REVIEW

Retinal pathology as biomarker for cognitive impairment and Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia. Furthermore, over the last few decades, there has been a shift towards identifying earlier stages of AD, which include mild cognitive impairment (MCI). Improved methods of screening and early detection are essential to identify cognitively normal individuals who have a high risk of developing MCI and AD, so that interventions can be developed to delay the progression of specific disease-related pathologies. Thus far, novel biomarkers that have been examined include structural and functional neuroimaging as well as biochemical analysis of cerebrospinal fluid. However, in spite of these efforts, there is still an urgent need for unravelling additional novel biomarkers for AD and MCI. As the retina shares many features with the brain, including embryological origin, anatomical (such as microvascular bed) and physiological characteristics (such as blood-tissue barrier), it has been suggested that the retina may provide an easily accessible and non-invasive way of examining pathology in the brain. While most AD-related pathology occurs in the brain, the disease has also been reported to affect different regions of the retina, including the macular region and optic disc. Studies have suggested that retinal pathology, such as deposits in the macular region, decreased retinal nerve fibre thickness, and optic disc cupping and retinal microvascular abnormalities may be related to AD and cognitive impairment. This article presents a review of current literature on retinal involvement in AD and MCI.

INTRODUCTION

As a result of rapid demographic ageing, the burden from common age-related brain diseases, such as dementia, is expected to rise exponentially.[1 2] Currently, the global prevalence of dementia is estimated to be as high as 24 million, and is predicted to double every 2 decades.[1] In terms of costs, in the USA alone, dementia is associated with an estimated healthcare cost of US$ 172 billion per year.[1] Alzheimer's disease (AD) is the leading cause of dementia, and is characterised by a progressive decline in cognitive function, which typically begins with deterioration in memory. Among regional populations of individuals aged >60 years, the prevalence of AD ranges from 6.4% in North America and Western Europe to 4.9% in Latin America, and 4.0% in China. In contrast, for mild cognitive impairment (MCI), which is considered a transitional stage to early AD, a much wider range has been reported (3–42%).[1 2]

Although substantial progress has been made over the past few decades in understanding AD, our ability to translate this into clinical benefits remains limited, as demonstrated by the diagnostic uncertainty inherent to the present criteria to diagnose AD, and the fact that currently only symptomatic treatments are available for clinically diagnosed AD.[1 3] It can be argued that improved methods of screening and early detection are essential to identify cognitively normal individuals who have a high risk of developing MCI and AD, so that interventions can be developed to delay the progression of specific disease-related pathologies. Over the last few decades, there have been major advances in unravelling novel biomarkers for AD and MCI using state-of-the-art neuroimaging and biochemical analysis of the cerebrospinal fluid (CSF). Although clinical symptoms of dementia become manifest late in the course of the disease, it has been shown that the underlying subclinical pathology (such as cerebral atrophy and white-matter lesion on MRI, changes in Aβ-42 in the CSF) is widespread in the population and may be present many years before symptoms of cognitive impairment.[1 3] However, in spite of these efforts, there is currently no definitive ante-mortem diagnosis for AD, and therefore, there is still an urgent need for unravelling novel biomarkers for AD and MCI. Over the last decade, advances in retinal imaging have opened new possibilities of using the retina as a template to examine pathology in the brain, and thereby elucidate novel biomarkers for AD and MCI. In this review, we provide a comprehensive update on the role the retina may play in providing novel biomarkers for AD and MCI.

METHODOLOGY

References were identified through PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) with the search terms: 'retina AND dementia' (280 references found), 'retina AND Alzheimer's disease' (258), 'retinal AND dementia' (469), 'cognitive impairment AND retina' (47) between January 1970 and February 2012. The references from identified articles and the authors' own files were also searched for relevant publications. Only papers published in English were reviewed. The final list of 68 references was chosen on the basis of relevance to the topic covered in this article.

BIOMARKERS FOR ALZHEIMER'S DISEASE

Currently, a diagnosis of 'probable' AD is made using the NINCDS-ADRDA criteria, and is only

possible when the condition has progressed and considerable neurological damage has already occurred.[4] These criteria largely depend on the exclusion of other causes of dementias. Although the NINCDS-ADRDA criteria have been reported to have a high diagnostic accuracy rate (80–90%), these data are derived from studies in specialised expert research centres, and mostly from patients in later stages of the disease.[5 6] The clinical diagnostic accuracy is probably lower in patients in the earlier stages of AD, especially in those with MCI, when specific symptoms other than memory disturbances are absent or indistinct.

