Original Article

Regional Analysis of Inner Retinal Layer Changes in Multiple Sclerosis with and without Optic Neuritis

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Abstract

Objectives: The study aimed to investigate inner retinal changes in multiple sclerosis (MS) patients by comparing them with healthy controls. The study also aimed to assess regional differences of inner retinal layer involvement in eyes with and without optic neuritis (ON).

Materials and Methods: This retrospective, cross-sectional study consisted of 141 eyes of 74 relapsing-remitting MS patients and 80 eyes of 40 healthy controls. The study group was separated into two subgroups according to the presence of ON history. Peripapillary retinal nerve fiber layer (pRNFL) thickness, total macular thickness, and thicknesses of the macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), and inner nuclear layer were compared between the MS and healthy control groups and between eyes with and without ON history.

Results: Mean pRNFL, total macular, mRNFL, GCL, and IPL thicknesses were significantly thinner in the MS group than in the control group ($p<0.001$) and in eyes with ON compared to those without ON ($p<0.05$). Comparison of inner retinal layer thicknesses in the inner 3-mm ring subfields of the ETDRS grid revealed significant thinning in all subfields of the GCL and IPL of eyes with ON ($p<0.05$). The inferior subfield demonstrated the highest difference.

Conclusion: The study demonstrated that GCL and IPL thinning is a robust and reliable biomarker in all MS patients. The thinning was significantly greater in eyes with ON than in eyes without ON. The study also documented that the inferior region showed significantly greater GCL and IPL thinning in eyes with previous ON attacks.

Keywords: Multiple sclerosis, optic neuritis, optical coherence tomography, retinal ganglion cell, retinal nerve fiber

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Introduction

Multiple sclerosis (MS) is a degenerative disorder affecting the brain and spinal cord. It is a chronic demyelinating disease and frequently involves the visual pathways. Inflammation of the optic nerve, termed optic neuritis (ON), can be the initial presentation of MS. About 28% of patients with ON develop MS within 10 years.[1] In addition, autopsy findings revealed 90% optic nerve involvement in over 90% of MS patients.[2] Another postmortem study detected inner retinal atrophy in about 79% of MS patients and correlated the severity of retinal atrophy with overall brain weight at the time of autopsy.[3]

Optical coherence tomography (OCT) is a simple, cost-effective, and reliable tool for retinal visualization. OCT enables the acquisition of retinal images in three dimensions and cross-sections. It measures all retinal layers separately, including the peripapillary retinal nerve fiber layer (pRNFL). Retinal findings on OCT are strongly associated with brain tissue changes in MS patients.[4] In addition, several studies have confirmed the important place of OCT in both the diagnosis and monitoring of MS, even in the absence of ON.[5,6]

This study primarily aimed to investigate changes in the inner retinal layers in MS patients with and without ON compared to healthy controls. The secondary aim was to assess regional differences in the inner retinal layers in MS patients.

Materials and Methods

This retrospective, cross-sectional study was approved by the Scientific Research Ethics Committee of the Health Sciences University Türkiye (date: March 23, 2021, no: E-46418926-050.01.04-1592) and was conducted according to the principles of the Declaration of Helsinki. People with MS were referred

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from the MS unit of the neurology department for routine ophthalmological assessments. MS was diagnosed by a specialist neurologist based on the 2010 McDonald criteria. The study group was separated into two subgroups, those with and those without a history of ON. Patients with an ON history of less than six months were excluded. Healthy people who presented to the outpatient clinic for routine eye examination or because of refractive error formed the control group.

Exclusion criteria were glaucoma, refractive errors more than 4 diopters, any retinal disorders affecting the optic nerve and macular layer structure, any ophthalmological disorder that prevented good quality retinal imaging (e.g., corneal opacities, dense cataract, nystagmus), and a history of intraocular surgery other than uncomplicated phacoemulsification surgery performed at least 6 months earlier.

