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Evaluation of Inner Retinal Layers in Patients with Multiple Sclerosis or Neuromyelitis Optica Using Optical Coherence Tomography

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Abstract

Purpose—To evaluate the thickness of the inner retinal layers in the macula using frequency domain-optical coherence tomography (fd-OCT) in patients with demyelinating diseases.

Design—Cross sectional study

Participants—301 eyes of 176 subjects were evaluated. Subjects were divided in 5 different groups: controls, neuromyelitis optica (NMO), longitudinally extensive transverse myelitis (LETM), multiple sclerosis with (MS-ON) and without (MS non-ON) history of optic neuritis, respectively.

Methods—The individual layers from macular fd-OCT cube scans were segmented with an automated algorithm, and then manually hand-corrected. For each scan, we determined the thickness of the retinal nerve fiber layer (RNFL), the combined retinal ganglion cell and inner plexiform layers (RGCL+), and the inner nuclear layer (INL).

Main outcome measures—Macular RNFL, RGCL+ and INL thickness

Results—The RNFL was significantly thinner than controls for all patient groups ($p < 0.01$). Macular RGCL+ thickness was significantly thinner than controls for the NMO, MS-ON and MS non-ON ($p < 0.001$ for the 3 groups). The INL thickness was significantly thicker than controls for the NMO ($p = 0.003$) and LETM ($p = 0.006$) patients but not for MS-ON or MS non-ON. While the RNFL and RGCL+ were not significantly different between the NMO and MS-ON groups, the NMO patients had a significantly thicker INL than the MS-ON ($p = 0.02$) patients.

Conclusion—Macular RNFL and RGCL+ demonstrate axonal and neural loss in MS, either with or without ON, and in NMO patients. In addition, the INL thickening occurs in NMO and LETM patients and study of this layer may hold promise for differentiating between NMO and MS.

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Multiple sclerosis (MS) and neuromyelitis optica (NMO) are both inflammatory, autoimmune, demyelinating diseases that can present with optic neuritis (ON) and/or transverse myelitis. Usually the ON in NMO is more recurrent and severe when compared to MS.¹ The myelitis in NMO characteristically extends more than 3 vertebral bodies and is then called longitudinally extensive transverse myelitis (LETM), while in MS it rarely extends over two vertebral bodies.² Previously thought to be a rare subtype of MS, the identification of the NMO-immunoglobulin G (IgG) autoantibody³ has provided evidence that they are different diseases.⁴ We also know that a water channel protein, aquaporin-4 (AQP4) is the target of auto antigen in NMO.⁵ The AQP4 is usually found in astrocytes in the nervous system (e.g., optic nerve and spinal cord), but also is found in other supporting cells, such as the retina Mueller cells.⁶

Optical coherence tomography (OCT) is a technology that can be used to detect a large array of retinal abnormalities including those resulting from axonal loss in diseases affecting the anterior optic pathway including MS and NMO.⁷⁻¹⁰ Over the last years several studies have suggested that peri-papillary retinal nerve fiber layer (RNFL) and macular thickness analysis may be used to detect axonal loss in MS and to monitor treatment efficacy. It has also been suggested that OCT abnormalities can help differentiate MS from NMO patients based on the severity of axonal loss and the existence of subclinical damage in MS and not in NMO patients.^{9, 11} Most studies have quantified axonal loss based on OCT measurements of the peri-papillary RNFL,^{8, 10, 11} while some have also evaluated macular full thickness measurements, another indirect indicator of axonal loss.^{7, 9, 12, 13}

Recently with the advent of segmentation of OCT-measured macular measurements, different retinal layers have been studied in MS patients. Saidha, Syc, Durbin et al demonstrated a thinning of the retinal ganglion cell layer (RGCL) in all MS subtypes. This RGCL thinning correlated better with visual loss and neural disability than did changes in RNFL thickness.¹⁴ Another recent paper from the same authors discussed the possibility of a primary retinal neuro-pathology in MS patients and demonstrated that in part of these patients the inner and outer nuclear layers are thinner than normal controls.¹⁵

Several questions about the effects of MS and NMO on macular layer thickness remain open. For example, does MS really affect other retinal layers and what is the extent of RGCL thickness loss? Also, little is known about the thickness of retinal layers in NMO or LETM (NMO-spectrum) versus those in MS patients, as well as the effect of the positivity for anti-aquaporin 4 antibody on the thickness of retinal layers, specifically the inner nuclear layer where the Mueller cell bodies are located.

