Evaluation of retinal nerve fiber layer thickness in Alzheimer disease using spectral-domain optical coherence tomography

Alime GÜNEŞ[1,*], Seden DEMİRCİ[2], Levent TÖK[1], Özlem TÖK[1], Serpil DEMİRCİ[2]
[1]Department of Ophthalmology, Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey
[2]Department of Neurology, Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey

Background/aim: To evaluate the retinal nerve fiber layer (RNFL) thickness in patients with Alzheimer disease (AD) and to compare the results with those of healthy controls.

Materials and methods: Forty patients (mean age: 75.02 ± 6.34 years; 23 women) with untreated AD and 40 age-, sex-, and education-matched healthy patients were examined in this case-control prospective study. All patients underwent detailed ophthalmic and neurological examination. The Mini Mental State Examination (MMSE) was performed and RNFL thickness was measured using spectral-domain optical coherence tomography. The association between RNFL and MMSE score was also assessed.

Results: The average RNFL thickness was 84 ± 7.0 μm in AD patients and 107 ± 6.3 μm in healthy subjects (P < 0.001). The mean MMSE score was 21.9 ± 2.13 in AD patients. There was no significant correlation between the RNFL thickness and MMSE score.

Conclusion: Patients with AD had reduced RNFL thickness in all quadrants compared with the control group. This finding suggests that RNFL thickness analysis may be useful in the early diagnosis of AD.

Key words: Alzheimer disease, retinal nerve fiber layer thickness, optical coherence tomography

1. Introduction

Alzheimer disease (AD) is a common age-related and progressive neurodegenerative disorder that influences 67 in 1000 people over the age of 65, more than 26 million people worldwide (1,2). Clinically, it is characterized by progressive cognitive impairment and loss of learning and executive functions (3).

Furthermore, visual symptoms have been reported in AD, such as reduction of visual acuity, color blindness, and alteration of spatial resolution (4). Although these symptoms can be explained by involvement of posterior visual pathways and primary and associative visual cortices, it has been shown that the retina might play a role, too (5).

Neuropathological characteristics of AD are extracellular senile plaques that are principally formed by β-amyloid peptides, intracellular neurofibrillary tangles, and selective neuronal degeneration (6). In the early stage of AD, pathologic alterations occur in the entorhinal cortex and hippocampal complex. It is reported that the eye, particularly the retina, is also affected (7).

The retinal changes associated with AD include degeneration and loss of neurons, reduction of the retinal nerve fibers, increase in optic disk cupping, retinal vascular tortuosity and thinning, and visual functional impairment (7). In addition, deposition of amyloid peptides has been shown in retinal tissue in AD patients (6).

Despite intensive research on the pathogenesis and treatment of AD, there remains a need for new research models for simple and accessible procedures to diagnose AD.

Optical coherence tomography (OCT) enables cross-sectional imaging of the retina and is able to measure the retinal nerve fiber layer (RNFL) thickness (8). Recent OCT studies have described a loss of the RNFL thickness in patients with AD (9–15).

In this study, we evaluate the RNFL thickness in patients with AD and compare the results with those of healthy controls, and we also assess the association between RNFL thickness and Mini Mental State Examination (MMSE) score.

2. Materials and methods

Forty patients (23 women) with untreated AD and 40 age-, sex-, and education-matched healthy patients were

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* Correspondence: dralimesefer@hotmail.com

included in this case-control prospective study. The study was approved by the Süleyman Demirel University Department of Medical Sciences ethics committee and followed the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all patients or from their legal representatives.

Subjects with glaucoma, intraocular pressure higher than 21 mmHg, refractive error higher than ±3 spherical diopters (D), optic neuropathy, optic disk anomaly, age-related macular degeneration, vitreoretinal diseases, history of ocular trauma, corticosteroid usage, diabetes mellitus, Raynaud phenomenon, sleep apnea, alcohol abuse, or smoking were excluded.

AD patients were selected from the registry. AD was diagnosed according to the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (16). For the study, only the actual MMSE scores were taken in consideration. All patients and healthy controls underwent detailed ophthalmological and neurological examination on the same day. The ophthalmological examination included refraction, best-corrected visual acuity (BCVA), Goldmann applanation tonometry, slit lamp biomicroscopy, dilated fundus examination, axial length (AL) measurement with A scan ultrasonography (Sonomed, Microscan, 100 A), central corneal thickness (CCT) measurement by ultrasonic pachymeter (Sonomed PacScan 300AP + Biometric pachymeter), and RNFL thickness measurement by spectral-domain OCT (Spectral OCT SLO, OPKO / OTI Instrumentation). Temporal, nasal, inferior, and superior quadrant peripapillary RNFL thicknesses were determined by OCT. Visual acuities were measured with logarithm of the minimum angle of resolution (LogMAR) units. One eye of each subject was randomly selected for analysis.

Besides ophthalmological examination, a thorough neurological examination was performed. Association between RNFL and MMSE score was evaluated.

