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Neurodegeneration in ocular and central nervous systems: optical coherence tomography study in normal-tension glaucoma and Alzheimer disease*

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Background/aim: To evaluate, in vivo, the optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) in patients with normal-tension glaucoma (NTG) and those with Alzheimer disease (AD) in comparison with healthy subjects.

Materials and methods: This cross-sectional study included 18 patients with NTG, 20 with AD, and 20 control subjects. An ophthalmologic examination and OCT scans of both eyes were performed in all patients.

Results: There was a significant reduction in peripapillary RNFL thickness and macular GCC thickness and a significant increase in the global loss volume (GLV) rate in both the NTG and AD patients when compared to the control subjects ($P = 0.004$, $P = 0.006$, $P < 0.001$, respectively). The statistical evaluation showed no difference in any RNFL or GCC parameters between the AD and NTG groups ($P > 0.05$). There was a negative correlation between disease duration and average RNFL and GCC thicknesses ($r = -0.350$, $P = 0.027$ and $r = -0.471$, $P = 0.002$, respectively) and a positive correlation between duration and GLV ($r = 0.427$, $P = 0.006$) in the AD group.

Conclusion: The average RNFL thickness, GCC thickness, and GLV rates may help in the diagnosis of AD as an additional examination and may provide some important clues about the duration of the disease.

Key words: Optical coherence tomography, Alzheimer disease, normal-tension glaucoma, retinal nerve fiber layer, ganglion cell complex

1. Introduction

Glaucoma is among the leading causes of blindness worldwide. As an optic neuropathy, glaucoma is characterized by progressive retinal ganglion cell death. Elevated intraocular pressure is the only commutable risk factor for glaucoma. However, despite the effective control of intraocular pressure (IOP), the progression of visual field loss suggests that IOP-independent mechanisms may also play a role in glaucomatous degeneration in patients having normal-tension glaucoma (NTG) (1,2).

Based on the similarities between glaucoma and neurodegenerative diseases, including the selective loss of neuron populations and common mechanisms of cell injury and death, a contemporary hypothesis has implicated glaucoma as a neurodegenerative disease (3). The IOP-independent mechanisms that cause degeneration in NTG may be similar to the mechanisms at work in neurodegenerative diseases. Some studies have speculated that excessive valsalva, *Helicobacter pylori*, and, lately, optineurin might be common risk factors for both NTG and Alzheimer disease (AD) (4–6).

AD is a neurodegenerative disorder of the central nervous system that has an approximately 10% incidence rate in the elderly population. It is characterized by progressive deterioration in cognitive functions, changes in personality, and impaired ability to perform daily activities (7). Some ocular abnormalities, including the disturbance of color vision, eye movement, contrast sensitivity, and motion perception, are observed in patients with AD (8,9). Several studies also report a measurable decline in the retinal nerve fiber layer (RNFL) thickness in AD patients (10,11).

The results of pathological studies that have evaluated the retina and optic nerve of patients with AD reveal widespread axonal degeneration, RNFL thinning, and reduction in the number of retinal ganglion cells (RGCs)

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(12). There remain, however, controversial results about the type of axon loss; while some authors point out a loss of the larger-diameter axons, others report unaffected myelinated axons (12,13).

In addition to pathological evaluation, another method that enables the distinguishing of retinal layers and analysis of RNFL and RGCs in vivo is optic coherence tomography (OCT), an objective method for the evaluation of the degeneration of retinal layers in ophthalmological and neurological disorders (14,15). In recent years, spectral-domain OCT instruments have enabled automatic measurements of the macular ganglion cell complex (GCC) thickness, which represents the thickness of the nerve fibers, ganglion cells, and inner plexiform layer (16). Recent reports have shown that a significant decrease in the retinal ganglion cell number can occur prior to detectable visual field deficits (17,18), and the measurement of macular GCC thickness is expected to be a useful method by which to detect glaucoma at an earlier stage because of the high RGC density of the macula. After the measurement is taken, the thickness of the GCC is compared with a normative database, revealing the percent loss of these layers. To date, there have been no reports evaluating GCC thickness and percentage loss in AD patients. Yet GCC evaluation can provide important data and may aid in the discovery of the similarities and differences between these 2 neurodegenerative disorders.

In the present study, we evaluated and compared, in vivo, the OCT analysis of peripapillary RNFL and GCC thickness in patients with neurodegenerative disorders (NTG and AD) and in healthy subjects.

2. Methods

This cross-sectional study was conducted between April 2014 and June 2014 and included 18 patients with NTG, 20 patients with AD, and 20 healthy subjects. All patients had a Snellen best-corrected visual acuity of 6/10 or above, had –4 to +3 diopters of spherical refractive error or ≤ ±3 diopters of cylindrical refractive error, were not diagnosed with uveitis or retinal optic nerve diseases (except glaucoma), and were not diagnosed with ocular media opacities or severe cataracts. Corrected IOP values through the central corneal thickness (CCT) were calculated for all study patients according to the formula that Tsai et al. described in their study (Corrected IOP = Measured IOP – (CCT – 545) / 50 × 2.5 mmHg) (19). This study was conducted in accordance with the amended Declaration of Helsinki, and ethical clearance was obtained from the Local Human Research Ethics Committee. Informed consent was obtained from both patients and healthy subjects.

