Optical coherence tomography helps differentiate neuromyelitis optica and MS optic neuropathies

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ABSTRACT

Objective: To evaluate the retinal nerve fiber layer (RNFL) thickness and macular volume in neuromyelitis optica (NMO) spectrum patients using optical coherence tomography (OCT).

Background: OCT can quantify damage to retinal ganglion cell axons and can identify abnormalities in multiple sclerosis and optic neuritis (ON) eyes. OCT may also be useful in the evaluation of patients with NMO.

Methods: OCT and visual function testing were performed in 26 NMO spectrum patients with a history of ON, 17 patients with isolated longitudinally extensive transverse myelitis (LETM) without ON, 378 patients with relapsing-remitting multiple sclerosis (RRMS), and 77 healthy controls at 2 centers.

Results: Substantial RNFL thinning was seen in NMO ON eyes ($63.6\ \mu\text{m}$) relative to both RRMS ON eyes ($88.3\ \mu\text{m}$, $p < 0.0001$) and control eyes ($102.4\ \mu\text{m}$, $p < 0.0001$). A first episode of ON was estimated to cause $24\ \mu\text{m}$ more loss of RNFL thickness in NMO than RRMS. Similar results were seen for macular volume. ON also was associated with more severe visual impairment in NMO spectrum patients than in RRMS patients. Eyes in the LETM group and unaffected NMO eyes were not significantly different from controls, though conclusions about these subgroups were limited by small sample sizes.

Conclusions: Optical coherence tomography (OCT) shows more severe retinal damage after optic neuritis (ON) episodes in neuromyelitis optica (NMO) than in relapsing-remitting multiple sclerosis. Identification of substantial retinal nerve fiber layer loss ($>15\ \mu\text{m}$) after ON in a non-multiple sclerosis patient should prompt consideration of an NMO spectrum condition. OCT may be a useful tool for the evaluation of patients with NMO. *Neurology*® 2009;73:302-308

GLOSSARY

CI = confidence interval; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **IgG** = immunoglobulin G; **LETM** = longitudinally extensive transverse myelitis; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica; **OCT** = optical coherence tomography; **ON** = optic neuritis; **RNFL** = retinal nerve fiber layer; **RRMS** = relapsing-remitting multiple sclerosis.

Neuromyelitis optica (NMO; Devic disease) is an autoimmune disease that predominantly affects the spinal cord and optic nerves. Patients with NMO often experience recurrent episodes of optic neuritis (ON) that can cause severe visual impairment. Previously thought to be a rare subtype of multiple sclerosis (MS), the identification of the NMO-immunoglobulin G (IgG) autoantibody has provided strong evidence that NMO is a distinct disorder.¹

Optical coherence tomography (OCT) has been used to measure the thickness of the retinal nerve fiber layer (RNFL) and the macular volume in patients with MS and other conditions. The RNFL consists of retinal ganglion cell axons that coalesce to form the optic nerve. The macular volume is determined by the number of retinal ganglion cell bodies, photoreceptors, and other cell types. Previous studies found a significant decrease in the mean RNFL thickness and macular volume in MS eyes with and without a history of ON.²⁻⁷ Moreover, abnormalities

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were identified in all MS subtypes,⁶ and RNFL thinning was found to correlate with brain atrophy in MS.⁸

We used OCT to evaluate the retinas of patients with NMO, patients with longitudinally extensive transverse myelitis (LETM) without a history of ON, patients with relapsing–remitting MS (RRMS), and healthy controls. The goals of this study were 1) to compare the effect of optic neuritis on RNFL thickness, macular volume, and visual function in patients with NMO and RRMS; 2) to determine whether LETM patients without a history of ON have subclinical changes on OCT; and 3) to identify OCT findings that suggest a diagnosis of NMO.

