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Eye as a window to the brain: Review of retinal changes in Alzheimer's dementia

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ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disease causing significant morbidity and mortality in the elderly, affecting million worldwide. Diagnosis of AD is mainly by clinical symptoms, use of tests to detect loss of higher mental functions, and confirmed by neuroimaging studies such as magnetic resonance imaging and positron emission tomography. Current research in AD aims at early detection of pathological changes in the brain and development of disease-modifying drugs. Testing the effectiveness of these drugs requires the development of a noninvasive and cost-effective screening tool. Retinal changes in patients with AD mirror those found in the brain and offers a window for early detection of AD before cognitive changes set it. This article reviews the pathological correlation between retinal changes and AD and the current advances in retinal imaging to detect AD.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative condition and the most common cause of dementia in the elderly. AD is characterized by mild memory loss in the initial stages, progressing to a debilitating disease with the affected person's inability to carry out daily living activities and eventually death. The onset of symptoms is usually after 60 years, with a doubling risk every five years of life after 65 years. In 2020, the prevalence of AD was reported to be around five million and projected to triple in the next 40 years. AD is the 5th leading cause of mortality among adults aged 65 years and above [1]. AD often goes undetected in the early stages, with diagnosis delayed by 2-3 years after the onset of the symptoms. Brain imaging studies such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans reveal changes several years before the onset of symptoms [2]. However, these imaging studies are costly, time-consuming, and ineffective as screening tools for early disease detection. Recent research has focused on applying noninvasive and cost-effective ways to detect AD in its early stages [3]. Retina tissue, a neural component of the human optical system, of patients with AD, has been recently reported to manifest pathological changes similar to that seen in the brain of these patients. Retina offers a unique way to detect patients with AD as retinal changes precede brain changes by several years. In addition, retinal imaging is easier and more cost-effective than brain imaging [4]. This review provides the basis for the link between AD and retinal changes, the fundamental pathological similarities between AD and retinal degenerative disease, and the application of using the retina as a window to diagnose AD in its early stages.

Development of brain and visual system

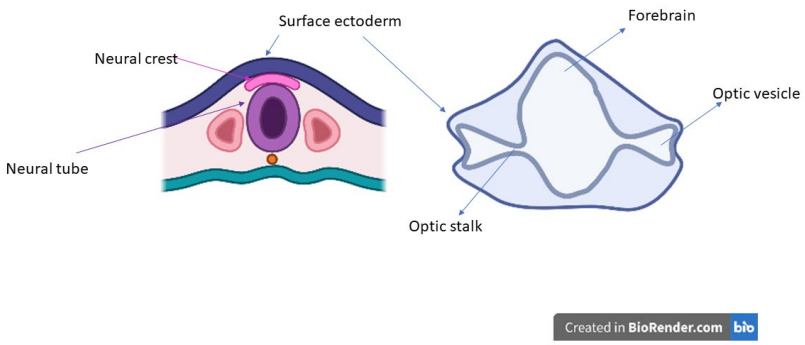

Figure 1. Developing brain (left) and eye (right) showing the optic vesicle develops from the Prosencephalon part of the neural tube

The retinal layer of the human eye is an extension of the developing brain. Retinal neurons and central nervous system neurons are derived from common progenitors. The brain develops from the specialized primordial form of ectoderm called the neuroectoderm. The cells in the neuroectoderm replicate to form a ridge-like structure called the neural crest, with the depression between the crests forming the neural fold. The neural fold enlarges and converts to a tube-like structure which is the primitive central nerve system. The cranial end of the neural tube enlarges and develops three bulges: Prosencephalon, Mesencephalon and Rhombencephalon. Prosencephalon splits into two parts: Telencephalon, which develops into the cerebral cortex, and Diencephalon, which forms the thalamus and the hypothalamus. In humans, about four weeks after fertilization, eyes begin to develop as optic grooves on either side of the developing Prosencephalon. After the neural tube closes, the optic grooves elongate to form an outpouching from the forebrain to form optic vesicles, which invaginates on itself to form an optic cup, and forms the retinal layer of the human eye [5].