The purpose of this study was: 1. to evaluate the thickness of the RNFL, RGCL and inner nuclear layer (INL) in the macula using high resolution optical coherence tomography (fd-OCT) in patients with MS, either with history of ON (MS-ON) or without history of ON (MS non-ON), patients with NMO (affected with ON) or LETM (NMO-spectrum, without ON); 2. to understand how the changes seen with these different diseases compare to each other and to controls.

Methods

Study design and sampling

This was an observational, prospective cross-sectional study. Participants were recruited from the Department of Neurology of the University of São Paulo Medical School. Approval from the Institutional Review Board Ethics Committee was obtained for the study. The study followed the principles of the Declaration of Helsinki and informed consent was

obtained from all participants. This study is registered on www.clinicaltrials.gov, under identifier NCT01024985 (accessed December 2, 2009).

A total of 84 eyes from 45 normal controls and 217 eyes from 131 patients were evaluated. Eyes of patients were divided in four different groups: 1- NMO; 2- LETM; 3- MS-ON; 4- MS non-ON. For specific comparisons groups, 1 and 3 were sub-divided in having one or more than one episode of ON.

All patients had their diagnosis confirmed by the treating neurologist (D.C.). MS diagnose was based on McDonald criteria¹⁶ The diagnosis of NMO was based on the revised diagnostic criteria of Wingerchuck et al.¹. All patients had previous episodes of ON and acute transverse myelitis with MRI, showing contiguous spinal cord lesion involving more than 3 vertebral segments. Fifteen (46%) patients had positive NMO-IgG anti aquaporine-4 antibody. LETM patients were included because it is considered a spectrum within the same disease as NMO^{9, 17, 18}. LETM patients are therefore considered the equivalent of NMO patients, but without the history of ON. In our study, inclusion criteria for LETM were: monophasic or recurrent occurrence of sensory, motor or autonomic dysfunction attributable to the spinal cord with bilateral signs or symptoms and progression to nadir between 4 hours and 21 days; inflammation within the spinal cord demonstrated by cerebrospinal fluid (CSF) pleocytosis or elevated IgG index or gadolinium enhancement on MRI; and spinal cord MRI abnormality extending three or more vertebral segments. Ten (35%) patients with LETM had positive anti-NMO antibody titers.

The neurologic exclusion criteria for all patients were extra-axial compressive etiology by neuroimaging, central nervous system manifestation of infectious diseases and brain MRI abnormalities other than those suggestive of MS or NMO.

Disease duration, number of ON crisis and disease-specific therapies was ascertained for each patient. History of ON episodes was determined for eyes of MS and NMO patients by self-report and physician report, and confirmed by medical record review. Patients whose most recent attack of ON had occurred less than 6 months prior were not included in the study. Normal controls consisted of normal healthy volunteers recruited from among the hospital staff.

Optical Coherence Tomography and segmentation technique

Subjects underwent fd-OCT scanning of the macular area without dilating the pupil, using commercially available equipment (3 D OCT-1000®, Topcon Corp., Tokyo, Japan) on the same day of the ophthalmic evaluation. The authors reviewed the images with respect to their subjective and objective quality.

The scanning protocol involved the acquisition of a set of 3 high-definition OCT images of the macula in a raster pattern covering a 6-mm area with a scan density of 512×128 in ~ 3.5 seconds (27,000 A scans/sec) (Figure 1A). Criteria for acceptable 3D OCT-1000® fundus images included: an absence of large eye movements, defined as an abrupt shift completely disconnecting a large retinal vessel; a consistent signal intensity level across the scan; and an absence of black bands (caused by blinking) throughout the examination.