METHODS Patients. Subjects were recruited from The Johns Hopkins Multiple Sclerosis and Transverse Myelitis Centers and the University of Texas Southwestern Multiple Sclerosis Center. Subjects were divided into 4 groups. Group 1 was patients diagnosed with an NMO spectrum disorder who had a history of optic neuritis. This group included 26 patients, of whom 19 (73%) had “definite NMO” as defined by the 2006 criteria of Wingerchuk et al.⁹ “Definite NMO” is defined by these criteria as a history of ON, history of acute myelitis, and 2 of 3 supportive criteria: 1) a contiguous spinal cord MRI lesion extending over at least 3 vertebral segments, 2) a brain MRI that does not meet criteria for MS, and 3) NMO-IgG seropositivity.⁹ Four patients in group 1 (15%) had ON and were NMO-IgG positive without a history of myelitis, and 3 (12%) were considered by an experienced clinician to have NMO but did not meet the above criteria because their myelitis was less than 3 vertebral segments. When analyzed separately, results for the subset meeting criteria for “definite NMO” did not differ from the other patients in this group, so these patients were analyzed together. Group 2 included patients with isolated LETM, defined as myelitis spanning 3 or more vertebral segments without evidence of MS and without a history of ON. Group 3 was patients with RRMS based on McDonald criteria.¹⁰ Group 4 was healthy controls. All patients undergoing evaluation for a possible NMO spectrum disorder during the time period of the study were asked to participate. The RRMS cohort was an unselected convenience sample of patients with MS evaluated in the Johns Hopkins Multiple Sclerosis Center. Healthy controls were recruited from patient’s families and volunteers. Informed consent was obtained from all participants, and the study was approved by the local institutional review boards. Patients were excluded from analysis if they had a history of glaucoma, diabetes, or retinal disease, which might otherwise affect OCT measurements. Scans performed in the 3-month period after acute ON were excluded from analysis to minimize the effect of optic disk swelling on OCT measurements. Data on number of ON episodes was available for a subset of patients (the Hopkins cohort).

Optical coherence tomography. The OCT scanning protocol has been described previously in detail.⁶ Retinal imaging was performed using a Stratus OCT-3 device with OCT 4.0 software (Carl Zeiss, Meditec, Dublin, CA). RNFL scans were obtained with the “Fast RNFL Thickness” protocol, and macular volume

was determined using the “Fast Macular Thickness” scan. Only scans with signal strength of 7 or above (maximum 10), indicating a high-quality scan, were considered acceptable for analysis. OCT scanning failed in 8 eyes (both eyes in 3 patients and one eye in 2 patients) in the NMO group because of blindness. Imaging quality was ensured by validation of optic disk centering by the technician. Macular volume results were available for a subset of patients (80%) because this testing was added to the protocol after the initiation of the study.

Visual function testing. Visual function testing was performed using retroilluminated eye charts. Both full-contrast Early Treatment Diabetic Retinopathy Study (ETDRS) charts and low-contrast (1.25% contrast) Sloan letter charts were used. Testing was performed monocularly, and subjects were asked to use their habitual distance glasses or contact lenses. Standard testing protocols were used. Charts were scored letter-by-letter, so that the number of letters identified correctly (maximum 70) constituted the summary measure. Snellen equivalents were also determined for descriptive purposes based on full-contrast visual acuity (ETDRS chart) scores.

Statistical analysis. Nonparametric statistical methods were used because of the small sample sizes. The Wilcoxon rank sum test was used for pairwise analyses. To maintain independence of all observations, a single eye was analyzed from each patient. In analyses of ON eyes, the ON eye was chosen. In subjects where both eyes had the same history of optic neuritis, the right eye was randomly chosen for use. There was no difference in the results when the left eye was used. Multivariate linear regression models were created to control for disease duration and age. A regression with a linear spline was used to model RNFL thickness as a function of number of ON episodes. Statistical significance was defined as $p < 0.05$. All analyses were performed using STATA 10.0 (StataCorp, College Station, TX).

RESULTS Patient characteristics are described in table 1. Twenty-six patients were included in the group of NMO spectrum patients with a history of ON. Seventeen patients were identified with isolated LETM. The frequency of NMO-IgG positivity was 60% in the NMO spectrum with ON group and 24% in the LETM group. These groups were compared with 378 patients with RRMS and 77 healthy controls. There was a history of ON in 41% of the RRMS group and none of the LETM or control subjects.

Optic neuritis eyes. The RNFL thickness for each group is shown in table 1 and figure 1. ON eyes in the NMO spectrum group had a mean RNFL thickness of 63.6 μm compared with 102.4 μm in controls ($p < 0.0001$). This represents a 38% absolute difference in the RNFL thickness between NMO ON eyes and controls. In NMO spectrum patients, the RNFL was also considerably thinner in ON eyes than in non-ON eyes (63.6 vs 97.9 μm , $p = 0.002$). The difference in RNFL thickness between ON and non-ON eyes is much greater in NMO spectrum patients than in RRMS (34.3 μm in NMO vs 9.6 μm in RRMS). Data for macular volume measurements are shown in table 1 and figure 2. ON eyes in the NMO spectrum group also

