), OCT Angiography (OCT-A), pupillometry, and eye-tracking, along with electrophysiological methods like Electroretinography (ERG) and Pattern Electroretinography (PEV), are being utilized to investigate potential ocular biomarkers. Further, tear fluid analysis has suggested that presence of amyloid-beta (Aβ) protein might reflect neurogenerative processes, providing a non-invasive window into disease progression.

Exploring ocular changes as potential early indicators of Alzheimer's Disease (AD), we aimed to provide an overview of promising biomarkers for earlier diagnosis and intervention. Our review further investigates the connections between AD and other ocular degenerative diseases such as age-related macular degeneration (AMD) and glaucoma, uncovering shared pathogenic pathways that could offer new therapeutic targets. To establish the sensitivity and specificity of these ocular biomarkers, comprehensive studies are required. Moreover, larger, longitudinal studies are essential to confirm the effectiveness of ocular assessments in the preemptive diagnosis of Alzheimer's Disease.
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Introduction

Alzheimer's disease (AD), the primary cause of dementia, stands as the most prevalent neurodegenerative disorder precipitating cognitive decline among the elderly (1,2) Individuals afflicted with AD exhibit a broad spectrum of cognitive impairments that manifest early on with significant episodic memory loss, alongside a progressive decline in semantic c memory, language capabilities, inhibitory control, attention, visuospatial functions, and executive abilities (3). Beyond these well-documented symptoms, AD patients also experience less recognized visual disturbances, such as impairments in stereopsis, color vision, contrast sensitivity, and motion detection (4).

The neuropathological signature of AD includes the accumulation of extracellular beta-amyloid (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, which collectively contribute to neuronal cell death (5,6) Notably, these pathological changes can commence decades prior to the clinical manifestation of symptoms and the formal diagnosis of the disease (7–9). Although therapeutic interventions in the later stages of AD are often ineffectual due to the irreversible nature of neuronal damage, there is consensus that early intervention might decelerate the disease's progression (2,10).

Definitive diagnosis of AD traditionally relies on post-mortem brain analyses. However, existing diagnostic methods such as cerebrospinal fluid (CSF) biomarkers and positron emission tomography (PET) imaging allow for the early detection of neuropathological alterations. Despite their utility, these methods are invasive, expensive, and not universally accessible, thus limiting their use for widespread early screening (2,11,12).

Intriguingly, the retina—developmentally an extension of the central nervous system (CNS)—comprising retinal ganglion cells (RGCs) whose axons form the optic nerve, presents a promising frontier for research (13). A burgeoning corpus of research suggests that AD shares pathogenetic mechanisms with ocular degenerative diseases such as

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age-related macular degeneration (AMD) and glaucoma, hinting at the potential of ocular structures to mirror cerebral pathology (10,14,15). As a result, ocular imaging tools are emerging as non-invasive, cost-effective, and widely accessible modalities that could play a crucial role in the early identification of Alzheimer's disease, akin to their established utility in other conditions such as diabetic retinopathy (10,16,17).

This review aims to delve into the shared pathogenetic factors between AD and certain ocular diseases and to explore specific ocular changes that could serve as sensitive biomarkers for AD. Through this examination, we aspire to uncover new insights into the disease and propose potential non-invasive diagnostic strategies for its early detection.

General characteristics

Patients with AD often exhibit a range of ocular alterations that parallel central nervous system degeneration. Notably, structural changes in the eye, such as thinning of the retinal nerve fiber layer (RNFL) and the ganglion cell layer (GCL), are well-documented. These changes affect multiple retinal components including melanopsin-containing retinal ganglion cells (mRGCs) and overall macular volume, suggesting a widespread retinal involvement (18–20).

