ORIGINAL ARTICLE

Optical Coherence Tomography in Patients with Relapsing-Remitting Multiple Sclerosis without Optic Neuritis: A 20-Month Longitudinal Study

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ABSTRACT

Optical coherence tomography is supported and used as a technique for visualisation of neuro-axonal loss in multiple sclerosis, but there are also a few studies expressing the opposite view. The aim of our study was to investigate retinal nerve fibre layer and optic nerve head parameters in patients with multiple sclerosis without a history of prior optic neuritis and symptoms of a new clinical attack during the follow-up for a total of 20-month period. Full ophthalmic evaluation was performed for all of the participants. The baseline retinal nerve fibre layer and macular thicknesses and focal and global loss of macular volume values were significantly lower in the eyes of the patients with multiple sclerosis compared with the healthy controls. No significant change between baseline and follow-up scans were found in all optical coherence tomography parameters in the multiple sclerosis group. Statistical analyses revealed significant retinal nerve fibre layer and macular thickness differences between baseline and second measurements in the controls. No significant difference in percent change between baseline and second measurements was observed between the patient and control groups. We conclude that whereas healthy subjects have an age-related tendency toward a decrease in retinal nerve fibre layer thickness, patients with multiple sclerosis patients are likely to pass through different stages of retinal thinning and thickening due to subclinical optic neuritis and, as a result, we could not detect any statistically significant change between baseline and second measurements in our multiple sclerosis patients.

Keywords: Multiple sclerosis, optical coherence tomography, retinal nerve fibre layer thickness

INTRODUCTION

Multiple sclerosis (MS) is the most common disabling neurodegenerative disease that has been traditionally categorised as an autoimmune inflammatory demyelination of the central nervous system (CNS). However, in the recent few years, several studies demonstrated the presence of axonal degeneration even in the initial stages of MS.^{1–4} Axonal loss is an irreversible process and is related to permanent disability observed in MS; therefore, the monitoring of axonal loss is important for the follow-up of the

disease and the development of a targeted treatment strategy.²

Retinal cell axons are part of the CNS, and do not have a myelin sheath until they penetrate the lamina cribrosa, thus the investigation of retina might be ideal for visualising the processes of neuroaxonal degeneration and understanding mechanisms of brain tissue damage in multiple sclerosis.⁵

One of the relatively novel techniques for investigation of retina is optical coherence tomography (OCT). OCT is a non-invasive technique that allows direct visualization and measurement of retinal nerve

fibre layer (RNFL) thickness, macular volume, and optic disc parameters with micron-scale resolution.⁶ OCT has the advantages of being quantitative and easy to use.⁷ The current OCT technology uses the spectral domain (SD-OCT), which offers improved accuracy and a simple-to-use and cost-effective tool over the previous time-domain OCT.⁸

In recent years, OCT has been widely used for visualisation of axonal loss in some neurodegenerative diseases, especially in MS. Several studies demonstrated axonal loss measured by OCT in patients with MS, even in the absence of any reported optic neuritis (ON).^{8–10} On the other hand, some longitudinal studies found that RNFL thickness measured by OCT did not decrease significantly in MS patients during the follow-up period.^{11,12} It is known that RNFL thickness of healthy individuals without any history of neurological or ocular disorders decrease over time.¹³ In this research, our aim was to study RNFL and optic nerve head parameters in a cohort of relapsing-remitting (RRMS) subtype of MS patients without a history of prior ON and new clinical attack during the follow-up of 20 months in comparison with the healthy subjects.

METHODS

This study was performed at the Departments of Neurology and Ophthalmology of Kafkas University, Medical Faculty, Kars, Turkey. The study adhered to the tenets of the Declaration of Helsinki. It was approved by the local ethical committee (2011/13) and the patients and control subjects were recruited into the study after giving written informed consent.

Full ophthalmological evaluation, including best-correct visual acuity, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy with a three-mirror contact lens, funduscopy, automated visual field examination, and OCT was performed in all of the participants of the study.