Retinal structure

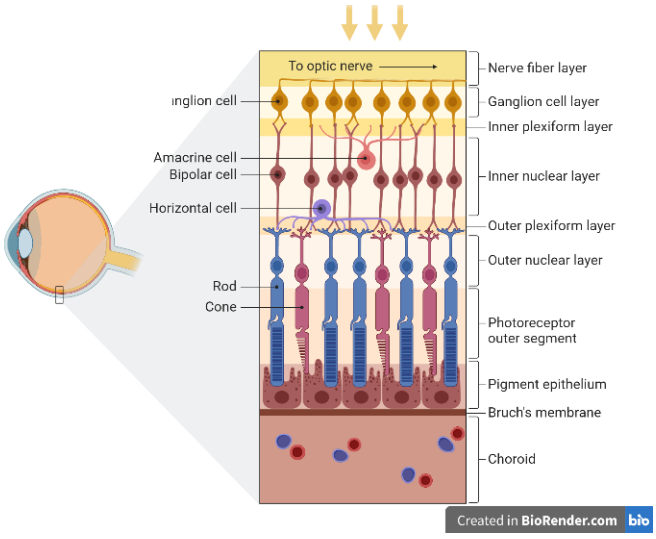

Figure 2. Schematic structure of retina showing the multi-layered configuration of cells and synaptic connections between the layers

The human retina is a transparent membrane with several layers of neurons interconnected by synapses. The primary light sensitive cells are the photoreceptors: cones that are predominantly active under light conditions and rods primarily active in dark. The nucleus of the photoreceptors forms the outer nuclear layer (ONL). Light processed by rods and cones is converted to an electrical signal, passed on through a series of interneurons located at the inner nuclear layer (INL), and then onto the retinal ganglion cells (RGC). From RGC, the signal is carried by its axon, the retinal nerve fiber layer (RNFL). There are six million ganglion cells in the human retina, and their axons form the optic nerve. The axons in the optic nerve then relay the information to the cortical neurons in the occipital cortex of the human brain [6].