2.1. Patients with glaucoma

The group of patients with glaucoma included those diagnosed with NTG with a median IOP of 20 mmHg or less in 10 baseline measurements, typical glaucomatous optic disc damage with or without asymmetry, nerve fiber bundle defects, glaucomatous visual field defects, and an open angle in the gonioscopy (20). All patients were under medical treatment and had low IOP measurements (<16 mmHg) for at least 1 year, and at least 3 check-ups. All glaucoma subjects had undergone reliable visual field analysis (Humphrey Visual Field Analyzer (Carl Zeiss Inc., Dublin, CA, USA) using the Swedish interactive thresholding algorithm standard 30-2 perimetry). Inclusion criteria covered patients who did not have neurological disorders and patients determined as having mild glaucoma due to the visual field mean deviation (MD) parameter. Disease severity was classified according to the following categories: mild glaucoma (MD > −6 dB), moderate glaucoma (−12 dB < MD < −6 dB), and severe glaucoma (MD < −12 dB) (21).

2.2. Patients with Alzheimer disease

The patients of the AD group were selected from those diagnosed in the Marmara University Neurology Department, according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) (22), and those who received cholinesterase inhibitors and/or NMDA receptor antagonists for treatment. Inclusion criteria covered patients who did not have any neurological diseases other than AD, whose IOP was 20 mmHg or less, who did not have glaucomatous damage in the optic disc, who did not have a history of glaucoma in the family, and who did not have any ophthalmic pathology other than refractive errors. AD patients were grouped into the following disease severity levels: normal (MMSE score of 26 or over), mild (MMSE score of 21–26), mild to moderate (MMSE score of 15–20), moderate (MMSE score of 10–14), and severe (MMSE score below 10) (23).

2.3. Control group

The control group included subjects who did not have any ophthalmic pathology (except for refractive errors), whose IOP was 20 mmHg or less, who were not diagnosed with glaucomatous damage in the optic disc, who did not have a history of glaucoma in the family, and who did not have any neurological disorders.

The ophthalmologic examination of both eyes included Snellen best-corrected visual acuity testing, a slit-lamp examination of the anterior segment, and a gonioscopy and fundus examination using indirect ophthalmoscopy. The IOP of all patients was measured using the Goldmann applanation tonometer, while CCT measurements were taken using ultrasonic pachymetry (Tomey, SP-3000, Germany). The AD cases were clinically assessed and all fulfilled the NINCDS/ADRDA criteria for probable AD (22). Patients with AD were examined by a neurologist and the severity of the disease was evaluated using the

MMSE test. OCT scans (RTVue - 100 5.1 fourier-domain OCT - Optovue Inc., Fremont, CA, USA) were performed without pupil dilation. During scanning, we gave full priority to maintaining high signal strength index values (>50). RNFL and GCC thickness measurements were analyzed in all cases.

2.4. RNFL

The analysis of the peripapillary RNFL was performed using an optic nerve head and a 3-dimensional disc program. The RNFL thickness map was obtained from the area with a diameter around the disc center of 3.45. Thickness measurements of the cases were analyzed according to the following quadrants: temporal (temporal-upper, temporal-lower), superior (superior-temporal, superior-nasal), nasal (nasal-upper, nasal-lower), and inferior (inferior-temporal, inferior-nasal). Additionally, the average RNFL thickness and the thickness of superior and inferior hemispheres were assessed.

2.5. GCC

The scans were centered 1 mm temporal to the 7-mm-square area of fovea (where GCC is the highest). The average GCC thickness, superior GCC thickness, inferior GCC thickness, focal loss volume (FLV, %), and global loss volume (GLV, %) were analyzed on the significance map.

Data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS) Windows version 17.0. The mean ± standard deviation and ratio values were used for the descriptive statistics of the data. Data distribution was tested using the Shapiro–Wilk test ($P < 0.05$), and a visual inspection of their histograms, Q–Q plots, box plots, skewness, and kurtosis was performed (24). All the demographic parameters except CCT and all the OCT parameters except superior-nasal quadrant RNLF thickness, GCC thickness, FLV, and GLV were nonnormally distributed. Pearson's correlation was used for analyzing the normally distributed data, and Spearman's correlation was used for analyzing the nonnormally distributed data. An analysis of variance and Kruskal–Wallis tests were used to identify the differences among groups (Tukey test or Mann–Whitney U test was used as a post hoc test when needed), whereas proportional data were analyzed using the chi-square test. P values < 0.05 were considered statistically significant.

3. Results

Both eyes of the participating patients and the control subjects were evaluated. The mean ages in patients with NTG, those with AD, and those in the control group were 53.6, 73.6, and 73.3 years, respectively ($P < 0.05$). The distribution of sex did not differ among the 3 groups ($P > 0.05$). The average duration of disease and treatment was 38.2 ± 32.2 months (range 3–120 months) in patients with NTG and 59.3 ± 51.6 months (range 3–180 months) in patients with AD ($P > 0.05$). The corrected visual acuity, refractive errors (spherical, cylindrical, and spherical equivalent), CCT, and IOP measurements were similar in all 3 groups ($P > 0.05$). The demographic data are summarized in Table 1.