Functional impairments are also evident, with alterations observed in several electrophysiological measures. These include varied electroretinogram (ERG) responses, diminished amplitudes in pattern ERG (pERG), and disruptions in visual evoked potentials (VEP) and multifocal ERG (mfERG), which collectively indicate compromised retinal and optic pathway functionality(18,21) Furthermore, the retinal microvasculature exhibits significant changes such as hypoperfusion in both superficial and deep capillary plexuses, which may mirror cerebral microvascular damage in AD (22–24).

AD patients also experience a spectrum of visual sensory deficits. These include reductions in color vision, contrast sensitivity—particularly at lower spatial frequencies—and visual acuity. Such sensory impairments are often accompanied by physical changes like reduced choroidal thickness and alterations in the optic nerve, including changes in the cup-disk ratio and axonal density (20,25).

Interestingly, visual field defects, particularly in the inferior hemifield, and deficits in visual spatial attention and motion perception are prominent, affecting patients' abilities to navigate their environments effectively (20). Cognitive impairments manifest in difficulties with reading, object recognition, and eye movement coordination, further complicating the visual challenges faced by these patients (26–28).

The timing and specificity of these visual impairments in the context of AD progression are subjects of ongoing debate. While some researchers argue that visual functions deteriorate in the later stages of the disease, others suggest these impairments manifest earlier and correlate with cognitive decline (29–32). However, not all scholars agree on the specificity of these visual symptoms to AD, with some contesting the direct correlation between cognitive performance and visual manifestations such as color vision, visual field, and acuity (29,33).

Contrast sensitivity, in particular, might be preferentially affected in the right visual field and is considered by some to be an early indicator of the disease, potentially offering a window into the neurodegenerative processes of AD before other symptoms become apparent (32,34).

Beta-amyloid deposits in ocular structures

Amyloid-beta (Aβ) deposits, a key pathological feature of AD, manifest not only in the brain but also extensively in ocular structures. As has been detected in the RGC layer, retinal nerve fiber layer RNFL, inner plexiform layer (IPL), and inner nuclear layers (INL) (35–37). These deposits are also evident in the aqueous humor and the lens, significantly contributing to the increased incidence of supranuclear cataracts (33,38,39).

Further, Aβ has been found in the walls of blood and choroidal vessels, Bruch's membrane, the outer plexiform layer (OPL), the outer segments of photoreceptors, within the retinal pigment epithelium (RPE), as well as in the optic disc and drusen (40–42). Notably, Aβ is present in the cornea (43).

In the retina, the beta-amyloid precursor protein (APP)—a precursor to Aβ—is extensively expressed, indicating its potential as a marker for diffuse axonal injury, which reflects broader neurodegenerative processes affecting ocular tissues (41,43).

Hyperphosphorylated tau, another neuropathological marker of AD, has been identified within the retina specifically in the RGC, RNFL, INL, IPL, and OPL. These findings highlight a widespread cellular disruption caused by tau pathology, mirroring cerebral manifestations of AD (29,44–46).

Interestingly, differences in Aβ and tau levels have been observed in the vitreous humor of patients with glaucoma and AD, with reduced Aβ and increased tau levels suggesting potential diagnostic markers for ocular manifestations of neurodegenerative diseases (35,42,47).

Aβ predominantly accumulates in the melanopsin-containing RGCs and the Edinger-Westphal nucleus (EWN), contributing to pupillary alterations. Additionally, Aβ and neuritic plaques aggregating in the pulvinar nucleus of the thalamus and the superior colliculus have been linked to abnormalities in eye movements, illustrating a profound connection between ocular motor control and AD neuropathology (48).

The concentration of Aβ plaques is primarily found in the peripheral regions of the superior quadrant of the retina, though some evidence also points to potential inferior localization. This concentration correlates with a reduction in RNFL thickness, underlining the impact of these plaques on retinal health (21,49).

Despite significant evidence supporting the presence of Aβ in ocular tissues, some studies report no detectable Aβ deposits within the retina and lens, challenging their role as universal biomarkers for AD (22,50,51). This variability underscores the necessity for more research to elucidate the reasons behind the inconsistent presence of Aβ and to assess its potential for diagnosing and monitoring Alzheimer's disease through ocular examinations.

