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ALZHEIMER'S DISEASE: EARLY NEURODEGENERATION INDICATORS IN THE RETINA – A NARRATIVE REVIEW

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ABSTRACT

Clinical Relevance

Retinal imaging provides a non-invasive method for the early diagnosis of Alzheimer's disease. Early identification of RNFL thinning, impaired vasculature, and electrophysiological alterations through routine examinations can be helpful in referrals, risk stratification, and follow-up for early intervention. This allows optometrists to have an important impact on neurodegenerative diseases.

Background

Convergence of Research Evidence Related to Retinal Biomarkers in Early Alzheimer's Disease (AD): The aim of this work is to provide an overview of the most recent research evidence regarding retinal biomarkers for identifying very early changes associated with AD. Additionally, the purpose of this work is to provide a comprehensive view of the emerging diagnostic value for multimodal retinal imaging technologies.

Methods

A review of peer-reviewed studies investigating the effects of structural retinal changes, vascular changes and electrical functional changes of the retina on the neurophysiology of patients with AD has been conducted. The evidence from Optical Coherence Tomography (OCT); OCT-angiography (OCT-A), hyperspectral imaging, adaptive optics, electroretinography (ERG), visual evoked potentials (VEP), pupillometry and deep learning-based Photoretinal Analysis have been collected and reviewed to create a framework for the early detection of Alzheimer's Disease based on retinal characteristics.

Results

Study results identified that AD has been associated with patterns of retinal thinning cross modally across the RNFL, Ganglion Cell Layer, Ganglion Cell Complex and varying degrees of micro vascular degeneration based upon findings observed in OCT-A. Study results also identified the presence of amyloid-β and tau proteins expressed physiologically within retinal tissue based on Molecular Imaging and an increase in response latency and reduction in amplitude of pERG and spVEP responses when compared to normal healthy controls suggestive of increased neurodegeneration of the posterior retina experienced by AD subjects. AI diagnostic models demonstrated a significant improvement in early detection of AD by identifying latent structural or spectral characteristics that were undetectable by human observer methods.

Conclusions

The findings regarding retinal neuroimaging indicate that the retina offers a unique vantage point for the detection of pathological retinal changes that mimic the changes that occur with neurodegeneration as seen in AD. The development of next generation retinal imaging technology will enable retinal biomarkers to evolve from an experimental tool to a standard method for the noninvasive identification of greater than preclinical amounts of retinal change associated with Alzheimer's Disease. As such, optometrists due to their access to a broad range of patients and their frequency of patient contact will be pivotal in the adoption and integration of retinal neuro diagnostics into future dementia-related treatment pathways.

KEYWORDS: *Alzheimer's disease, Retina, Optical Coherence Tomography, OCT-A, Retinal biomarkers, Amyloid-β, Tau, Electrophysiology, Artificial intelligence, Neurodegeneration.*

INTRODUCTION

Alzheimer's disease (AD) represents the leading cause of dementia globally and is characterized by synaptic failure, neuronal loss, and progressive cognitive impairment. Amyloid-β (Aβ) deposits, hyperphosphorylated tau, neuroinflammation, and microvascular dysfunction are the neuropathological hallmarks that develop silently for many years prior to clinical manifestation. Throughout this latent phase, patients remain unnoticed and possibilities for treatment diminish. Positron emission tomography and cerebrospinal fluid analysis are two widely recognized instances for conventional methods for diagnosis that are too costly, intrusive, and unfeasible for screening large populations.[7,8,39,51]

The neural tube gave rise to the retina, which shares morphological, physiological, and embryological similarities

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with the brain. It contains neurons, glial cells, microglia, and an intricate vasculature analogous to cerebral tissue. Retinal evaluations offer a rare opportunity to visualize living neural tissue noninvasively. Mounting evidence demonstrates that individuals with AD show distinctive retinal abnormalities, including thinning of the RNFL and GCC layers, microvascular rarefaction, retinal amyloid deposition, electrophysiological dysfunction, and alterations detectable by artificial intelligence (AI)–based analysis.[1,6,23,24,27]

In this review, contemporary research is organized into a multimodal diagnostic framework comprising structural, vascular, molecular, functional, and computational domains. A parallel objective is to highlight the evolving role optometrists will assume as early detectors of systemic neurodegenerative diseases. [7,22,23]

