Abstract: The retina is part of the central nervous system (CNS), and therefore, in Alzheimer's disease (AD), retinal and optic nerve degeneration could take place. This degeneration leads to neurofunctional changes that can be detected early and followed up throughout the evolution of the disease. As opposed to other CNS structures, the eye is easily accessible for in vivo observation. Retinal organization allows for the identification of its different neurons, and in consequence, detection of minimal changes taking place during neurodegeneration is possible. Functional vision studies performed on AD patients in recent years have shown how visual acuity, contrast sensitivity, color vision, and visual integration vary with the progression of neurodegeneration. The development of optical coherence tomography in ophthalmology has meant a breakthrough in retinal exploratory techniques, allowing the obtention of high-resolution images using light. This technique enables retinal analysis in the earliest stages of AD, being considered as a biomarker of neuronal damage. Given AD's high prevalence and its expected increase, it is important to
perform easy tests that cause minimal discomfort to the patients at a low cost while offering abundant information on the stage of the disease.

**Keywords:** Alzheimer’s disease; biomarker; neurodegeneration; retina; visual system

### INTRODUCTION

Alzheimer’s disease (AD) is recognized by the World Health Organization as a global public health priority. AD is the single principal cause of dementia, between 50 and 75%, and is primarily a condition of aging, roughly doubling in prevalence every 5 years after age 65 (1). The incidence of AD increases with age, and the prevalence is growing as a result of the aging of the population (2); however, there are no disease-modifying therapies currently available, and none have been successful in late-stage clinical trials (3).

Late-onset AD is likely to be driven by a complex interplay between genetic and environmental factors, implicating inflammatory, cholesterol metabolism and endosomal-vesicle recycling pathway (4) and the presence of the APOE+4 allele (5). In addition, AD is frequently associated with vascular dysfunctions and inflammation (6). In particular, it is now recognized to play a key role in AD pathogenesis the microglial activation in response to amyloid deposition (7).

The basis of AD has not been fully elucidated. However, the progressive accumulation of β-amyloid (Aβ) plaques and abnormal forms of phosphorylated tau (tau tangles) within and outside of neurons and neuroinflammation, both of which could lead to neuronal loss and synaptic dysfunction (8), are considered to be the neuropathological hallmarks (9–11).

The “amyloid cascade hypothesis” (12) is based on the progressive deposition of fibrillar Aβ as diffuse plaques, which activates an inflammatory response, altered ion homeostasis, oxidative stress, and altered kinase/phosphatase activity, leading to the formation of NFTs and widespread synaptic dysfunction and neuronal death (13). Recently, it has been demonstrated that an Aβ plaque environment can accelerate the templated spread of tau pathology (14, 15).

Hyperphosphorylation of tau has numerous pathogenic effects. It reduces tau’s affinity for microtubules and increases its possibility to aggregate and fibrillize (16). This impact leads to weakening of microtubules with consequent axonal transport failure and neurodegeneration (15).

In the past decade, remarkable advances have been made in disease-specific biomarkers based on the detection of amyloid or neurodegeneration. With the knowledge that the pathological changes occur years previous to symptoms, the arrival of biomarkers of Aβ and tau pathology, and nuclear imaging measures of atrophy, diagnostic criteria have evolved to allow for the diagnosis to be made both earlier and with increased molecular specificity.

These biomarkers not only enable the diagnosis of AD in the stage of dementia but also beforehand, in the prodromal stages of AD. However, these biomarkers are not applicable as population-wide screening tools because they are invasive, not easily applicable and expensive.
Eye Function and Structure in Alzheimer’s Disease

Eye and Brain: Symbiotic Relationship

Over the last few decades, in neurodegenerative diseases of the central nervous system (CNS), the importance of ophthalmic examination has reportedly increased. It is not surprising that the retina, as an extension of the CNS, is impaired in patients with CNS degeneration (17). The eye has unique physical structures and is host to specialized immune responses similar to those in the brain and spinal cord (18–20). In fact, abnormal results were found in AD patients in test exploring visual processing/visual pathways and also in those examining the retina (17).

