Optical coherence tomography differs in neuromyelitis optica compared with multiple sclerosis

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ABSTRACT

Background: Neuromyelitis optica (NMO) is associated with destructive inflammatory lesions, resulting in necrosis and axonal injury. Disability from multiple sclerosis (MS) is due to a combination of demyelination and varying axonal involvement. Optical coherence tomography (OCT), by measuring retinal nerve fiber layer (RNFL) as a surrogate of axonal injury, has potential to discriminate between these two conditions.

Methods: Included were 22 subjects with NMO or NMO spectrum disorders and 47 with MS. Seventeen subjects with NMO and all with MS had a remote history of optic neuritis (ON) in at least one eye, at least 6 months before OCT. Linear mixed modeling was used to compare the two diagnoses for a given level of vision loss, while controlling for age, disease duration, and number of episodes of ON.

Results: After ON, NMO was associated with a thinner mean RNFL compared to MS. This was found when controlling for visual acuity (56.7 vs 66.6 μm , $p = 0.01$) or for contrast sensitivity (61.2 vs 70.3 μm , $p = 0.02$). The superior and inferior quadrants were more severely affected in NMO than MS.

Conclusions: Optic neuritis (ON) within neuromyelitis optica (NMO) is associated with a thinner overall average retinal nerve fiber layer compared to multiple sclerosis, with particular involvement of the superior and inferior quadrants. This suggests that NMO is associated with more widespread axonal injury in the affected optic nerves. Optical coherence tomography can help distinguish the etiology of these two causes of ON, and may be useful as a surrogate marker of axonal involvement in demyelinating disease. *Neurology*® 2009;72:1077-1082

GLOSSARY

CIS = clinically isolated syndrome; **CS** = contrast sensitivity; **EDSS** = Expanded Disability Status Scale; **MS** = multiple sclerosis; **NMO** = neuromyelitis optica; **OCT** = optical coherence tomography; **ON** = optic neuritis; **RNFL** = retinal nerve fiber layer; **VA** = visual acuity.

Neuromyelitis optica (NMO) is a demyelinating condition with predilection for optic nerve and spinal cord.^{1,2} The disease course can be devastating and distinct from multiple sclerosis (MS).³ The destructive pathology includes necrosis, cavitation, and hyalinized vessels.⁴⁻⁸ Axonal injury is often present, and may occur to a greater extent compared with MS. With MS, the optic nerve pathology contributing to vision loss may include demyelination with some preservation of axons.

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Table	Summary of the multiple sclerosis and neuromyelitis optica cohorts	
	Multiple sclerosis	Neuromyelitis optica
No. (MS/CIS)	47 (36/11)	22
Age, y, mean (range)	42.3 (22–65)	42.9 (24–64)
F/M, %	83/17	77/23
Episodes of ON, mean (median, range per eye)*	0.97 (1, 0–5)	1.61 (1, 0–6)
Nerves affected by ON (%)	65 (69)	30 (68)
Years from 1st episode ON, mean per eye (range)	8.6 (0–41)	9.4 (1–33)
IV glucocorticoids for optic neuritis, %*	39	77
Disease duration, y, mean (range)	10.4 (1–41)	9.6 (1–33)
EDSS, median (mean, range)*	2.0 (2.7, 0–7)	4.0 (4.5, 0–8.5)
Visual acuity, median (range)*	20/20 (20/13–CF)	20/25 (20/15–NLP)
5% Contrast sensitivity, logMAR, median (range)*	0.3 (–0.1–1.0)	0.6 (0.1–1.0)
RNFL all eyes, μm , unadjusted mean $\pm$ SD**	80.7 $\pm$ 19.3	70.5 $\pm$ 26.2
RNFL affected eyes, μm , unadjusted mean $\pm$ SD*	76.5 $\pm$ 2.4	54.8 $\pm$ 3.7

*Statistically different at $p \leq 0.05$ by t test, Wilcoxon test, or χ^2 test.

**All eyes, both affected and unaffected, averaged together.

MS = multiple sclerosis; CIS = clinically isolated syndrome; ON = optic neuritis; EDSS = Expanded Disability Status Scale; CF = count fingers; NLP = no light perception; RNFL = retinal nerve fiber layer.

Optical coherence tomography (OCT) utilizes scanning infrared light to image the retina.⁹ The thickness of the retinal nerve fiber layer (RNFL) can be measured accurately via optical interferometry.^{10,11} Using histopathology, a correlation has been demonstrated between optic nerve axonal count and the thickness of the RNFL.¹² Optic atrophy and RNFL thinning are noted features in many patients with MS.^{13–15}

Even without a history of optic neuritis (ON), the RNFL by OCT in MS is typically thinner than in normal controls.¹⁶ RNFL correlates with visual function,^{17–21} gray and white matter brain volumes,^{22,23} and overall disability in MS.²⁴ The use of OCT has been proposed as a potential biomarker of axonal degeneration in MS.²⁵

The following investigation sought to describe the differences in RNFL thickness between NMO and MS. Our hypothesis is that since NMO is associated with severe relapses, less recovery, more destructive lesions, and more axonal injury than MS, it will have a thinner RNFL in those who have had ON after adjusting for visual outcome.