All statistical analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to report the age, spherical equivalent (SE), BCVA, intraocular pressure (IOP), CCT, and AL and descriptive analysis was presented as mean ± standard deviation. The distribution of continuous variables and normality were evaluated by the Shapiro–Wilk test. The independent t-test was used to compare the differences between the groups. Correlations among analytes were assessed by calculating Spearman correlation coefficients. $P < 0.05$ was regarded as statistically significant.

3. Results
The mean age was 75.02 ± 6.34 years (range: 65–83 years) in AD patients and 74.15 ± 5.76 years (range: 67–86 years)

in healthy controls (P = 0.52). The patient and control groups were similar regarding age, SE, BCVA, IOP, CCT, and AL (Table 1). All AD patients had newly diagnosed dementia, and the mean disease duration was 1.92 ± 0.85 years (range: 1–4 years).

Table 1. Comparison of data (mean ± standard deviation) in AD patients and controls.

	AD (n = 40 eyes)	Control (n = 40 eyes)	P-value*
Age (years)	75.02 ± 6.34	74.15 ± 5.76	0.52
SE (D)	–0.15 ± 1.79	0.25 ± 1.08	0.25
BCVA	0.14 ± 0.20	0.10 ± 0.17	0.39
IOP (mmHg)	15.15 ± 3.81	14.64 ± 2.43	0.51
CCT (μm)	526.5 ± 32.9	533.3 ± 36.1	0.40
AL	23.23 ± 0.78	22.88 ± 0.79	0.07

SE: Spherical equivalent, D: diopter, BCVA: best corrected visual acuity, IOP: intraocular pressure, CCT: central corneal thickness, AL: axial length.

RNFL was significantly thinner in AD patients than in controls. The average RNFL thickness was 84.0 ± 7.0 μm in AD patients and 107.1 ± 6.3 μm in healthy subjects (P < 0.001). This RNFL thinning was significant in all quadrants (Table 2).

Table 2. Mean retinal nerve fiber layer thickness (μm) in patients with AD and healthy controls (mean ± SD) Mean RNFL thickness (μm).

Location	AD (n = 40 eyes)	Control (n = 40 eyes)	P-value*
Average	84.0 ± 7.0	107.1 ± 6.3	<0.001
Nasal	67.7 ± 17.0	85.4 ± 13.5	<0.001
Temporal	66.6 ± 15.0	80.2 ± 16.7	0.001
Superior	104 ± 14.2	126.5 ± 14.0	<0.001
Inferior	101.3 ± 16.2	135.9 ± 16.3	<0.001

The mean MMSE score was 21.90 ± 2.13 (range: 19–25) in AD patients, and this was not significantly correlated with the RNFL thickness.

4. Discussion
AD is one of the most frequent major public health problems because of the rapid increase of the aging population. AD is the most common cause of dementia and is more common in women than men, with rates 1.5 times higher in women (17). Visual function is affected in most AD patients and this leads to decrease in quality of life in AD (13).

Current treatments can regulate the course of the disease and/or ameliorate some symptoms, but there is no cure, and the disease inevitably progresses in all patients. The most crucial approach is early diagnosis and early intervention (18). Generally, AD patients have a normal neurologic examination except for the cognitive examination in the early stages (19).

RNFL thinning may be the earliest finding of AD, even before memory impairment. Several recent studies reported a loss of RNFL thickness in early stages of AD patients (9–15). However, the results of these studies are controversial. Berisha et al. (10), Chi et al. (11), and Kesler et al. (12) showed significant reduction in only the superior quadrant thickness of RNFL in patients with AD. Parisi et al. (9) and a metaanalysis (13) showed that RNFL thickness decreased in AD patients in each quadrant. A recent study has found significant reduction of RNFL thickness in AD patients compared to healthy individuals (14). The result of a current study suggested that RNFL could serve as a biomarker of mild cognitive impairment and AD (15).

Similar to previous reports, our results demonstrate a reduction of RNFL thickness on average and in all quadrants of AD patients compared with healthy controls.

The reason for the reduction of RNFL thickness in AD is likely the death of retinal ganglion cell axons in addition to retrograde degeneration resulting from loss of cortical neurons (6). The defects detected by OCT in a patient group with mild symptoms further supports that these defects may be specific to AD.

In addition, there was no significant correlation between the RNFL thickness and MMSE score in our study.

In this study, all patients were newly diagnosed and were in the early stage of AD. This may be significant, for differences may not be so prominent in late-stage AD because RNFL thickness is reduced by age. The subjects were not using any medications. This is important because drugs can have beneficial effects on stabilizing and slowing the progression of the disease.

The important limitation of our study is the relatively small sample. Therefore, further prospective randomized larger studies are needed to evaluate these observations.

In conclusion, this study confirms that RNFL thickness is reduced in AD patients compared with the control group. As a measure of neuronal degeneration, OCT should occur as a standard part of the evaluation of patients in early AD.

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