The neuroinflammatory changes could be detected using a routinely diagnostic technique used in ophthalmology, the optical coherence tomography (OCT). OCT allows to see the anatomic detail of pathological changes in the retina and optic nerve. Changes in OCT measurements have been used to study the course of neurodegenerative diseases such AD (21–25), suggesting that the data compiled may be useful as a biomarker in diagnosing and treating neurodegenerative disease.

The retina is made up of specialized neuron layers that are interconnected via synapses (photoreceptors, bipolar cells, horizontal cells, amacrine cells, interplexiform cells and ganglion cells) (18, 26). In the eye, the light that enters is captured by the photoreceptor cells in the outer retina, initiating a cascade of neural signals that finally reach the retinal ganglion cells (RGCs), whose axons form the optic nerve. These axons project to the lateral geniculate nucleus in the thalamus and to the superior colliculus in the midbrain, whose information is then transmitted to specialized visual processing centers in the brain that provide a perception of the world.

The first study, showing postmortem anomalies in the optic nerve of patients with AD, demonstrated not only widespread axonal degeneration but also a reduction in the number of RGC and the thickness of nerve fiber layer (NFL), with a 25% decrease of ganglion cell layer (GCL) (27–29). More recent OCT studies also found a decrease in the thickness of inner retinal layers (NFL and GCL) (30–41).

The presence of Aβ plaques in GCL could explain the RGC degeneration in the AD course (19, 27, 42). In fact, it has been demonstrated that most of the Aβ plaques deposited in the retina are located in the GCL (43, 44). Deposits of Aβ trigger a neurotoxic effect in the RGC, inducing apoptosis (45). This apoptosis is dose- and time-dependent (45). Some pieces of evidence showed that Aβ expression is greater in the central retina than in the periphery of the eye of an AD mouse model (46). As in the brain, Aβ deposits in the retina have the classical plaque structure, forming clusters along the blood vessels (47). Aβ accumulations were located inside and around melanopsin retinal ganglion cells (mRGC) and more evident in the superior quadrant of the retina (47).

In the last few years, it was found that mRGCs also showed a significant loss in postmortem AD retinas (47). These cells represent the 1–2% subpopulation of RGC that are intrinsically photosensitive (47, 48). The mRGC send ambient light information to the hypothalamus nucleus via the retinohypothalamic tract (48), regulating circadian rhythms, pupil size, sleep alertness, and pineal melatonin synthesis (49–51). This mRGC loss could contribute to circadian dysfunction in AD (47). Indeed, its presence in the early stages of AD of circadian dysfunction was postulated as the worst prognostic value in AD (47).
All these retinal changes could be responsible, in part, for the visual deficit that occurs in AD patients. The acetylcholine decrease is also characteristic of this disease, and therefore contributes to the visual deficit that occurs in AD patients because acetylcholine is essential for the correct visual process of healthy retinas (52).

**VISUAL FUNCTIONAL TESTS IN THE EXPLORATION OF AD**

Aging affects visual function because light transmission diminishes inside the eye, whereas the scattering of light increases. With age, there is not only a decrease in the density of photoreceptors in the retina, but there is also less efficiency in phototransduction and photopigment regeneration (53). In addition to aging, visual processing is affected in AD patients. The brain’s visual areas are involved in AD pathology (in the dorsal and ventral regions), worsening the perception of movement; angular and color discrimination; and form and face identification (54–60). There are several tests such as the visual acuity test, and the contrast sensitivity and color vision test to explore this visual processing in the ophthalmology practice.

**Visual acuity**

Visual acuity (VA) is a measure of the spatial resolution of the visual system to detect and discriminate an object. In patients with AD, it is very important to choose the correct VA test. It was demonstrated that VA tests present better values if the letters are isolated (61).