Alzheimer's disease: Pathology

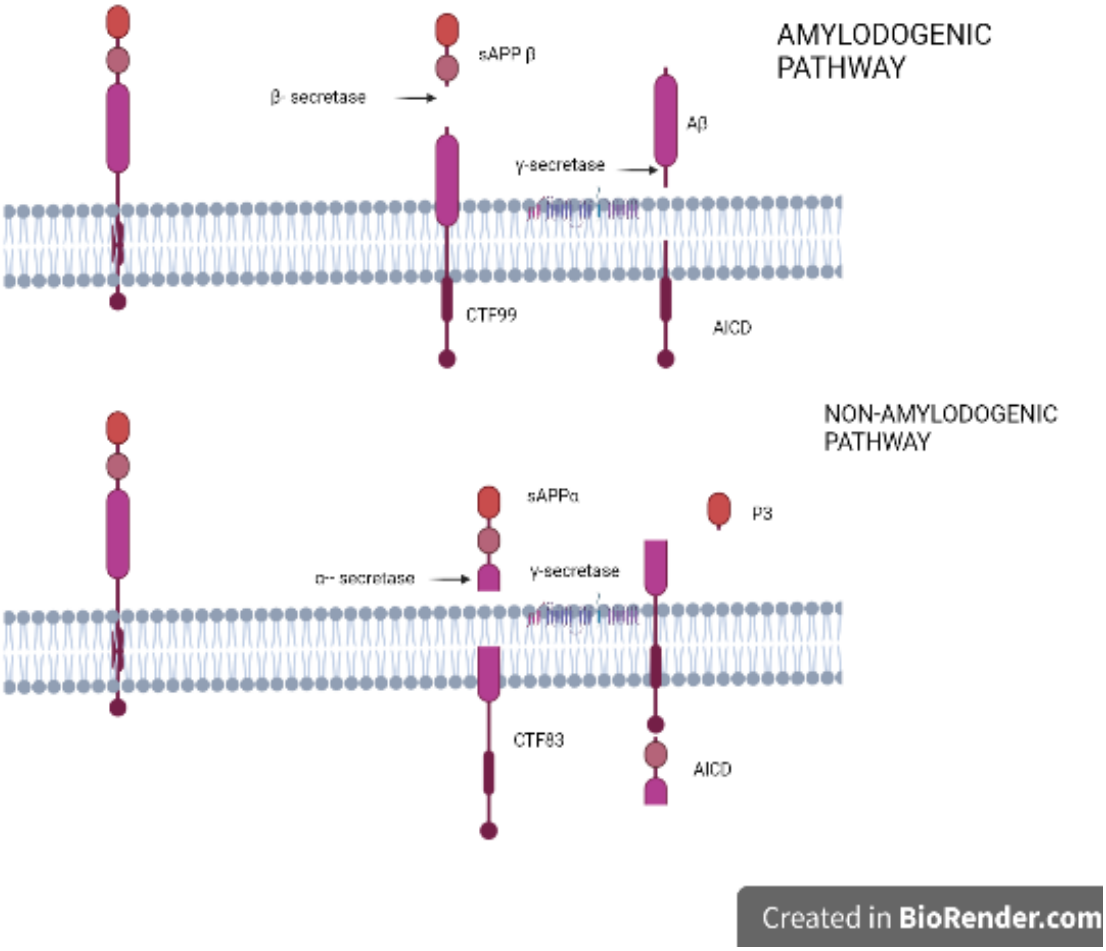

Figure 3. Schematic diagram showing the two pathways through which amyloid precursor protein (APP) gets processed in the neurons

Alzheimer's disease is characterized by generalized cortical atrophy, most prominent in the medial temporal lobe and the hippocampus. Microscopically, the presence of amyloid plaques in the extracellular space and neurofibrillary tangles within the neurons is the key feature for diagnosis of AD. Amyloid plaques are formed by the extracellular non-vascular accumulation of Aβ40 and Aβ42 peptides [7]. These peptides accumulate because of abnormal amyloid precursor protein (APP) processing by β- and γ-secretases. APP, an integral membrane protein, is concentrated

in synapses and is involved in cell growth, synapse formation, and neuroplasticity. APP has three major isoforms, APP770, APP751, and APP695. APP695 is mainly neuronal, with other forms localized non-neuronally. APP is processed in two pathways: on the cell surface, APP is cleaved initially by α-secretase and then γ-secretase, a process that does not produce Aβ peptides. In another path, APP gets internalized into endosomes and cleaved by β -secretase, forming soluble APP (sAPPβ) which is then cleaved by γ-secretase to generate Aβ peptides [7,8]. The accumulation of Aβ peptides is toxic to the neurons resulting in neuronal apoptosis, loss of synaptic terminals, and synaptic dysfunction.

Another neuropathological feature of AD is the presence of neurofibrillary tangles (NFTs), abnormal accumulation of hyperphosphorylated tau proteins. Tau protein, belongs to the family of microtubule-associated proteins (MAPs), helps to stabilize microtubules, and plays a significant role in axonal transport. In humans, tau protein is encoded by MAPT gene located on chromosome 17. The gene has 16 exons which are alternatively spliced to form six tau isoforms. Tau, in its native form is unfolded and its function is regulated by phosphorylation. In phosphorylated form, it is released from the microtubules, which are then disassembled. Aβ peptides cause hyperphosphorylation of Tau proteins leading to misfolding and aggregates into an insoluble, double helical form called paired helical filament (PHF), which is the precursor of NFTs [8.9].

Retinal pathology in AD

Retina cells express APP, abnormal processing of which has been implicated in retinal degenerative diseases. Similar to its role in the brain, APP is believed to help in retinal synaptogenesis, especially in the INL, where the interneurons, amacrine cells synapse with bipolar and ganglion cells. Postmortem examination of retina in AD patients co-labelled with Aβ-specific monoclonal antibodies has revealed Aβ plaques distributed in retinal tissues [10]. The retinal Aβ had a distinctive globular configuration compared with a classic central core and radiating fibrils as seen in Aβ plaques in AD. The distribution in retinal tissue was perivascular as opposed to a non-vascular distribution of Aβ plaques in AD. A recent study has revealed more neuronal distribution around melanopsin retinal ganglion cells (mRGCs), a subtype of retinal ganglion cells which regulate circadian rhythm and pupillary reflex. The presence of Aβ plaques is higher in AD patients compared to age-matched controls, provides evidence that there is a common pathogenetic mechanism for neuronal degeneration in both retina and the brain of patients with AD [11]. In addition to Aβ plaques, abnormally phosphorylated Tau(pTau) protein has been detected in inner retinal layers of AD patients [12]. Several transgenic mice models of AD have demonstrated the age-dependent increase in the deposits of retinal Aβ plaques in the inner nuclear layer (INL)and ganglion cell layers (GCL) of the retina [13,14]. In addition to Aβ plaques, pTau and NFTs have been observed in INL and GCL of retina from AD transgenic mice. In addition to the presence of biomarkers, Aβ plaques, and NFTs in retinal patients of AD and transgenic AD mice models, there is neuronal degeneration of retinal cells like that seen in AD [14,15]. Histological examinations of postmortem retinas from AD patients have shown photoreceptor degeneration and retinal ganglion cell degeneration with subsequent retrograde degeneration of its axon leading to optic atrophy [16]. Photoreceptor and ganglion cell degeneration are the hallmark of two retinal conditions, macular degeneration, and glaucoma.