Increasing incidence of AD in the population worldwide, along with the need to manage the disease before significant cognitive symptoms arise, calls for a sensitive and specific screening technology to identify high-risk individuals prior to irreversible brain damage. Biomarkers that have shown promise for the detection of AD and MCI include structural and functional neuroimaging, biochemical analyses of blood and CSF samples, and finally, genetic factors.[1 7 8]

MRI has revealed subclinical structural brain changes, which are important indicators of future adverse neurological events. Atrophy of the brain, in particular the hippocampus, is a strong predictor of AD and cognitive decline.[9 10] More recently, new techniques for quantitative neuroanatomic measurement, including cortical thickness analysis, are becoming available, which show that cortical thinning was associated with a nearly tripled risk of cognitive decline.[11] Furthermore, advances in neuroimaging techniques, such as functional MRI (fMRI) can visualise neuronal activity either during rest or in association with a task that activates specific brain regions.[12] However, inter- and intra-individual variability limits the use of these technologies in the differential diagnosis of dementia-causing disorders. Nevertheless, fMRI can facilitate the characterisation of functional abnormalities in specific diseases. People with AD exhibit reduced brain activity in the parietal and hippocampal regions, in comparison with healthy controls.[12] In addition, some studies have found different neuronal activity patterns in healthy controls and patients with MCI.[1] Overall, although MRI scanning is crucial in assessing preclinical processes, it remains a time-consuming and expensive technique. Moreover, some patients have contraindications for undergoing MRI scanning, such as claustrophobia, cardiac pacemakers and allergic reactions to contrast materials.

Another promising technique is positron emission tomography (PET) imaging employing ligands, such as Pittsburgh Compound-B (PIB), which selectively bind to Aβ-plaques enabling plaque load to be imaged in vivo.[13] Furthermore, CSF biomarkers have been shown to be the most accurate of the biomarkers investigated to date, with AD being associated with decreased Aβ-42 levels and increased total and phosphorylated τ levels in the CSF.[14 15] With specificity at 90%, the mean sensitivity of these three CSF biomarkers to discriminate between AD and normal ageing ranges between 80% and 86%. However, the specificity of both, τ protein and Aβ-42 levels are not optimum, because abnormal levels are also found in other dementias.[16 17] In contrast, high concentrations of phosphorylated τ protein have only been found in patients with AD. Finally, the sensitivity of these biomarkers tends to vary widely among studies, both, with different and the same ELISA methods.[16] Several studies have also examined the performance of these biomarkers in patients with mild AD or MCI, showing that abnormal levels are already found in the early phase of AD, with sensitivity and specificity figures in the range of those found for AD cases. However, the clinical applicability of these biomarkers is limited by the lack of standardisation of the assays.[16 17] Furthermore, these procedures are invasive, and patient acceptance may be low. Finally, in terms of genetic markers, certain mutations in amyloid precursor protein, presenilin-1 and presenilin-2, are known to cause early-onset familial AD.[18 19] For sporadic AD, one major susceptibility gene has been discovered, namely the apolipoproteine E ε4 gene.[20] This gene has been implicated in modulating the metabolism and aggregation of Aβ. Recent large genome-wide association studies have revealed additional novel genetic loci that are related to AD, although the effect sizes are small.[21] Hence, genetic profiling is emerging as a technique for predicting the risk of an individual contracting AD.

In spite of these efforts, there is still no clinically validated biomarker available for AD. As the retina shares many common aspects with the brain, including histological, physiological and embryological features, retinal imaging has emerged over the last decade as a non-invasive and direct technique for assessing brain pathophysiology.