**Contrast sensitivity and color vision**

The contrast sensitivity (CS) test assesses the capacity of the visual system to distinguish an object from the background in which it is placed. The CS test allows us to ascertain the integration of the information of the ganglion cells receptor field and their cortical processes. CS is measured by a threshold curve in which the spatial frequencies examined are depicted. Color vision is an illusion created by the interactions of the neurons in our brain. It is intimately linked to the perception of form where color facilitates detecting borders of objects (62). Parvo- and magnocellular ganglion cells are located in the GCL and lead to two different visual pathways that identify color and contrast (63). Parvocellular ganglion cells are smaller and more numerous than other retina ganglion cells, with smaller receptor fields located in the macular retinal area. They give rise to the parvocellular visual pathway, specialized in pattern identification and color; and it is most sensitive to high spatial frequency (51). The magnocellular pathway originates in magnocellular retina ganglion cells, which are larger and more numerous, and have larger receptor fields that are more sensitive to low spatial frequencies (63). There is a third type of ganglion cell that is called koniocellular, which receives information from short wave cones. Koniocellular cells are also sensitive to blue–yellow tones (64, 65). CS is a really important visual function. Even several studies showed that a CS loss is the best predictor of the ability of elders to perform daily life activities (66, 67).
Visual fields

The visual field (VF) refers to the total space in which objects can be seen in the side (peripheral) vision as your eyes are focused on a central point. The fovea, where the cone photoreceptor density is at its highest, is the area of greatest sensitivity. The visual sensitivity comes down further from the fovea. Traditional perimetry is carried out under photopic conditions, and therefore, rod photoreceptors do not contribute to the visual field (68). The normal visual field extends to approximately 60° nasally, 90° temporally, 60° superiorly and 70° inferiorly. In the area of the optic nerve head, temporal part of the VF, exists a blind spot that indicates an area with no photoreceptors (69).

Visual integration

Identifying a visual stimulus requires not only physical input analysis but also the contact between the neuronal representations of the stimulus and the memories that the perceivers have accumulated through their life experiences with the objects. Object identification arises from the dynamic interaction between a sensorial/physical process (upstream processing) and a cognitive process (downstream processing). Spatial frequency is an important physical property of the image. The extraction of visual sensory characteristics follows a course to a fine processing scheme where the low spatial frequency represents the overall information about the shape and orientation of the stimulus, while the high spatial frequency corresponds to the configuration information and fine details (70–75).

OPHTHALMOLOGICAL METHODS FOR RETINAL ANALYSIS

Over the past decade OCT has evolved as one of the most important tests in ophthalmic practice. It is a non-invasive imaging technique that provides high-resolution, cross-sectional images of the retina.

Optical coherence tomography

OCT was first demonstrated for cross-sectional retinal imaging in 1991 by a Massachusetts Institute of Technology (MIT) team (76). OCT synthesizes cross-sectional images from a series of laterally adjacent depth-scans giving a non-invasive clinical tool to evaluate the structural anatomy and the evaluation of the integrity of the retina.

Optical coherence tomography angiography

Optical coherence tomography angiography (OCTA) is a promising new method for visualizing the retinal vasculature and choroidal vascular layers. A key advantage of OCTA over traditional fluorescein angiography is that it provides depth-resolved information without contrast. The basis of OCTA is to repeatedly scan a region and then examine the resultant images for changes. Stationary tissue
structures will show little change, whereas moving structures, such as blood flowing through vessels, can show changes between images. Contrast is generated based on the difference between moving cells in the vasculature and the static surrounding tissue. This imaging technique can be performed in patients for whom fluorescein angiography or indocyanine green angiography may not be indicated (77). OCTA is clinically used as an en face imaging modality, which is generated by summarizing the flow information within the depth range encompassed by the current scheme. This scheme subdivides the retinal circulation into two plexuses and choroidal circulation into two slabs. Angiograms, which are similar to fluorescein angiography or indocyanine green angiography, are also produced (78).