AD, Macular degeneration and Glaucoma: common pathogenetic mechanism

Age-related macular degeneration (AMD) is a progressive degeneration of photoreceptors and retinal pigment epithelium (RPE). AMD is the leading cause of blindness in the western world. AMD is associated with the accumulation of degenerative material called drusen between the RPE and its basement membrane, eventually leading to a degeneration of overlying photoreceptors. Pathological examination of drusen has shown the presence of Aβ protein, suggesting a link with AD [17,18].

Glaucoma is a progressive ocular condition characterized by loss of RGC and thinning of its axons, the retinal nerve fiber layer (RNFL) of the retina. Glaucomatous RGC cell death is typically a result of elevated intraocular pressure (IOP), usually regulated by the flow of aqueous humor within the eye. Sustained elevation of IOP leads to slowing of axonal conduction within RNFL, causing accumulation of Aβ and p-tau in RGCs, resulting in neuronal degeneration. Loss of RGC leads to axonal loss, thinning of RNFL, and optic atrophy, which leads to blindness [18,19].

Common to AD, AMD and glaucoma is the predominant amyloidogenic processing of APP. However, the underlying mechanism by which the amyloidogenic pathway takes over the non-amyloidogenic path is not clearly understood. Both genetic and epigenetic factors have been believed to trigger an increase in the β- over α-secretase activity of APP processing. After the Aβ peptides form in the extracellular space, they exert their neuronal toxicity by causing synaptic dysfunction, oxidative stress with mitochondrial dysfunction, and neuroinflammation with glial activation [20].

Aβ peptides and synaptic dysfunction

Glutamate is the principal excitatory neurotransmitter in the brain and exerts its actions through either fast-acting ionotropic or slow-acting metabotropic receptors. Ionotropic receptors consist of three subfamilies: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, kainate receptors, and N-methyl-D-aspartate receptors (NMDARs). Glutamate acting through NMDAR involves Calcium (Ca2+) as a secondary messenger. It plays an essential role in synaptic plasticity, enabling either long-term potentiation (LTP, increase in synaptic connections) or long-term depression (LTD, decrease in synaptic connections). LTP and LTP facilitate higher mental functions of the brain, such as learning and memory [21]. Under stressful conditions, there are excessive glutamate levels, leading to abnormal NMDAR activity, which causes an excessive influx of Ca2+ into the neurons. Increased Ca2+ levels lead to neuronal death, damage to endothelial cells of blood vessels, and disrupt the blood-brain barrier. Aβ peptides (especially Aβ 1-42) cause synaptic dysfunction by triggering aberrant excitatory neural network activity through abnormal NMDAR stimulation and increased Ca2+ levels, leading to neuronal degeneration in the brain and retina [20,22].

Aβ peptides and oxidative stress

Aβ interacts with several mitochondrial proteins, including proteins of the outer mitochondrial membrane, intermembrane space, inner mitochondrial membrane, and the matrix, and causes dysfunction of critical enzymes involved in oxidative stress [20,23]. Abnormal interaction causes impairment of oxidative phosphorylation and an increase in reactive oxygen species (ROS) production. In addition, Aβ peptides bind to intracellular metal ions such as iron, copper, and zinc, modulators of intracellular oxidative stress. Excessive ROS produced increased levels of carbonylated proteins, 4-hydroxynonenal (4-HNE) and oxidized bases (i.e., 8-oxo-2-dehydroguanine, 8-hydroxyadenine, 5-hydroxyuracil), indicating oxidation of cellular proteins, lipids, and DNA, respectively [23]. Alteration of membrane proteins and cellular machinery leads to increased neuronal membrane permeability, decreased ATP production and finally, neuronal death. Oxidative stress also reduces the clearance of Aβ peptides from within the neurons' intracellular space, further increasing their levels and cascading downstream neuronal damage. In AMD and glaucoma, Aβ dysregulates mitochondria-associated proteins such as pyruvate dehydrogenase, disrupting the electron transfer chain. Abnormal mitochondrial electrical activity and ROS increase lead to photoreceptor and retinal ganglion cell death [20,24].

