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REVIEW

Ocular amyloid imaging at the crossroad of Alzheimer's disease and age-related macular degeneration: implications for diagnosis and therapy

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Abstract

Alzheimer's disease (AD) and age-related macular degeneration (AMD) are important disorders of aging, but significant challenges remain in diagnosis and therapy. Amyloid-beta (Aβ), found in the brain and a defining feature of AD, has also been observed in the retina in both AD and AMD. While current diagnostic modalities for detecting Aβ in the brain are costly or invasive, Aβ in the retina can be noninvasively and conveniently imaged using modern photonic imaging systems such as optical coherence tomography (OCT). Moreover, since many of these retinal changes occur before degenerative changes can be detected in the brain, ocular amyloid biomarkers could be utilized to detect AD as well as AMD in their earliest stages when therapy may be most effective in halting disease progression. Novel technologies to quantify retinal biomarkers have the potential to facilitate early diagnosis and noninvasive monitoring of disease progression with important therapeutic implications.

Keywords Alzheimer's disease · Amyloid beta · Optical coherence tomography · Retinal imaging

Abbreviations

Aβ	Amyloid-beta
AD	Alzheimer's disease
AMD	Age-related macular degeneration
aMCI	Amnestic mild cognitive impairment
APP	Amyloid precursor protein
ARIA-E	Amyloid-related imaging abnormalities-edema
BEAM	Brain–eye amyloid memory study
CSF	Cerebrospinal fluid
ERG	Electroretinogram
FAF	Fundus autofluorescence
GC-IPL	Ganglion cell-inner plexiform layer
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tau
OCT	Optical coherence tomography
PET	Positron emission tomography
RNFL	Retinal nerve fiber layer
RPE	Retinal pigment epithelium
VEP	Visual evoked potential

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Introduction

Alzheimer's disease (AD) and age-related macular degeneration (AMD) are common and devastating disorders of aging. More than 43 million people worldwide are living with dementia, most often secondary to AD [1], whereas an estimated 170 million people globally are affected by AMD [2], an important retinal degenerative disease. Unfortunately, there is currently no curative therapy for AD. Treatments are available to relieve symptoms but these are moderately beneficial at best. Similarly, while the introduction of anti-angiogenesis therapy has helped prevent blindness and restore vision in exudative or wet AMD [2], there remains

no effective treatment for the majority of patients with non-exudative or dry AMD. Recent research has pointed to potential shared links between AD and AMD that may offer new insights into the development of novel biomarkers for both diseases.

The hallmark pathology of AD involves the progressive accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFT) comprised of hyperphosphorylated tau protein in the brain. In AD, Aβ has also been found in the retina, which is part of the central nervous system [3]. Interestingly, retinal pathology in AD mirrors Aβ deposition in AMD. With the advent of advanced imaging technology such as optical coherence tomography (OCT), it is now possible to identify the effects of Aβ accumulation through non-invasive imaging of ocular structures in live patients. Fully elucidating the role of amyloid in the eye and brain in these two disorders could potentially lead to the development of amyloid-based ocular disease biomarkers as well as more effective therapies for both diseases.

This review article will detail the recent findings of Aβ-related ocular biomarkers in human subjects and animal models of AD and AMD, and the prospects of novel ocular imaging technologies as biomarkers for these important aging diseases. Searches on PubMed between 1980 and May 2018 using a combination of terms "Alzheimer's disease", "macular degeneration", "amyloid beta", "Aβ" and "ocular imaging" were completed to identify references for this review. There were no language restrictions. The final references were selected based on relevance to the topics covered in this review.

Amyloid-β peptide and the retina

Presence of amyloid-β peptide in the retina of animal and human models of AD

Aβ plaques have been observed in the retinas and retinal microvasculature of AD transgenic mouse models [3–8] and the *Octodon degus*, a wild-type rodent native to Chile and a natural model of sporadic AD [9]. Importantly, Aβ plaques were seen in the retina of one of the murine models at 2.5 months of age, 2–3 months before the same deposits were observed in the brain [3]. These animal models also demonstrated a significant reduction in visual function and visuospatial recognition as compared to normal controls [8, 10, 11], supporting a role for Aβ toxicity in the retina. Aβ was shown to exert its effect in the retina by upregulating the expression of an inflammatory cytokine (MCP-1), a microglia marker (F4/80) and apoptotic profiles in the ganglion cell layer [4] consequently inducing microglia infiltration and astrogliosis in the retina [5, 7]. Consequently, retinal ganglion cell dendritic atrophy preceding cell loss [6], inner retinal thinning, reduction of axonal density in the optic nerve and reduced scotopic threshold response amplitudes representing deficient inner retinal function [12] have been observed in transgenic mouse models when compared to wild-type controls.

In humans without AD, the presence of tau proteins and amyloid precursor protein (APP) was demonstrated in the inner layers of the normal young and aged retina. Aβ, in contrast, was not found in normal young retinas but was scantily deposited within drusen-like subretinal pigment epithelium (RPE) deposits in normal old retinas [13]. The presence of Aβ plaques in post-mortem retinas in humans with AD has also been investigated by several groups. Even though multiple animal models of AD have reported the presence of Aβ plaques, it is important to note that results from human studies using post-mortem retinas from AD patients have been heterogenous, with some studies showing the lack of retinal Aβ plaques in AD.