The local structural thickness was determined for the individual B-scans of the cube scan. In particular, for each B-scan, the boundaries of anatomical layers were determined using a previously validated automated segmentation algorithm,¹⁹ which was then hand-corrected using manual segmentation via a custom program as previously described,²⁰⁻²² a technique which has been shown to provide reliable and repeatable results²³. The hand-correction was done by an experienced operator who was blind to the patient's diagnose during the

segmentation process. Figure 1B shows the borders segmented and the regions for which we calculated thickness values: RNFL, RGCL combined with the inner plexiform layer (IPL), and INL. Because the boundary between the RGCL and the IPL can sometimes be hard to determine, we measured the combined RGCL+IPL (RGCL+) instead of measuring each of these layers separately. For each cube scan, we segmented 128 B-scans and obtained the thickness for each evaluated layer, including 3 separate measurements corresponding to the macular RNFL, the RGCL+ and the INL thickness. A pseudo-color thickness map of these layers is shown in Fig. 2 for the average of the controls, MS-ON and NMO patients.

Visual function testing

Subjects underwent a complete ophthalmologic examination including best-corrected monocular visual acuity assessment and SAP. Visual acuity was assessed with ETDRS charts at 3.2 m (Lighthouse Low-Vision Products, Long Island City, NY). Snellen equivalents were also recorded for ETDRS VA measurements. SAP was conducted with a Humphrey Field Analyzer (Carl-Zeiss Meditec, Dublin, CA) using the Swedish Interactive Threshold Algorithm (SITA-standard 24.2 program) and a Goldmann size III stimulus on a 31.5-apostilb background. Perimetry was performed on the same day as OCT testing.

For all patients and controls, ophthalmological inclusion criteria for the study were best corrected visual acuity of 20/200 or better in at least one eye, refractive errors less than 5.00 diopters sphere or 4.00 diopters cylinder, intraocular pressure < 22 mmHg, and reliable VF. A reliable VF test was defined as one with fewer than 33% fixation losses, false positive or false negative responses. The ophthalmologic exclusion criteria were history of clinically apparent optic neuropathies other than ON, history of intraocular pressure elevation, clinical signs of glaucomatous optic neuropathy, and optic disc anomaly.

Data analysis and statistics

Analysis was performed using SPSS version 19.0. Generalized estimating equation (GEE) models, accounting for age and within patient inter-eye correlations, were used to examine the macular RNFL, RGCL+ or INL thickness of the different groups. For all statistical tests, type I error for significance was set as $P < 0.05$.

Results

A total of 301 eyes were evaluated and separated in 5 groups. NMO: Forty-six eyes from 29 patients with NMO (anti-NMO positive = 22 eyes, only one episode of ON = 33 eyes); LETM: 56 eyes from 29 patients with LETM (anti-NMO positive = 20 eyes); MS-ON: 41 eyes of 29 patients with MS previously affected with ON (MS-ON, only one episode of ON = 28 eyes); MS non-ON: 74 eyes of 44 patients without previous episodes of ON (MS non-ON); and, Controls: 84 eyes of 45 controls. Table 1 shows the demographic data of all individuals studied.

Table 2 and Fig. 3A show macular RNFL thickness measurements for each group. Average macular RNFL thicknesses were significantly reduced in NMO ($p < 0.001$), LETM ($p = 0.003$), MS-ON ($p < 0.001$) and MS non-ON ($p = 0.008$) eyes when compared with normal controls. NMO eyes were significantly smaller than those from LETM ($p < 0.001$) or MS non-ON ($p < 0.001$) eyes, but were not significantly different when compared to MS-ON eyes ($p = 0.254$). LETM eyes were significantly thicker than MS-ON ($p = 0.009$) and not significantly different than MS non-ON eyes ($p = 0.628$). Finally, macular RNFL thickness measurements of MS-ON were significantly different than those of MS non-ON eyes ($p = 0.002$).