A Glimpse into the Brain through the Retina

The retina isn't just another eye structure—it actually comes from the same embryologic tissue as the brain. Because of this shared origin, it carries many of the cell types we usually associate with the central nervous system. You'll find: [1,4,6]

- Neurons
- Glial elements
- Resident microglia
- Intricate network of vessels

And here's the important part: since its architecture mirrors that of the brain, the retina tends to mirror its vulnerabilities too. In Alzheimer's disease, for instance, several pathologic changes seen in the brain also turn up in retinal tissue, including:

- Deposits Of Amyloid-B (Aβ) [2,31,39]
- Abnormal Tau Build-Up [30,39]
- Inflammatory Activity [27,47]
- Loss Or Damage Of Axons [11,12,47]
- Small-Vessel Dysfunction [3,10,25,40,41]

Retinal Structural Clues in Alzheimer's disease

1. RNFL (Retinal Nerve Fiber Layer) thinning - Various studies show evidence how the OCT (Optical Coherence Tomography) shows a clear decrease in RNFL thickness for people who have mild cognitive impairment (MCI). In fact, an individual with MCI has observable RNFL thinning that continues as the disease progresses. It has also been shown that RNFL thickness correlates with cognitive testing scores, such as the MMSE and MoCA, showing a corresponding decrease in scores when RNFL becomes thinner. It is also noteworthy that thinning of RNFL occurs first in the superior and inferior quadrants of the retina.. [5,11,12,13,14]

2. Damage to the Ganglion Cell Layer (GCL) and Ganglion Cell Complex (GCC)

Ganglion cells are very vulnerable to amyloid toxicity; therefore, they are often the first cells that are affected in the disease process. Some points found in research about GCL and GCC include: [4,12,36] 1. GCL thinning may be apparent even before the individual recognizes cognitive decline and 2. The measurement of GCC may differentiate an MCI patient from a healthy aged individual better than RNFL thickness. The presence of tau-related pathological changes cause a decrease in synaptic activity in the IPL (Inner Plexiform Layer) which interrupts communication patterns before there are widespread neuronal losses.

Retinal Microvascular Biomarkers (OCT-Angiography)

OCT-A studies show Alzheimer's-related changes such as: [3,10,15,16,33,34]

- Reduced **superficial capillary plexus density**
- Enlarged **foveal avascular zone (FAZ)**
- Capillary dropout around the macula
- Vessel tortuosity and microvascular rarefaction

These reflect cerebral hypoperfusion and blood–brain barrier dysfunction—key elements of AD pathology.

MOLECULAR RETINAL BIOMARKERS

Retinal Amyloid-β [2, 9, 17, 31, 46]

Multiple imaging technologies identify Aβ aggregates in vivo:

- **Hyperspectral imaging** detects amyloid through spectral signatures.
- **Curcumin-aided fluorescence imaging** visualizes plaques with high sensitivity.
- **Adaptive optics scanning laser ophthalmoscopy (AOSLO)** enables ultra-high-resolution visualization of amyloid deposits.

Retinal amyloid burden corresponds strongly with cerebral amyloid PET findings.

Tau Pathology

Tau deposition has been identified in human retinas, particularly within the inner plexiform and ganglion cell layers. Tau's usefulness as an early biomarker is further demonstrated by the observation that it seems to break down synaptic function prior to significant death of neurons.[30]

Oxidative Stress & Metabolism [50]

Enhanced oxidative stress in AD retinas has been detected by recent redox imaging investigations. The systemic mitochondrial failure seen in the course of AD correlates with these changes in metabolism.

Electrophysiological Biomarkers

Pattern ERG [19]

Even when OCT looks normal, people with AD have substantially decreased pattern ERG amplitudes, which indicate RGC abnormalities. relying on late-stage atrophy, these nutritional deficiencies are the result of early synaptic disruptions.[19]

Visual Evoked Potentials (VEP)

Slowed signal conduction along the visual pathway is represented by delayed P100 latency, this has been often reported in AD.[18,45]

Pupillary Light Reflex (PLR)

PLR alterations include:

- Reduced constriction amplitude
- Prolonged latency
- Impaired cholinergic responses

Given its accessibility, pupillometry holds promise for widespread screening.