Among the studies that have found Aβ plaques in post-mortem retinas of AD patients, most have originated from one research group. Koronyo–Hamaoui and collaborators detected Aβ plaques by curcumin staining in the post-mortem retinas of eight AD human patients and five suspected early stage AD patients, but not in five age-matched controls [3]. Additionally, Aβ plaques were found earlier in the retina than in the brain and accumulated with disease progression [3]. In a subsequent study, the same group found substantial Aβ deposition in five AD retinas while no or minimal Aβ immunoreactivity was detected in five control retinas [14]. More recently, Koronyo and colleagues used whole mount techniques to demonstrate increased Aβ immunoreactivity and deposits in the retinas of AD patients when compared to age- and sex-matched controls [15]. Of note, they showed that Aβ plaques were more frequently found in the periphery of the superior quadrant and were uncommon in the macula. Cross-sectionally, diverse Aβ deposits, often associated with blood vessels, were found most commonly in the ganglion cell layer [15].

In contrast, other groups have failed to consistently detect retinal Aβ deposition in AD patients. Tsai et al. demonstrated Aβ plaque-like structures in only two of six AD human whole mount retinas and none in the six age-matched control eyes [16]. Schon and collaborators did not find fibrillary accumulations of Aβ in six post-mortem AD retinas. Similarly, Ho et al. examined eyes from 11 AD cases and six age-matched controls and did not observe amyloid deposits in the lens, retina or other ocular structures in AD eyes [18]. Hinton and colleagues also failed to find amyloid in the retinas of four AD patients [20] and Leger et al. did not find intraretinal amyloid in eyes of older patients including two AD patients [21]. Lastly, Jiang et al. completed a meta-analysis of five of the aforementioned studies and found significant statistical heterogeneity between their

results, which was thought to be due to the fact that the first study by Koronyo-Hamaoui and coworkers used five antibody clones, in contrast to the other four studies which used only one clone [19]. The authors concluded that this meta-analysis did not provide sufficient evidence to suggest whether pathological accumulation of retinal Aβ could be used as a diagnostic tool for AD.

The heterogeneity of results from these human studies may reflect a lack of consistency in retinal whole mount techniques and immunohistochemical methods [22]. Given the limitations in pathological assessment of Aβ deposition and the limited availability of autopsy retinas for larger studies, in vivo detection of retinal Aβ through optical imaging may be the next logical area of inquiry.

Association of AD with changes in the retina

Despite the controversy surrounding Aβ deposition in postmortem human retinas, many studies have demonstrated other structural retinal changes in AD patients [22]. There have been multiple histopathological reports of retinal ganglion cell loss and optic nerve degeneration in AD patients [20, 23, 24]. However, a few studies have contradicted these results and shown that retinal ganglion cell density and axon number in optic nerve are unaffected in AD [25, 26].

Nevertheless, there is a large body of evidence demonstrating that the retina is affected in AD. Retinal nerve fiber layer (RNFL) abnormalities were previously demonstrated on red-free photographs [27] and since OCT became commercially available in the mid 1990s, there have been many clinical studies that have confirmed this finding using OCT. OCT provides an in vivo cross-sectional view, direct microstructural analysis and live imaging of the neural retina, which is central nervous system tissue (Fig. 1).

Some studies have found thinning of the RNFL (Fig. 2), axons of the ganglion cells, in the superior quadrant with corresponding inferior visual field deficits in patients with mild cognitive impairment (MCI) or prodromal AD, and AD [28, 29]. Liu and colleagues noted that RNFL thickness was decreased in the superior quadrant in MCI and then appeared to progress to the inferior quadrant in severe AD [30]. Using histopathological methods, Koronyo and collaborators showed that Aβ accumulation occurred most commonly in the innermost retinal layers in the periphery of the superior quadrant and this coincided with atrophy of the ganglion cell layer, inner nuclear layer and outer nuclear layer in AD patients [15]. Anatomically, cell ganglion axons from the superior retina project through parietal lobe of optic radiation to the cuneal gyrus area of the primary visual cortex, while axons from the inferior retina project to the lingual gyrus area. Armstrong and collaborators had found a higher density of senile plaques and neurofibrillary tangles in the cuneal gyrus than the lingual gyrus, which would explain the inferior visual field defect and superior RNFL thinning in some AD patients [31].

Meanwhile, Lu and colleagues found that the RNFL is thinner in both the superior and inferior retina even in patients with early AD [32]. However, most other studies showed RNFL thinning in all quadrants in patients with MCI and AD [33–36]. Two meta-analyses of seven and six studies, respectively, further demonstrated that RNFL thickness was reduced in all quadrants in patients with MCI and AD compared to controls [37, 38]. Of note, Knoll and coauthors documented RNFL thickening in early cognitive impairment [38] while our group used multivariate regression analysis