Table 1. Basic demographic data (values expressed as mean ± standard deviation).

	NTG (n = 36)		AD (n = 40)		CONTROL (n = 40)		P**	
AGE (years)	53.6 ± 7.1*		73.6 ± 10.7		73.3 ± 9.6		**<0.001**	
	M/F		M/F		M/F			
SEX	8 (45%) / 10 (55%)		7 (35%) / 13 (65%)		6 (30%) / 14 (70%)		0.420	
DURATION (months)	38.2 ± 31.7		59.9 ± 50.5		-		0.133	
	OD (n = 18)	OS (n = 18)	OD (n = 20)	OS (n = 20)	OD (n = 20)	OS (n = 20)	OD	OS
SPHERICAL (D)	0.04 ± 1.1	0.08 ± 0.93	–0.06 ± 1.5	0.06 ± 1.31	–0.18 ± 1.24	–0.33 ± 1.35	0.933	0.488
CYLINDER (D)	0.16 ± 0.47	0.04 ± 0.65	0.15 ± 0.58	0.20 ± 0.60	0.10 ± 0.73	0.10 ± 0.73	0.907	0.846
SPHER-EQUIV (D)	0.12 ± 1.12	0.10 ± 1.01	0.01 ± 1.69	0.16 ± 1.48	–0.13 ± 1.39	–0.28 ± 1.58	0.801	0.519
VA (logMAR)	0.01 ± 0.03	0.01 ± 0.02	0.03 ± 0.04	0.03 ± 0.04	0.03 ± 0.04	0.03 ± 0.04	0.191	0.087
IOP (mmHg)	13.77 ± 1.86	13.50 ± 1.42	12.90 ± 1.33	13.75 ± 0.71	12.95 ± 1.09	13.60 ± 1.18	0.211	0.858
CCT (μm)	550.2 ± 27.9	550.6 ± 27.9	553.5 ± 13.2	553.9 ± 15.1	549.5 ± 13.3	550.7 ± 12.0	0.690	0.801

* Mann–Whitney test: NTG versus AD ($P < 0.01$) and NTG versus control ($P < 0.01$) **All P values were derived from a Kruskal–Wallis test. P values with bold characters are < 0.05

In Table 1, n stands for number of eyes; NTG stands for normal-tension glaucoma, AD stands for Alzheimer disease; M stands for male; F stands for female; OD stands for right eye; OS stands for left eye; and D stands for diopter. In addition, DURATION indicates the disease and treatment duration; SPHERICAL indicates the refractive error spherical component; CYLINDER indicates the refractive error cylindrical component; SPHER-EQUIV indicates the refractive error spherical equivalent; VA stands for visual acuity; IOP stands for intraocular pressure; and CCT stands for central corneal thickness.

The statistical analysis was initially performed on both eyes and later on the right and left eyes separately. The analysis of the average RNFL including both eyes revealed a significant difference among the 3 groups (P = 0.004). With the paired comparisons, RNFL in the NTG patients was thinner than in the control group patients (P < 0.001), while it was similar to that in the AD patients (P = 0.823). The average RNFL in the AD patients was also significantly thinner when compared to the controls (P = 0.002). The superior-nasal quadrant also demonstrated a significant thinning in the NTG and AD groups when compared to the controls. RNFL and GCC data and statistical analysis including both eyes are given in Table 2. However, the statistical evaluation showed no difference in any RNFL parameters between the AD and NTG groups (P > 0.05) (see Table 2).

The average GCC thickness was significantly thinner in the NTG and AD groups when compared to the control group (P < 0.05). In addition, GLV rates in the AD and NTG groups and the FLV rate in the AD group were higher compared to the controls (P = 0.006; P < 0.001). Yet there was no significant difference between the NTG and AD patients in the paired comparison regarding mean GCC and GLV rates for both eyes (P = 0.632, P = 0.346) (see Table 2).

When only the right eyes were considered, analysis regarding average RNFL thickness did not reveal a significant difference among the 3 groups. The superior-nasal quadrant showed a significant thinning in both the NTG and AD groups when compared to the controls. The upper-temporal quadrant was thicker in the AD than in the NTG patients, and that was the only statistically significantly difference shown regarding quadrants between these 2 groups for the right eyes. The average GCC thickness differed among the 3 groups (P = 0.008). The average GCC in the NTG and AD groups was significantly thinner than that in the control group in paired comparisons (P = 0.011 and P = 0.005, respectively). In addition, GLV in the NTG and AD groups was higher compared to that in the control group (P = 0.002 and P = 0.001, respectively). There was no significant difference between the NTG and AD patients regarding mean GCC, FLV, or GLV rates (P = 0.781, P = 0.75, and P = 0.465, respectively). The FLV rate was higher in the eyes of patients with AD when compared to those of the control group patients (P = 0.007), but there was no significant difference between the FLV rate in patients with NTG and those in the control group (P = 0.460). Table 3 presents the results of the RNFL and GCC thickness analyses for both right and left eyes.