The inclusion criteria for the study were MS based on revised McDonald criteria, visual acuity $\geq 20/30$, refractive error < 5 D equivalent sphere or 3 D of astigmatism, and intraocular pressure < 21 mm Hg.¹⁴ All the patients were under immunomodulatory treatment (interferons or glatiramer acetate) and were in remission at the time of follow-up. Demographic variables including age, gender, and neurological status including Expanded Disability Status Scale (EDSS) were determined in all of the patients.¹⁵ We did not include data for disease duration in our study, because some patients were not able to give reliable data about the onset of the disease.

Patients having a history of ON, chronic uveitis, retinitis pigmentosa, ocular trauma, high myopia, previous ocular surgery, and any diagnosed ocular or

neurological conditions other than MS were excluded from the study.

Healthy relatives of the patients and hospital staff with no history of MS or other neurological and ophthalmological diseases were included as the control group.

The original cohorts consisted of 27 patients with RRMS and 27 healthy controls. Both eyes of the patients and controls were examined. The first examination was conducted in February 2011. The second investigation was conducted in October 2012. During the follow-up, 2 patients developed ON, 3 patients developed a new MS attack, 1 patient's disease transformed into a secondary progressive MS subtype, and 5 patients refused a follow-up control examination. These patients were excluded from the study. Sixteen MS patients and 15 controls were admitted for the second examination.

OCT was performed through undilated pupil using the RTVue version 4.0 (Optovue, Fremont, CA, USA). Only scans that reached signal strength of at least ≥ 6 , which indicate a high quality scan, were accepted for the analyses. The RNFL scan pattern completes four circular scans in 0.15 seconds at a diameter of 3.45 mm, targeted around the optic nerve head. Peripapillary RNFL thickness was measured in each eye as an average and by superior and inferior hemispheres. Ganglion cell complex (GCC) thickness in macular region was obtained by GCC scan protocol, which consists of one horizontal scan followed by 15 vertical scans, centred 1 mm temporal to fovea. Macular thickness included an average and superior and inferior thicknesses, and focal loss volume (FLV) and global loss volume (GLV) values. FLV is a parameter that provides a quantitative measurement for the amount of significant GCC loss. FLV is the total sum of significant GCC loss (in volume) divided by the map area, which provides a percent of significant tissue loss for volume. GLV is the sum of the pixels where the fractional deviation map value is < 0 , and then divided by the total area to give a percent loss of GCC thickness. Only average (not superior or inferior thickness) RNFL and GCC values were used for statistical analyses. Optic nerve head volume measurement (NHV) was obtained by a protocol that consists of 12 radial line scans and 13 concentric rings, centred on disc.

Statistical Analyses

Statistical analysis was performed using SPSS Statistics Base 13.0 (SPSS, Chicago, IL, USA). Quantitative data were given as mean $\pm$ SD and categorical data were given as percentages. Normal distribution was determined using the Shapiro-Wilk test. Mann-Whitney *U* test for comparisons between the two groups, Wilcoxon test for differences

between baseline and last values of scalar variables, and χ^2 test for categorical variables were used as appropriate. Percent changes were calculated for demonstrating difference between baseline and last values, and Mann-Whitney *U* test was used to determine percent change differences between the two groups. A *p* value below 0.05 was accepted as significant. Exact *p* values were provided for all test results.

RESULTS

Thirty-two eyes of 16 RRMS patients were compared with 30 eyes of 15 healthy individuals. Demographic and clinical data of the patients and healthy controls are shown in Table 1.

The baseline average RNFL, GCC, FLV, and GLV values were significantly lower in the eyes of MS patients compared with controls ($p < 0.001$ for all comparisons) (Table 2). Baseline and 20-month follow-up OCT examinations of MS patients and healthy participants were compared. No significant change between the baseline and follow-up scans were found in any OCT parameters in the MS group (Table 3). Statistical testing revealed significant RNFL, GCC, and FLV differences between the baseline and second measurements in the controls ($p = 0.035$, 0.030 , and

<0.001 , respectively) (Table 4). Table 5 shows mean percent changes of average RNFL and GCC thicknesses and NHV, FLV, and GCC parameters between the baseline and final measurements. No significant differences in percent change between the baseline and second measurements were noted in the patient and control groups.