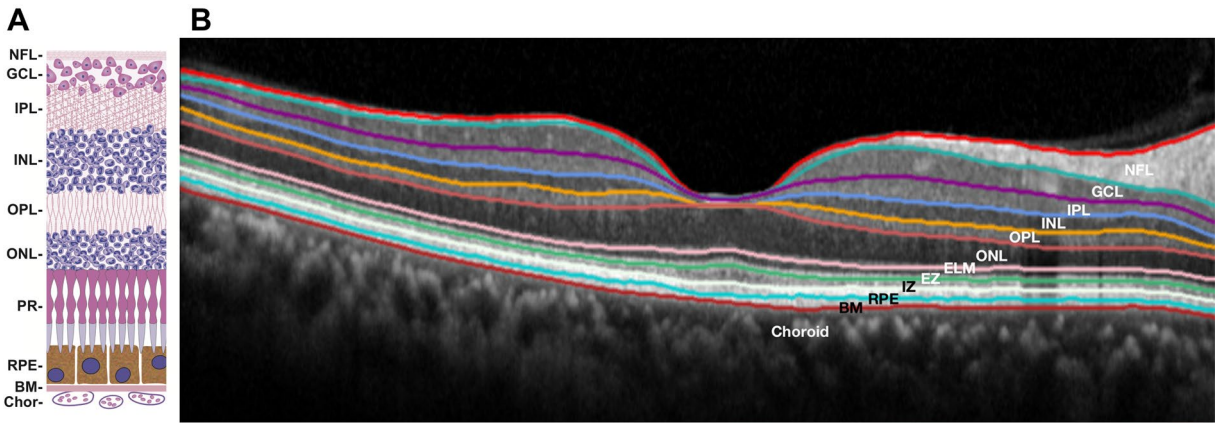

Fig. 1 Structure of human retina: schematic diagram (**a**) and retinal optical coherence tomography image with segmented layers (**b**). The nerve fiber layer (NFL) and ganglion cell layer (GCL) are of most interest to AD investigators. Other labeled structures include inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), external limiting membrane (ELM), photoreceptors (PR), ellipsoid zone (EZ), interdigitation zone (IZ), retinal pigment epithelium (RPE), Bruch's membrane (BM) and choroid (chor). 1A reproduced with permission from Malek G et al. *Cell Mol Life Sci*. 2014;71(23):4617–4636 [108]

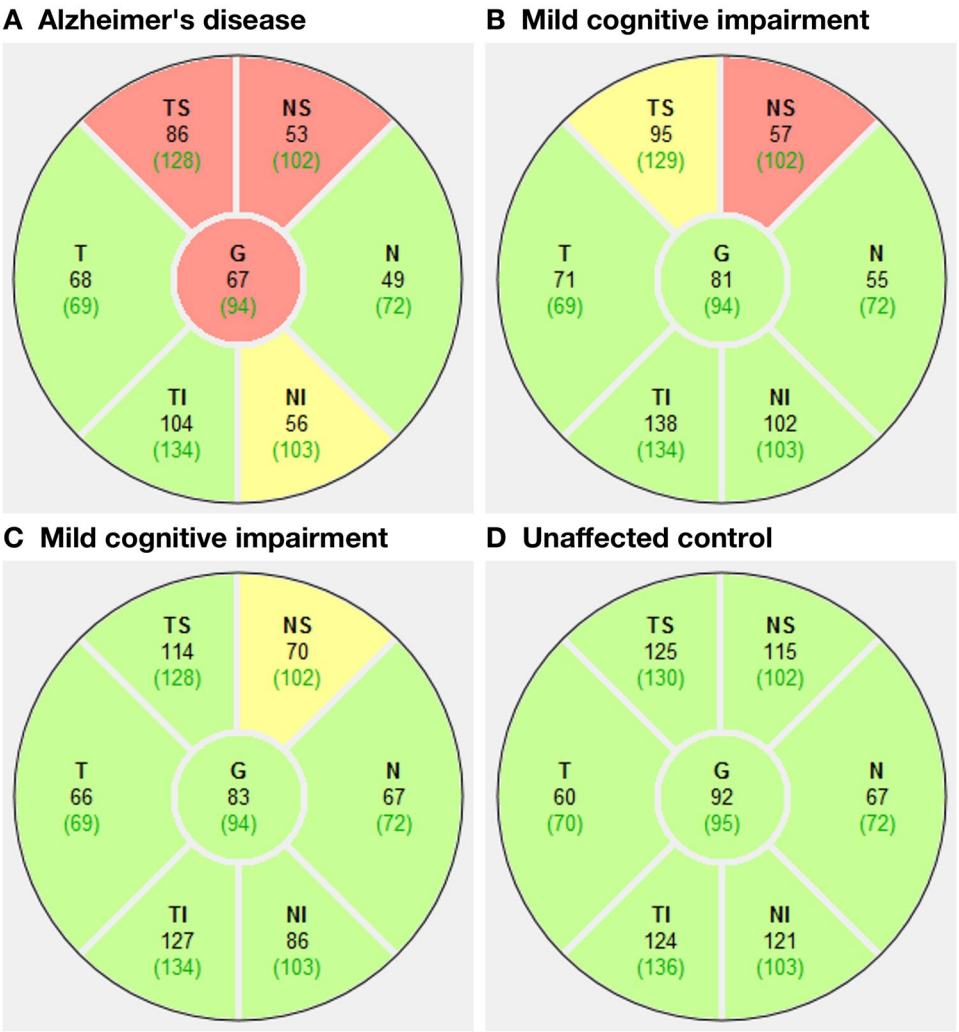

Fig. 2 Examples of quadrant-specific retinal nerve fiber layer (RNFL) abnormalities surrounding the optic nerve in patients with AD (**a**), mild cognitive impairment (**b, c**), and control subjects (**d**). Spectral domain optical coherence tomography (Spectralis; Heidelberg Engineering, Germany) measures RNFL in the peripapillary region with circular scans centered around the optic nerve head. The RNFL is then automatically segmented and analysis printouts classify global (G) and regional [temporal (T), superotemporal (TS), superonasal (NS), nasal (N), inferonasal (NI) and inferotemporal (TI) sectors] RNFL measurements into green, yellow or red categories. Green denotes within normal limits (5th–95th percentile), yellow denotes borderline (1st–5th percentile) and red denotes outside normal limits (below 1st percentile) RNFL thickness compared to an age-matched normative database

to show that specific areas of thickening were adjacent to areas of thinning in the macula of AD and MCI patients [39]. These results suggest that dynamic changes occur in the inner retina during AD progression, specifically a phase of inflammation and gliotic reactive changes of neural tissue is followed by thickening of the RNFL prior to degeneration and thinning [38, 40]. These dynamic changes may be responsible for some of the variability in RNFL thinning reported by different studies. The use of different OCT models has also been postulated to account for some of the variability in results [41].