Table 2. Retinal nerve fiber layer and ganglion cell complex thickness analysis for both eyes (values expressed as mean ± standard deviation).

		NTG (n = 36)	AD (n = 40)	CONTROL (n = 40)	P**
RNFL thickness (μm)	ST	123.1 ± 21.2	116.6 ± 18.5 *	131.9 ± 18.9	**0.002**
	SN	107.7 ± 20.6 *	109.3 ± 18.8 *	118.9 ± 14.9	**0.002**
	IT	135.6 ± 21.1	129.1 ± 21.8	136.4 ± 13.8	0.323
	IN	123.7 ± 31.1	115.8 ± 22.6	122.8 ± 28.2	0.629
	NU	89.1 ± 17.3	88.7 ± 16.4	94.1 ± 14.8	0195
	NL	76.3 ± 16.4	76.1 ± 12.4	81.5 ± 13.3	0.072
	TU	78.0 ± 11.6	83.4 ± 14.8	83.6 ± 11.9	0.071
	TL	77.8 ± 12.0	82.5 ± 11.3	84.2 ± 12.1	0.098
	Avg RNFL	101.4 ± 13.8 *	99.8 ± 10.3 *	108.4 ± 14.9	**0.004**
GCC thickness	Avg GCC (μm)	91.6 ± 9.4 *	90.1 ± 10.0 *	98.7 ± 6.3	**<0.001**
	FLV (%)	1.6 ± 2.9	2.9 ± 2.9 *	0.6 ± 0.6	**0.006**
	GLV (%)	8.9 ± 7.8 *	10.4 ± 8.3 *	3.3 ± 2.7	**<0.001**

*The difference compared to controls is P < 0.01

** All P values were derived from a Kruskal–Wallis or Mann–Whitney U statistical test. P values with bold characters are <0.05.

In Table 2, n refers to the number of eyes; NTG stands for normal-tension glaucoma; AD stands for Alzheimer disease; OD stands for right eye; OS stands for left eye; ST stands for superior-temporal; SN stands for superior-nasal; IT stands for inferior-temporal; IN stands for inferior-nasal; NU stands for nasal-upper; NL stands for nasal-lower; TU stands for temporal-upper; TL stands for temporal-lower; Avg RNFL stands for average retinal nerve fiber layer; Avg GCC stands for average ganglion cell complex; FLV stands for focal loss volume; and GLV stands for global loss volume.

When only the left eyes were considered, the average RNFL thickness differed among the 3 groups (P = 0.018). The average RNFL in the NTG and AD patients was thinner than that in the control subjects (P = 0.04 and P = 0.007). Except in the inferior-temporal quadrant, RNFL thickness parameters in the NTG and AD groups were similar in the left eyes (see Table 3).

The average GCC thickness was thinner in the NTG and AD patients when compared to the control subjects (P < 0.01). GLV rates in the NTG and AD groups were higher when compared to the controls (P = 0.005 and P = 0.003, respectively). GCC, FLV, and GLV was similar in the NTG and AD patients (P = 0.715, P = 0.248, and P = 0.569, respectively) (see Table 3).

There was a moderate negative correlation between disease duration and average RNFL thickness (r = −0.350, P = 0.027), a strong negative correlation between duration and average GCC thickness (r = −0.471, P = 0.002), and a strong positive correlation between duration and GLV rate (r = 0.427, P = 0.006). However, there was no correlation between MMSE score and OCT parameters within the AD group (P > 0.05).

4. Discussion

The similarities between neurodegenerative disease of the central nervous system and glaucoma have been reported in earlier studies (3–6,25–27). Visual impairment is also often demonstrated in AD patients (8,9). The challenge in early diagnosis is canalizing researchers to assess ocular examination methods for use in screening AD changes. In this study, we compared the retinal structural changes caused by 2 different neurodegenerative diseases affecting ocular and central nervous systems and analyzed neuronal damage in vivo. To our knowledge, there has been no previous comparative study of OCT findings in the retinal layers and in vivo neuron damage in neurodegenerative disorders concerning the ocular and central nervous systems.

The present study indicated a significant reduction in peripapillary RNFL thickness and macular GCC thickness and a significant increase in GLV rate, in both the NTG and AD patients, when compared to the control subjects. Within the AD group, there was a moderate negative correlation between disease duration and average RNFL thickness, a strong negative correlation between

Table 3. Retinal nerve fiber layer and ganglion cell complex thickness analysis for right and left eyes (values expressed as mean ± standard deviation).