DISCUSSION

Our longitudinal study demonstrated that baseline RNFL and GCC thicknesses were significantly decreased in the MS group compared with the healthy controls. Similar results have been shown in the previous studies.^{8,16,17} Also, baseline FLV and GLV values significantly increased in MS patients compared with controls. FLV and GLV parameters have not been investigated in the similar studies. Our MS patients did not demonstrate significant progressive impairment in any of the OCT values studied after the 20-month follow-up period. Contrary to this finding, the healthy controls revealed a statistical significant change in RNFL, GCC, and FLV parameters at the end of the follow-up period. However, no statistically significant mean percent changes between the first and second measurements of any OCT values were found in the control and patient groups.

TABLE 1 Demographic and clinical characteristics of MS patients and healthy controls.

		Control eyes (<i>N</i> = 30)	Patients eyes (<i>N</i> = 32)	<i>p</i>
Age (years)	Mean $\pm$ SD	31.07 $\pm$ 4.45	32.5 $\pm$ 5.06	0.213
	Median (min-max)	30.00 (25-38)	32.00 (23-41)	
Gender	M/F	10 (33.3%)/20 (66.7%)	6 (18.8%)/26 (81.3%)	0.307
EDSS	Mean $\pm$ SD		1.81 $\pm$ 0.19	
	Median (min-max)		1.5 (1.0-3.0)	

MS = multiple sclerosis; EDSS = Expanded Disability Status Scale. $p \leq 0.05$ was accepted as significant.

TABLE 2 OCT values of MS patients and healthy control at the baseline evaluation.

		Baseline OCT values		<i>p</i>
		Control eyes (<i>N</i> = 30)	Patients eyes (<i>N</i> = 32)	
RNFL (μ m)	Mean $\pm$ SD	116.10 $\pm$ 11.23	101.44 $\pm$ 12.52	<0.001
	Median (min-max)	109.80 (102.94-137.45)	99.66 (78.00-122.72)	
GCC (μ m)	Mean $\pm$ SD	101.28 $\pm$ 7.80	89.24 $\pm$ 9.58	<0.001
	Median (min-max)	99.16 (90.07-124.08)	88.36 (70.30-108.80)	
NHV (mm^3)	Mean $\pm$ SD	0.28 $\pm$ 0.19	0.25 $\pm$ 0.16	0.622
	Median (min-max)	0.21 (0.09-0.96)	0.21 (0.02-0.80)	
FLV (%)	Mean $\pm$ SD	0.48 $\pm$ 0.36	2.25 $\pm$ 2.04	<0.001
	Median (min-max)	0.39 (0.007-1.35)	1.51 (0.05-7.24)	
GLV (%)	Mean $\pm$ SD	1.89 $\pm$ 1.76	8.49 $\pm$ 6.69	<0.001
	Median (min-max)	1.01 (0.20-5.82)	7.31 (0.39-24.39)	

MS = multiple sclerosis; OCT = optical coherence tomography; RNFL = retinal nerve fibre layer; GCC = ganglion cell complex; NHV = optic nerve head volume; FLV = focal loss volume; GLV = global loss volume. $p \leq 0.05$ was accepted as significant.

TABLE 3 Baseline and 20-month follow-up OCT parameters in MS group.

		OCT values (Patients eyes; N = 32)		<i>p</i>
		Baseline	20 months	
RNFL (μm)	Mean ± SD	101.44 ± 12.52	99.48 ± 12.53	0.350
	Median (min–max)	99.66 (78.00–122.72)	98.95 (77.00–123.60)	
NHV (mm ³)	Mean ± SD	0.25 ± 0.16	0.25 ± 0.17	0.797
	Median (min–max)	0.21 (0.02–0.80)	0.20 (0.03–0.76)	
GCC (μm)	Mean ± SD	89.24 ± 9.58	88.94 ± 10.55	0.695
	Median (min–max)	88.36 (70.30–108.80)	86.58 (70.30–107.80)	
FLV (%)	Mean ± SD	2.25 ± 2.04	2.44 ± 2.11	0.627
	Median (min–max)	1.51 (0.05–7.24)	1.64 (0.21–8.17)	
GLV (%)	Mean ± SD	8.49 ± 6.69	9.22 ± 7.07	0.550
	Median (min–max)	7.31 (0.39–24.39)	9.29 (0.52–25.39)	

MS = multiple sclerosis; OCT = optical coherence tomography; RNFL = retinal nerve fibre layer; GCC = ganglion cell complex; NHV = optic nerve head volume; FLV = focal loss volume; GLV = global loss volume. $p \leq 0.05$ was accepted as significant.