Even though multiple studies have shown evidence of ganglion cell loss and RNFL thinning in AD, it remains challenging to translate these findings into clinical practice. These biomarkers cannot yet be used for the early detection of AD because glaucoma, another common ocular disorder affecting approximately 66 million patients worldwide [42], also presents with ganglion cell loss and RNFL thinning. To date, clinicians are limited by a lack of evidence-based guidelines on how to best differentiate RNFL loss due to glaucoma versus AD. In fact, the two conditions may be linked: some studies have reported that OAG patients were more likely to develop dementia [42, 43]. The pathobiology for open angle glaucoma and that for AD have been thought to be connected by retinal neurodegeneration as a final common pathway. A systematic review of ten studies that investigated the association between AD and OAG concluded that the results were highly heterogeneous and most studies were limited by small sample size and inadequate design [44]. Larger and higher quality association studies, preferably with longer follow-up are, therefore, needed to elucidate the presence and type of relationship between AD and OAG.

A recent study also found that ganglion cell-inner plexiform layer (GC-IPL) thinning on OCT correlated with atrophy in the temporal and occipital regions of the brain on magnetic resonance imaging [47]. Since the retina is a developmental outgrowth of the diencephalon, and considered by some authors to be a part of the central nervous system, one possibility is that the retina is vulnerable to the same

neuroinflammatory injury that causes neurodegenerative disease in the brain [48]. A second hypothesis is that neuronal dysfunction in the brain of a person with AD may lead to nerve loss in the retina via Wallerian-like degeneration [49].

Amyloid-β peptide is also identified in the retina of age-related macular degeneration

Aβ is also implicated in the pathogenesis and progression of another common and devastating degenerative disease, AMD. Studies have shown that retinal ganglion cells, the inner nuclear layer of the retina and RPE (Fig. 1) express APP and have the capability to produce Aβ even under normal/healthy conditions [50, 51]. However, Aβ deposits do not usually accumulate in the subretinal drusen, hallmarks of AMD, until old age. This suggests a disruption of the balance between the synthesis and clearance of Aβ aggregates that occurs with age [52]. In fact, Aβ accumulations have been observed in different reservoirs surrounding the aging retina. These include the immediate environment around the RPE, the vitreous humor, the coating of the outer segments of photoreceptors and in subretinal drusen [52].

Furthermore, studies with human post-mortem eyes have shown that Aβ in the retina correlated with increasing age and higher subretinal drusen loads, suggesting that Aβ may be associated with more advanced stages of AMD [53, 54]. Specifically, confocal immunofluorescence and ultrastructural analysis of these eyes showed that Aβ was found in vesicular components within drusen known as 'amyloid vesicles', in both macular and peripheral retina [51, 53, 54]. In-depth analysis of amyloid vesicles revealed that they consisted of a highly organized interior with concentric ring like layers bound by a dense outer shell [51, 53]. Immunostaining also revealed that toxic oligomeric Aβ forms were localized centrally within drusen in close proximity to the inner collagenous layer of Bruch's membrane while Aβ protofibrils and mature fibrils were more likely to accumulate towards the outer periphery and shell of amyloid structures within drusen [51–54].

Aβ may induce AMD-related changes in the retina through a combination of mechanisms. In human RPE cultures, Aβ promotes a pro-inflammatory milieu through upregulation of pro-inflammatory cytokines including IL-1β, IL-8 and IL-33 [55, 56]. In drusen, Aβ peptide also co-localizes with activated complement components involved in inflammatory responses [51, 53, 57, 58]. In addition, Aβ may target the barrier property of RPE by inducing damage by reactive oxygen species, triggering cellular senescence and impairing mitochondrial activity [52, 59]. Moreover, exposure of RPE cultures to Aβ caused an increase of pro-angiogenic vascular endothelial growth factor (VEGF) and concomitant decrease in anti-angiogenic pigment epithelium derived factor (PEDF) [60]. VEGF plays a crucial role in the pathogenesis of choroidal neovascularization and anti-VEGF treatments now form the mainstay of therapy for exudative AMD.

Despite findings of increased Aβ deposition in the retina in both AMD and AD, the recent publication by Koronyo and colleagues pointed out that Aβ deposition in both diseases may be secondary to distinct processes [15]. In their work, curcumin–amyloid deposits in AD patients were found in the periphery in the absence of maculopathy and in one patient in the outer retina above intact RPE and Bruch's membrane. This finding differs from AMD, in which drusen occurs in the macula and are sub-RPE deposits that are accompanied by RPE disruption and Bruch's membrane thickening [15]. The study was, however, limited by its inability to exclude the existence of subretinal pseudodrusen structures in AD patients. Another important caveat to consider is that peripheral changes can also occur in AMD. AMD patients with intermediate to advanced maculopathy were demonstrated to have a two-fold increased risk of peripheral drusen and pigment changes [61].