VISUAL AND OCULAR ABNORMALITIES IN ALZHEIMER'S DISEASE

Visual disturbance may be an early complaint of patients with AD, and studies have reported reduced visual performance on tests including visual field, colour vision, contrast sensitivity, visual attention, motion perception, visuo-spatial construction, visual memory and fixation problems.[22] However, none of these abnormalities are specific to AD. Histopathologically, these visual deficits in AD have generally been attributed to neuronal damage in the visual pathways of the brain. Indeed, there is evidence that during the pathogenesis of AD, plaques and tangles occur in vision-processing brain regions prior to their occurrence in the hippocampus.[23] Thus, visual disturbance may precede memory impairment. Several studies examining visual function in patients with AD, including clinical and electrophysiological assessments, showed that visual impairment experienced by some patients with AD primarily resulted from involvement of primary visual and association cortex, rather than changes in the retina or optic nerve.[22 24] More recently, using fMRI and diffusion-weighted imaging, it has been shown that patients with amnestic MCI may already have visual spatial processing problems arising from neurodegeneration in the visual pathways.[25] However, apart from alterations in the central visual regions, specific pathological changes have been reported in the eye. Ocular abnormalities that have been reported to accompany AD include: enhanced pupil response to cholinergic drops,[26 27] altered pupil flash response,[28] Aβ proteins which have also been found to exist in the lens (both, Aβ-40 and Aβ-42), aqueous humour (Aβ-40) and vitreous humour (Aβ-42).[29 30] However, the exact link between the presence of Aβ proteins in these tissues and AD remains to be determined.

RETINAL BIOMARKERS FOR ALZHEIMER'S DISEASE

The retina, which is a direct extension of the brain, shows the strongest link with AD pathology. Embryologically, the retina is an extension of the diencephalon, and both are highly metabolically active tissues and share similar patterns of vascularisation, including a barrier function, auto-regulation and relatively low-flow and high-oxygen-extraction systems.[31] The retina consists of multiple layers of neural and photoreceptor cells, along with nerve fibres and vasculature (figure 1). The optic disc is the interface between the retina and the optic nerve, and is the location at which blood vessels and retinal nerve fibres leave the retina. Retinal morphology reported to be altered in

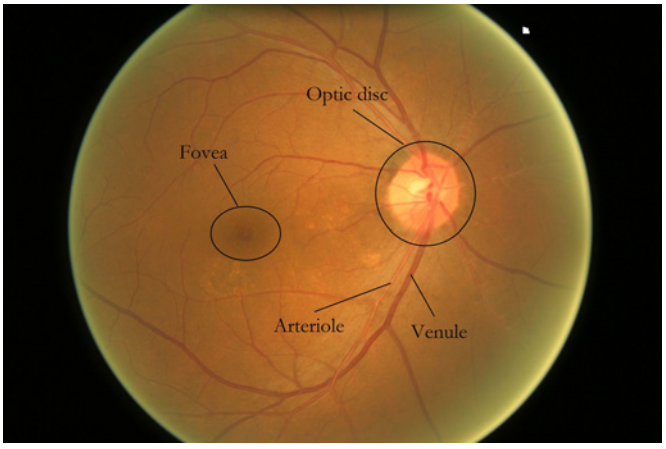

Figure 1 Retinal photograph showing the optic disc, fovea, retinal arterioles and venules.

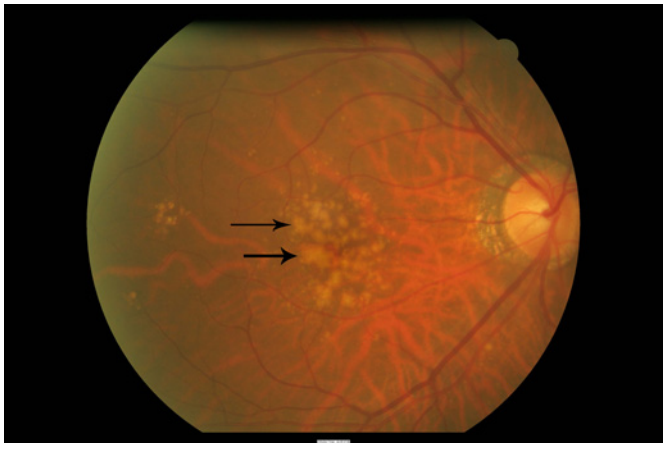

Figure 2 Early stage of age-related macular degeneration showing drusen, extracellular deposits, in the macular region (black arrows).

AD and MCI includes changes to the macular region, retinal vasculature, optic disc, retinal cell loss and thinning of the retinal nerve fibre layer (RNFL) (table 1).

