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Mini Review

# Window to the Central Nervous System - Advanced Retinal Imaging for Early Diagnosis of Alzheimer's Disease

**Chang LYL[1,2,3]*, Black JM[1,2,3] and Acosta ML[1,2,3]**

[1]Department of Optometry and Vision Science, University of Auckland, New Zealand

[2]New Zealand National Eye Centre, University of Auckland, New Zealand

[3]Centre for Brain Research, University of Auckland, New Zealand

***Corresponding author:** Chang LYL, Department of Optometry and Vision Science, University of Auckland, New Zealand, 85 Park Road, Grafton, Auckland, New Zealand

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**Abstract**

More than a century has passed since the first case of Alzheimer's disease (AD) was described, but unfortunately establishing a probable clinical diagnosis still remains a challenge, and is often a long process of excluding other possible causes of dementia. There is a demand for an accurate, accessible, and preferably non-invasive tool for more timely and effective diagnosis. The eyes, especially the retina and optic nerve have received considerable attention in recent years with advanced digital imaging as a route for researchers to catch a glimpse of the central nervous system (CNS) in vivo. In this mini review, we aim to firstly, describe current diagnostic protocols for AD, and secondly, discuss the technology, specificity, and current research surrounding retinal imaging for AD diagnosis.

**Keywords:** Retina; Ganglion cell; Aβ plaque; Alzheimer's disease

## Abbreviations

CNS: Central Nervous System; AD: Alzheimer's disease; Aβ: Amyloid-beta; NINCDS: National Institute of Neurological and Communicative Disorders and Stroke; ADRDA: Alzheimer's disease and Related Disorders Association; OCT: Optical Coherence Tomography; HRT: Heidelberg Retinal Tomography; RNFL: Retinal Nerve Fibre Layer; MCI: Mild Cognitive Impairment; RGC: Retinal Ganglion Cell; POAG: Primary Open Angle Glaucoma; GCL: Ganglion Cell Layer; Tg: Transgenic

## Introduction

Alzheimer's disease (AD) is the most common type of dementia, as a result of neurodegeneration in the brain, and affects an estimated 36 million people worldwide [1]. AD is characterized by amyloid-beta (Aβ) plaque, and hyperphosphorylated tau aggregation in the brain, causing neuro-inflammation and neuronal death [2]. Current clinical diagnosis for AD relies primarily on patients self-presenting to clinicians when memory loss and cognitive decline become apparent. According to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's disease and Related Disorders Association (ADRDA) criteria for AD diagnosis [3] this condition is characterised by progressive deterioration of cognition and memory in comparison with the individual's previously known level of cognitive function-which is often noticed first by a family member or caregiver. Unfortunately, these symptoms often suggest that significant irreversible damage to the brain has already occurred. Also, the clinical tests utilized mostly require subjective response of the patient, which is challenging when the patient is uncooperative or simply lacks attention or energy at the time of examination– making clinical diagnosis inaccurate, and impossible for the severity of disease to be determined. Medical imaging and analysis such as positron emission tomography, structural magnetic resonance imaging, and cerebrospinal fluid study have the advantage of being independent from patient response, meaning that results are less likely to be confounded, and add more reliability to clinical diagnosis. These specialized tests are however less accessible, more expensive, and invasive for the patient.

There is a niche for tests that are independent from patients' cognitive input, economical, easy-to-administer for clinical use, and widely available. Visual function testing and ocular imaging have great potential in becoming an alternative or assistive tool for such measures in AD patients, as visual processing areas in the brain and visual information processing in the retina are known to be affected in early stages of AD. We are optimistic that such non-invasive imaging techniques through the eyes may one day provide opportunities for early diagnosis and intervention in order to preserve cognition and achieve more successful treatment outcomes [4,5].

### The role of digital ocular imaging in AD – correlation between AD and glaucoma

In recent years numerous studies have utilized digital ocular imaging such as spectral domain optical coherence tomography (OCT) and Heidelberg retinal tomography (HRT) for the examination of the retinal nerve fiber layer (RNFL, axons of retinal ganglion cells) in AD [6,7] and patients with mild cognitive impairment (MCI) [7], which is considered the prodromal phase of AD [8]. Amnestic MCI in particular has been identified with higher conversion rate to AD, with 43-48.7% progressing to AD over 30-36 months, reported by Fischer et al. and Lee et al. [9,10]. Many have found that MCI and AD patients do in fact have thinner RNFL compared to healthy controls, suggesting that cortical degeneration may be reflected by degeneration of the retinal ganglion cells (RGC) [6,7].

As RNFL thinning and RGC death are pathognomonic for glaucoma, and are often detected by digital retinal imaging, it has




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been proposed that the visual signs and symptoms seen in glaucoma patients are also experienced by AD patients [11]. Furthermore, the two conditions have been found to have common characteristics in their pathophysiology. A correlation between primary open angle glaucoma (POAG) and AD has also been demonstrated by studies identifying an increased incidence of POAG among AD patients [12,13], but no increased risk of developing AD in POAG patients [14]. It can be interpreted from these studies that AD patients are more prone to developing glaucoma, but not vice versa. It is however intriguing whether the POAG observed in AD is due to a pathological mechanism identical to that of POAG in individuals without AD. A recent study looking at the volume of certain brain regions by MRI and retinal degeneration in AD patients has found that reduction in grey matter volume of the occipital and temporal lobes was associated with retinal thinning spanning from the ganglion cell layer (GCL) to inner plexiform layer [15]. It was suggested that retinal thinning may be secondary to degeneration in the brain, causing retrograde degeneration of the optic nerve and RGC [15]. Hence retinal thinning in the elderly may not merely indicate POAG, but serve as an indicator for risk of cognitive decline. This information prompts revision of the pathology and diagnostic protocol of POAG in the elderly, especially in those showing signs and symptoms of cognitive impairment.