Since elevated levels of Aβ are found in the retinas in both AD and AMD, there have been multiple large population-based studies that have investigated the comorbidity between the two diseases, and the results have been contradictory. Some studies have found an association between AMD and AD, senile dementia or cognitive impairment [57, 62–64] while others have not [65, 66]. Some authors have suggested that the association more specifically applies to dry or non-exudative AMD [63, 64, 67]. In a manuscript which showed no relationship between AMD and AD, the authors studied only exudative AMD patients since all the AMD patients in their cohort had received anti-VEGF therapy [66].

Amyloid-β peptide in other ocular structures in AD

Although the lens and the brain have different embryonic tissue origins, the lens being derived from the surface ectoderm and the brain from the neuroectoderm, it is interesting to note that Goldstein et al. identified Aβ peptide in the lenses of AD patients in similar concentration levels as found in the brain [68]. To date, the mechanism by which Aβ accumulates in the lens remains unclear. AD patients were also found to have a specific supranuclear equatorial cataract not found in controls, with increased Aβ deposition in the lens fibers [68]. A follow-up study found similar cataracts in Down syndrome patients, who have a third copy of chromosome 21 causing a triplication of the APP gene and increased Aβ levels [69]. Transgenic mice studies supported the association between AD pathology in the brain and lens [70]. However, other human histopathological studies have failed to demonstrate the presence of Aβ in the lens of AD

subjects [18, 71]. In addition, Bei et al. failed to detect any significant difference in cataract type and opacities in the lens in the earliest pre-clinical stages of AD, at a time that would be most useful for diagnosis [72].

It remains unclear why some studies have found Aβ in specific areas of the cataractous lens of AD subjects, while other studies have failed to show this association. Nevertheless, spurred by promising results from some of these studies, Kerbage and colleagues completed a clinical trial to test the utility of a Fluorescent Ligand Eye Scanning (FLES) system designed to detect amyloid levels in the lens of patients with cognitive impairment [73, 74]. This multicenter phase II trial enrolled 20 AD subjects and 20 age-matched controls [73, 74]. All subjects received a topical aftobetin-hydrochloride ointment, an amyloid binding ligand. The Sapphire II laser device was then used to measure fluorescence emissions of aftobetin-hydrochloride bound to Aβ aggregates from the lens. All patients also received Amyvid PET to measure brain plaque density. The trial showed that clinical diagnosis by FLES had a higher sensitivity (85%) and specificity (95%) for differentiating AD from normal controls than the Amyvid PET (both sensitivity and specificity of 80%) [74].

Retinal imaging as a potential biomarker for AD

Drug development for the prevention of AD has been impeded by lack of fully validated biomarkers of early pathological changes. Current diagnostic modalities for detecting pathological changes in pre-clinical or prodromal AD are limited by cost and exposure to radiation (amyloid PET), invasiveness (CSF biomarkers), as well as suboptimal specificity and sensitivity (serum amyloid) [75]. MRI volumetry and fMRI can detect hippocampal atrophy and functional brain network changes, respectively, but neither is fully validated as a prognostic biomarker. Thus, there remains considerable interest in the development of peripheral biomarkers for pre-clinical and prodromal AD.

Imaging of the retina has become possible with the advent of sophisticated, high-resolution, inexpensive, fast, and non-invasive optical imaging. Because optical imaging of the retina achieves greater than 100 times the resolution of MRI, retinal imaging biomarkers may be as sensitive and specific as serum/CSF amyloid or genetic tests, and may be more sensitive, more specific, and less costly than MRI or PET imaging. The higher resolution photography achievable with retinal imaging could greatly facilitate early dementia detection [76].

Another benefit of using ocular biomarkers in the diagnosis of AD is the reported early manifestation of visual function defects and retinal changes in AD. Patients with early AD experience abnormalities in visual acuity [77], contrast sensitivity [78], color perception [79], visual field due to RNFL loss [80], and motion perception [81]. Many of the retinal findings associated with AD have been detected early in disease course and may even occur before degenerative changes are seen in the brain [3], which would be an asset to the early diagnosis of AD. Specifically, patients with MCI or prodromal AD were found to already have thinning of the RNFL [28–30, 32–36] and retinal amyloid plaques [82]. Furthermore, RNFL thinning in AD has been correlated with electroretinogram (ERG) findings, suggesting visual dysfunction in the disease [34]. In fact, pattern ERG and pattern visual evoked potentials (VEP) were noted to be abnormal in early stages in AD when the ophthalmologic exam findings are unimpressive [83]. This highlights that the dysfunction of the retinal ganglion cells and optic nerve in early AD may not be apparent on routine eye exams [83].

Other potential ocular biomarkers for AD

In addition to quadrant-specific RNFL loss previously discussed [9, 24–29], clinical studies have demonstrated ganglion cell layer loss [23, 76], reduced macular volume [35, 40], and decreased macular pigment [45] and choroidal thickness [46] in patients with MCI and AD. In addition, AD may share several clinical and pathological features with AMD, including peripheral retinal abnormalities such as drusen and pigment changes seen on color fundus photographs of AD patients [84]. Recent clinical studies have shown a significant difference in presence of hard drusen in the peripheral retina of AD patients (Fig. 3) [85, 86]. However, as discussed earlier in this review, not all authors agree that the pathophysiology and morphology of retinal Aβ and 'drusen' deposition in AD are similar to that in AMD [15]. As noted by Koronyo et al., peripheral deposition in the absence of maculopathy is not found in AMD, but may occur as a distinct process in AD. Furthermore, while the deposits in AD were found within the retina with an intact RPE and Bruch's membrane [15], deposits in AMD are typically found under the RPE with disruption of the RPE and Bruch's membrane.