Age-related macular degeneration and Alzheimer's disease

There have been a number of studies suggesting that age-related macular degeneration (AMD), a common age-related eye disease in up to 6% of people aged 60–75 years, and 20–30% in those aged >75 years, is related to dementia and cognitive decline. Drusen, extracellular deposits presumably derived from the degenerating photoreceptors and retinal pigment epithelium, are an early sign of AMD (figure 2).[32 33] While there are similarities between these extracellular deposits in the retina and the brain, evidence from studies that have examined the link between AMD and AD is inconclusive.[32] In the Rotterdam Study, data suggested that AMD predicted the 2-years risk of AD in participants >75 years of age.[34] However, this relationship was partially explained by shared cardiovascular risk factors. In a cross-sectional analysis of the Atherosclerosis Risk In Communities Study (ARIC), it was found that persons who performed worse on the Word Fluency Test were more likely to have early AMD. However, other neuropsychological tests were not related to AMD.[35] Another cross-sectional analysis from the Blue Mountains Eye Study showed that persons with late AMD were more likely to have cognitive impairment, as defined by the Mini-Mental State Examination, even after excluding vision-related tasks from the Examination.[36] Data from the Cardiovascular Health Study among 2088 participants aged 69–97 years showed that early AMD was observed in 16.3% of the individuals with AD, and in 15.6% of the individuals without AD, confirming a lack of any significant association between AD and AMD.[37] Histopathologically, although amyloid-associated proteins, τ and amyloid precursor proteins are expressed in the retina, immunoreactivity against tangles or amyloid plaques has not been consistently found in drusen.[32 33]

Table 1 Summary of retinal abnormalities possibly related to Alzheimer's disease

Part of the retina	Retinal abnormalities possibly related to Alzheimer's disease
Macula (fovea)	Drusen, extracellular deposits containing amyloid-associated proteins, tau and amyloid precursor proteins
Optic nerve	Loss of retinal nerve fibre layer thickness with depletion of retinal ganglion cells and optic nerve axons
	Optic disc pallor
	Optic disc cupping
	Neuro-retinal rim thinning
Retinal microvasculature	Retinopathy signs
	Retinal vascular calibre

Open-angle glaucoma and Alzheimer's disease

There are fewer data on the relationship between AD and optic nerve damage, in particular, that related to open-angle glaucoma, another common age-related eye disease. Open-angle glaucoma affects 1.4–4.2% of people >40 years of age, and is characterised by optic disc cupping (figure 3). The loss of RNFL thickness in AD is linked to a depletion of retinal ganglion cells (RGC) and optic nerve axons.[38–41] RGCs are the final common pathway that transfers visual information through the retinal nerve fibres and then the optic nerve into the brain. Initial postmortem histopathological studies have shown widespread axonal degeneration and reduction in the thickness of the nerve fibre layer in the retina and optic nerves of patients with AD.[42–44] Furthermore, Sadun and Bassi's work also suggested that the primary degeneration in the eyes of patients with AD may be involving the large M-cell axons.[45] Their findings are consistent with RGC dysfunction and support the notion that optic nerve damage occurring in AD preferentially affects the larger, faster-

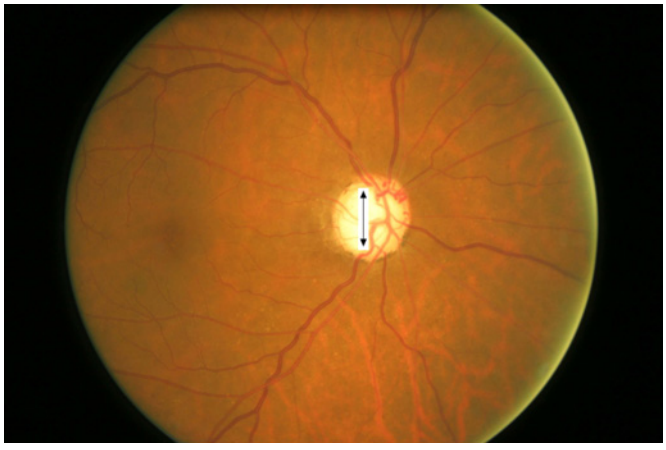

Figure 3 Optic disc cupping as seen in open-angle glaucoma. Arrow showing the upper and lower border of the cup.