All participants underwent a complete ophthalmologic examination. Retinal spectral-domain OCT (SD-OCT) was done with Spectralis (software version 6.16.2, Heidelberg Engineering, Heidelberg, Germany). Images were obtained by a trained technician. Images precisely centered on the fovea with good quality were recorded. Scanning was performed in a 30x20 degree cube consisting of 25 raster lines at 240 µm intervals. Retinal layers were determined automatically (Figure 1a). Thicknesses of the total macula and inner layers including the macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), and inner nuclear layer (INL) were recorded in each of the nine subfields in the Early Treatment Diabetic Retinopathy Study (ETDRS) grid (Figure 1b). The mean total macular thickness and the thicknesses of each inner retinal layer were obtained from the average of the thicknesses of the nine subfields. Volumes were also calculated automatically by SD-OCT. Mean peripapillary RNFL (pRNFL) thickness was determined from the average of sixteen successive B scans surrounding the optic disc (diameter 3.5 mm, 768 A-scans) (Figures 1c and 1d).

Statistical Analysis

The data were analyzed statistically using IBM SPSS version 20.0 (IBM Corp, Armonk, NY, USA) software. The fit of the data to normal distribution was determined visually and analytically (Kolmogorov-Smirnov test). Descriptive statistics for variables with normal distribution were presented as mean and standard deviation. Comparisons between two groups were made using independent samples t-test. One-way analysis of variance (ANOVA) was used to compare multiple groups. Welch statistics were used when the variances were not homogeneous. Tamhane's T2 or LSD tests were used in post-hoc analyses according to whether the variances were homogeneous or not. Comparison of categorical variables was made with Pearson chi-square test. A p-value less than 0.05 was accepted as statistically significant.

Results

The study included 141 eyes of 74 patients with relapsing-remitting MS and 80 eyes of 40 healthy controls. Gender and age characteristics were similar in the MS and control groups, while the MS group had significantly lower visual acuity ($p<0.001$). The mean MS duration was determined as 10.88±7.45 years. Demographic properties, Expanded Disability Status sale scores, and best-corrected visual acuity (BCVA) of the groups are summarized in Table 1.

Within the MS group, 46 eyes had a positive history of ON and 95 eyes had a negative history. MS patients with ON were 5.48 years younger on average than those without ON ($p<0.05$). Although the mean BCVA in patients with ON was 0.07 (decimal) lower than that in patients without ON, this difference was not statistically significant ($p=0.126$). The mean number of ON attacks was 1.46±0.88.

pRNFL measurements were significantly thinner in the MS group than in the control group ($p<0.001$) (Table 2). When the subgroups with and without ON were compared with each

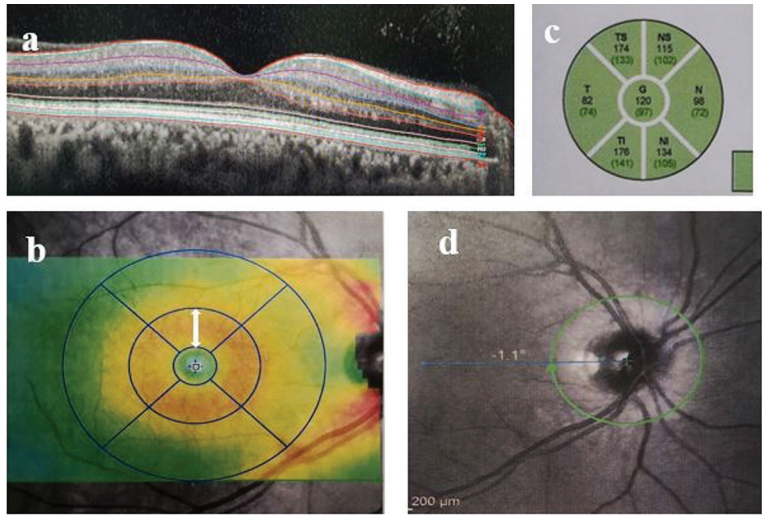

Figure 1. a) Automatic segmentation of the macular retinal layers by spectral domain optical coherence tomography; b) Nine subfields of the macula in the ETDRS (Early Treatment Diabetic Retinopathy Study) grid. The white double arrow shows inner and outer boundaries of the inner 3-mm annulus; c,d) Peripapillary retinal nerve fiber measurement

other and the control group, pRNFL measurements also showed significant differences between all groups (p<0.05, p<0.001, p<0.001) (Table 2).

The mean total macular, mRNFL, GCL, and IPL thicknesses were significantly thinner in the MS group compared to the control group (p<0.001) (Table 2). The mean INL thickness was greater in the MS group, but the difference was insignificant (p=0.171) (Table 2). Consistent with the thickness results, mean macular, mRNFL, GCL, and IPL volumes were statistically lower in the MS group compared to the control group (p<0.001), while the mean INL volume did not differ significantly (p=0.067) (Table 2).