Table 1 Demographic data, retinal nerve fiber layer thickness, and macular volumes

Diagnosis	No. of patients	Age, mean (SD), y	NMO-IgG positive, %	History of ON, %	ON status	No. of eyes analyzed	RNFL thickness, μm			Macular volume, mm^3		
							Mean (SD)	Median (range)	p Value vs controls	Mean (SD)	Median (range)	p Value vs controls
NMO spectrum with ON	26	41 (13)	60	100	ON eyes	22	63.6 (20.3)	57.4 (31.0–99.4)	<0.0001	5.83 (0.75)	5.68 (4.32–7.12)	<0.0001
					Non-ON eyes	8	97.9 (18.3)	96.0 (73.4–121.9)	0.5	6.63 (0.54)	6.75 (5.81–7.20)	0.5
LETM	17	45 (14)	24	0	Non-ON eyes	17	96.3 (14.3)	96.9 (50.0–112.8)	0.2	6.69 (0.39)	6.65 (6.05–7.41)	0.2
RRMS	378	39 (10)	—	41	ON eyes	157	88.3 (16.5)	87.4 (44.4–129.5)	<0.0001	6.38 (0.49)	6.35 (5.05–7.69)	<0.0001
					Non-ON eyes	338	97.4 (13.9)	99.1 (44.4–144.7)	0.01	6.63 (0.47)	6.65 (5.06–8.14)	0.009
Controls	77	38 (12)	—	0	Non-ON eyes	77	102.4 (11.0)	102.2 (80.8–128.1)	—	6.83 (0.34)	6.81 (6.12–7.57)	—

RNFL = retinal nerve fiber layer; NMO = neuromyelitis optica; IgG = immunoglobulin G; ON = optic neuritis; LETM = longitudinally extensive transverse myelitis; RRMS = relapsing-remitting multiple sclerosis.

had a lower mean macular volume compared with controls (5.83 vs 6.83 mm^3 , $p < 0.0001$).

To compare the effect of ON in patients with NMO and RRMS, the mean RNFL thickness and macular volume of ON eyes were compared. The RNFL was thinner in NMO ON eyes than RRMS ON eyes (mean 63.6 vs 88.3 μm , $p < 0.0001$). Macular volume was also lower in the NMO group relative to RRMS (5.83 vs 6.38 mm^3 , $p = 0.001$). This difference could result from either a greater severity or a greater number of ON episodes in patients with NMO compared with patients with RRMS. Because NMO ON eyes did have a greater number of ON events than RRMS eyes, an additional comparison was performed in the subset of eyes that experienced only 1 episode of ON. Using a multivariate linear regression analysis to control for age and disease duration, a single episode of ON was estimated to cause 24 μm more RNFL loss in NMO than in RRMS ($p < 0.001$). Thus, ON episodes are associated with greater retinal damage in NMO than in RRMS. In patients with a history of unilateral ON, the proportion of patients with a difference in RNFL thickness between the ON and non-ON eye of $>15 \mu\text{m}$ was 75% in patients with NMO and 24% in patients with RRMS.

An analysis of the effect of the number of ON episodes on RNFL thickness found that the first episode of ON caused greater thinning of the RNFL than subsequent episodes in both NMO and RRMS. Using a multivariate linear regression model, a single episode of ON was estimated to cause a 31- μm decrease in RNFL thickness in patients with NMO (95% confidence interval [CI] 21–42 μm , $p < 0.001$) and a decrease of 10 μm in RRMS (95% CI 6–13 μm , $p < 0.001$). Subsequent episodes of ON in the same eye were estimated to each cause an additional loss of 10 μm of RNFL thickness in NMO ($p = 0.026$) and a nonsignificant change in the RRMS group. When stratified by NMO-IgG status, no difference was seen in RNFL thickness between the antibody-positive and antibody-negative NMO groups ($p = 0.94$).

Non-optic neuritis eyes. In eyes without a history of ON, the RNFL was mildly thinner in all groups relative to controls. This difference was only significant for RRMS eyes (97.4 μm for RRMS, 97.9 μm for NMO, 96.3 μm for LETM vs 102.4 μm for controls; table 1). The number of non-ON eyes was much larger in the RRMS group ($n = 338$), than the NMO ($n = 8$) and LETM ($n = 17$) groups. Consequently, the lack of statistical significance in the NMO and LETM groups may be due to small sample sizes. Similar results were seen for macular volume (table 1).