FUNCTIONAL CHANGES IN AD

Nowadays, it is known that, in AD, in addition to altering brain structures, the involvement of the different regions of the visual system also occurs, with a manifestation of distinct symptoms and signs that can be detected by clinical history and ophthalmological studies.

VA has proven to be a controversial test in AD. Studies have not found an alteration in AD patients (79–86), and others have found VA loss and linked them to visual hallucinations (87, 88) (Table 1). Moreover, these alterations of VA are

| TABLE 1 | Eye changes in AD patients |
| --- | --- |
| **Visual alterations** | References |
| Visual acuity | 87, 88 |
| Contrast sensitivity | 82, 84, 85, 90–102, 103, 104 |
| Visual field | 105–109 |
| Color vision | 58, 84, 93, 110, 113–116 |
| Visual integration | 93, 117 |
| **Structural alterations** | |
| Retinal Aβ deposition | 19, 27, 42–47 |
| Optic nerve | 27–29 |
| Macular thickness | |
| Inner retinal layers | 30–41, 138, 140–145 |
| Outer retinal layers | 135 |
| Peripapillary thickness | 21, 24, 30–38, 120–127 |
| Retinal vascularization | 148–150 |
| Choroid thickness | 125, 148, 151–153 |

AD: Alzheimer’s disease; Aβ: beta-amyloid
related to difficulties in writing and reading (89). On the other hand, recent studies have found that CS testing is a more sensitive tool than VA testing to identify the subclinical impairment of visual function (90, 91). CS precedes the development of dementia at 10 years of the longitudinal follow-up in a well-phenotyped, prospective, community-based cohort (90, 91). It has been shown that the CS function is affected in AD patients. The impairment ranges from a reduction in all spatial frequencies (85, 92–99) to a greater decline in high (92, 93, 98, 100) or low spatial frequencies (82, 84, 101, 102). Such discrepancies in the affected frequencies could be due to differences among the CS test used as well as the patients included in the studies (17, 66). Recent works show that CS is the main manifestation during the initial disease stage. There is a progressive impairment throughout the disease course (93, 103, 104) (Table 1). CS impairment in AD has consequences for cognitive abilities and daily functions, given that the most affected spatial frequencies are the higher frequencies corresponding to macular function (17). The presence of reduced CS years before the clinical onset of dementia suggests that this association is not simply a consequence of later stage dementia. Furthermore, reduced CS can precede the clinical onset of cortical or subcortical dementia neurodegeneration (90).

Visual field test requires significant cooperation from the patient. Therefore, the reports of VF and AD are scarce, and most are case reports (17, 68). However, it has been observed that decreased VF sensitivity correlated with cognitive impairment. A large prospective study of threshold VF perimetry in patients with probable AD demonstrated that the most common VF abnormality was bilateral inferior constriction of the VF in an arcuate-like pattern (105, 106). AD patients underwent a diffuse sensitivity loss and defects that involved the central field. In 39% of AD patients, the density of plaques and tangles was greater in the cuneal compared with lingual gyri, supporting the theory that cortical disease is responsible for the VF loss (105). Recent findings show that the side of the homonymous defect is predicted by lateralized occipital atrophy (107–109) (Table 1).

Another manifestation of AD is the fluctuations in color perception, which are mainly errors in color recognition due to the involvement of the parvocellular pathway (110).

