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Review Article

Retinal Alterations as Early Biomarkers of Neurodegenerative Diseases and Cognitive Impairment in The Older Adults

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Abstract

Alterations in imaging studies of the retina, i.e., optical coherence tomography, fundus images, flowmetry and retinal oximetry are indicators of neurodegenerative diseases such as Alzheimer's, Parkinson's, vascular dementia, amyotrophic lateral sclerosis, among others [1-4]. This imaging studies give an in vivo, non-invasive, and fast diagnostic alternative, which can potentially lead to treatment improvement and better preparation of the patients and their families to the severe stages of these diseases [5,6].

Keywords: Retina, Older adults, Cognitive Impairment, Neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Schizophrenia, Multiple sclerosis, Vascular dementia, Lewy body dementia, Ganglion cells, Optical coherence tomography, Fundoscopy, Beta amyloid plaques, Age related macular degeneration

Introduction

The retina is the nervous layer of the eyeball, sharing its embryological origin with the central nervous system [1,7,8]. This opens a plethora of possibilities for evaluation of the brain and its alterations through retinal imaging, since it is a part of the central nervous system that can be seen *in vivo*, in a fast and non-invasive manner, using imaging studies such as optical coherence tomography, fundoscopy, doppler flowmetry and retinal pulse oximetry [2,7,9]. In these studies, we can evaluate alterations in vascularization, pathological protein accumulations, inflammation, changes in the thickness of retinal layers, among other data [2,5,10,11]. The neurodegenerative diseases in which these imaging methods have been applied to geriatric patients are Alzheimer's disease, which is the leading cause of dementia, present in 10 to 15% of those over 65 years of age [9,12-15]; vascular dementia, which is the second cause of dementia [2,16-18]; Parkinson's disease, which is the second most frequent neurodegenerative disease, present in approximately 1% of this population [3,10]. Other neurodegenerative diseases in which the usefulness of retinal studies has been demonstrated are amyotrophic lateral sclerosis [19-22], Lewy body dementia [3,12,23,24], multiple sclerosis [1,2,10,25,26], schizophrenia [1,27,28], and Huntington's disease [4,29,30]. The study of retinal alterations could be an *in vivo* biomarker of these diseases, helping to establish the diagnosis as early as possible, which opens the door to timely care, delaying severe symptomatology and reducing complications, as well as creating new effective treatments [5,6]. It also provides the

opportunity for the patient and family members to make decisions regarding housing, finding primary and auxiliary caregivers, financing, choice of treatment and advance directives before severe functional and cognitive impairments make it impossible for the patient to decide [5,6].

Methods

We used a systematic search in Pubmed, Google Scholar and Clinical Key literature databases under the concepts of: "Retina and cognitive deficiency", "Retina and neurodegeneration", "Macular degeneration and Alzheimer's", "Retina and Alzheimer's", "Retina and Parkinson's", "Retina and amyotrophic lateral sclerosis", "Retina and dementia" taking into account only articles written between 2014 and 2019 in Spanish and English, including clinical studies, clinical trials, narrative reviews, meta-analyses and systematic reviews.

Content

The retina is the nervous layer of the eyeball and shares its embryological origin with the central nervous system [1,7,8]. Its formation starts from migratory pluripotential cells of the neuroectoderm of the diencephalic part of the neural tube, from which the central nervous system derives [1,7,31]. Because of this common origin, retinal microvasculature provides an insight into the cerebral vasculature [2,13,15]. Since retina and brain contain neurons, microglia, and astrocytes that confers them the same blood barrier [13,15,32]. Retina tissues are susceptible to changes when brain neurodegeneration occur [5,13,33] and can be an approach for the study, diagnosis, and prognosis in diseases such as Alzheimer's, Parkinson's, Lewy body dementia, amyotrophic lateral sclerosis, multiple sclerosis, schizophrenia, among others [1,4,10,20,27,34].

Alzheimer's Disease

Since its first description in 1906 by the German psychiatrist Alois Alzheimer, ocular affections were observed in these patients, although usually attributed to damage in the visual cortex, numerous recent studies, and analyses [1,2,7,12,29,35] pointed out alterations in the retina that could be considered as biomarkers, since they manifest themselves before the memory deficit and cognitive deterioration [7,12,13]. The diagnosis of this disease is characterized by the formation of "senile plaques" of beta-amyloid protein and neurofibrillary tangles of tau protein in the brain found by necropsy [9,12,13,34]. Thus, retinal imaging methods are considered as an option for *in vivo*, noninvasive diagnosis of this disease [1,9,13,34,36].