Visual function testing. Visual acuity was tested with both standard and low-contrast eye charts. The OCT

Figure 1 Box plots of retinal nerve fiber layer thickness by disease type and optic neuritis status

RNFL = retinal nerve fiber layer; ON = optic neuritis; NMO = neuromyelitis optica; LETM = longitudinally extensive transverse myelitis; RRMS = relapsing-remitting multiple sclerosis.

findings correlated well with the results of visual function testing. Visual acuity was worst in ON eyes of NMO spectrum patients. Using full-contrast charts, the mean number of correct letters in this group was 27 out of a possible 70, compared with 54 in RRMS ON eyes and 59 in control eyes ($p = 0.001$ vs RRMS, $p = 0.001$ vs controls; table 2). This corresponds to a visual acuity of 20/60 for the NMO ON eyes, 20/20 for the RRMS ON eyes, and 20/16 for controls. The relationship between RNFL

thickness and visual acuity in NMO ON eyes is shown in figure 3. Graphically, it appears that on a standard vision chart there is a threshold RNFL thickness of approximately 60 μm , below which visual acuity becomes very poor.

Performance on low-contrast eye charts followed the same pattern (mean: 4 correct letters for NMO ON eyes, 6.5 letters for RRMS ON eyes, and 16 letters for control eyes). On low-contrast charts, the NMO ON eyes differed from controls ($p \leq 0.0001$) but not from

Figure 2 Box plots of macular volume by disease type and optic neuritis status

ON = optic neuritis; NMO = neuromyelitis optica; LETM = longitudinally extensive transverse myelitis; RRMS = relapsing-remitting multiple sclerosis.

Table 2 Visual function testing results

Group	100% Contrast chart			1.25% Contrast chart		
	Mean no. of correct letters (SD)	Median no. of correct letters (range)	p Value vs controls	Mean no. of correct letters (SD)	Median no. of correct letters (range)	p Value vs controls
NMO spectrum and LETM						
ON eyes	27 (29)	14 (0-68)		4 (9)	0 (0-27)	<0.0001
Non-ON eyes	59 (10)	61 (27-69)	0.26	18 (11)	18 (0-36)	0.5
RRMS						
ON eyes	54 (15)	57 (0-70)	0.003	6.5 (8)	2 (0-32)	<0.0001
Non-ON eyes	59 (8)	60 (12-70)	0.23	13 (10)	13 (0-36)	0.98
Controls	59 (5)	60 (42-69)	—	16 (8)	15 (0-35)	—

Each chart contains 70 letters.

NMO = neuromyelitis optica; LETM = longitudinally extensive transverse myelitis; ON = optic neuritis; RRMS = relapsing-remitting multiple sclerosis.

RRMS ON eyes ($p = 0.11$). Non-ON eyes in the NMO spectrum and LETM groups were combined for analysis and compared with non-ON eyes in RRMS and controls. Using both standard and low-contrast eye charts, there were no significant differences among these groups in the number of correct letters identified.

DISCUSSION Patients with NMO often have severe episodes of ON which can, in some cases, lead to blindness. In MS, ON is also common; however, the attacks tend to be less severe and have a better prognosis. This study used OCT to show that the RNFL is significantly thinner in NMO eyes that have experienced ON than both control eyes and MS ON eyes. The severe thinning of the RNFL is presumably due to degeneration of the retinal ganglion cell axons. Macular volume, which in part reflects the num-

ber of retinal ganglion cell bodies, is also significantly decreased in NMO ON eyes. Furthermore, visual acuity testing is grossly abnormal in NMO ON eyes when compared with control and RRMS ON eyes. Together, these data suggest that ON is a more destructive process with greater potential for causing visual disability in NMO than in MS. We also found that the first episode of ON seems to cause the greatest amount of RNFL thinning in patients with NMO and RRMS, with a lesser degree of thinning occurring in subsequent episodes of ON. One possible explanation for this is that after an episode of ON, axons may make up a smaller percentage of the RNFL, such that subsequent ON episodes cause a smaller amount of RNFL change.

In NMO spectrum eyes without a history of ON, we found that the mean RNFL thickness and macular volume were slightly lower than controls, but the difference was not significant. The sample sizes in these groups were small, so the possibility remains that there is a true small difference in OCT values for this group relative to controls. If a true difference does exist, one could speculate either that ON causes a small degree of retinal damage to the contralateral eye or that the retinal abnormalities were due to an ON-independent process. A larger cohort would be needed to evaluate this.

