Research Article

Integrity of the nerve fiber layer of the retina in Alzheimer's disease

Abstract

Introduction: With the aging of the population, neurodegenerative diseases has become increasingly common, especially Alzheimer's disease. One of the ocular characteristics of this disease is the loss of axons of retinal ganglion cells. With the advancement of new diagnostic methods, such as the measurement of the nerve fiber layer of the retina by optical coherence tomography, we can now predict the prognosis of these patients. The objective of this study is to compare the differences in the thickness of retina between normals and patients with Alzheimer's disease.

Methods: This cross-sectional, non-interventional study was conducted at Hospital do Servidor de São Paulo State with 35 eyes of patients with Alzheimer's Disease and 36 eyes of healthy subjects. All subjetcts and patients had had complete ophthalmologic examination and the nerve fiber layer was measurement by optical coherence tomography.

Results: Differences were observed in retinal nerve fiber layer statistics of patients with Alzheimer's disease, when compared to healthy subjects.

Conclusion: The retinal nerve fibers has a lower thickness in patients with Alzheimer's disease compared to a group of healthy subjects.

Keywords: alzheimer disease, retina, tomography, optical coherence

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Introduction

With the increase in the life expectancy of the world population there was a greater attention to the diagnosis and treatment of neurodegenerative diseases. Although there is an exponential increase in the number of neuroprotective drugs for diseases, the inverse is seen in relation to the biomarkers and diagnostic neurodegenerative process. Among the neurodegenerative diseases associated with age, Alzheimer's disease is the most frequent, with cognitive and neuropsychiatric disorders resulting in progressive disability and eventual incapacitation.[1,2]

Alzheimer's disease was first described in 1906 by Alois Alzheimer, a physician psychiatrist and german neurophysiologist who, when performing the necrological study of the brain of a patient who died at 51 years of age with dementia symptoms, she observed generalized atrophy of the cerebral cortex, more pronounced in the hippocampus, observed in elderly brains. Already at that time Alzheimer described changes such as neurofibrillary tangles (Tau Protein) and senile plaques (accumulation of beta amyloid protein), which killed neurons and reduced connections synaptic.[3–5]

The visual symptoms reported in the early stages of Alzheimer's disease, include difficulties with reading, finding objects, depth perception, spatial perception in movement, color recognition and sensitivity to contrast. Previous reports have attributed these symptoms to degeneration in the cortex, however, there is growing evidence that anterior visual pathways are involved in Alzheimer's disease, particularly in the form of degeneration of the optic nerve and loss of retinal ganglion cells, suggesting that these changes may contribute to visual impairment. These mainly due to the deposition of amyloid Beta protein (Ab), histopathological marker of Alzheimer's disease, in the retinal cells of these patients.[6,8,14]

The mechanism by which amyloid beta protein can cause the death of neurons of the retina is not fully understood, however, mechanisms similar to those occurring in the brain have been demonstrated in the eye. In the retina, changes related to Alzheimer's disease include degeneration and loss of neurons, reduction of retinal nerve fiber layer, optic disc excavation, retinal vascular narrowing and tortuosity, and functional impairment.[7,9]

Optical coherence tomography (OCT) involves a non-invasive high resolution, widely used in ophthalmology. OCT technology allows quantification of the layer thickness of nerve fibers and other layers which has been of enormous value for the early identification of glaucoma and, more recently, from other diseases affecting the layer of nerve fibers. A beam of light is directed to the tissue of interest and is reflected by the microstructures according to thickness, distance and reflectivity. The breadth and delay of this reflected beam are determined by a Michelson interferometer, so you can measure the different layers. Simply put, the OCT uses a principle that resembles ultrasound, being light in the place of sound. The source of the light used for image acquisition is a superluminescent diode with high spectral band, which reaches a wavelength of 870nm, allowing high.[11] Optical coherence tomography has been used to study a variety of neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis), multiple sclerosis and optic neuromyelitis.[7,9,10] In Alzheimer's disease the degeneration of ganglion cell axons may decrease the thinning of the nerve fiber layer of the retina.[5,7]

The objective of this study was to compare the thickness diferences of normals subjects retinal nerve fibers between with Alzheimer's disease patients.