Regardless of the controversy surrounding the similarities between AD and AMD, it is important to note that several studies have demonstrated the presence of increased peripheral retinal Aβ deposits/drusen in AD [15, 85, 86] and wide-field photography has been employed to identify peripheral drusen that may suggest a high risk of developing AD [85, 86]. Most recently, the design of a wide-field OCT with wavefront sensorless adaptive optics for enhanced imaging made identification and three-dimensional localization of the peripheral retinal drusen possible with great precision in subjects with MCI [87] (Fig. 4). An extension of this system,

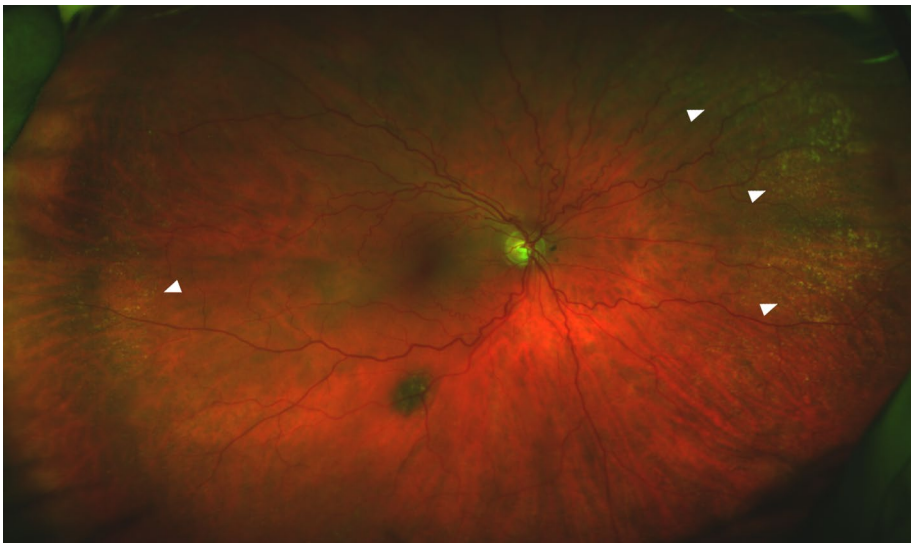

Fig. 3 Wide-field (200°) retinal image taken using Optos 200Tx (Optos Inc., Dumfermline, UK) depicts peripheral drusen or amyloid plaques (arrowheads) in an AD patient

wavefront sensorless adaptive optics wide-field OCT angiography [88] can potentially be used to quantify vascular biomarkers in AD. Another promising related technology is based on the polarization properties of Aβ plaques in the retina using polarization sensitive OCT [89] and other optical imaging modalities [90]. Further, combination of OCT and angle-resolved low coherence interferometry technologies can be potentially used to directly quantify the pathological changes in the structural characteristics of retinal cells [91].

Another promising new technology that employs optical imaging following administration of curcumin has shown the ability to noninvasively detect individual retinal Aβ plaques in live mice [3]. Retinal Aβ inclusions were identified before plaques were detectable in the brain, and increased retinal plaque formation was seen with disease progression [3]. Preliminary data from a pilot study of 40 patients conducted in Australia using retinal imaging with curcumin as a fluorochrome showed 100% sensitivity and 80.6% specificity for AD diagnosis [92]. Recently, Koronyo and coauthors tested several commercially available curcumin brands and determined that a solid-lipid formulation had the best tissue bioavailability and maximum signal to noise ratio [15]. This curcumin formulation was then given orally to patients. Imaging with a scanning laser ophthalmoscope illustrated increased curcumin fluorescent spots in the retinas of live AD patients when compared to matched controls [15]. A representative OCT examination of the retina of an AD patient revealed that the curcumin fluorescent spot (thought to be indicative of Aβ deposits) was found at the outer retinal layers [15]. Since the histological examination of postmortem retinas in the same report had demonstrated that Aβ accumulation occurred most frequently in the innermost retinal layers [15], further studies are needed to determine the range of location and morphology of curcumin–amyloid deposits on OCT examination in live AD patients.

Potential role of ocular biomarkers in anti-amyloid therapeutics

Since Aβ has been thought to play a central role in AD pathogenesis, recent clinical drug development has focused on the amyloid cascade by targeting Aβ clearance and Aβ production. Unfortunately, many of these anti-amyloid therapies have been limited by low drug efficacy and significant side effects.

Immunotherapy that targets Aβ clearance includes active and passive immunization. After animal studies by Schenk et al. showed successful amelioration of Aβ loads after active immunization [93], the first human trial of an Aβ vaccine, AN-1792 was initiated. Unfortunately, phase II clinical trials of the vaccine were halted after 6% of patients developed autoimmune meningoencephalitis [94]. Moreover, the phase II data did not show a positive effect on preventing cognitive decline even though the vaccine appeared to decrease Aβ deposition [95]. Thus, it was hypothesized that successful Aβ plaques and NFT removal may not stop progression of disease after the pathological cascade of neuronal toxicities begin [96].