TABLE 4 Baseline and 20-month follow-up OCT parameters in control group.

		OCT values (Control eyes; N = 30)		<i>p</i>
		Baseline	20 months	
RNFL (μm)	Mean ± SD	116.10 ± 11.23	114.98 ± 11.17	0.003
	Median (min–max)	109.80 (102.94–137.45)	109.30 (102.66–136.50)	
NHV (mm ³)	Mean ± SD	0.28 ± 0.19	0.26 ± 0.18	0.052
	Median (min–max)	0.21 (0.09–0.96)	0.19 (0.08–0.96)	
GCC (μm)	Mean ± SD	101.28 ± 7.80	100.36 ± 7.78	0.021
	Median (min–max)	99.16 (90.07–124.08)	98.79 (91.28–125.42)	
FLV (%)	Mean ± SD	0.48 ± 0.36	0.51 ± 0.35	0.013
	Median (min–max)	0.39 (0.007–1.35)	0.41 (0.002–1.46)	
GLV (%)	Mean ± SD	1.89 ± 1.76	1.90 ± 1.67	0.497
	Median (min–max)	1.01 (0.20–5.82)	1.18 (0.11–5.43)	

MS = multiple sclerosis; OCT = optical coherence tomography; RNFL = retinal nerve fibre layer; GCC = ganglion cell complex; NHV = optic nerve head volume; FLV = focal loss volume; GLV = global loss volume. $p \leq 0.05$ was accepted as significant.

TABLE 5 Mean percent change of OCT values (%/20 months) in MS patients and controls.

		OCT values		<i>p</i>
		Control eyes (N = 30)	Patients eyes (N = 32)	
RNFL (μm)	Mean ± SD	−0.009 ± 0.016	−0.057 ± 0.173	0.390
	Median (min–max)	−0.006 (−0.05–0.02)	−0.040 (−0.33–0.46)	
NHV (mm ³)	Mean ± SD	−0.045 ± 0.143	0.483 ± 1.572	0.767
	Median (min–max)	−0.061 (−0.35–0.23)	0.00 (−0.88–6.78)	
GCC (μm)	Mean ± SD	−0.009 ± 0.019	−0.005 ± 0.15	0.439
	Median (min–max)	−0.009 (−0.06–0.03)	−0.028 (−0.19–0.39)	
FLV (%)	Mean ± SD	0.096 ± 0.410	3.759 ± 1.13	0.921
	Median (min–max)	0.076 (−0.71–1.60)	0.031 (−0.82–5.92)	
GLV (%)	Mean ± SD	0.074 ± 0.293	1.56 ± 4.18	0.714
	Median (min–max)	0.009 (−0.46–0.93)	0.13 (−0.92–18.82)	

MS, multiple sclerosis; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer; GCC, ganglion cell complex; NHV, optic nerve head volume; FLV, focal loss volume; GLV, global loss volume. $p \leq 0.05$ was accepted as significant.

The limited number of prospective longitudinal studies that investigated RNFL thickness in MS patients reported controversial results about changes in macular and peripapillary RNFL thicknesses

over time. Some studies that investigated MS patients (not only patients without a previous history of ON, but even patients with history of ON) found that RNFL and macular thicknesses were not statistically

reduced over time.^{11,12} Henderson *et al.* studied 34 patients with progressive MS on two occasions with a median interval of 575 days and 18 healthy controls with a median interval of 656 days. The MS patients had significant decreases in the baseline RNFL thickness and macular volume of their clinically unaffected eyes compared with controls. No significant decrease in RNFL thickness was observed between the baseline and follow-up values in either patients or controls.¹¹ Serbecic *et al.* prospectively studied 37 RRMS and secondary progressive MS patients on two occasions with a median interval of 22.4 ± 0.5 months and did not find any significant changes between the baseline and follow-up RNFL patterns.¹² Another study reported no significant change in RNFL over 2 years in 46 MS patients without comparative data from healthy controls.¹⁸ These studies support our results of almost stable RNFL thickness in MS patients during relatively short follow-up period.