conducting RGCs along with their retinocortical projections.[45] Another postmortem study by Blanks *et al* demonstrated a 25% decrease in RGCs at the level of the macular region, while other studies have found no significant changes.[42 46 47]

More recently, optical coherence tomography (OCT) has become available, which is a non-invasive technology that allows in vivo cross-sectional retinal imaging; hence, it is widely used to assess open-angle glaucoma and macular diseases.[48–51] Using these novel technologies, clinical studies have shown that there is a reduction of RNFL thickness in AD, and suggested that this morphological abnormality is related to a retinal dysfunction, as revealed by abnormal pattern electroretinogram responses.[48–51]

Peripapillary RNFL thinning in AD was found specifically in the superior quadrant in patients compared with control subjects. There were no significant differences in the inferior, temporal or nasal RNFL thicknesses between these groups.[48–51] In line with those observations, another study reported that the RNFL thickness is thinner not only at the superior, but also at the inferior quadrant compared with control subjects.[49] All these findings may imply that retinal damage in patients with AD may be localised preferentially to the superior and inferior quadrants. However, the exact mechanisms underlying these differences are yet unknown. Finally, more recently, it was shown that subjects with MCI already have reduced RNFL thickness compared with age-matched control subjects, suggesting that these retinal changes may occur in the early stages of development of AD.[48]

With respect to the optic nerve head, retinal photography and scanning laser ophthalmoscopy have both been used to demonstrate optic disc abnormalities in AD, including optic disc pallor, pathological disc cupping and thinning of the neuroretinal rim.[41 52] Some of these optic disc morphologies found in AD are more specifically found in eyes with open-angle glaucoma, such as peripapillary RNFL thinning, optic disc cupping and visual field loss. It has been suggested that AD accelerates the progression of glaucoma symptoms: a >10% per year decay in visual field and optic disc cupping were demonstrated in patients with glaucoma who were later diagnosed with AD, whereas, an average 3% per year decay in visual field was observed in patients with glaucoma who did not develop AD.[53] Furthermore, cup-to-disc ratios in patients with AD were reported to be increased by 39–43% when compared with those in the control group. Finally, the proportion of primary open-angle glaucoma in patients with AD (24%) was much higher than that in the control group (10%). However, increased rates of visual field defects and/or optic disc cupping are not specific for AD, and have also been reported in Parkinson's disease.[54]

Retinal microvascular abnormalities and Alzheimer's disease

AD is known to have a vascular component with small-vessel disease, microinfarction and cerebral amyloid angiopathy.[1] Given the homology between the retinal and cerebral microvasculatures, it is not unexpected that changes in the retinal vasculature might also occur in AD.[31] Several large population-based studies have shown that retinal vascular changes are associated with subclinical and clinical cerebrovascular diseases, including stroke and cognitive impairment. In ARIC, Cardiovascular Health Study and the Rotterdam Study, which examined community-based cohorts of middle-aged and elderly predominantly healthy people, retinal vascular changes, including retinopathy signs and retinal vascular calibres, were associated not only with incident stroke, but also with subclinical MRI-defined changes, including cerebral infarction, white-matter lesions and atrophy.[55–58] Furthermore, in the ARIC study, in patients without stroke, retinal vascular changes were associated with poorer cognitive function.[57] In the Rotterdam Study, it was observed that larger retinal venular calibre was associated with an increased risk of dementia and, in particular, vascular dementia, which is in line with observations in stroke and cerebral small-vessel disease.[56 58] However, these data did not support a role for vascular pathology underlying retinal venular widening in the aetiology of AD.[58] Overall, the link between retinal microvascular abnormalities and AD remains inconclusive.

FUTURE DIRECTIONS

Inferences from presently available studies should be made with caution due to several methodological limitations. First, except for studies examining retinal vascular abnormalities,[55–58] so far, most studies including histopathological and clinical studies using OCT had small sample sizes.[32 33 42 43 48–51] Second, these studies used a case-control design, which does not allow proper assessment of the temporal relationship between retinal changes and AD. Furthermore, in a case-control setting, the concomitant occurrence of ocular diseases, such as AMD and open-angle glaucoma in patients with AD, may further reduce the sensitivity and specificity of retinal changes (such as retinal nerve fibre layer thickness) to detect AD. In order to assess whether these retinal changes predict AD, longitudinal studies are needed in which patients without eye diseases are included at baseline, and subsequently followed for the occurrence of AD. Third, most previous studies included patients with AD, who lacked complete phenotyping, for example, MRI, to assess cerebrovascular disease. Finally, apart from AD, studies on retinal involvement need to be extended to incorporate other diseases, which may cause cognitive impairment, such as vascular dementia, frontotemporal dementia, Parkinson's disease dementia and diffuse Lewy-Body disease.