Tear Biomarkers

The presence of amyloid-beta (Aβ) in tears, as reported in various studies, offers an intriguing perspective on its potential as a biomarker for Alzheimer's Disease (AD) (52–54) This raises fundamental questions about the origin and mechanism of Aβ production and release in tears, which, while not fully understood, invites several hypotheses based on our current understanding of AD pathology and lacrimal gland biology.

Amyloid-beta is primarily produced in the brain, but its detection in peripheral systems like tears suggests that it could be either circulated systemically or produced locally. One theory is that the lacrimal glands, which are responsible for tear production, might undergo similar amyloidogenic processes observed in the brain. These glands could possess the enzymatic machinery necessary to process amyloid precursor protein (APP) into Aβ, akin to what occurs in neurodegenerative changes in the brain (16). This is supported by the knowledge that other peripheral tissues, such as skin and mucosal glands, also express APP and might process it into Aβ under certain conditions.

Another possibility is that Aβ in tears reflects systemic changes associated with AD, including inflammation and neurodegeneration that might influence various body systems, including the lacrimal apparatus. Changes in the permeability of blood-retinal and blood-lacrimal barriers, which are a characteristic of systemic diseases, might facilitate the transport of Aβ from blood to tears.

This concept is underscored by research, such as the studies by Gijs et al. and Gharbiya et al., which not only detected higher levels of Aβ in tears of AD patients compared to controls but also suggested a potential diagnostic role for these findings (16,55). The detection of elevated Aβ levels in tear fluid reflects a systemic manifestation of AD, suggesting that the pathological processes in the brain could be mirrored in the lacrimal glands.

Understanding how Aβ is produced and released into tears could significantly enhance its utility as a biomarker (56). If further research confirms that Aβ levels in tears accurately reflect central nervous system changes, this could pave the way for developing non-invasive diagnostic tools that leverage tear samples for early detection and monitoring of AD progression. This approach offers a promising avenue for research, potentially leading to a simple and accessible method for diagnosing and monitoring Alzheimer's Disease.

Ocular movements

AD patients often experience various visual dysfunctions, with many reporting difficulties in reading, which can be attributed to abnormal eye movements and diminished visual attention (43,57,58).

One of the most well-documented signs in AD patients is dysfunction in saccadic eye movement (59). Numerous studies have reported increased latency in initiating prosaccades, reduced prosaccade velocity, increased latency in executing antisaccades, and a higher error rate in antisaccades among AD patients (3,60,61). However, other authors have noted no significant impairment in prosaccades among AD patients (61). Antisaccade paradigms, such as the rate of antisaccade errors, have been suggested to be more specific and thus useful in distinguishing AD patients from controls (3,62,63).

Additionally, fixation and smooth pursuit movements are also compromised in AD. Patients have displayed less accuracy and longer response times in visual search tasks, with prolonged fixation durations while searching for a target and difficulty maintaining fixation on both still and moving targets (57,64). Fixation instability in AD patients has been linked to their inability to suppress reflexive or intrusive saccades and may also reflect difficulties in acquiring and processing visual inputs (57,58,65). Evidence suggests that fusional vergence is impaired in AD patients, potentially due to damage in premotor cells located in the midbrain near the oculomotor nucleus, resulting in smaller and irregular convergence angles compared to controls and patients with other forms of dementia (57,65). A progressive slowing of vertical saccades has consistently been observed in AD patients, correlating with autopsic findings of neurofibrillary pathology in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) (66).

Research also indicates reduced depth perception and stereopsis, loss of contrast sensitivity, and diminished color perception in AD (18,42,64). Moreover, AD patients show impairments in head-eye coordination and exhibit different facial and ocular movements compared to controls (67,68).