The subgroups with ON and without ON demonstrated significant thinning and volume loss in the total macula, mRNFL, GCL, and IPL in comparison with the control group (p<0.001) (Table 2). The mean INL thickness and volume were thicker in both MS subgroups than in the control group, but only the subgroup with ON showed a statistical significance (p<0.05) (Table 2). When the subgroups with and without ON were compared with each other, the thicknesses and volumes of all layers except the INL were significantly lower in the subgroup with ON (p<0.05) (Table 2).

Comparison of total macular and inner retinal layer thicknesses in the inner 3-mm ring subfields of the ETDRS grid revealed significant thinning in all subfields in the GCL and IPL of eyes with ON (p<0.05) (Figure 2a, b). The greatest difference was in the inferior subfields of the GCL and IPL (6.481 µm, p<0.001; 4.115 µm, p<0.001, respectively). Total macular thickness showed statistically significant thinning in the inferior, nasal, and temporal subfields (p<0.05) but not the superior subfield (p=0.071) (Figure 2a). mRNFL showed no significant differences between the two subgroups in any subfield (Figure 2b). The INL was thicker in all subfields in eyes with ON, with statistically significant differences in the superior, temporal, and nasal subfields (Figure 2b).

BCVA (decimal) showed weak to moderate positive correlation with total macular thickness (r=0.338, p<0.001) and pRNFL (r=0.297, p<0.001), mRNFL (r=0.425, p<0.001), GCL (r=0.472, p<0.001), and IPL thickness (r=0.488, p<0.001).

Discussion

The present study demonstrated significant thinning in all inner retinal layers except the INL in the eyes of people with MS. This study also revealed that GCL and IPL thinning was greater in eyes with ON compared to those without ON, and this thinning was significantly greater in some regions.

OCT measurements of the retina have been proposed as biomarkers in the diagnosis and follow-up of MS.[7] pRNFL and macular GCL/IPL measurements in particular were recommended for MS diagnosis and monitoring.[5,8] The cause of retinal changes was initially thought to be retrograde neurodegeneration secondary to demyelination.[9] A recent study also supported the mechanism of anterograde neurodegeneration affecting the visual pathways.[10] Pietroboni et al.[11] found significant reductions in mRNFL, GCL, IPL, and GCL + PL thickness in the very early clinical stages of MS without a history of ON. The current study showed significant thinning of the pRNFL, mRNFL, GCL, and IPL in MS patients compared with healthy controls, independently of ON history. These findings are consistent with studies suggesting there is both anterograde and retrograde transsynaptic neurodegeneration in MS.

Comparison based on ON history showed that total macular, pRNFL, mRNFL, GCL, and IPL thicknesses were significantly reduced in eyes with ON. On the other hand, the change in INL did not show statistical significance. Consistently, the total macular, mRNFL, GCL, and IPL volumes showed statistically significant reductions in ON eyes. Similarly, Seitz et al.[12] found a significant decrease in total macular, mRNFL, and GCL + PL umes in patients with ON compared to those without ON. The study by Seitz et al.[12] included patients with a mean disease duration of 2.2±3.5 years, whereas our study included late-stage cases with a mean disease duration of 10.88±7.45 years. Another study also reported significant thinning of the total macula, mRNFL, GCL, and IPL in eyes with ON compared to those without ON, in line with the current study.[13]

Table 1. Demographic characteristics and best-corrected visual acuity levels of the study and control groups

	Multiple sclerosis (n=141 eyes)	**Control (n=80 eyes)**	**p**	**ON– (n=95 eyes)**	**ON+ (n=46 eyes)**	**Control (n=80 eyes)**	**p**
Gender, n (%)	Male: 60 (42.6) Female: 81 (57.4)	Male: 40 (50) Female: 40 (50)	0.285*	Male: 40 (42.1) Female: 55 (57.9)	Male: 20 (43.5) Female: 26 (56.5)	Male: 40 (50) Female: 40 (50)	0.558*
Age (years)	41.6±10.0	41.8±14.0	0.934**	43.44±9.78	37.96±9.74	41.8±14.0	[1]**0.031**‡ [2]0.762‡ [3]0.205‡
BCVA (decimal)	0.94±0.19	1.00±0.00	<0.001**	0.96±0.14	0.89±0.25	1.00±0.00	[1]0.332‡ [2]**0.046**‡ [3]**0.033**‡
Expanded Disability Status Scale	4.52±1.42	-		4.52±1.31	4.50±1.70	-	0.937**