Our results concur with French¹¹ and Caribbean¹² studies of OCT in NMO spectrum patients. They found significant thinning of the RNFL in patients with NMO, although they did not stratify eyes by history of ON. In agreement with our results, a small group of NMO-IgG-positive LETM patients were analyzed in the French study and no OCT abnormalities were found. They identified a strong correlation between RNFL thickness and Expanded Disability Status Score in patients with NMO.

Figure 3 Number of correct letters on a standard ETDRS letter chart in NMO spectrum eyes with a history of optic neuritis as a function of RNFL thickness

ETDRS = Early Treatment Diabetic Retinopathy Study; NMO = neuromyelitis optica; RNFL = retinal nerve fiber layer.

There are several potential limitations to our study. First, blindness due to severe episodes of ON prevented successful OCT scanning in 8 eyes in the NMO group. It is likely that these eyes had the most dramatic changes in retinal architecture. Consequently, the true average OCT values in NMO ON eyes may be even more severe than what was estimated in our cohort. Second, because of relatively small sample sizes it is not possible to rule out small differences between groups that otherwise seem similar. Third, it is possible that our population of patients with NMO is more severely affected than the general NMO population because all subjects were recruited from academic referral centers. However, most patients with this uncommon condition are referred to academic centers, and all patients being evaluated for an NMO spectrum condition at the study sites were asked to participate in the study to minimize selection bias.

The identification of the NMO-IgG antibody has greatly advanced our understanding of NMO and related conditions. The antibody has a 54% to 71% sensitivity and >90% specificity for NMO.¹³⁻¹⁵ NMO-IgG is also positive in 25% of recurrent ON patients without MS and 38% to 80% of patients with isolated LETM.¹⁴⁻¹⁷ Evidence is mounting that NMO is a distinct condition, rather than simply a rare subtype of MS. In support of that idea, we found a greater degree of retinal damage after ON in NMO than in MS. Our study did not have sufficient power to definitively determine whether unaffected NMO eyes are abnormal, but retinal damage in NMO seems to be predominantly or exclusively the result of destructive ON episodes. This differs somewhat from MS, where OCT can detect retinal abnormalities even in patients with no history of ON (such as patients with primary progressive MS).⁶ These results are consistent with the observation that patients with NMO rarely convert to a secondary progressive course and that disability in NMO primarily results from relapses,¹⁸ whereas in MS, disability can result either from inflammatory relapses or slowly progressive axonal degeneration.¹⁹

In some circumstances, OCT may be a useful adjunct for differentiating ON due to NMO from ON due to MS or isolated ON. In a patient with ON and a brain MRI not suggestive of MS, clinical characteristics such as a bilateral presentation, recurrent ON, or poor visual recovery may suggest a diagnosis of NMO. In addition, more severe thinning of the RNFL in a patient with history of ON should prompt consideration of NMO. We found that in patients with prior unilateral ON, a >15- μ m difference in RNFL thickness between the two eyes was more likely to occur in NMO (75%) than in RRMS

(24%). Consequently, in patients who do not meet diagnostic criteria for MS, NMO-IgG testing should be considered when there is a history of ON that was bilateral, was recurrent, resulted in poor visual recovery, or left them with a >15- μ m difference in RNFL thickness between the eyes when measured >3 months after the event. Earlier diagnosis of NMO has the potential to decrease future disability through earlier initiation of systemic immunomodulatory treatment.

AUTHOR CONTRIBUTIONS

Statistical analysis was performed by J.N. Ratchford.

DISCLOSURE

J.N.R. has served as a consultant for Teva Neuroscience and receives research support from the Partners Multiple Sclerosis Center in the form of a Clinical Fellowship Award. M.E.Q., A.C., and T.F. report no disclosures. E.F. serves as a consultant for and on the speakers' bureaus of Biogen-Idec, Teva Neuroscience, and Athena Diagnostics. L.J.B. has served on a scientific advisory board for Biogen-Idec, has served as a consultant for Biogen-Idec, and receives research support from the NIH/National Eye Institute (grant K24 018136) and the National Multiple Sclerosis Society (grants RG 3208-A-1, RG 3428-A/2, TR 3760-A-3). P.A.C. has served as a consultant for EMD Serono, Teva Neuroscience, Novartis, Biogen-Idec, Amplimmune, Vertex, Eisai, and Diogenix, and receives research support from EMD Serono, Teva Neuroscience, Biogen-Idec, and the National Multiple Sclerosis Society. D.A.K. has received research support from Niveda in the form of a sponsored research agreement, and serves as a consultant for and holds stock options in Niveda, for which he is a founding member.

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