Methods

The present study is classified as descriptive, prospective, cross-sectional, non-interventional and comparative study of a series of patients with Alzheimer's disease, held at the Hospital do Servidor Público de São Paulo (HSPE) - IAMSPE.

The basic principles contained in the Helsinki Declaration of 1964, and Resolution No. 196 of October 10, 1996 of the National Council all patients signed the informed consent form. The study was approved by the Ethics and Research Committee of the Institute of HSPE-IAMSPE. The inclusion criterion was the diagnosis of Alzheimer's disease by the neurology clinico f HSPE-IAMSPE.

The exclusion criteria were

a. Any retinal disease.

b. Optic nerve diseases such as glaucoma, optic neuritis or neuropathy ischemic disease.

c. Opacity of means which may prevent an adequate signal in the examination of image.

d. Diagnosis of dementia for any cause other than Alzheimer's disease.

e. A debilitating illness or disability that would prevent the OCT from being carried out.

Patients with Alzheimer's Disease were referred by the neurology clinic of the HSPE, diagnosed and accompanied by a single neurologist (N.L.R.S.). All patients underwent ophthalmologic evaluation with visual acuity, evaluation of extrinsic ocular motility, biomicroscopy of the anterior segment, measurement of intraocular pressure with Goldmann tonometer as well as funduscopy under drug mydriasis. The thickness of the nerve fiber layer was evaluated by Optical coherence (OCT) with Cirrus SD-OCT (Carl Zeiss Meditec, Dublin, CA.). Examination was performed after pupillary dilation to obtain the best signal. Discarded exams with a sign less than six. The means of the quadrants temporal, nasal, inferior and superior peripapillaries were obtained with the optic protocol disc 200 x 200 cube scan.

Descriptive and exploratory analyzes of the data were performed. As a measure arithmetic mean (or median) and as a measure of the standard deviation (Dp) and coefficient of variation (CV) were used. To the comparison between the data sets (control x Alzheimer's disease; quadrants) we used the t test for the parametric data and the MannWhitney test, for the non-parametric. The significance was 5%. To test yourself homogeneity between proportions was used Fisher's exact test. The level of the significance level used for the tests was 5%. These analyzes were carried out in the SigmaPlot statistical software.

Results

While respecting the inclusion and exclusion criteria, they were eligible for this study of 35 patients with Alzheimer's disease (20 patients) and 36 eyes of normal subjects (20 normal subjects). Table 1 shows the distribution of patients with Alzheimer's disease and normal subjects by sex and age. Table 2 shows the comparison of the overall thickness of the fiber layer of the retina of normal subjects and Alzheimer's disease patients.

There was also a statistically significant difference ($p < 0.05$) in the evaluation of the retinal nerve fiber layer of all quadrants when analyzed separately (Table 3).

Table 1 Distribution of patients with Alzheimer's disease and normal subjects by sex and age

		Groups	
		Alzheimer disease	Normal subjects
Age (years)		78.7±5.74	7.,8±5.2
Sex	Female	11 (55%)	7 (35%)
	Male	9 (45%)	13 (65%)

Table 2 Comparison of the overall thickness of the retinal nerve fiber layer between the patients with Alzheimer's disease and normal subjects

	Groups		
	Alzheimer disease	Normal subjects	p
RLF (µm)	85.3±9.2	100.5±10.2	<0.001*

RLF: retinal layer fibres; *: statiscally significant value

Table 3 Comparison of the thickness of the retinal nerve fiber layer between patients with Alzheimer's disease and normal subjects

	Groups		
	Alzheimer disease	Normal subjects	p
Inferior RLF (µm)	109.8±16.6	130.9±15.1	<0.001 *
Superior RLF (µm)	102.3±14.9	125.2±11.8	<0.001 *
Nasal RLF (µm)	67.1±12.1	77.9±9.5	<0.001 *
Temporal RLF (µm)	62.2±11.5	68.1±12.5	0..42 *

RLF: retinal layer fibres; *: statiscally significant value

Discussion

In this descriptive, prospective, cross-sectional, non-interventional study, we compared the thickness of the nerve fiber layer of the retina by the method of optical coherence tomography between the eyes of patients with Alzheimer's and eyes of healthy subjects.