BCVA: Best-corrected visual acuity, ON: Optic neuritis
[1]ON- vs. ON+, [2]ON- vs. control, [3]ON+ vs. control. *Pearson chi-square test, **Independent samples t-test, ‡One-way ANOVA, Welch, post-hoc Tamhane's T2

Table 2. Comparison of peripapillary retinal nerve fiber layer thickness and total macular and inner retinal layer thicknesses and volumes between the control group and the multiple sclerosis (MS) group overall and the MS subgroups with optic neuritis (ON+) and without optic neuritis (ON-)

	MS (n=141)	Control (n=80)	p	ON- (n=95)	ON+ (n=46)	Control (n=80)	p
pRNFL (µm)	83.34±14.79	100.59±8.43	**<0.001***	86.37±14.33	77.09±13.86	100.59±8.43	[1]0.001‡ [2]<0.001‡ [3]<0.001‡
Total macular thickness (µm)	296.02±16.71	309.50±13.03	**<0.001***	298.37±16.41	291.15±16.45	309.50±13.03	[1]0.048‡ [2]<0.001‡ [3]<0.001‡
mRNFL thickness (µm)	22.18±4.79	26.72±1.98	**<0.001***	22.72±4.85	21.14±4.55	26.72±1.98	[1]0.030† [2]<0.001† [3]<0.001†
GCL thickness (µm)	32.02±6.39	40.65±3.33	**<0.001***	33.27±6.15	29.61±6.23	40.65±3.33	[1]<0.001† [2]<0.001† [3]<0.001†
IPL thickness (µm)	28.45±4.69	33.68±2.35	**<0.001***	29.18±4.93	27.05±3.87	33.68±2.35	[1]0.003† [2]<0.001† [3]<0.001†
INL thickness (µm)	34.86±4.67	34.09±2.36	**0.171***	34.33±5.03	35.90±3.71	34.09±2.36	[1]0.120‡ [2]0.972‡ [3]**0.012**‡
Total macular volume (mm^3)	8.20±0.47	8.56±0.37	**<0.001***	8.27±0.48	8.06±0.43	8.56±0.37	[1]0.032‡ [2]<0.001‡ [3]<0.001‡
mRNFL volume (mm^3)	0.72±0.17	0.89±0.07	**<0.001***	0.75±0.17	0.69±0.17	0.89±0.07	[1]0.026† [2]<0.001† [3]<0.001†
GCL volume (mm^3)	0.90±0.15	1.11±0.09	**<0.001***	0.93±0.15	0.84±0.14	1.11±0.09	[1]<0.001† [2]<0.001† [3]<0.001†
IPL volume (mm^3)	0.77±0.11	0.90±0.06	**<0.001***	0.79±0.12	0.74±0.09	0.90±0.06	[1]0.007† [2]<0.001† [3]<0.001†
INL volume (mm^3)	0.98±0.12	0.95±0.06	0.067*	0.97±0.14	1.00±0.09	0.95±0.06	[1]0.419‡ [2]0.609‡ [3]**0.012**‡

pRNFL: Peripapillary retinal nerve fiber layer, mRNFL: Macular retinal nerve fiber layer, GCL: Ganglion cell layer, IPL: Inner plexiform layer, INL: Inner nuclear layer
[1]ON-vs. ON+, [2]ON-vs. control, [3]ON+ vs. control . *Independent samples t-test, †One-way ANOVA, post-hoc LSD, ‡One-way ANOVA, Welch, post-hoc Tamhane's T2

The present study also compared differences in the inner 3-mm subfields of the ETDRS grid in eyes with and without a history of ON. Regional comparison of inner retinal layer changes revealed the greatest difference in the inferior subfield. The nasal and temporal subfields followed the inferior subfield in terms of the difference in total macular, GCL, and IPL thickness between the two subgroups. Thinning of the GCL in the inferior macula has also been implicated as a sign of early glaucomatous damage.[14,15] Hood et al.[15] introduced a macular vulnerability zone to define the most susceptible area of retinal ganglion cells in early glaucoma. This zone corresponds to the inferior macula. The axons of the retinal ganglion cells in the zone extend into the inferotemporal part of the optic disc, which is known to be vulnerable to glaucomatous damage. Our finding of profound ganglion cell loss in the inferior macula may indicate a similar mechanism of optic nerve involvement in MS. Özbilen et al.[16] reported regional differences in the inner retinal layers in MS patients and consistent with our study, they observed the greatest difference in ganglion cells in the inferior 3-mm subfield of ETDRS ring in their study comparing eyes with ON and without ON.