With the continuous advancement in retinal imaging techniques, there remains scope for further exploring the link between retinal pathology and dementia. There are efforts underway to develop tools that allow non-invasive detection of amyloid plaques, both, in mouse models and patients with AD. However, current non-invasive detection of amyloid plaques are of limited resolution and availability. An alternative non-invasive approach is to visualise amyloid plaques in AD and patients with MCI at high resolution using state-of-the-art optical imaging of the retina.[33] Initial studies suggest that in vivo non-invasive monitoring of AD pathology via optical imaging with high resolution and specificity is feasible through the retina.[33] The development of novel ligands will further enhance in vivo detection of amyloid plaques in the retina and the brain.

Thus far, the time-domain OCTs, which are capable of measuring the total retinal nerve fibre layer thickness, are successfully being used in research settings assessing damage to the optic nerve head in both, ophthalmology (glaucoma) and neurology (optic neuritis in multiple sclerosis; AD).[59] More recently, spectral-domain OCT (resolution up to 5 μm) is becoming available making it possible to measure different structural retinal sublayers (such as retinal nerve fibre layer, ganglion cell layer, inner and outer nuclear layers, inner and outer plexiform layers, photoreceptor; figure 4).[59] Future studies may also elucidate whether specific retinal sublayers may be more closely related to pathology in the brain than the total retinal nerve fibre layer thickness measurements. Moreover, apart from the retinal sublayers and the optic disc, OCT

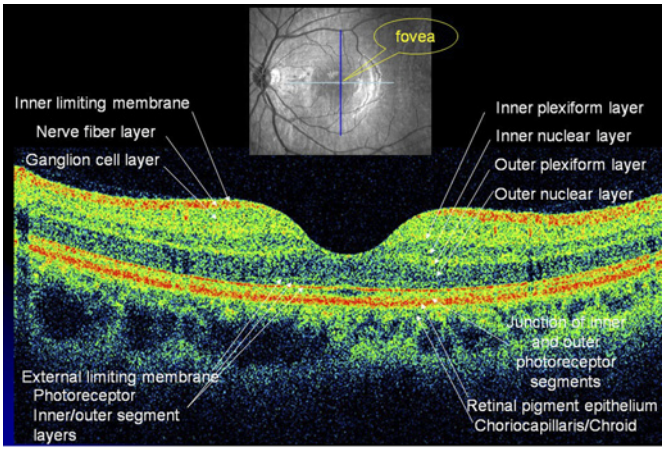

Figure 4 Optical Coherence Tomography scan showing a cross-sectional image of the different retinal layers around the fovea.

provides data on the retinal thickness in the macular region. A recent cross-sectional study among patients with Parkinson's disease (PD) and atypical Parkinsonian syndromes, including multiple-system atrophy, progressive supranuclear palsy and corticobasal syndrome, used spectral-domain OCT with manual segmentation to measure the peripapillary RNFL and macular thickness. The mean peripapillary RNFL did not significantly differ between these groups. In contrast, the mean macular thickness in progressive supranuclear palsy patients presented a significant reduction compared with both, controls and patients with PD, while the reduction observed in multiple system atrophy and corticobasal syndrome failed to reach statistical significance.[60] Studies, so far, have not specifically examined the role of reduced thickness in the macular region in relation to AD. Future studies using OCT technology in patients with AD also need to focus on the macular region. Finally, with respect to OCT, efforts are currently underway to develop algorithms that allow fully automated segmentation of retinal sublayers.[61] In the study of multiple sclerosis, it has already been shown that these fully automated segmentation techniques show comparable results in a faster and more reproducible way than those provided by fully manual or computer-assisted manual segmentation techniques.[61] The development of quantitative and reproducible biomarkers using these OCT segmentation techniques may also be useful in the study of AD, not only in terms of detecting small and subtle retinal changes in the preclinical stages of AD, but also in the evaluation of treatment effects in clinical trial settings.