Aβ peptides and neuroinflammation with glial activation

Inflammatory markers and glial cells, which are involved in phagocytosis and repair mechanisms, surround Aβ plaques in postmortem AD brains. Pro-inflammatory cytokines such as TNFα, and IL-1β have been shown to shift the microglial morphology from phagocytic M2 to more towards M1 phenotype, which is more cytotoxic to the neuronal cells [20]. In retinal cells, Aβ peptides have been shown to cause complement activation, upregulating pro-angiogenic factors such as vascular endothelial growth factor (VEGF). VEGF causes the growth of new blood vessels in the subretinal space, which bleed and scar, causing damage to the RPE and photoreceptors [20]. Activated microglia have also been reported closely surrounding the optic nerve head of glaucomatous eyes [25].

Manifestations of AD in the eye: Use of non-invasive imaging and Implications for diagnosis

Current diagnostic modalities for AD include the use of brain imaging techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET), or findings of specific biomarkers in the cerebrospinal fluid (CSF) or serum [2]. These imaging modalities are expensive, time-consuming, and require the use of radioactive tracers. Retinal imaging has been considered a low-cost and simpler diagnostic modality to diagnose AD. Clinically, several ocular features have been described in AD patients. These include a change in pupillary size, altered pupillary response, early formation of a cataract, retinal and choroidal thinning and increased cupping of the optic nerve head [26]. The most specific finding is the retinal and optic nerve head findings. The retina offers a unique opportunity for noninvasive and repetitive imaging. The introduction of optical coherence tomography (OCT) in 1991 for noninvasive imaging of the retina and optic nerve in vivo was a milestone development in ocular imaging [27].

The OCT device uses the principle of interference of two low-coherent light rays, one reflected from the tissue and the other a reference light ray. The interference pattern generates a reflectivity pattern of the tissue imaged, and an Amplitude (A) scan is generated based on the strength of the reflected signals. Several hundred A-scans are combined to get a high resolution, two-dimensional, cross-sectional Brightness (B) scan of the retina [27,28]. The first generation, time-domain (TD)OCT scanned 400 A-scans per second with generated B-scan images having an axial resolution of 10 μm. Spectral-domain OCT (SD-OCT), also known as Fourier-domain OCT, increases the speed of data collection by a factor of 100 (40,000 A-scans per second), leading to improved resolution of B-scan images [29]. The advantage of SD-OCT is the quick acquisition time preventing motion artifacts from gathering high-quality images. One commercially available SD-OCT, Spectralis (Heidelberg Engineering, Vista, California, USA), with Trutrack technology provides repeatable measurement of the same points on the retina over time. Newer developments with OCT technology include Swept-source OCT (SS-OCT) which provides deeper imaging of the eye and provides information about choroid thickness, and OCT-Angiography (OCT-A), which give the images of the retinal and choroidal vessels without the need to inject any contrast dye intravenously [30,31].

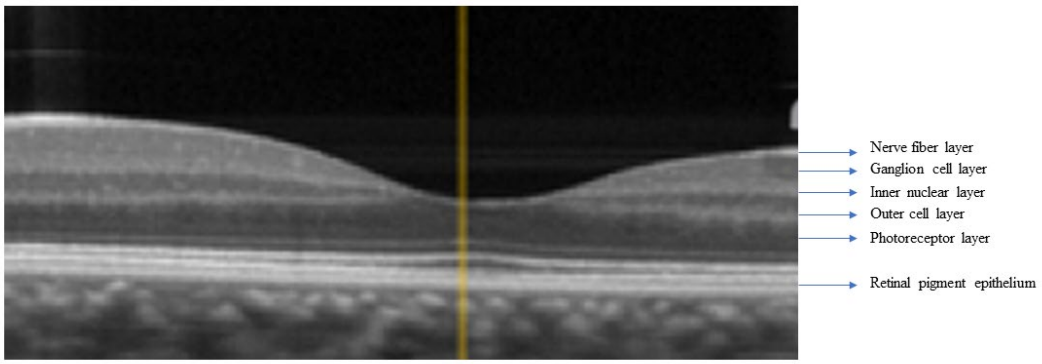

Figure 4. Cross-sectional optical coherence tomography (OCT) image of the retina showing different layers