In the color perception, some studies using the Farnsworth test and Ishihara test found no differences between AD patients and control group (96, 111, 112). On the other hand, some tritan-axis defects were found, showing a correlation with the cognitive decline (58, 84, 93, 113, 114). The discrepancy in the results of both studies may be due to the fact that each study used a different color vision method. A recent investigation showed that the Ishihara color vision test could discriminate between AD and vascular dementia (115). The Ishihara test may involve dorsal cortical pathways that extend from the occipital to the parietal lobes. In the Ishihara test, the patients have to identify a number occulted in a pattern made up of small color forms with different tones. AD patients usually present simultagnosia caused by an occipitoparietal dysfunction, and therefore, they cannot recognize the pattern that is presented in the Ishihara test. The problem does not lie in the color sense, but in the inability to reconstruct the pattern (115). Using the Farnsworth-Munsell 100 hue test, a significantly decreased color discrimination was found in AD. In addition, the number of color discrimination errors was inversely related to Mini-Mental State Examination scores (MMSE) (110). Some studies using the Farnsworth color testing methods, not influenced
by dorsal stream dysfunction, suggest that AD patients tend to have tritan color defects (58, 93) while others have found a protanomaly (116) (Table 1).

The perception digital test (PDT) is a sensitive method in mild AD patients developed for evaluating their visual-perception disorders (117). The test is designed to assess the visual recognition of familiar situations. PDT has a significant correlation with the cognitive decline of the AD patient, indicating that patients with mild AD have significantly more failures in PDT than controls (93, 117) (Table 1).

**STRUCTURAL CHANGES IN AD**

The retinal nerve fiber layer (RNFL), RGC and inner retinal layers are considered indirect biomarkers of the CNS, allowing the prediction of brain pathology in patients suffering from different neurological diseases (118, 119). Many studies focus on the thickness of segmented peripapillary RNFL (superior, inferior, nasal, and temporal) in patients with AD comparing them with controls. Some works showed a decrease in the peripapillary RNFL thickness in all areas (30, 31, 34, 36–38). However, others authors found that the peripapillary RNFL thinning occurred in the inferior and superior regions (35, 39, 40), while other works demonstrated that peripapillary RNFL thinning appeared only in the superior region (120–124). Some studies reported thinning in the RNFL associated with a progressive cognitive decline (21, 24, 123, 125, 126) (Table 1). The variance in peripapillary RNFL thickness reported in AD might be due to differences in disease progression among patients studied since patients with greater peripapillary region alteration were those with a more advanced stage of AD. In any case, thinner peripapillary RNFL indicates fewer RGCs in AD, which confirmed the differences in OCT measurements in AD patients (127). The loss of RGCs is matched with the pathologic cascade hypothesis in AD, which affects both the cerebral neuron and the RGCs in the retina (36). This whole peripapillary RNFL controversy is the result of studies based on small size samples and important methodological heterogeneity (37, 128–130). In line with this hypothesis, pattern electroretinography showed a decrease in their wave response, suggesting that RGCs are directly involved in AD (38, 92, 131–133).

Some authors did not show any statistical significance with respect to the macular outer retinal thickness analysis between the neurodegenerative disease and control groups (134). However, other studies in the context of early AD observed a loss in the outer nuclear layer that could suggest retrograde transsynaptic degeneration (135). In AD, most of the studies have been done with OCT, and they have focused on the inner retinal layers, whereas less attention has been devoted to the outer retinal layers. The discrepancy in results could be due to technical variability, examination time and OCT interpretation (129, 136, 137). By using human postmortem tissue in the eyes of severe AD patients with confirmed neuropathology, different patterns of thinning in the superior-nasal and superior-temporal regions of the retina relative to the optic nerve have been found. Also, they found a gradient of thickness reduction whereby thinning was greatest for the inner layers of the retina, followed by the outer layers of the retina (138). This thickness profile matches the distribution of the retinal Аβ deposits in the mid- and
far-periphery of the superior quadrants of these tissues as previously demonstrated (19, 28, 29, 47, 139).

In the last few years, some studies focusing on the analysis of patients with mild cognitive impairment (MCI) found a thinning in the macular inner layers (140). By contrast, a macular volume increase was found in MCI compared with controls in others works (141). This finding could be explained as a possible inflammation and gliosis prior to neurodegeneration.