Visual impairment in Alzheimer's disease has been the focus of research in the world, since the transparency of the unique opportunity to glimpse the pathological process of the disease through the study of central nervous system cells accessible by a non-invasive examination.

In a meta-analysis study Coppola G, et al, (2015) evaluated 11 studies on peripapillary nerve fiber layer in patients with Alzheimes disease, in which 380 patients with Alzheimes disease and 293 healthy controls, after combined analysisof the studies reached the conclusion that the layer of nerve fibers of patients with Alzheimes disease is tuned in relation to healthy individuals[7]. The present study corroborate the result found by this author, demonstrating overall thinning of retinal layer fibres in patients with Alzheimes disease.

In a bibliographic review, Jindahra and Plant (2011) discuss several articles that the degeneration of ganglion cells and the layer of nerve fibers in patients with Alzheimes disease, prior to the existence of the OCT through histological analysis and retinography, until after the appearance of this with detailed in vivo analysis, the same have also come to the conclusion that there is a strong literary that there are significant changes in the nerve fiber layer of patients with Alzheimes disease[15], as observed in this study.

Bambo M.P. (2014) in a prospective, cross-sectional study as well as analyzed 57 eyes of patients with AD and identified all quadrants analyzed, demonstrating overall thinning of the nerve fibers,[8] a finding also found in the present study.

Different hypotheses about the cause of thinning in the fiber layer in Alzheimer's disease have been formulated, however, to the more accepted is based on the fact that the pathophysiological process of Alzheimer's Disease occurs not only in the cerebral cortex, but in various areas of the central nervous system, including the retina, through the deposition of tau protein and the peptide amyloid. However, the deposition of proteins associated with Alzheimer's Diseade and its precursors in the retina is observed not only in this disease, but also in pigmentary retinitis, age-related macular degeneration, other diseases, in addition to the normal aging process.

A second hypothesis considers a secondary lesion of retina, by a mechanism of retrograde transsynaptic degeneration, that is, of the genicular body towards the retina.[15-19]

The third hypothesis accepted for this process is based on the fact that the glaucoma develops most commonly in patients with Alzheimer's disease. Considers that the pathophysiological process of Alzheimer's disease and the normal tension glaucoma are similar in the cryptic lamina, and are due to a high pressure gradient of the cerebrospinal fluid. The pressure gradient at the crimping blade level is determined by the difference between intraocular and retrobulbar pressure, cerebrospinal fluid pressure. A decrease in the retrobulbar gradient, both by decreased brain volume and decreased of cerebrospinal fluid production, injury of the optic nerve axons and retrograde results in the thinning of the layer of retinal nerve fibers in patients with Alzheimer's Disease.[15–19]

Recent studies demonstrate a correlation between the severity of the disease and the degree of thinning in the nerve fiber layer. Studies such as De Garcia et al.[20] observed that in patients with mild Alzheimer's disease, this thinning is less significant when compared to more severe cases. Our study did not divide patients by severity, however, since it is a tertiary care hospital, the cases of the outpatient clinic were more severe, this may explain the greater thinning in the evaluated patients.

Conclusion

In the present study, anatomical alterations were verified and corroborated of patients with Alzheimer's disease. Regarding the thickness of the layer of retinal nerve fibers determined by examination of the optical coherence tomography, a decrease was observed when compared to a group of healthy subjects of the same age group. Since the decrease in thickness occurred globally and segmented.

However, longitudinal studies with greater casuistry deserve attention, due to their scarcity and the rich content they will bring. Studies that can improve optical coherence tomography as a diagnostic and follow-up resource in patients with Alzheimer's disease.

Acnowledgement

None.

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Author declare tehr is no conflit of interst towarrds the manucript.

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