There is growing evidence of a distinct subgroup of AD patients affected by the visual variant of Alzheimer's disease (VVAD), who predominantly exhibit visual dysfunctions, especially in reading or writing activities (19,69).

Anomalies in ocular movement observed in AD patients can be detected using eye-tracker devices, and some have been proposed as potential markers for disease or progression (58,70,71). However, the specificity of these documented visual defects in AD needs to be established, as similar anomalies have been observed in healthy older individuals and in other neurological conditions such as Parkinson's Disease (PD), Vascular Dementia, Fronto-Temporal Dementia, and Lewy Body Dementia (42,57,72).

Pupillary features

AD patients have frequently been reported to exhibit anomalies in pupillary size and responses to light and dark conditions. Pupillometry, as a result, has been proposed as a potential diagnostic marker for early disease detection.

Research indicates that AD patients generally present with a smaller resting pupil diameter, slower dilation velocity, shorter latency, and lower amplitude response to pupillary light reactions, along with diminished darkness reflex responses compared to controls (23,50,65). Conversely, an increase in pupillary size in AD patients has also been observed (2). Some studies have documented a hypersensitive pupil response to a dilute (0.01%) solution of the cholinergic antagonist tropicamide in AD patients compared to healthy controls (73–75), while others have reported a decrease in amplitude and latency of the light reflex response following

tropicamide drop instillation (57,75,76). Yet, other researchers did not find significant anomalies in pupil response to dilute tropicamide in AD patients relative to controls (77).

Furthermore, it is reported that instillation of the cholinergic agonist pilocarpine results in greater pupil constriction in AD patients than in non-clinical controls (38,50,76). Several pupillary anomalies observed in AD patients, such as variations in pupil size and a weaker light reflex, have been found to correlate with the severity of dementia (35,57).

Attempts to explain these abnormal pupil responses in AD patients point to neurodegenerative changes leading to neuronal loss not only in the basal forebrain but also in the Edinger-Westphal nucleus (EWN) and the locus coeruleus (LC), which are responsible for parasympathetic and sympathetic supply to the iris, respectively (48,57,78). The variability in the involvement of the LC and EWN in the neurodegenerative process might account for the differences observed in the pupillary responses of individual AD patients (75).

Finally, it is noted that the anomalies in pupil responses are not specific to AD, as similar abnormalities can also be observed in Parkinson's Disease (PD), vascular dementia, and Down's syndrome (23,50)

Retinal findings

Studies have found that the RGC layer is significantly thinned across all quadrants in Alzheimer's patients (35,78–81). This thinning has been particularly noted in the superior (2,82,83) and inferior quadrants (48,82), as well as in the temporal foveal region (21,84) and parafoveal area (35,80,85). Additionally, authors have reported damage to the axons of the optic disc (41,57,86,87), with a tendency for more pronounced thinning toward the macula, supero-temporally to the optic nerve (87).

Similarly, the RNFL has been found to be thinned across all four retinal quadrants (24,37,88), with pronounced alterations in the superior quadrant most frequently reported (89). Some researchers argue that the RNFL is thinnest nasally, while others highlight the temporal area as more affected (90,91), and yet others suggest a greater thinning supero-nasally compared to supero-temporally (92).

A reduction in peripapillary RNFL (pRNFL) thickness has also been noted across all quadrants (31), especially in the superior (80) and, according to some findings, also in the inferior quadrant (93). The reduction in pRNFL thickness might be more significant in the superior quadrant during the early stages of dementia, with potential expansion to the inferior quadrant as the condition progresses (41,94).

Reports also indicate that changes in the macular RNFL may occur earlier than those concerning pRNFL (41). It has been suggested that thinning in the superior quadrant during early stages correlates with inferior visual field loss (49). However, contrasting findings propose that alterations in the lower quadrant may manifest at the onset of dementia (95), with predominant changes in the inferior quadrant in later stages affecting cognitive functions (49). Despite these varied findings, the late course involvement of RNFL contrasts with other studies proposing it as a potential early biomarker for the disease (80,94).