OCT images have been used to develop a normative database of retinal thickness and choroidal thickness and show an age-dependent reduction in thickness [32]. In addition, segmentation algorithms can identify different densities of nuclear layers with varying reflectivity patterns on OCT images and allow the measurement of individual retinal layers. Retinal layers which are relevant to evaluating changes in AD include the retinal nerve fiber layer (RNFL) and retinal ganglion cell (RGC) layer [33]. Several studies have reported that retinal thickness and mean total macular volume in all macular quadrants are lower in AD patients than in control subjects [34]. RNFL layer thickness around the optic nerve head has been reported to be reduced in patients with AD, especially those with cognitive impairment. RNFL thickness indirectly measures RGC impairment, the primary area of involvement in the retina in patients with AD [35]. It is difficult on OCT images to delineate RNFL and GCL separately except in the macular area, devoid of RNFL, and studies have measured GCL thickness in the macula. Macular GCL thickness has been found to correlate with AD severity based on cognitive impairment on the Mini-Mental Score Examination (MMSE) score [35,36]. In patients with AD, the volume of GCL was significantly decreased [37]. One of the limitations of GCL thickness is its non-specificity.

GCL abnormalities have also been reported with non-AD dementia, strokes, and other neurodegenerative diseases, including multiple sclerosis. To increase the specificity, a functional testing of the retina, multifocal ERG (mERG), has been combined with retinal thickness on OCT. mERG evaluates electrical activity within the 30 degrees of the retina compared to ERG, which is a global retinal response. The electrical wave generated has an initial negative deflection (N1), followed by a positive deflection (P1) and a second negative deflection (N2) [38]. In addition to the amplitude of the wave, implicit time, the time needed for the electrical response to reach maximum amplitude, is a sensitive indicator of outer retinal function. In a cross-sectional study of 49 participants, Byun et al reported that a combination of delayed implicit time noted on mERG and GCL thickness on OCT correlated well with the presence of Aβ peptides deposition on PET scan in cognitively normal individuals with AD related neurodegeneration. Based on their results, they reported that retinal structural changes on OCT and functional changes on mERG can be used as retinal biomarkers for early detection of amyloid deposition in cognitively normal individuals with AD [39]. Similar to pathological reports of outer retinal damage at the level of photoreceptors, OCT images have revealed decreased reflectivity of the photoreceptor inner and outer segments to light stimulus in patients with early-onset AD compared to age-matched controls [40].

OCTA has been reported the vascular density was significantly lower in superficial retinal capillary vascular plexus (SRCP) in those with AD [41]. The reduction in vascular network is consistent with pathological reports from postmortem studies of the retina in AD patients, which has revealed a vascular distribution of amyloid plaques compared to non-vascular distribution in the brain [13]. In AD mouse models, Aβ peptides have been found in the retinal and choroidal vasculature suggesting that Aβ may be implicated in alterations in blood flow [13.14]. In another study, DRCP (deep retinal capillary plexus) densities correlated better with significant reduction compared to SRCP densities in AD patients compared to healthy controls [42]. OCTA changes have also been reported to be used as a biomarker to detect preclinical AD, that is, patients who are biomarker positive by PET scan and are cognitively normal. OCTA images reveal that foveal avascular zone (FAZ), the central area of retina, normally devoid of retinal capillaries, has been suggested to be increased in patients with preclinical AD; however, these changes are still disputed [43,44].

OCT changes reflect neuronal loss in the retina, which indicates that the disease is well under progression. Imaging techniques have enabled in-vivo imaging of retinal Aβ plaques in live animals using a curcumin-based amyloid probe for labeling amyloid and a modified scanning laser ophthalmoscope (SLO) to observe the curcumin fluorescence within the retinal layers of the mice. Curcumin has natural fluorescence, high affinity to Aβ peptides, and has been shown to be non-toxic on systemic administration [45]. In fact, studies have reported that curcumin has anti-oxidative and anti-inflammatory properties and growing evidence that it reduces Aβ peptides oligomer production [46]. Proof of human trials have shown that oral curcumin ingested over several days by AD patients, followed by retinal images taken by SLO camera have shown increased fluorescent intensity in the retina at days 1 and 10 compared to baseline, correlating with amyloid deposits in the retina. The retinal deposits could be quantified and

compared among AD patients, non-AD dementia patients, and controls, showing a significant increase among AD patients. OCT was then used to obtain high-resolution cross-sectional images of the area of retinal deposit and revealed the amyloid deposits were localized to the outer retina above the level of RPE. The amyloid deposits were distributed along the peripheral retina, consistent with histological distribution. The authors also reported curcumin-positive deposits in the outer retina in patients with AMD, further proving that drusen deposits in patients with AMD also have amyloid deposits [45, 47].