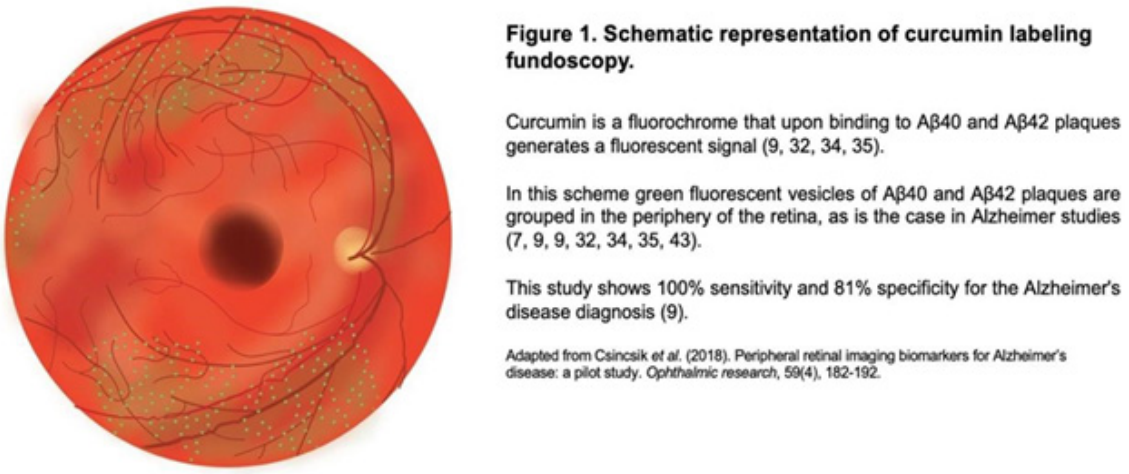
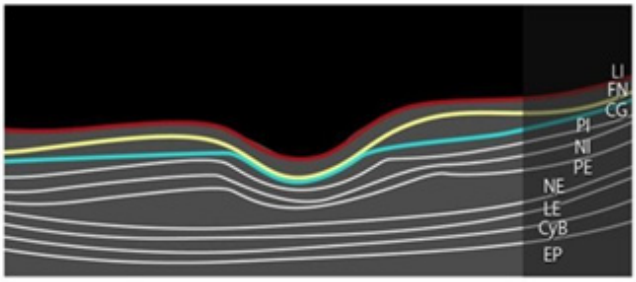


Figure 1: Schematic representation of curcumin labelling fundoscopy.

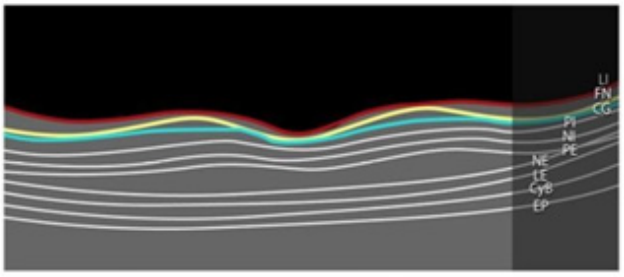
The first study to be discussed is fundoscopy with curcumin labeling, a fluorochrome that passes the blood-retinal barrier and upon binding to beta-amyloid plaques generates a fluorescent signal [9,29,32,34] (Figure 1). The presence of beta-amyloid protein and its amyloid precursor protein (APP) can be found as a normal part of aging [9,35], however neurotoxic proteins beta-amyloid protein40 (Aβ40) and beta-amyloid42 (Aβ42) aggregates are not found in geriatric patients without this disease [32,34,35,37-39]. These plaques have been found in the brain 15 to 20 years before the symptomatologic onset of Alzheimer's disease, and studies have found these plaques in the retina years before in the brain, so they can be used as biomarkers leading to anti-amyloid treatments years before the onset of the brain disease [7,9,31,32,34,35,38]. Retinal Aβ40 and Aβ42 plaques, called "amyloid vesicles" [9], are associated to age-related macular degeneration, since in this disease we can find beta-amyloid protein within the drusen that characterize it [9,13,32,37,40,41]. The main difference is that in macular degeneration its drusen are found below the pigment epithelium in the macular region and there is disruption of Bruch's membrane; while in Alzheimer's disease the aggregates are found above the pigment epithelium in the periphery of the retina and Bruch's membrane is intact [8,9,13,31,34,41-44] (Figure 1).