Table 2 and Fig. 3B show results of comparison of RGCL thickness measurements in each group. When compared to normal controls, average macular RGCL+ thicknesses were significantly smaller in NMO eyes ($p<0.001$), MS-ON ($p<0.001$) and MS non-ON ($p<0.001$) eyes. No significant difference was observed between measurements of LETM eyes and controls ($p=0.370$). NMO eyes were significantly smaller than LETM eyes ($p<0.001$), but not than MS-ON ($p=0.996$) or MS non-ON ($p=0.064$) eyes. LETM eyes were significantly thicker than MS-ON ($p<0.001$) and MS non-ON ($p<0.001$). No significant difference was observed between MS-ON and MS non-ON eyes ($p=0.64$).

Table 2 and Fig. 3C show results of comparison of INL thickness measurements in each group. The NMO ($p=0.026$) and LETM ($p=0.007$) eyes had thicker INL, while the thicknesses of the INL for MS ON ($p=0.911$) and MS non-ON ($p=0.376$) did not differ from controls. Also NMO ($p=0.004$) or LETM ($p=0.001$) were thicker when compared with MS ON ($p=0.023$, $p=0.006$, respectively) or with MS non-ON ($p=0.004$, $p=0.001$, respectively.) There was no significant difference between MS ON and MS non-ON ($p=0.440$).

We also evaluated separately eyes with one single episode of ON, comparing two groups, MS patients (28 eyes) and NMO patients (33 eyes) with normal controls data. The results are shown on Table 3. Measurements were significantly thinner than controls regarding macular RNFL thickness ($p<0.001$ for both groups of eyes) and RGCL+ thickness ($p<0.001$ and $p=0.006$, respectively) measurements. However, when evaluating INL thickness measurements, the NMO group of eyes with a single ON episode was significantly thicker ($p=0.04$), but the MS group demonstrate no significant difference ($p=0.82$) compared to controls. When compared to each other, MS-ON with one episode and NMO with one ON episode, there was no significant difference in RNFL ($p=0.21$) and RGCL+ ($p=0.75$), but the INL was also statistically thicker ($p=0.03$) in the NMO group. In this two groups with one episode of ON we also compared the peri-papillary RNFL and we found that the NMO with one episode was significantly thinner ($p<0.001$) than MS with one episode.

Discussion

In a large population of patients with either NMO spectrum or MS using fd-OCT, we found that both macular RNFL and RGCL+ were statistically thinner in MS with or without ON when compared to normal controls. These findings are consistent with the hypothesis that optic nerve demyelination results in retrograde axonal degeneration, culminating in ganglion cell death²⁴. It also helps supports the notion that axonal and neuronal loss is present even in eyes of MS patients without clinical history of ON. These results are similar to a recent study²⁵ in which RGCL thickness was found to be reduced in 4 eyes with MS ON and 12 eyes with MS non-ON. The findings are also in agreement with a number of previous studies²⁶⁻²⁹, which evaluated the peri-papillary RNFL or the full-thickness macular measurements, but not specifically the RGCL, in patients with MS.

In addition to confirming the occurrence of axonal loss in MS patients, our study provides also speaks to the current debate about the presence of primary retinal pathology in MS patients. Recent studies have evaluated the INL and outer nuclear layers, as well as the RGCL of MS patients. In an anatomopathologic study, Green et al demonstrated a loss of INL neurons (neurons from bipolar, horizontal and amacrine cells) in post mortem studies of MS patients³⁰. Subsequently, Saidha et al¹⁵ subdivided the MS patients using OCT data and created a new group, which they named macular thinning predominant (MTP). MTP patients had normal peri-papillary RNFL and the average macular thickness below the 5th percentile. This new group had significant thinning of both the inner and outer nuclear layers of the retina when compared to normal controls¹⁵. In a different study the same authors found evidence that the INL and ONL thickness did not differ according to ON history¹⁴. Based

on these findings, Saidha et al have hypothesized that a primary process, independent of optic neuropathy, is targeting retinal neurons in some MS patients.