A study suggests that in AD, the macula is the first retinal region to be affected, covering all internal quadrants and one outer temporal quadrant (19,80). A reduction in macular thickness and volume has been described (19). Notably, macular thinning is mostly observed in the RNFL and the superior quadrant, but not in the fovea (96). Other studies indicate that foveal thickness and macular volume are primarily reduced in all internal quadrants and only in the outer temporal quadrants(48,93). One study highlights that macular thickness is diminished in all segments except the inferior outer one (96).

Reports detail a thinning of the RNFL, RGC, IPL, ONL, and OPL in the macula (25,97). It is suggested that RGC and IPL thinning may precede RNFL thinning (31). Another study claims that retinal thickness is decreased across all layers except the ONL (98). Yet another acknowledges that total retinal thickness and macular thickness are reduced in all sectors (99).

One study has noted that macular thinning is particularly pronounced in the inferior, temporal, and nasal quadrants, more so in the inner segments around the fovea (57). However, some research indicates that the thinning of RNFL, GCL, and IPL does not occur in the inferior outer quadrant (85).

Thinning of other retinal layers such as the INL, IPL, and ONL in the macula is reported to be less severe compared to the RNFL or RGC, possibly due to lower localization of AB deposits in these layers (94). Thinning of INL and ONL is more severe toward the optic nerve, especially supero-nasally, and in the inferior sectors (11). Further, the inner retina is more involved than the outer retina (100).

Another study acknowledges a thinner superior-nasal retina compared to the superior-temporal one (87). Interestingly, a thickening of the IPL, especially at the onset of the disease, has been reported by another study, although without statistical significance (101). Further studies claim that RGC, IPL, INL, and ONL are thinner mostly superior-temporally toward the macula (87).

A correlation between cognitive impairment as Mini-Mental State Examination (MMSE scores), the severity of the disease, ERG alterations, and the localization of AB deposits has been widely described (34,88,94). However, not all studies confirm a link with cognitive performance (81). Subjects with lower MMSE scores seem to have reduced levels of AB and tau deposits (47), and macular parameters and those of inner retinal layers are more frequently correlated with the MMSE scores, rather than the pRNFL(96). Nonetheless, a strong correlation between pRNFL and MMSE was noted in one study (50). A link between RNFL loss and venous retinal alterations has also been found (100), as well as a correlation between vascular retinal alterations and cognitive characteristics (23). A recent study has considered a higher risk for the development of these alterations in those with clinically unimpaired ApoE ε4 gene carriers (102).

Loss of mRGC, especially in the inferior periphery as well as in the foveal and parafoveal areas, has been described and might occur in the early stages (103). The mRGC that have not been lost are damaged and have abnormal morphology (104). Alterations of mRGC are involved in the impairment of contrast sensitivity, pupillary light response, and circadian disturbances (36).

Vascular Alterations and Optical Coherence Tomography Angiography Findings

Patients with Alzheimer's disease (AD) commonly exhibit distinct vascular abnormalities in the retina, including diminished retinal blood flow and increased vessel tortuosity (65,97,105) Additionally, there's a notable reduction in vascular complexity and fractal dimension, alongside elevated blood oxygen saturation levels (18,21,106). Notably, decreased perfusion is particularly pronounced in the radial peripapillary capillaries of the optic nerve head, as well as the parafoveal and macular regions, with some studies noting an increase in venous diameter alongside a decrease in arterial calibers (18,79).

The correlation between reduced retinal blood flow and the thinning of the ganglion cell layer (GCL) highlights the potential link between ocular and cerebral vascular pathology(107). Such retinal vascular changes are significant as they may mirror cerebral hypoperfusion, a common feature in AD and may even precede the clinical onset of dementia symptoms (34,95,97). Patients with a higher density of Aβ plaques in the retina tend to show increased retinal vein tortuosity compared to those with fewer plaques (18).