		NTG		AD		CONTROL		P**	
		OD (n = 18)	OS (n = 18)	OD (n = 20)	OS (n = 20)	OD (n = 20)	OS (n = 20)	OD	OS
RNFL thickness (μm)	ST	123.7 ± 21.6	122.4 ± 21.3	116.4 ± 18.0	116.8 ± 19.5 *	129.1 ± 17.7	134.7 ± 20.1	0.108	**0.014**
	SN	107.4 ± 19.6 *	107.9 ± 22.1	107.7 ± 17.1 *	110.9 ± 20.6	120.9 ± 12.4	117.0 ± 17.2	**0.006**	0.179
	IT	129.9 ± 17.6	141.3 ± 23.1	131.4 ± 23.3	126.7 ± 20.6	135.8 ± 10.1	136.9 ± 17.0	0.652	0.080
	IN	126.1 ± 30.5	121.3 ± 32.3	120.8 ± 23.7	110.8 ± 20.8	124.3 ± 26.9	121.3 ± 30.0	0.923	0.592
	UN	92.3 ± 16.1	85.8 ± 18.4	88.0 ± 18.2	89.5 ± 14.7	92.6 ± 16.3	95.6 ± 13.4	0.816	0.085
	LN	83.1 ± 15.8	69.6 ± 14.4 *	77.9 ± 12.6	74.2 ± 12.3	80.7 ± 15.0	82.3 ± 11.8	0.499	**0.009**
	UT	79.8 ± 14.1	76.2 ± 8.6	90.2 ± 13.8 *	76.7 ± 12.7	82.8 ± 9.4	84.4 ± 14.2	**0.031**	0.085
	LT	76.3 ± 14.7	79.3 ± 8.6	84.1 ± 9.9	80.9 ± 12.5	81.8 ± 10.4	86.6 ± 13.6	**0.046**	0.292
	Avg RNFL	102.3 ± 14.1	100.4 ± 13.9	101.3 ± 10.4	98.3 ± 10.3 *	106.0 ± 8.8	110.7 ± 19.1	0.190	**0.018**
GCC thickness	Avg GCC (μm)	91.4 ± 10.4 *	91.7 ± 8.5	90.5 ± 9.9 *	89.8 ± 10.3 *	99.7 ± 6.9	97.6 ± 5.5	**0.008**	**0.023**
	FVL (%)	2.0 ± 3.8	1.2 ± 1.6	3.3 ± 3.1 *	2.6 ± 2.9	0.7 ± 0.7	0.5 ± 0.2	**0.002**	0.263
	GVL (%)	9.6 ± 8.3 *	8.1 ± 7.4 *	10.5 ± 7.6 *	10.2 ± 9.1 *	3.4 ± 2.9	3.1 ± 2.5	**0.001**	**0.004**

* The difference compared to controls is P < 0.01

** All P values were derived from a Kruskal–Wallis or Mann–Whitney U statistical test. P values with bold characters < 0.05

In Table 3, n stands for number of eyes; NTG stands for normal-tension glaucoma; AD stands for Alzheimer disease; OD stands for right eye; OS stands for left eye; ST stands for superior-temporal; SN stands for superior-nasal; IT stands for inferior-temporal; IN stands for inferior-nasal; NU stands for nasal-upper; NL stands for nasal-lower; TU stands for temporal-upper; TL stands for temporal-lower; Avg RNFL stands for average retinal nerve fiber layer; Avg GCC stands for average ganglion cell complex; FVL stands for focal loss volume; and GLV stands for global loss volume.

duration and average GCC thickness, and a strong positive correlation between duration and GLV.

It is also noteworthy that patients in the NTG group were significantly younger than those in the AD and control groups. It is well known that there is an age-dependent decrease in RNFL thickness, with 10 years of aging leading to an approximate 4-μm decrease in RNFL thickness measured with OCT (28). Under these circumstances, despite the younger age of the NTG group, the average RNFL thickness in the subanalysis was less than that of the control group. This result confirms the structural changes and RNFL thinning in the NTG group as a result of the glaucomatous process.

The present study also revealed that the average RNFL thickness was significantly less in the AD group when compared with the control group. There was no difference between the AD and NTG groups. Another important finding was the different results obtained in average RNFL when the eyes were evaluated separately. One possibility is the limited sample size of the groups. Another possible explanation is the asymmetric involvement nature of the disease in the eyes. Contrary to RNFL thickness, GCC parameters were not affected by laterality or sample size and demonstrated similar results in both eyes.

Our findings confirm the results of previous pathologic studies (12,29) and other studies that used in vivo RNFL evaluation methods (30,31); these studies also show widespread axonal degeneration, a reduction in the number of optic nerve fibers, and a decrease in retinal ganglion cells in patients with AD. Tsai et al. and Hedges et al. also demonstrated increased optic disc cupping and decreased thickness of the retinal nerve fiber layer and neuroretinal rim in their studies, which utilized the subjective evaluation of fundus photographs for analyses of optic nerves of AD patients (31,32). Parisi et al. (30) used OCT to show that morphologic abnormality resulted in RNFL thinning and suggested that these changes are related to retinal dysfunction as revealed by abnormal pattern-electroretinogram (PERG) responses. There are controversial results about the type of axon loss that occurs, however. Some authors point out a predominant loss of the larger-diameter axons and loss of the largest class of retinal ganglion cells (M-cells) (29), while others report that myelinated axons are unaffected (12,13). Iseri et al. emphasize that the loss of retinal ganglion cells may be a primary process or a consequence of retrograde neurodegeneration occurring in the cortical regions (33).

In another study (30), researchers compared 17 AD patients (average age 70.4 years) with normal age-matched controls and reported a significant reduction in RNFL thickness in AD patients when compared to controls; this difference was correlated to abnormal PERG responses. The mean RNFL thickness was 99.9 ± 8.9 μm in the control group, but 59.5 ± 16.7 μm in the AD patients in their study.