In the current study, we did not find evidence for this process. In particular, the INL thickness was not statistically different from the normals. However, it is important to note that we evaluated patients with relapsing-remitting MS (both with and without previous episodes of ON) and did not restrict our analysis to the MPT group of patients selected by Saidha et al. In theory, our group of MS eyes without ON could contain some patients that meet the criteria to MTP. Therefore, the fact that we did not find a difference in the MS groups compared to controls regarding INL thickness does not exclude the existence of primary retinal neuronal pathology in the disease. Rather, this demonstrates that if there is INL thinning, it is occurring in a small subset of patients. It is also important to note that while we measured the INL, Saidha et al measured the INL plus the outer plexiform layer, although it seems unlikely to make a difference. In any case, clearly more work is needed here.

The current study is also the first to evaluate separately the RGCL and the INL of patients with NMO or LETM. Several previous studies have demonstrated severe peripapillary RNFL^{9, 11, 31, 32} or full-thickness macular⁹ thinning in NMO eyes. Our findings of significantly reduced macular RNFL and RGCL+ layers when compared to normal controls is in agreement with the current thinking that optic neuritis in NMO is associated with significant neuronal loss. Similar to what was found in MS eyes, the results show *in vivo* evidence of neural loss in NMO patients, which presumably is also caused by axonal degeneration after the optic nerve insult.

Some have also asked whether patients with LETM (NMO spectrum, without previous ON) have subclinical episodes of demyelination, as has been documented for MS patients. In the present study, our macular segmentation analysis demonstrated significant reduction of macular RNFL in these patients compared to controls. These findings support the idea that subclinical damage also occurs in LETM. On the other hand, there was no difference when the RGCL+ was evaluated, a somewhat surprising finding since presumably RGCL should also be reduced when the RNFL is damaged. A possible explanation is related to the fact that the thickest parts of RNFL plot in the macular scan (figure 2, red arrows) are associated with ganglion cells that fall largely outside the macula scan. Alternatively it is possible that even though axonal loss existed due to subclinical optic nerve damage, RGC layer degeneration had not occurred by the time of OCT examination.

While findings in RGC and macular NFL in NMO or LETM show similarities with what is found in MS patients, analysis of INL showed strikingly different findings in NMO-spectrum compared to both controls and MS patients. Both in NMO and LETM patients there was a significantly increase in INL thickness when compared to controls or MS patients (Table 2). NMO and LETM patients are known to be associated an autoantibody called NMO-IgG³, which targets the most abundant water channel protein in the CNS aquaporin 4 (AQP4)³³. It is also known that such water channel membrane protein is found in supporting cells, such as astrocytes and the Mueller cells in the retina. The damage to AQP4 has been implicated in the pathogenesis of cerebral edema³⁴ and associated with reversible edema of brain regions, such as the hypothalamus and periventricular structures³⁵. The deletion of AQP4 has also been implicated as cause of Mueller cells swollen in mice³⁶. In one study, a hypoosmolar solution induced rapid swelling and sodium influx into Mueller cells in AQP4 null mice but not in wild-type mice, suggesting that water flux through AQP4 is involved in the rapid Mueller cell volume regulation in response to osmotic stress and that deletion of AQP4 results in swelling of the glial cells of the retinal tissue³⁶. Because the AQP4 loss in NMO has a unique pattern and is unrelated to stage of demyelinating

activity³⁷, the fact that both our NMO and LETM patients had thicker INL than controls suggests that in addition to the demyelination of the optic nerve, direct damage to the retina might also be involved in the pathophysiology of these diseases. The presence of AQP4 receptors in Mueller cells, which have the body cell located in INL, may be a possible site of this occurrence. Therefore, we speculate that the increase in thickness of INL might represent an intracellular edema caused by the dysfunction/deletion of AQP4 in Mueller cells in both NMO and LETM patients. Further OCT, and ideally anatomopathologic, studies analyzing eyes of patients with the NMO spectrum of disease are necessary to clarify this issue. Future OCT studies analyzing NMO patients throughout ON episodes would also be of interest to help understand if the demyelization process is directly associated with a possible damage caused by loss of AQP4 in Mueller cells.