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AI Based Retinal Biomarker Analysis

AI has grown into an innovative technology that will identify subtle retinal deficiencies that clinicians never sight: [20,21,38]

- Using retinal images, CNNs correctly distinguish between AD, MCI, and healthy controls.
- Beyond human resolution, deep-learning OCT analysis can identify minute structural alterations.
- Cognitive decline is significantly correctly anticipated by combined AI-OCT/OCT-A systems.

The clinical use of retinal biomarkers will likely be accelerated by AI's capacity to combine multimodal datasets.

Clinical Consequences: A New Direction in Optometric Practice

Optometrists are probably the ones closest to making retinal biomarkers part of everyday care. Most people already get an OCT scan or a quick fundus photo during a routine eye exam, so slipping biomarker assessment into that same appointment feels almost natural. It would not overhaul the clinic schedule or force anyone to reinvent how they work. Still, I imagine there will be a learning curve, because interpreting these newer metrics can feel a bit unfamiliar at first. Even so, the basic setup is already in place, and that gives optometrists a real advantage as these tools start finding their way into regular practice. Optometrists may ultimately: [22, 23, 24]

- Screen older adults for retinal indicators of Neurodegeneration
- Monitor longitudinal retinal changes
- Refer high-risk individuals for neurological evaluation
- Participate actively in multidisciplinary dementia care teams

For reliable use in clinics, consistent techniques for imaging and good training are necessary in order to ensure that conclusions stay the same regardless of the circumstances at hand.

Future Directions [42, 43, 49]

As the field progresses, an assortment of areas merit attention. In order to determine whether retinal alterations actually predict disease, long-term studies which monitor individuals until clinical conversion are still lacking. Additionally, researchers are attempting to integrate several retinal markers into a single algorithm; however, these models will have to find a balance between the functionality and complexity.

Both the need to validate results in more diverse populations and standardizing imaging settings across machines continue to be challenging issues. The integration of retinal imaging into primary-care dementia pathways is becoming more popular, but this change will need careful planning. Teams are simultaneously developing portable, less expensive instruments like early hyperspectral cameras, PLR devices, and small OCT units.

Retinal biomarkers may eventually be used as an early, accessible way to identify neurodegenerative change if the evidence keeps getting stronger, but that future still depends on thorough testing.

Conclusion

The retina has begun to resemble a small, surprisingly revealing window into the early phases of Alzheimer's. It is easily examined during a standard eye examination, but it has subtle structural thinning and blood flow disruptions that could be signs of more serious neurological changes. Researchers have also started to see tau and amyloid deposits in addition to slight alterations in electrophysiological responses. Furthermore, AI systems continue to discover oddly complex patterns that human observers might miss. These elements combine to produce a multimodal fingerprint that is, to be honest, still evolving and imperfect.

This fingerprint could grow sharper and more clinically reliable as new imaging technologies and analytical techniques are developed. However, there are moments when I question how quickly these developments can be put into practice outside of research labs. The promise is there, although the path can be slow and uneven. What seems clear, however, is that optometrists will have a meaningful role in this shift. They are often the first professionals people visit for concerns that seem minor at first glance, perhaps just a new pair of glasses. Because of that, they are in a unique position to notice early retinal changes that might otherwise go unnoticed. If population-level dementia screening based on retinal markers ever becomes routine, it will likely be shaped, at least in part, by the judgment and day-to-day experience of these frontline clinician.[47,48]

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Conflict of Interest

Concerning the design, preparation, or publication of this manuscript, the authors declare that they have no conflicts of interest. The content of this work was not influenced by any financial or personal relationships.

Ethics Statement

There are no new clinical trials, identifiable data, or human subjects in this narrative review of earlier research. Thus, informed consent and Institutional Review Board (IRB) approval were not necessary.

Data Availability Statement

This review doesn't include any new data or analyses. All the information used in this article originates from existing, publicly available sources.

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Figure captions

Figure 1. Anatomical representation of the human visual pathway from retina to visual cortex.
Figure 2. Mechanisms of retinal and cerebral neuroinflammation in Alzheimer's disease.
Figure 3. Retinal biomarker pathways in Alzheimer's disease.
Figure 4. Optic nerve changes and their visual manifestations.