Iseri et al. (33) conducted a similar study of 14 patients with AD (mean age 70.1 years) and 15 age-matched controls (mean age 65.1 years). They found that the mean RNFL thickness was significantly lower in the AD group (87.46 ± 23.78 μm) when compared to the control group (113.16 ± 6.72 μm). The RNFL thickness was significantly reduced in all quadrants except temporal quadrants. They also reported that the retinal thickness of the macula in AD patients was less than that of the controls; thinning was observed in the superior and nasal quadrants. They found a significant correlation between MMSE scores and concluded that macular volume measured by OCT may be useful in evaluating the effect of disease severity on RNFL. No correlation was revealed between any of the OCT parameters and MMSE scores in the present study. The OCT results of Iseri et al.'s study showed an overall decrease in quadrants that was similar to our data, but our quadrant findings did not show a significant difference. The maximal RNFL thinning occurred in the superior-nasal quadrant in the current study.

The mean RNFL thickness of the AD group and that of the control group varied between studies (30,32,33). We found an RNFL thickness of 99.8 ± 10.3 μm in the AD patients, 101.4 ± 13.8 μm in the NTG patients, and 108.4 ± 14.9 μm in the control subjects. Our results were similar to the findings reported by Iseri et al. (33). The variance between our study and that by Parisi et al. may be due to the duration of AD in the study patients. Moreover, differences in OCT devices and measurement techniques used in each study may contribute to the differing results.

Glaucoma is an optic neuropathy usually associated with elevated IOP, but a subset of glaucomatous patients experience glaucomatous optic nerve changes despite having a normal IOP. This subset is determined to have NTG (34). Previous studies have shown that AD and glaucoma have many common features (35), such as being slow, chronic neurodegenerative disorders in which incidence increases with age (36). In addition, cortical degeneration in visual association areas is a characteristic of AD. Tau and beta-amyloid peptides, derived from amyloid precursor proteins, form neurofibrillary tangles and neuritic plaques, the pathologic hallmarks of AD in the lateral geniculate nucleus and superior colliculus (37). The cerebrospinal fluid level of b-amyloid (1–42) was found to be decreased and tau levels to be increased in AD patients when compared to healthy subjects (38,39). Yoneda et al. (39) investigated the pathogenesis of glaucoma and diabetic retinopathy and found that b-amyloid (1–42) levels were significantly decreased and tau levels significantly increased in the vitreous fluid of AD patients when compared to a control group. These

results are consistent with the hypothesis that these neurodegenerative disorders in the specified ocular diseases might share a common mechanism with AD (39). McKinnon et al. (40), in a rat glaucoma model, detected a build-up of an antibody in RGCs and the activation of caspases-3 and abnormal amyloid precursor protein processing, mechanisms that are similar to those at work in AD. Their study suggests a different hypothesis by which to explain RGC death in glaucoma that mimics AD at the molecular level (41).

Recent studies revealed that glaucoma patients have significantly smaller retinal vessel diameters than those without glaucoma (42,43). Retinal abnormalities were also detected in early AD even before cognitive changes were observed (44,45). Retinal vessel signs are therefore a new possible common risk factor underlying the 2 diseases. Retinal and cerebral vascular dysregulation may induce low perfusion pressure and may be the a risk factor underlying pathogenesis (45,46).

Glaucomatous damage also affects the retinal ganglion cell body and dendritic structures other than axons. Recently, GCC has been emphasized as important for the early diagnosis of glaucoma (47). Our data revealed a significant decrease in GCC thickness and an increase in FLV and GLV rates in patients with NTG and AD ($P < 0.05$). Interestingly, only left eyes failed to show a significant difference in FLV rates ($P = 0.263$). These results suggest the damage of retinal ganglion cells in NTG and AD patients. Blanks et al. similarly reported a 25% decrease in neurons in the ganglion cell layer of the foveal and parafoveal retina in postmortem pathologic analysis (10). To our knowledge, the current study was the first to report a decrease in GCC thickness in vivo in patients with AD. Sen et al. previously evaluated patients with Parkinson disease in which GCC layer thickness did not differ among patients receiving or not receiving treatment as well as control subjects ($P = 0.304$) (48).

The present study revealed a moderate negative correlation for disease duration with average RNFL thickness, a strong negative correlation between duration and average GCC thickness, and a strong positive correlation between duration and GLV for AD patients. This finding suggests that the duration of the disease is the most important parameter affecting the RNFL, GCC thickness, and GLV. These 3 parameters may be useful in anticipating the duration of the disease in newly diagnosed AD patients. However, there was no correlation between the MMSE score and any of the OCT parameters, suggesting that there is no relationship between the severity of the disease and OCT findings in patients diagnosed with AD; therefore, it may be possible to detect retinal changes in the early stages of the disease, before clinical findings even become visible. Iseri et al. also showed a correlation between the reduction of RNFL thickness and modifications of the PERG, but it was not correlated with MMSE scores (33).