As both diseases, MS and NMO, may present with optic neuritis, considerable work has been done to differentiate these diseases. The OCT also has been used for this purpose, specifically the average of peri-papillary RNFL^{9, 11} and the macular volume⁹. However, as far as we know, no one has compared the RCGL or the INL of these two entities. We found that the macular RNFL and RGCL+ are not able to differentiate between these diseases. To avoid bias related to number of previous episodes, we did the same comparison in patients with only one previous episode of ON and the results were similar. As NMO affects the peri-papillary RNFL more than MS does, as evidenced in this study and in previous work^{9, 11}, perhaps, NMO cause more diffuse damage in fibers, while in the macular area both diseases have the same effect in RNFL and RGCL+. On the other hand, the INL was thicker in NMO than in MS with ON perhaps due to the involvement of AQP4 in NMO patients. In any case, we suggest that the peri-papillary RNFL and the macular INL measures will help differentiate between MS and NMO.

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Figure 1.

Above: A grey-scale raw Topcon 3D fd-OCT 1000® B-scan in the macular area. Below: A schematic representation of a B scan where the different color lines correspond to the retinal layer boundaries as identified during our segmentation process as follows: red line = inner limiting membrane; green line= outer boundary of the RNFL; pink line= outer boundary of inner plexiform layer; blue line = outer boundary of inner nuclear layer.
 RNFL=retinal nerve fiber layer; RGCL+ = retinal ganglion cell plus inner plexiform layer;
 INL= inner nuclear layer

Figure 2.

Pseudo-color thickness map generated from cube scan based on the thickness of the layers evaluated. A. Controls; B. Multiple sclerosis with optic neuritis; C. Neuromyelitis optica. Red arrows represent the thickest part of RNFL which ganglion cells fall largely outside the macula.

RNFL=retinal nerve fiber layer; RGCL+ = retinal ganglion cell plus inner plexiform layer; INL= inner nuclear layer

Figure 3.

Panels A to C represent box plots illustrating the inter-quartile range for macular retinal nerve fiber layer (panel A), retinal ganglion cell layer + inner plexiform layer (panel B) and inner nuclear layer (panel C). * represents $P < 0.05$ when compared with controls.

RNFL=retinal nerve fiber layer; RGCL+ = retinal ganglion cell plus inner plexiform layer; INL= inner nuclear layer; NMO= neuromyelitis optica; LETM= longitudinally extensive transverse myelitis;

MS-ON= multiple sclerosis with optic neuritis; MS non-ON= multiple sclerosis without optic neuritis

Demographic characteristics of patients with neuromyelitis optica, longitudinally extensive transverse myelitis, multiple sclerosis and normal controls

Table 1

	NMO	LETM	MS-ON	MS non-ON	Controls
Subjects	29	29	29	44	45
Eyes studied	46	56	41	74	84
Number of patients (eyes) with only one episode of ON	25 (37)	-	26 (34)	-	-
Age, yrs, mean (Standard deviation)	39.8 (11.1)	41.6 (11.9)	34.3 (8.7)	35.3 (10.2)	36.0 (12.5)
Gender Male/Female	2/30	10/19	4/26	7/44	10/35
Time from diagnosis in yrs (mean, median, range)	4.97, 4, 0 - 21	4.48, 5, 0 - 8	6.5, 5, 1-26	4.66, 3, 1-21	-
Number of patients (eyes) anti-NMO positive	15 (22)	10 (20)	-	-	-
Visual acuity [median (range)]	20/20 (20/16 - 20/200)	20/20 (20/16-20/25)	20/25 (20/16 - 20/200)	20/20 (20/16-20/25)	20/20 (20/16-20/25)
Visual Field Mean Deviation in dB, mean (SD)	- 9.8 (-7.8)	-1.5 (1.4)	- 3.7 (-3.4)	- 2.3 (-2.4)	-1.1 (1.1)