However, the observed alterations in vessel caliber and venular fractal dimensions, such as reduced retinal vessel density and increased venular tortuosity, are not universally confirmed across all studies focused on retinal changes in AD (21,36,97). Indeed, some research indicates a reduction in retinal vessel tortuosity, and one study reported an increase in retinal vessel density, particularly in the macular region and peripapillary retinal nerve fiber layer (RNFL) (11,20,45). Additionally, while some studies have noted a narrowing of retinal venules, others have found that a widening of retinal venules correlates with an increased risk of dementia (43,97).

Optical coherence tomography angiography (OCTA) is a recently introduced technique employed by ophthalmologists to examine the characteristics of retinal vessels at high resolution. This imaging method has revealed a reduction in retinal capillary density in both the superficial capillary plexus (SCP) and the deep capillary plexus (DCP), as well as in the radial peripapillary capillaries layer (24,97,108). A lower flow density has been observed in the SCP, but not in the DCP, according to some findings, while other studies report this reduced flow density also in the DCP, but not in the SCP (105,109). Contrarily, a few researchers have found that patients with amyloid-beta (Aβ) plaques exhibited higher vessel density compared to those without these deposits (18,82). Meanwhile, other studies have identified no significant differences in vessel density between healthy controls and patients with Alzheimer's disease (AD) (14,110).

However, a few authors argue that there is no statistical significance in the findings related to the DCP, and other researchers have stated that microvasculature alterations are not observed in the SCP. The foveal avascular zone (FAZ) area is reported to be larger in patients with AD, accompanied by a dropout of vasculature within the fovea (111,112). However, there is no consensus on this finding as several studies report no differences in FAZ area between patients with AD and healthy controls, and some even report no reduction in FAZ (113).

Another study has established a positive correlation between retinal vascular density and the reduction of RNFL thickness in patients with AD (114). This correlation extends to include vascular density, choroidal thickness, FAZ enlargement, and MMSE scores (115).

Choroidal thickness

Numerous studies have reported a reduction in choroidal thickness (CT) in AD, particularly within a 1 mm radius around the fovea (25,113,116). Specifically, one study notes a more pronounced decrease in CT across all sectors, including the subfoveal area and extending 500 micrometers from the fovea (84,117). The macular and superior-nasal choroidal regions are frequently observed to be thinner in patients with AD, whereas the superior-temporal choroidal region tends to be thicker (118,119). However, there are conflicting reports, and this could also be attributed to the method of choroidal measurement by CT (120).

These variations in choroidal thickness may be associated with the retinal distribution of Aβ deposits, which are also found in choroidal vessels (121). One study highlights that choroidal thinning is evident only in the early stages of the disease and may relate to the cognitive performance of patients(80). In contrast, other findings suggest that a thinner choroid correlates with lower MMSE scores, indicating more advanced disease (107). Moreover, some authors have observed a thicker choroid in later stages of AD, while others report no correlation between CT and cognitive status (48). A possible link has been proposed between superior-temporal CT and increased vascularization in severe Alzheimer cases (119).

Despite these findings, the statistical significance of choroidal alterations as reported by many studies is contested by several authors who find no discernible difference in CT between patients with AD and healthy subjects (122).

Association with other ocular diseases

Age-Related Macular Degeneration

Several studies have identified a possible association between AD and AMD, noting that patients with AMD are at a greater risk of developing cognitive impairment, as evidenced by their poorer performance in neuropsychological tests compared to controls (33). Conversely, a higher incidence of AMD has been reported in patients with AD (123). Both diseases are age-related and share common risk factors including smoking, atherosclerosis, hypertension, obesity, and high cholesterol (124).