There is ongoing research to image beta-amyloid in vivo without using biomarkers such as curcumin. Hyperspectral (HS) imaging is based on the principle of acquiring an image across various wavelengths of light and combining the spectral data obtained with spatial data to develop a single data cube [48]. Each pixel in the HS image obtained has a reflectance spectrum of a single point across different wavelengths of light. Aβ peptides have a characteristic spectral signature that has been identified and developed in preclinical studies on mice AD models. It has been reported that signal strength is proportional to the amount of Aβ peptides in the tissue. The retinal images are taken with a specialized camera, Metabolic Hyperspectral Retinal Camera (MHRC). The study reported significant differences in the retinal reflectance spectra on images obtained from MHRC in individuals with substantial Aβ burden on brain PET imaging with mild cognitive impairment compared to age-matched PET-negative controls. Retinal imaging scores from MHRC correlated with brain Aβ load [49]. MHRC is a noninvasive, repeatable method to identify and quantify beta-amyloid load within the retina and indirectly provide a way to predict beta-amyloid within the brain, helping to screen individuals at risk of AD.

Discussion

The prevalence of Alzheimer's dementia is expected to burden society and health care worldwide. The quality of life in patients with AD is limited due to the progressive neurodegeneration compounded by visual disability due to blindness from associated visual conditions such as macular degeneration and glaucoma. Most patients with AD already have cognitive decline at the time of diagnosis with significant pathological changes in the brain.

Treatment of AD is aimed at treating the symptoms arising from cognitive decline. The two major classes of medications used for treatment include cholinesterase inhibitors and NMDA antagonists. Cholinesterase inhibitors increase the levels of acetyl choline, a neurotransmitter predominantly used by neurons to communicate across synapses. In AD, due to depletion of synapses, there is less acetylcholine and reduced interneuronal communication. Cholinesterase inhibitors, by inhibiting the enzyme, acetylcholine esterase, which typically degrades acetylcholine, increase its levels and moderately improve neuropsychiatric symptoms such as agitation and depression. Commonly prescribed cholinesterase inhibitors include donepezil, galantamine, and rivastigmine. However, these medications have side effects, which include diarrhea, nausea, loss of appetite, and sleep disturbances. NMDA antagonists work by reducing glutamate-induced excitotoxicity and neuronal death. Memantine, the currently approved medication, slows the progression of symptoms with moderate to severe Alzheimer's disease. Memantine is sometimes used in combination with a cholinesterase inhibitor, and its side effects include dizziness and confusion. However, both these medications have no effect on the progression of AD.

The treatment of AD is moving from symptomatic treatment to developing novel medications that can modify the course of the disease. In 2021, the Food and Drug Administration (FDA) approved aducanumab (Aduhelm) to treat some cases of Alzheimer's disease. Aducanumab is a monoclonal antibody directed against beta-amyloid. The drug was approved for mild cases of AD and has shown some effect in reducing the beta-amyloid load in the brain, although results have been controversial. The medication is expensive, costing more than $50,000 per patient per year and additional costs for diagnostic tests like PET scans. Other disease modifying drugs that are being developed include other monoclonal antibodies donanemab and solanezumab; beta-amyloid production blockers, which inhibit beta and gamma-secretase and prevent amyloidogenic processing of APP; and tau aggregation inhibitors. Currently, more than 100 drugs are being evaluated in various stages of clinical trials for the treatment of AD. Newer biomarkers are needed to test the efficacy of these drugs. Apart from neuroimaging biomarkers, several se-

rum biomarkers being reported for early diagnosis and monitoring of AD spectrum disease progression include amyloid β1-42 (Aβ1-42), t-Tau, p-Tau181, and neurofilament light chain (NFL). Serum biomarkers are cost-effective compared to expensive neuroimaging tests. However, they are still invasive and not 100% specific. Clinical trials combine two or more biomarkers, mixing fluidic analysis with imaging techniques to achieve high specificity and keep it cost-effective, noninvasive, and repeatable. Retinal imaging techniques are at the forefront of research to identify patients with AD before cognitive decline and develop a lasting cure for the disease.

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