Accumulations of beta-amyloid protein in the retina cause a neuroinflammatory state increasing the expression of cytokines such as MCP-1, which stimulates apoptosis in the ganglion layer and gliosis [9,36,37]. Other cytokines such as IL-1β, IL-8, IL-3 damage the barrier properties of the pigment epithelium, leading to an inflammatory state, mitochondrial damage, accumulation of reactive oxygen species and hyperproduction of vascular endothelial growth factor [9,16,35]. Accumulation of Aβ40, Aβ42 and tau protein lead to neuronal and synapse loss in retinal layers, causing neurodegeneration [12,37,38,45]. Tau protein, which impairs synapses, mainly accumulates in the ganglion cell, inner plexiform, inner nuclear and outer plexiform layers, which can also be assessed by fundoscopy with fluorescent labeling [12,32,46].

In Alzheimer's disease, the first sign of disease in the retina is the thinning of the nerve fiber layer in the macular and peripapillary region [10,11,22,33,47], of at least 17. 5% (30), as the disease progresses, there is thinning in the internal limiting and ganglionic layers up to 25% at the level of the fovea [47], and in more advanced patients it has been observed that the thinning reaches the internal plexiform and internal nuclear layers [9,10,11,31,48]. These thinning is observed in optical coherence tomography, another *in vivo*, noninvasive, high-resolution method that allows measuring the thickness of the retinal layers and macular volume [2,5,31,46] (Figure 2).



A. Schematic of an optical coherence tomography of a healthy person (10, 11, 31 33, 47). LI=internal limiting; FN=nerve fiber layers; CG=ganglion cell layer; PI=internal plexiform; NI=internal nuclear; PE=external plexiform; NE=external nuclear; LE=external limiting; CyB= cone and rod layer; EP= pigment epithelium.



B. Schematic of an optical coherence tomogram of a person with Alzheimer's disease showing thinning of the innermost layers, mainly the ganglion cell layer and the nerve fiber layer.

Adapted from Santos CY, Johnson LN, Sinoff SE, et al. Change in retinal structural anatomy during the preclinical stage of Alzheimer's disease. Alzheimer Dement (Amst). 2018 Feb 7:10: 196-209

Figure 2: Schematic representation of an optical coherence tomography.

The most frequently findings in different studies are the thinning of the ganglion cell and nerve fiber layers, optic nerve atrophy, reduction of macular volume and pigment, and choroidal thinning; these alterations become more evident as the disease progresses [2,9,11,13,29,33,36,43,47,49-55]. Patients with greater thinning of the ganglion cell and nerve fiber layers, with greater reduction in macular volume when subjected to the mini-mental examination scored 10 or lower, indicating severe cognitive impairment [11-13,47]. Alterations in the retinal microvasculature in Alzheimer's disease have been associated with increased memory impairment, decreased speed of thinking, and alterations in executive functions [2,56]. Alterations such as the reduction blood flow, smaller venular and arteriolar diameter due to accumulation of collagen and β-amyloid plaques in the vascular walls that increase the stiffness of their walls, and elevated oxygen saturation in venules and arterioles evaluated by oximetry [13,15,18,34,56].

In addition to the similarities noted between drusen in age-related macular degeneration and amyloid vesicles in the retina in Alzheimer's disease, there are other associations between the two diseases [16,37,40,57,58]. Patients with age-related macular degeneration have been found to be at increased risk for senile dementia, cognitive impairment and even Alzheimer's disease, and this risk may be as high as 50% in individuals aged 69 to 97 years [16,37,40,59,60]. Six percent of patients with non-exudative age-related macular degeneration develop senile dementia or Alzheimer's disease [16] and show greater cognitive impairment by the brief cognitive impairment test [59,60], poorer memory retention [59] and greater impairment in executive functions [16]. Betaamyloid plaques, contained in retinal drusen, stimulate an increase in vascular endothelial growth factor, increasing the risk of exudative macular degeneration in patients with Alzheimer's disease [16]. Another interesting relationship between the two diseases is still under study; it has been observed that the administration of ranibizumab, an inhibitor of vascular endothelial growth factor, reduces the risk of senile dementia and Alzheimer's disease [61].