Pathogenically, AD and AMD are linked through mechanisms that lead to extracellular deposits of amyloid-beta (AB) and cell death in both the retina and brain. These mechanisms include increased oxidative stress, complement activation, mitochondrial damage, failure of the glymphatic system, and dysfunction of proteasomal and lysosomal systems (125). Both diseases are characterized by the presence of extracellular deposits—amyloid plaques in AD and drusen in AMD—which share common components such

as AB, clusterin, vitronectin, apolipoprotein E, complement components, and inflammatory mediators (126).

Interestingly, some studies have noted the deposition of drusen and pigment color changes in the temporal and peripheral retina of AD patients in the absence of maculopathy (23). This contrasts with AMD, where drusen primarily occurs in the macula, suggesting different processes in AB deposition (49).

Genetic similarities between AMD and AD have also been explored, with findings pointing to shared genetic polymorphisms such as complement factors, and ApoE gene variants (48). Pathway analysis has further indicated that clathrin-mediated endocytosis (CME) signaling, LXR/RXR activation, and the atherosclerosis signaling pathway are common to both AMD and AD (127).

However, it is important to note that a few studies have not been able to confirm any association between AD and AMD or evidence of a common genetic background, highlighting the variability and complexity in the relationship between these two conditions (128).

Glaucoma

AD and glaucoma are both neurodegenerative and chronic conditions with a strong age-related incidence, progressively leading to irreversible neuronal cell death (46,129). Several studies have reported an increased rate of primary open-angle glaucoma (POAG) occurrence in AD patients and an increased risk of AD in POAG patients, suggesting an association between these two pathologies (50,130,131). It has also been observed that almost all AD patients with POAG exhibit normal tension, and more severe progression of glaucoma symptoms and glaucomatous optic neuropathy has been found in AD (38,132).

Despite this evidence, other authors have not supported the association between POAG and AD, or have even found a decreased rate of AD in POAG patients compared to control subjects (130,133). The relationship between glaucoma and AD has been supported by biological and mechanistic features they share. Altered cerebrospinal fluid (CSF) circulatory dynamics have been suggested as a common pathogenetic factor in both AD and glaucoma. Specifically, CSF circulatory failure can induce a lowering of intracranial pressure (ICP), potentially creating an abnormally high trans-lamina cribrosa pressure difference leading to glaucomatous damage. Additionally, it has been reported that a substantial proportion of AD patients have very low ICP, explaining their higher risk of developing glaucoma (134,135).

A role for Aβ in the pathogenesis of glaucoma has been proposed. Evidence indicates that caspase activation and abnormal processing of amyloid precursor protein (APP), events leading to Aβ production in AD, may also contribute to glaucoma pathogenesis (46,132). Lastly, a higher frequency of pseudoexfoliation syndrome (PEX) in AD patients and a higher frequency of AD in PEX patients have been reported. Both pathologies are considered conformational diseases as they share amyloid-like material deposition in different sites (136,137).

Conclusions

This review investigated ocular alterations as potential biomarkers for AD, highlighting the potential of non-invasive and cost-effective diagnostic tools such as Optical Coherence Tomography (OCT), OCT Angiography (OCT-A), pupillometry, tears collection, eye-trackers, and electrophysiological examinations. These tools offer promising avenues for early detection of AD, potentially allowing for interventions before significant neuronal loss occurs.

Additionally, the review explored connections between AD and ocular degenerative diseases like Age-related Macular Degeneration (AMD) and glaucoma, identifying shared pathogenic mechanisms and risk factors. Such similarities could help elucidate the underlying pathways of these diseases, opening possibilities for new therapeutic targets.

However, the presence of similar ocular changes in other types of dementia and studies involving limited participant numbers calls for further research. There is a need for longitudinal studies with larger sample sizes to establish the sensitivity and specificity of these ocular biomarkers for AD. Understanding these relationships and enhancing diagnostic accuracy are crucial for advancing treatment strategies and improving outcomes for patients with AD and related disorders.

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