NMO= neuromyelitis optica; LETM= longitudinally extensive transverse myelitis; MS= multiple sclerosis; ON= optic neuritis; MS-ON= multiple sclerosis with optic neuritis; MS non-ON= multiple sclerosis without optic neuritis; SD= standard deviation

Optical coherence tomography thickness measurements (in μm) of different retinal layers in eyes of patients with multiple sclerosis, neuromyelitis optica, longitudinal extensive transverse myelitis and normal controls

Table 2

OCT parameters	NMO mean (SE) (n=51)	LETM mean (SE) (n=53)	MS-ON mean (SE) (n=45)	MS non-ON mean (SE) (n= 74)	Control mean (SE) (n=82)	NMO versus LETM P-value	NMO versus MS non-ON P-value	LETM versus MS non-ON P-value	LETM versus MS non-ON P-value	MS-ON versus MS non-ON P-value
Macular layer										
NFL	28.3 (1.3) *	34.9 (0.8) *	30.6 (1.4) *	35.5 (0.7) *	37.9 (0.6)	p<0.001 [†]	p=0.254	p=0.009 [†]	p=0.628	p=0.002 [†]
RGCL+	61.7 (2.0) *	71.4 (1.0)	61.7 (1.5) *	64.4 (0.8) *	70.3 (0.8)	p<0.001 [†]	p=0.996	p<0.001 [†]	p<0.001 [†]	p=0.64
INL	32.9 (0.6) *	32.8 (0.4) *	31.4 (0.4)	31.0 (0.3)	31.4 (0.3)	P=0.837	p=0.023 [†]	p=0.006 [†]	p=0.001 [†]	p=0.440

Generalized estimated equations (GEE).

* P < 0.05 compared with controls.

[†] P < 0.05 when two groups compared OCT= optical coherence tomography; NMO= eyes in patients with neuromyelitis optica; LETM= eyes in patients with longitudinally extensive transverse myelitis; MS= multiple sclerosis; MS-ON= eyes in patients with MS and optic neuritis. MS non-ON= eyes in patients with MS without optic neuritis; NFL= nerve fiber layer; RGCL+ = retinal ganglion cell plus inner plexiform layer; INL= inner nuclear layer; SE= standard error

Table 3

Optical coherence tomography thickness measurements (in μm) in eyes of patients with multiple sclerosis or neuromyelitis optica with only one episode of optic neuritis and in normal controls

OCT parameters	NMO (1) eyes (SE) (n=33)	MS-ON (1) eyes (SE) (n=28)	Control eyes (n=82)	NMO(1) versus MS-ON(1) P-value
Layer				
Macular RNFL	29.6 (1.4) *	32.3 (1.6) *	38.1 (0.6)	p=0.208
Macular RGCL+	64.1 (2.2) *	63.2 (1.8) *	70.5 (0.8)	p=0.746
Macular INL	33.1 (0.7) *	31.4 (0.3)	31.5 (0.4)	p=0.027 [†]
Peri-papillary RNFL	88.9 (3.6) *	100.7 (3.5) *	108.2 (1.2)	p=<0.001 [†]

Generalized estimated equations (GEE). SE= standard error

* P < 0 .05 compared with controls.

[†] P < 0.05 when two groups compared OCT= optical coherence tomography; NMO(1)= eyes in patients with neuromyelitis optica with one episode of optic neuritis; MS-ON(1)= eyes in patients with MS and one episode of optic neuritis. RNFL= retinal nerve fiber layer; RGCL+ = retinal ganglion cell plus inner plexiform layer; INL= inner nuclear layer