### Novel retinal imaging techniques - the pursuit to identifying unique features in AD retina

Considering the aforementioned literature, it remains a challenge to determine whether the glaucoma seen in AD patients is of the same pathophysiology as glaucoma seen in otherwise healthy individuals. Is it possible that the RNFL and RGC degeneration seen in AD give rise to a unique type of degenerative optic neuropathy, which is reminiscent of glaucoma? OCT and HRT are both clinical tools that evaluate anatomical changes in the retina – RNFL thinning, which is unfortunately not specific for AD, as it is also associated with glaucoma, Parkinson's disease and dementia with Lewy bodies [16]. There seems to be a new research direction towards detecting the molecular proteins and Aβ plaques associated with the pathology of AD, which has been found in the post-mortem retina of AD donors. However, their real value as a diagnostic technique remains controversial in the literature [17,18].

The work of Koronyo et al. [18] aimed to develop a more specific, non-invasive method to detect Aβ plaques in the retina of their transgenic AD mouse model APPSWE/PS1ΔE9 (AD-Tg mice), which addresses the molecular pathology. Histological evidence from animal models and post-mortem eyes of AD donors show presence of Aβ plaques in the retina, particularly in the inner retinal layers (RNFL and GCL), which forms direct physical connection with the CNS. In the study by Koronyo-Hamaoui et al. the AD-Tg mice had either intravenous or oral administration of curcumin (diferuloylmethane), a naturally occurring fluorescent compound which binds to the β-pleated sheet structure of Aβ plaques with high affinity. A review of curcumin, and its promises and limitations for clinical use has been described in the literature [19]. Both Aβ40 and Aβ42 isoforms of retinal plaques were successfully imaged, using an advanced optical imaging microscope for in vivo examination of the AD-Tg mice eyes. The curcumin bound plaques were imaged using filters that allowed excitation and emission at 550/25 and 605/70 nm. It was concluded by the authors that the presence of amyloid plaques could be detected by this non-invasive imaging technique, which was supported by comparable immunohistochemistry results. We acknowledge that in vivo retinal imaging using such imaging system is not able to distinguish the location of the plaques within the various retinal layers, but it will certainly be more informative with future development of animal retinal tomography, which would allow more sophisticated analysis. Nevertheless, the immunohistochemistry data with retinal cross-sections showed that the plaques were seen in the NFL/GCL, in most other retinal layers and even the sclera, which to our knowledge has never been reported before. Considering that RNFL and GCL are the location of degeneration in human AD and MCI, one would expect the presence of retinal plaques to be more concentrated in these inner retinal layers, which makes it seem unusual that plaques were also identified in the outer retinal layers. Following this interesting discovery by Koronyo et al. in their AD-Tg mice, an optical imaging device designed for human has been developed [20], and preliminary findings were presented by Frost et al based on 40 AD patients analyzed [20], that they were able to differentiate between AD and healthy controls with high sensitivity and specificity. We are looking forward to the full study finding in the near future, as a larger sample size is necessary to determine its true clinical value. This retinal amyloid imaging test is currently being used in a longitudinal research project under the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing [21], involving a multidisciplinary team of researchers, comparing data collected from AD patients, MCI patients and healthy volunteers at age 60 or older.

It is interesting to note that Aβ has also been detected in the glaucomatous retina in the form of soluble oligomers [22], and play an important role in the pathogenesis of glaucoma [23], by promoting RGC apoptosis [24], and disrupting neurotrophic axonal transport. Aβ plaques (Aβ42 isoform) have also been detected in a monkey model of chronic ocular hypertension [25], but similar findings have not been reported in human ocular hypertension or glaucoma. Aβ plaques found in AD have been considered to be the causative factor for neurodegeneration, whereas in the case of glaucoma they are considered to be the downstream event of inflammatory insult. The evidence in the literature is inconclusive to answer whether the presence and pattern of distribution of retinal Aβ plaques are exclusive to AD, or whether they are also found in human glaucoma or other neurological conditions. It will be interesting to answer the following questions: 1) Are retinal Aβ plaques also found in human glaucoma or other neurological conditions? 2) If retinal Aβ plaques are found in these conditions, would the pattern of distribution be different from AD patient?

## Conclusion

The eyes have great potential in becoming the organ for diagnosing neurodegenerative diseases of the CNS, and are likely to contribute to more effective diagnosis of AD. We are hopeful that ocular imaging, whether using readily available clinical tools (OCT, HRT), or by the more research-based, retinal plaque imaging system, are sensitive in setting AD apart from healthy normal controls. In the pursuit of validating the specificity of this retinal plaque imaging technique and with the advancement of retinal imaging technology, it may soon be possible to detect not only the presence, but the location of the plaques in vivo within the retinal layers. Answering these questions would help us understand whether the RNFL thinning

and optic neuropathy seen in AD are of the same pathophysiology as glaucoma or perhaps, a unique class of optic neuropathy downstream from pathology in the CNS.

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