Although animal studies of passive anti-Aβ immunization demonstrated acute memory improvement [97], human studies of bapineuzumab and solanezumab failed to demonstrate improvement in clinical outcomes in patients with mild-to-moderate AD [98, 99]. Multiple potential explanations exist for this. In both trials, up to 25% of patients classified as having mild AD did not have amyloid findings on PET, suggesting that they did not have AD [100]. While bapineuzumab decreased the rate of Aβ deposition seen on PET, solanezumab increased serum Aβ concentrations, suggesting migration of Aβ from the brain to the periphery [98, 99]. Epitope specificity might explain the lack of clearance for solanezumab [100]. The

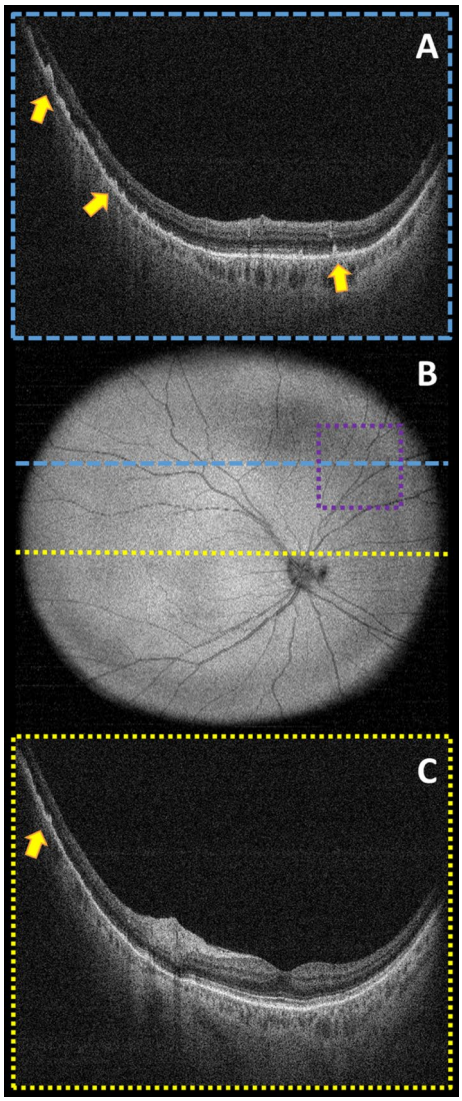

Fig. 4 Wide-field (65° or ~20.5 mm × 20.5 mm) OCT images taken from a subject with MCI. The colored lines in the wide-field image (**b**) correspond to the peripheral (**a**) and central (**c**) B-scan locations. The peripheral drusen deposits are marked with yellow arrows. Reproduced with permission from Polans J et al. *Biomedical Optics Express*. 2017;8(1):16–37 [87]

N terminal region of Aβ is exposed on the surface of Aβ fibrils, therefore, N terminal antibodies like bapineuzumab can recognize both soluble and insoluble Aβ. Meanwhile, middle and C terminal regions are masked in fibrils so C terminal antibodies like solanezumab can only target soluble Aβ and are less effective in plaque clearance. Regardless, neither bapineuzumab nor solanezumab resulted in robust overall Aβ clearance [98, 99]. Moreover, dosing of the antibodies was decreased due to concerns about amyloid-related imaging abnormalities related to vasogenic edema (ARIA-E) and the doses used were thought to be inadequate to achieve therapeutic effect [98, 99].

Since Aβ peptides are generated by endoproteolytic cleavage of neuronal amyloid protein precursor (APP) by β-site APP-cleaving enzyme 1 (BACE1) and γ-secretase, therapies have been developed to target these enzymes with the goal to inhibit Aβ production [96]. The phase III study for verubecestat, a BACE1 inhibitor was terminated 5 months ahead of the scheduled completion date due to futility and an increased incidence of treatment-related adverse events (rash, falls and injuries, sleep disturbance, suicide ideation, weight loss and hair color change) [101]. Meanwhile, phase III trials for semagacestat, a γ-secretase inhibitor, were halted because treated patients demonstrated worsening cognitive assessment and increased risk of skin cancer compared to the placebo group [102]. The lack of clinical efficacy was thought to be due to the dosing regimen which achieved short pulses of full inhibition alternating with periods of normal activity instead of a more moderate continuous inhibition of enzymatic activity [103]. Moreover, treatment was started late relative to onset of disease. It has been shown that efficacy of BACE1 or γ-secretase decreased with aging and disease progression in murine models [96].

Although a large number of anti-amyloid drugs have failed in phase III clinical trials for AD dementia, the amyloid hypothesis continues to be a focus of treatment development and data from failed trials are being used to refine our model of AD pathogenesis [104]. Two of the main limitations in these trials have been attributed to inadequate dosing and late start of treatment relative to onset of disease. Part of the reason for failure of bapineuzumab and gantenerumab, also an anti Aβ antibody, in phase III trials was thought to be decreased antibody dosing to prevent ARIA-E. Since these trials, physicians and scientists have become more comfortable managing this side effect.. Recently, the phase 1B study showed that the humanized antibody aducanumab, at the highest dosing level, reduced brain amyloid fibrillary plaque levels (by PET scan) and slowed cognitive decline in patients with prodromal or early AD [105]. This agent is being tested in phase III trials and the results of this study will largely determine the field's enthusiasm for the amyloid hypothesis. Another antibody entering phase III trials, crenezumab, was built on an immunoglobin G4 (IgG4) backbone instead of an IgG1 backbone to reduce the overactivation of microglial cells in the brain, allowing high dosing without signs of ARIA-E [106].