BCVA demonstrated the highest correlation with GCL and IPL thicknesses, followed by mRNFL and total macular thickness. The lowest correlation was seen with pRNFL. Our findings corroborate previous studies reporting the robust association of GCL and IPL thinning with visual function in MS patients with and without ON history.[17,18,19] Narayanan et al.[20] observed a high correlation between multifocal visual evoked potential and GCL + IPL thickness, supporting the relation of GCL-IPL thickness to visual function in MS.

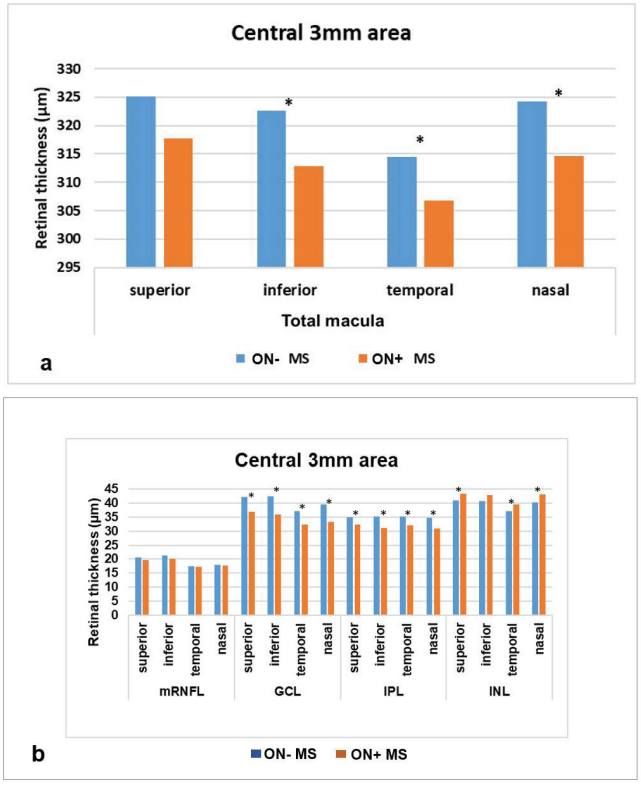

Figure 2. a) Total macular thickness in eyes with a history of optic neuritis (ON) demonstrated thinning in all inner 3-mm subfields of the ETDRS (Early Treatment Diabetic Retinopathy Study) grid. The thinning was statistically significant in the inferior, temporal, and nasal subfields; b) Comparison of inner retinal layers in the inner 3-mm subfields of the ETDRS ring. Ganglion cell layer (GCL) and inner plexiform layer (IPL) showed significant thinning in all subfields in eyes with ON history, while the inner nuclear layer (INL) showed significant thinning in the superior, temporal, and nasal subfields. Macular retinal nerve fiber layer (mRNFL) showed no significant difference in any subfield and inner nuclear layer (INL). *p<0.05

Study Limitations

The main limitation of the study is its retrospective nature. In addition, the study included cases with only one type of MS and did not compare different types.

Conclusion

Our study demonstrated that GCL and IPL thinning is a robust and reliable biomarker in all MS patients. However, the thinning in these layers was significantly greater in eyes with a history of ON than in eyes without ON. The study also documented that the inferior region showed significantly greater GCL and IPL thinning in eyes with previous ON attacks. This finding may guide future studies about the specific feature of the optic nerve involvement in MS.

Ethics

Ethics Committee Approval: This retrospective, cross-sectional study was approved by the Scientific Research Ethics Committee of the Health Sciences University Türkiye (date: March 23, 2021, no: E-46418926-050.01.04-1592) and was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally peer reviwed.

Authorship Contributions

Surgical and Medical Practices: B.K., Ş.S., Concept: B.K., Ş.S., N.D., S.D., M.S., Design: B.K., S.D., Data Collection or Processing: B.K., Ş.S., N.D., S.D., Analysis or Interpretation: B.K., Ş.S., N.D., S.D., M.S., Literature Search: B.K., Ş.S., N.D., Writing: B.K., Ş.S., M.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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