Parkinson's Disease

Retinal amacrine cells are interneurons that have synapses with the axons of bipolar cells and synapses with the dendrites

of ganglion cells, these synapses are found in the inner plexiform layer of the retina [11,29,62]. Amacrine cell bodies and nuclei are in the inner nuclear layer of the retina and release dopamine, which confers contrast sensitivity and color vision, because retinal cells contain D1 and D2 receptors [11,29,63]. The pathophysiology of Parkinson's disease consists of the loss of dopamine-producing cells and low concentrations of dopamine, mainly in the substantia nigra [3,11,29,64]. In the retina, loss of amacrine cells results in loss of dopamine and its functions, in addition to favoring accumulation of ubiquitin and α-synuclein, a protein associated with alterations in mitochondrial function and synaptic transmission [3,11,29,48,62]. Dopamine also regulates glutamate in the retina, so its deficit causes an elevation of glutamate, decreasing the synaptic reception capacity in the ganglion cells leading to nerve fibers atrophy that form the optic nerve [11,27]. The manifestations of this disease begin when 70-80% of the dopaminergic cells are lost, studies indicate that the loss of these cells before reaching these percentages, could give the opportunity to revert these effects with the administration of L-dopa, delaying and diminishing functional alterations in these patients [3,29].

The loss of retinal cellularity, particularly ganglion cells, can be assessed noninvasively by real-time imaging in a study called apoptotic retinal cell detection [3]. On optical coherence tomography, thinning of the macular region is evident mainly in the ganglion, inner plexiform, inner nuclear and outer plexiform layers [3,11,26,48,62]. It has been observed that the thinner the ganglionic and inner plexiform layers, especially at the macular level, the earlier and more severe the symptoms of the disease, this is associated with dopaminergic degeneration due to the loss of amacrine cells [3,23,29,62,64,65]. Fundoscopy with fluorescent labeling of αsynuclein, shows its accumulations in the inner nuclear and ganglion cell layers in Parkinson's patients, especially in the retinal artery wall, these patients show greater impairment in hippocampal synaptic function and behavioral disorders [3,2,29,64].

Amyotrophic Lateral Sclerosis

Characterized by accelerated neurodegeneration of upper and lower motor neurons, causing muscle atrophy [19-21,56]. Patients usually die within three to five years after the onset of symptomatology, due to respiratory muscle paralysis, so it is of vital importance to detect this disease as early as possible [19,21,22,26]. Optical coherence tomography shows thinning in the nerve fiber, ganglion, inner plexiform, inner nuclear and outer plexiform layers, mainly in the macular area [20-22,26,34]. When cells of these layers are lost, several functions are lost: with the loss of bipolar cells of the inner nuclear layer, the transmission of color vision through synapses with ganglion cells is impaired, which has been proven by the Hardy-Rand-Ritter test [4,20,26], by losing amacrine and horizontal cells of the inner nuclear layer, which regulate synaptic transmission between bipolar and ganglion cells by inhibition with GABA, the amount of this neurotransmitter is reduced in the retina, in the same way that it has been reduced in the brain of patients with this disease [19].

As for markers, the autophagy marker p62 has been found in bipolar cells in perinuclear inclusions [26] in the plexus layers of the retina [26] in the inner and outer plexiform layers, which are the layers where synapses happen. Another autophagy marker has been found in high concentrations, ubiquitin 2. Ubiquitin 2 is believed to be causing ganglion cell death [26]. The loss of the nerve fiber layer, composed of ganglion cell axons, is caused by retrograde synaptic degeneration, like the degeneration of upper and lower motor neurons that occurs in this pathology; also, one eye is more affected than the contralateral eye, as occurs in the motor involvement of amyotrophic lateral sclerosis [4,19,26]. Patients with greater nerve fiber layer loss had a familial form of the disease and greater hippocampal synaptic dysfunction, which when evaluated by the revised functional assessment scale for amyotrophic lateral sclerosis and the Rankin scale, greater functional severity was found [4,20,26].

Table 1: Other neurodegenerative diseases related to retinal alterations.