In addition, since many of these failed trials tested anti-Aβ drugs in patients with moderate AD (bapineuzumab, semagacestat, solanezumab), many experts believe that new clinical trials may benefit from targeting patients with earlier stages of disease. Alzheimer's Prevention Initiative (API), Dominantly Inherited Alzheimer Network (DIAN) and Anti-amyloid treatment in asymptomatic AD (A4) are three trials that were designed to initiate treatment in asymptomatic patients based on familial genetic risk or

PET amyloid positivity [106]. With further validation, the ocular biomarkers discussed in this review have the potential to detect AD-related changes in its earliest stages and may be useful to identify enrollees in future clinical trials when used alone or in combination with other CNS biomarkers.

A phase III trial of ocular amyloid imaging in AD, the Brain–Eye Amyloid Memory Study (BEAM, NCT02524405), is currently ongoing and will provide evidence as to the utility and accuracy of ocular biomarkers. This study aims to recruit 320 subjects with normal cognition, AD, MCI, subcortical vascular cognitive impairment, Parkinson's disease—MCI, Parkinson's disease—dementia and dementia with Lewy Bodies. All subjects will undergo SD-OCT to measure RNFL thickness, FLES using the Sapphire II system (device/ointment combination) to detect amyloid in the ocular lens, brain MRI and brain amyloid PET. A subset will also undergo speckle variance (SV)-OCT. Primary outcome measures include comparing RNFL thickness and ocular lens amyloid amongst the different subject groups and validating these results against brain MRI and brain amyloid PET. Secondary outcome measures include correlating retinal artery narrowing with covert lacunar infarcts on MRI and retinal venular widening with periventricular white matter hyperintensities on MRI. Data collection is expected to be completed in August 2018.

Analogous to AD, anti-Aβ immunotherapy has shown promising results in animal models of AMD [107]. Aβ peptide was identified in pathologic lesions in a murine model of AMD; APOE4-targeted replacement mice were fed a high fat, cholesterol (HFC)-enriched diet [107]. Ding et al. demonstrated that systemic administration of an anti-Aβ 40/42 bispecific antibody decreased Aβ load in sub-RPE deposits in this animal model, which correlated with preserved RPE morphology and retinal function [107]. Anti-Aβ immunotherapy is currently being studied as a therapeutic strategy in clinical trials of dry AMD. A Phase II trial with RN6G (NCT01577381) was terminated due to insufficient subject recruitment while a phase I trial with GSK933776 (NCT01424436) is ongoing. Noninvasive imaging of retinal amyloid burden, if validated in the future, may serve as a structural and biochemical measure of drug efficacy in these trials as well.

Conclusions

Observation of amyloid-related retinal biomarkers in AD and AMD subjects justifies additional research into the shared role of abnormal protein aggregates and associated inflammation in the brain and retina. The existence of Aβ in different reservoirs in the eye may explain why Aβ is associated with RNFL thinning, ganglion cell loss, and peripheral retinal deposits in patients with AD and macular subretinal and sub-RPE drusen and RPE abnormalities in patients with AMD. Regardless, novel imaging technologies and software to quantify retinal Aβ biomarkers will facilitate early diagnosis and noninvasive monitoring of both diseases. This is especially important in the era of amyloid hypothesis for Alzheimer's disease. Despite the failure of previous phase III anti-Aβ clinical trials, researchers remain enthusiastic about the potential of the amyloid hypothesis since the failures were thought to be due to inadequate drug dosing and late start of treatment [106]. The next cohort of clinical studies will, therefore, focus on testing an Aβ plaque clearing antibody or a potent BACE1 inhibitor (or a combination of both) in a pre-clinical AD population. Since Aβ has been shown to accumulate in the retina before it accumulates in the brain, the quantification of Aβ ocular biomarkers could revolutionize the field of anti-amyloid therapeutics by reliably identifying patients many years before the anticipated onset of AD. The results from the BEAM clinical trial examining RNFL thickness and lens amyloid deposition in AD will, therefore, be important. There is also a need for additional clinical trials investigating other potential ocular biomarkers such as wide-field photography and wide-field OCT imaging of peripheral Aβ deposits and drusen, optical imaging after curcumin administration and technology based on alternation of polarization properties. Meanwhile, in the field of AMD therapeutics, lessons from AD clinical trials could be applied to discover anti-Aβ drugs that could prevent blindness and restore sight.

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Compliance with ethical standards

Conflicts of interest SSO receives research funding from the International Retinal Research Foundation. EML has received research grants from Alzheimer's Association, Duke Institute for Brain Sciences and the National Eye Institute. HEW has received research grants from the Veterans Affairs Medical Center, National Institute on Aging and Alzheimer's Association. SF has received research grants from the National Institute of Health and Duke University, and holds US patent 8811745 and 9299155. PMD has received advisory fees from Avid/Lilly, Anthrotronix, Muses Labs, AstraZeneca, Cognoptix, Lundbeck/Takeda, Piramal, Genomind, Sonexa, Targacept, NeuroPro, Neurocog Trials, Forum, Holmusk, and T3D Therapeutics; research grants

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Ethical standards This articles does not contain any studies with human participants performed by any of the authors.

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