**CHANGES IN THE EARLY AD AND THEIR PROGNOSTIC VALUE IN THE DETECTION AND FOLLOW-UP**

In the most incipient AD stages, the macular RNFL thickness and total macular volume measured by OCT have better prognostic values in mild AD patients than in healthy subjects. The thickness of the inner superior macula seems to have the highest diagnostic value in early AD neurodegeneration. Possibly, the macular area is the first affected area of the retina, which may be due to the large number of ganglion cells in this retinal area (21, 24). Other studies have primarily assessed retinal thickness changes in the macula to explain the visual symptoms experienced by AD patients (138). The earliest detectable structural retinal change associated with AD is suggested to be a decrease in macular RNFL volume, and it is related to neocortical Aβ accumulation in the very early AD (135). In healthy eyes, the macular region of the retina is physiologically very active, and this hyperexcitation might be diminishing in the preclinical stage of AD (28). In support of this theory, postmortem histological studies have found pathological alteration of RGC in the macular region in AD patients (28, 47). In a meta-analysis of 17 studies comparing AD patients with healthy controls and in five studies comparing individuals with MCI with controls, there were significant decreases in the thickness of the macular region in all four quadrants compared to controls, thus suggesting that the degenerative process affects the entire macular region (130).

Another work, using a multivariate regression model show the existence of specific areas of thickening, interspersed with areas of thinning in the macula of AD and MCI patients. This finding supports the idea that inner retinal layers may be suffering dynamic changes during the course of AD progression (142). The retinal thickening in MCI was attributed to gliosis preceding neuronal loss and atrophy of the axonal projections in the RNFL (143). This theory has been supported by histopathology work, suggesting that gliosis precedes human AD pathology in the brain (144, 145). However, other studies in OCT suggested that the outer retinal thickness did not show any statistical significance between the neurodegenerative disease groups and controls (134). Other authors consider that many other findings have been described such as a reduction in macular volume, RGC layer thickness, choroid thickness and some vascular alteration. These results might be promising biomarkers for dementia staging and AD progression (146, 147).

In recent years, thanks to the development of the OCTA, several studies analyzed the retinal vascularization and the choroid. Most of the studies, published in moderate AD, have found a loss of the retinal vascular density in the macular area with slower blood flow and an increase in the foveal avascular
Figure 1 Areas under the ROC curves of the psychophysical tests (A–D) and macular OCT (E–F) in discriminating between mild AD patients and control subjects. (A) Visual acuity (dec), (B) contrast sensitivity, (C) Rue 28-hue color test, (D) perception digital test, (E) fovea and macular volume, and (F) inner macular quadrants. Modified from (A–D) Salobrar-Garcia et al., 2015 (93) and (E–F) Garcia-Martin et al., 2014 (21).
All these changes could be explained as a consequence of the amyloid angiopathy, which occurs in AD, in which amyloid deposits formed in the walls of the blood vessels. This process resulted in an ocular vascular occlusion and the diminishing of blood flow (120, 148, 149, 154).

It is possible that retinal AD biomarkers can only be obtained after having integrated various of the already cited biomarkers, which include both neuroretinal (such as RFNL, GCL, macular thickness) and retinovascular parameters (vessel morphology among others), in a composite biomarker (128).

The analysis of the ophthalmological tests prognostic value of AD showed that VA, CS, color perception, and visual integration (93) have a significant predictive value in early AD disease (Figure 1). The CS is the best predictive test in the diagnosis of the AD with an aROC between 0.857 and 0.755 (93), while the aROC curves of the OCT showed the best prognostic value is found in the macular area with values of $r = 0.821$ (21) (Figure 1). The focus must be centered on these tests to see the visual changes in the AD disease.

**CONCLUSION**

In conclusion, several alterations have been shown in the visual perception and the retinal structure in the eyes of AD patients, even in the earliest stages. The VA, CS, color perception, and visual integration tests, as well as macular OCT, have been altered in the early stages. When the disease progresses in the eyes of moderate AD patients, retina alteration reaches the peripapillary area, showing the progression of neurodegeneration in the eye.

**Conflict of interest:** The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this chapter.

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