With respect to the retinal microcirculation, there are presently efforts underway to examine novel retinal vascular parameters in relation to AD and MCI. These include both, local and global vascular topographic features, including the branching angles of blood vessels (figure 5A), retinal vessel tortuosity (figure 5B) and fractal dimension (figure 5C).[62] These new retinal vascular parameters indicate how optimally designed and developed the retinal microvascular system is, and therefore, may also reflect the state of the systemic and brain microcirculation.[62] Variations from the optimal geometry are known to occur in particular conditions, such as diabetes mellitus. Similar variations may occur in AD due to a vascular component, and need to be explored further. Finally, novel technologies, such as the dynamic vessel analysis of retinal vascular diameter in response to flickering light, are making it possible to examine dynamic and functional aspects of the retinal microcirculation.[63]

Finally, both, AMD and primary open-angle glaucoma are complex multifactorial eye diseases associated with both, genetic and environmental factors.[64–68] In recent years, the discovery of novel genetic (complement factor H gene for AMD) and neuro-inflammatory markers have provided crucial insights into the aetiology of these eye diseases. These recent advances could also provide novel directions for future research into the pathophysiology of AD.

CONCLUSION

The retina provides an ideal opportunity to explore the possibilities of elucidating novel non-invasive biomarkers for dementia and AD. Evidence is accumulating in support of AD-related changes in the retina; however, currently, all identified changes in the retina are non-specific for AD, and finding a sufficiently sensitive and specific retinal biomarker remains a major challenge. With the continuous development and advancement of retinal imaging techniques, there remains scope for retinal changes to be utilised as non-invasive biomarkers for AD. It is therefore essential that well designed, preferably longitudinal studies of retinal imaging be conducted in well-phenotyped populations, and correlated with other biomarkers for AD and vascular disease. Furthermore, future studies using animal models are required to demonstrate possible similarities in pathophysiological substrates that underlie changes in both, the retina and the brain, as seen in AD.

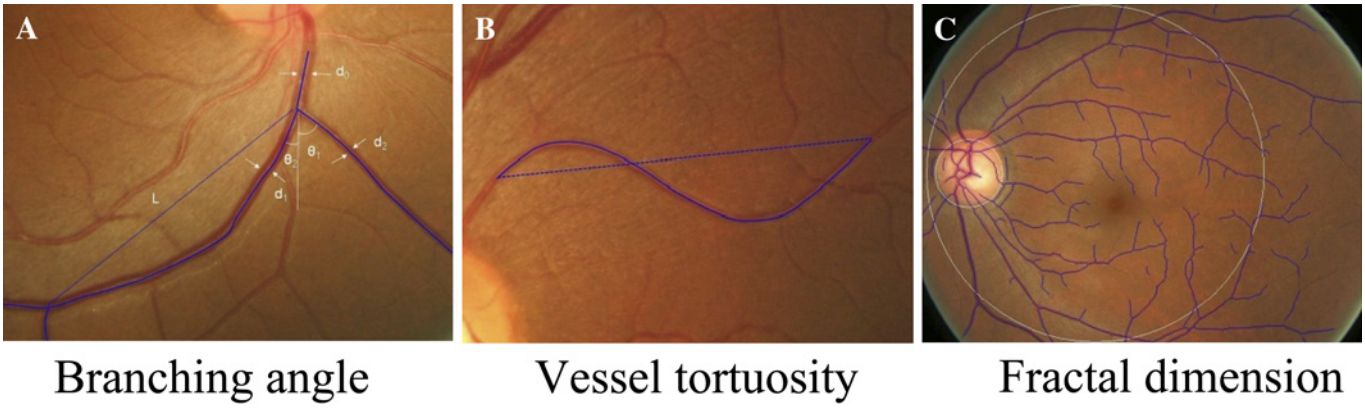

Figure 5 (A) Branching angle: the first angle subtended between two daughter vessels at each bifurcation. (B) Vessel tortuosity: measured as ratio of the straight distance of a vessel compared with actual length of the vessel. (C) Fractal dimension: retinal vascular tree is a 'self-similar' structure which can be summarised in terms of the fractal dimension quantifying the complexity of the whole branching pattern of the retinal vascular tree.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

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Retinal pathology as biomarker for cognitive impairment and Alzheimer's disease

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