According to these findings, OCT may be used as an objective marker by which to assess early neurodegenerative changes in AD. GCC measurements, which show early RGC damage in neurodegeneration, may be very important in detecting neurodegenerative disorders characterized by neuronal loss in early stages and may provide some clues about the disease duration. Further in vitro studies are needed to assess the common retinal changes between NTG and AD patients.

In conclusion, OCT is an easily repeatable and valuable instrument in the evaluation of peripapillary RNFL in both NTG and AD patients. The average RNFL, average GCC thicknesses, and GLV rates may aid in the diagnosis of AD as a supporting examination and may afford some important clues concerning the duration of the disease.

References

1. Araujo SV, Spaeth GL, Roth SM, Starita RJ. A ten-year follow-up on a prospective, randomized trial of postoperative corticosteroids after trabeculectomy. Ophthalmology 1995; 102: 1753–1759.
2. Jay JL, Allan D. The benefit of early trabeculectomy versus conventional management in primary open angle glaucoma relative to severity of disease. Eye 1989; 3: 528–535.
3. Gupta N, Yucel YH. Glaucoma as a neurodegenerative disease. Curr Opin Ophthalmol 2007; 18: 110–114.
4. Kountouras J, Zavos C, Gavalas E, Boziki M, Chatzopoulos D, Katsinelos P. Normal-tension glaucoma and Alzheimer's disease: *Helicobacter pylori* as a possible common underlying risk factor. Med Hypotheses 2007; 68: 228–229.
5. Wostyn P. Normal-tension glaucoma and Alzheimer's disease: hypothesis of a possible common underlying risk factor. Med Hypotheses 2006; 67: 1255–1256.
6. Liu Y-H, Tian T. Hypothesis of optineurin as a new common risk factor in normal-tension glaucoma and Alzheimer's disease. Med Hypotheses 2011; 77: 591–592.
7. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006; 368: 387–403.
8. Cronin-Golomb A, Corkin S, Rizzo JF, Cohen J, Growden JH. Visual dysfunction in Alzheimer's disease: relation to normal aging. Ann Neurol 1991; 29: 41–52.
9. Mendez MF, Tomsak RL, Remler B. Disorders of the visual system in Alzheimer's disease. Neurology 1990; 40: 439–443.

10. Blanks JC, Torigoe Y, Hinton DR, Blanks RH. Retinal pathology in Alzheimer's disease. I. Ganglion cell loss in foveal/parafoveal retina. Neurobiol Aging 1996; 17: 377–384.

11. Paquet C, Boissonnot M, Roger F, Dighiero P, Gil R, Hugon J. Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Neurosci Lett 2007; 420: 97–99.

12. Hinton DR, Sadun AA, Blanks JC, Miller CA. Optic-nerve degeneration in Alzheimer's disease. N Engl J Med 1986; 315: 485–487.

13. Davies DC, McCoubrie P, McDonald B, Jobst KA. Myelinated axon number in the optic nerve is unaffected by Alzheimer's disease. Br J Ophthalmol 1995; 79: 596–600.

14. Inzelberg R, Ramirez JA, Nisipeanu P, Ophir A. Retinal nerve fiber layer thinning in Parkinson disease. Vision Res 2004; 44: 2793–2797.

15. Altintas O, Iseri PK, Ozkan B, Caglar Y. Correlation between retinal morphological and functional findings and clinical severity in Parkinson's disease. Doc Ophthalmol 2007; 116: 137–146.

16. Kita Y, Kita R, Takeyama A, Anraku A, Tomita G, Goldberg I. Relationship between macular ganglion cell complex thickness and macular outer retinal thickness: a spectral-domain optical coherence tomography study. Clin Experiment Ophthalmol 2013; 41: 674–682.

17. Harwerth RS, Carter-Dawson L, Shen F, Smith EL III, Crawford ML. Ganglion cell losses underlying visual field defects from experimental glaucoma. Invest Ophthalmol Vis Sci 1999; 40: 2242–2250.

18. Kim NR, Lee ES, Seong GJ, Kim JH, An HG, Kim CY. Structure-function relationship and diagnostic value of macular ganglion cell complex measurement using Fourier-domain OCT in glaucoma. Invest Ophthalmol Vis Sci 2010; 51: 4646–4651.

19. Shih CY, Graff Zivin JS, Trokel SL, Tsai JC. Clinical significance of central corneal thickness in the management of glaucoma. Arch Ophthalmol 2004; 122: 1270-1275.

20. Anderson DR, Collaborative Normal Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998; 126: 487–497.

21. Hodapp E, Parrish RK II, Anderson DR. Clinical Decisions in Glaucoma. St. Louis, MO, USA: Mosby Year Book; 1993.

22. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939–944.

23. Hux MJ, O'Brien BJ, Iskedjian M, Goeree R, Gagnon M, Gauthier S. Relation between severity of Alzheimer's disease and costs of caring. CMAJ 1998; 159: 457–465.

24. Kim HY. Statistical notes for clinical researchers: assessing normal distribution (1). Restor Dent Endod 2012; 37: 245–248.

25. Ghiso JA, Doudevski I, Ritch R, Rostagno AA. Alzheimer's disease and glaucoma: mechanistic similarities and differences. J Glaucoma 2013; 22: 36–38.