In contrast, other longitudinal studies have shown reduction of the RNFL thickness in the MS patients during follow-up.^{10,16} Talman *et al.* reported progressive RNFL thinning in some patients with MS, even in the absence of ON, during a mean follow-up of 18 months in 299 patients.¹⁰ Another study, which investigated a large cohort of MS patients and healthy controls during a 2-year follow-up, reported greater decreases of RNFL thickness in the MS patients, but statistical differences were found only for the average RNFL thickness and not for other measures such as superior and inferior RNFL.¹⁶

Different studies have reported progressive, age-related decline of RNFL and macular thicknesses in healthy subjects determined by OCT or other non-invasive imaging in cross-sectional and longitudinal studies during short-term follow-up.^{11,19–22} Henderson *et al.* reported a significant reduction of macular volume in healthy controls over time.¹¹ Leung *et al.* studied RNFL thickness prospectively in healthy subjects and found age-related loss.¹⁹ Also, Kilic *et al.* reported a negative correlation between RNFL thickness and age.²² These findings were confirmed by histological studies demonstrating a significant association between age and RNFL thickness in normal subjects.^{23,24} Particularly, large baseline RNFL thickness was found to be associated with a faster rate of RNFL thickness loss.²⁰ Mean rate of change of average RNFL thickness in our control subjects was $-0.67 \mu\text{m}/\text{year}$ (95% confidence interval [CI]: 0.29 to 1.04). These values are similar to those previously reported.¹⁹

Then the question arises: Why did the RNFL and macular thicknesses in MS patients not significantly change during the observation period? Some studies have shown the presence of subclinical optic neuropathy in MS patients, which can be diagnosed by performing not only OCT, but such multiple tests as visual evoked potentials, visual field examination,

visual acuity, and colour vision.^{25–27} According to the literature, in the early stages of ON in MS patients, RNFL and macular thinning or thickening (swelling) can occur, along with different structural changes in optic disc morphology.^{27,28} The retina in MS patients passes through stages of minimal demyelination, remyelination, and gliosis, which can be verified only by biopsy.²⁹ Some researchers consider that OCT is relatively insensitive for revealing acute axon damage at the time of acute presentation and even later, and that non-neural tissue components in RNFL may obscure subtle degrees of axonal loss in MS.^{11,30} We think that some of our patients without pronounced visual symptoms or complaints could have had subclinical changes in the optic nerve during the follow-up period. It is known that thinning of the RNFL below $75 \mu\text{m}$ (injury threshold) might lead to a corresponding decline in objective visual function.³¹ Whereas healthy subjects have a tendency to age-related RNFL thinning, MS patients can likely pass through different stages of retinal thinning and thickening, which might be the reason why we could not find any statistically significant change between the baseline and second measurements in our MS patients. Even so, the MS patients in our cohort had a mean annual rate of average RNFL change of -1.17 (95% CI: -2.27 to 4.74) similar to the results reported in previous studies.^{10,11} In conclusion, ON might be present in subclinical (occult) form without typical symptoms or complaints.^{32,33} Our patients did not have any complaints, especially visual, during the follow-up period and had not been examined by OCT or another technique for early detection of subclinical optic neuritis in the inter-observational period. For these reasons, we think that RNFL in some of the patients might tend to thicken, which is related to possible subclinical optic neuritis, and thus did not significantly decrease in the follow-up period, whereas RNFL thickness in healthy subject gradually reduced. It is also possible that 20 months is not enough time to document progressive RNFL thinning in MS patients. Long-term observation will reveal RNFL and macular thinning, because during this period the amount of neuroaxonal loss could surpass factors that cause retinal thickening.

We think that studies with a larger cohort and longer follow-up periods are needed to establish more reliable results.

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