Disease	Alterations in the Layers of the Retina
Mild cognitive development	It is a stage considered prodromal to dementia, amnestic-like mild cognitive impairment is considered an early stage of Alzheimer's disease [1,15,39]. These patients show peripapillary thinning of nerve fibers and loss of macular volume on optical coherence tomography [1,2,7,31,36], low retinal blood flow, thinning of the choroid, and loss of macular pigment and volume [5,33,36]. The cognitive impairment of patients with these alterations has been evaluated with the Rey auditory-verbal learning test, obtaining worse results than older adults without these retinal alterations [36].
Multiple sclerosis	The pathology of this disease consists of demyelination and degeneration of the axons of the central nervous system [7,10]. The retina has unmyelinated axons that are part of the ganglion cells; in patients with this disease a thinning of the ganglion cell layers, and nerve fibers has been observed by optical coherence tomography, which indicates an axonal loss of the central nervous system. axonal loss of the central nervous system; the inner plexiform and inner nuclear layers are also thinned to a lesser extent [1,2,4,7,10,18,21,25,26,34]. Patients with greater retinal axon loss show greater ischemic retinal axon loss show greater physical disability using the expanded disability status scale, as well as greater cognitive deficits and poorer quality of life according to the multiple sclerosis-specific quality of life questionnaire MSQoL-54 [10].

Vascular dementia	Patients with increased diameter and tortuosity of retinal venules assessed by flowmetry, oximetry and angiography are at increased risk of vascular dementia [2,18,68].
Schizophrenia	In patients with at least 16 years of evolution of this disease, a thinning of the ganglion and nerve fiber layers has been observed [1,27,28,69]. The loss of ganglion cells causes a deficit in contrast sensitivity and color vision due to dopamine, glutamate and glycine dysregulation, similar to that mentioned in Parkinson's disease [27]. Other alterations have also been observed such as increased thickness of the venules in fundoscopy, as well as macular and choroidal thinning in optical coherence tomography [69]. These changes have also been observed in older adults with bipolar disorder [69].
Huntington's disease	The huntingtin protein, which causes this pathology, has been found in the retinal ganglion cell layer [4,29,30].

Lewy body dementia: The characteristic lesions of this disease are Lewy bodies and neurites, which are accumulations of αsynuclein [23,24]. These lesions can be evaluated by fundoscopy with fluorescent markings for α-synuclein, and are marked mainly in the outer plexiform, inner nuclear and ganglionic layers of the retina [23,24], these accumulations are associated with behavioral disorders [23,24]. Using an optical coherence tomography thinning in the nerve fiber layer is observed [12,18,66] in a comparative study with Parkinson's disease and Alzheimer's disease by *Moreno Ramos T, et al.* [67] where dementia due to Lewy bodies, presents the greatest thinning of this layer compared to the other two diseases. This thinning is associated with greater severity of dementia, since patients with these results obtained a severe deterioration in the Mattis dementia scale and in the mini-mental examination, compared with patients who did not show this thinning and their deterioration was mild [67] (Table 1).

Discussion

With the evidence demonstrated in the studies mentioned above, emphasizing those of *Santos CY, et al.* [7], *Koronyo Y, et al.* [32], *Koronyo-Hamaoi M, et al.* [34] and *Csincsik L, et al.* [43], it has been shown that it is possible to detect the changes of neurodegenerative diseases through the imaging study of the retina. Comparing normal aging changes with control groups, a significant difference is found. One limitation is that not all studies used scales such as mini-mental examination, Mattis dementia scale or some other method to assess the evolution of neurodegeneration and its symptomatology with respect to the changes observed in imaging studies. Studies such as *Rohani M, et al.* [4], *Satue M, et al.* [10], *Den Haan J, et al.* [11], *Mukherjee N, et al*. [21], *Knoll B, et al*. [36], *Cunha LP, et al.* [47], *Al Salem KM, et al.* (60), *Moreno Ramos T, et al.* [67] agreed that in imaging alterations the greater thinning of retinal layers according to the specific disease treated, the greater the evolution of neurodegeneration and therefore more severe symptomatology. It is worth mentioning that most of the studies referred to in this article do not mention the sensitivity and specificity of these diagnostic methods, so it is an important aspect that remains to be studied, because although it was shown that retinal manifestations can be found years before the symptomatologic onset of this group of diseases [3,5-7,9,12,13,29,31,32,34,35,38] the usefulness of these tests for early detection that can lead us to delay symptomatology, improve quality of life and even, in the future, implement new treatment options [5,6,61,68,69] still needs to be evaluated.

Conclusion

The study of the retina using imaging methods, such as fundoscopy and optical coherence tomography, is a noninvasive, *in vivo,* and rapid diagnostic aid for the neurodegenerative diseases mentioned in this article. Although its sensitivity and specificity has yet to be further evaluated, the retina opens possibilities for the early detection of these diseases. The benefits are the delay of severe symptomatology when treated early, preparation of the patient and family members for advanced stages, the opportunity for the patient to make decisions regarding treatment in severe stages, such as housing, care, financial and even the possibility of new treatment options in the future.

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