26. Kersey T, Clement CI, Bloom P, Cordeiro MF. New trends in glaucoma risk, diagnosis and management. Indian J Med Res 2013; 137: 659–668.

27. Danesh-Meyer HV, Levin LA. Neuroprotection: extrapolating from neurologic diseases to the eye. Am J Ophthalmol 2009; 148: 186–191.

28. Alamouti B, Funk J. Retinal thickness decreases with age: an OCT study. Br J Ophthalmol 2003; 87: 899–901.

29. Sadun AA, Bassi CJ. Optic nerve damage in Alzheimer's disease. Ophthalmology 1990; 97: 9–17.

30. Parisi V, Restuccia R, Fattapposta F, Mina C, Bucci MG, Pierelli F. Morphological and functional retinal impairment in Alzheimer's disease patients. Clin Neurophysiol 2001; 112: 1860–1867.

31. Tsai CS, Ritch R, Schwartz B, Lee SS, Miller NR, Chi T, Hsieh FY. Optic nerve head and nerve fiber layer in Alzheimer's disease. Arch Ophthalmol 1991; 109: 199–204.

32. Hedges TR, Perez Galves R, Speigelman D, Barbas NR, Peli E, Yardley CJ. Retinal nerve fiber layer abnormalities in Alzheimer's disease. Acta Ophthalmol Scan 1996; 74: 271–275.

33. Iseri P, Altınas O, Tokay T, Yuksel N. Relationship between cognitive impairment and retinal morphological and visual functional abnormalities in Alzheimer disease. J Neuro-Ophthalmol 2006; 26: 18–24.

34. Wostyn P, Audenaert K, De Deyn PP. Alzheimer's disease-related changes in diseases characterized by elevation of intracranial or intraocular pressure. Clin Neurol Neurosurg 2008; 110: 101–109.

35. Wostyn P, Audenaert K, De Deyn PP. Alzheimer's disease and glaucoma: Is there a causal relationship? Br J Ophthalmol 2009; 93:1557–1559.

36. Guo L, Salt TE, Luong V, Wood N, Cheung W, Maass A, Ferrari G, Russo-Marie F, Sillito AM, Cheetham ME et al. Targeting amyloid-beta in glaucoma treatment. Proc Natl Acad Sci USA 2007; 104: 13444–13449.

37. Leuba G, Saini K. Pathology of subcortical visual centers in relation to cortical degeneration in Alzheimer's disease. Neuropathol Appl Neurobiol 1995; 21: 410–422.

38. Engelborghs S, De Vreese K, Van de Casteele T, Vanderstichele H, Van Everbroeck B, Cras P, Martin JJ, Vanmechelen E, De Deyn PP. Diagnostic performance of a CSF-biomarker panel in autopsy-confirmed dementia. Neurobiol Aging 2008; 29: 1143–1159.

39. Yoneda S, Hara H, Hirata A, Fukushima M, Inomata Y, Tanihara H. Vitreous fluid levels of beta-amyloid(1–42) and tau in patients with retinal diseases. Jpn J Ophthalmol 2005; 49: 106–108.

40. McKinnon SJ, Lehman DM, Kerrigan-Baumrind LA, Merges CA, Pease ME, Kerrigan DF, Ransom NL, Tahzib NG, Reitsamer HA, Levkovitch-Verbin H et al. Caspase activation and amyloid precursor protein cleavage in rat ocular hypertension. Invest Ophthalmol Vis Sci 2002; 43: 1077–1087.

41. McKinnon SJ. Glaucoma: Ocular Alzheimer's disease? Front Biosci 2003; 8: 1140–1156.

42. Jonas JB, Nguyen XN, Naumann GO. Parapapillary retinal vessel diameter in normal and glaucoma eyes. I. Morphometric data. Invest Ophthalmol Vis Sci 1989; 30: 1599–1603.

43. Mitchell P, Leung H, Wang JJ, Rochtchina E, Lee AJ, Wong TY, Klein R. Retinal vessel diameter and open-angle glaucoma: the Blue Mountains Eye Study. Ophthalmology 2005; 112: 245–250.

44. Berisha F, Feke GT, Trempe CL, McMeel JW, Schepens CL. Retinal abnormalities in early Alzheimer's disease. Invest Ophthalmol Vis Sci 2007; 48: 2285–2289.

45. De la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. Stroke 2002; 33: 1152–1162.

46. Flammer J, Orgul S, Costa VP, Orzalesi N, Krieglstein GK, Serra LM, Renard JP, Stefánsson E. The impact of ocular blood flow in glaucoma. Prog Retin Eye Res 2002; 21: 359–393.

47. Firat PG, Doganay S, Demirel EE, Colak C. Comparison of ganglion cell and retinal nerve fiber layer thickness in primary open-angle glaucoma and normal tension glaucoma with spectral-domain OCT. Graefes Arch Clin Exp Ophthalmol 2013; 251: 831–838.

48. Sen A, Tugcu B, Coskun C, Ekinci C, Nacaroglu SA. Effects of levodopa on retina in Parkinson disease. Eur J Ophthalmol 2013; 24: 114–119.