METHODS This study was approved by the local Human Research Protection Office/Institutional Review Board, and all subjects provided informed consent. NMO was defined by three

of the four following criteria: ON, longitudinally extensive transverse myelitis, positive NMO-IgG,²⁶ and brain MRI not meeting diagnostic criteria for MS, as modified from criteria of Wingerchuk et al.²⁷ Any subject who met criteria for an NMO spectrum disorder was included, regardless of whether they had been affected by a clinical episode of ON. Five subjects in the NMO group did not have a clinical episode of ON, but all had a positive NMO-IgG. Four of the five had recurrent myelitis. All subjects with NMO and ON also had spinal cord involvement. An additional inclusion criterion was age 18–65 years. Exclusion criterion included no other ocular pathology that could affect vision. Out of the available cohort of 26 NMO subjects at this institution, 4 were excluded (one was under age 18, one was over age 65, one was lost to follow-up, and one had diabetic retinopathy). Subjects with MS included those with clinically definite MS by Poser criteria, along with clinically isolated syndrome (CIS) at high risk defined by an abnormal brain MRI. All subjects with MS had at least one prior episode of clinical ON in at least one eye, 6 months or more before inclusion. The 6-month cutoff was based upon a published, prospective study which demonstrated a plateau in the decline of the RNFL at this time.²⁸ Subjects with MS were preferentially recruited to have had ON with severe onset and poor recovery in order to match the visual acuity (VA) with the NMO cohort.

VA was measured by a Snellen 20-foot wall chart. Contrast sensitivity (CS) was measured by a 5% contrast sensitivity chart^{29,30} in an illuminated cabinet at 3 meters (Precision Vision, IL). Best vision was obtained with prescription glasses and pin-hole occluder. OCT measurements of RNFL were obtained by a trained technician on a Zeiss Stratus OCT III with v4.0 software. In those eyes with poor visual function, OCT was obtained by external fixation of the good eye as the technician assessed the quality of the scan.

Statistical analyses utilized linear mixed modeling to account for two eyes within a single individual. Disease duration, age, and number of episodes of ON per eye were controlled within the model. Models were used to compare the difference between eyes in NMO and MS, after a clinical episode of ON, based upon clinical outcomes of 1) visual acuity and 2) contrast sensitivity. Group comparisons used Student t test, Wilcoxon rank sum, or χ^2 analysis when appropriate. OCT was evaluated as the average overall RNFL, along with the RNFL for each quadrant. In order to create clustered boxplots for both unaffected and affected eyes, visual acuity after ON was categorized based upon the Ranges of Vision Loss by the International Council of Ophthalmology.³¹ Due to low numbers in the moderate ($n = 4$) and severe ($n = 8$) categories, these were combined with the profound cases to be categorized as severe.

RESULTS A total of 69 subjects were included in the study, 22 NMO and 47 MS (table). There were no differences between the two cohorts for age, gender, duration since first episode of ON, or overall disease duration. Subjects with NMO had a higher EDSS score, more use of IV glucocorticoids for ON, an increased number of episodes of ON per eye, a slightly worse contrast sensitivity and visual acuity, and a lower mean RNFL.

After a clinical episode of ON, the overall unadjusted mean RNFL for those with NMO was significantly lower than those with MS. Estimated means by a repeated measures mixed model yielded $54.8 \pm 3.7 \mu\text{m}$

Figure 1 Average retinal nerve fiber layer thickness in multiple sclerosis vs neuromyelitis optica controlled for visual acuity

Interquartile box plots demonstrate that the adjusted retinal nerve fiber layer is thinner in neuromyelitis optica for those eyes previously affected by optic neuritis ($p = 0.01$). Those categorized as normal had recovered to $\geq 20/25$ from previous optic neuritis.

for NMO and $76.5 \pm 2.4 \mu\text{m}$ for MS. Using the eye within an individual with the thinner RNFL, the odds of falling into the NMO group increased by 8% for every $1 \mu\text{m}$ decrease in RNFL thickness.

The model based upon VA, while also adjusting for age, disease duration, and number of episodes,

confirmed that NMO is associated with a thinner overall RNFL compared to MS. After a clinical episode of ON, the adjusted mean RNFL for NMO was $56.7 \pm 3.1 \mu\text{m}$, whereas it was $66.6 \pm 2.4 \mu\text{m}$ for MS (figure 1, $p = 0.01$). Examining the quadrants individually (figure 2) showed that the superior ($p < 0.01$) and inferior ($p = 0.03$) quadrants were thinner in NMO. The nasal ($p = 0.09$) and temporal ($p = 0.5$) were not different.

The model based upon CS, while also adjusting for age, disease duration, and number of episodes of ON, again confirmed that after ON, NMO is associated with a thinner RNFL compared to MS. The adjusted mean RNFL for NMO was $61.2 \pm 3.0 \mu\text{m}$, and was $70.3 \pm 2.2 \mu\text{m}$ for MS (figure 3, $p = 0.02$). Examining the quadrants individually (figure 4) showed that the superior ($p < 0.01$), inferior ($p = 0.03$), and nasal ($p = 0.03$) quadrants were thinner in NMO. The temporal ($p = 0.9$) quadrant was not different.

DISCUSSION This study demonstrated that following a remote episode of ON, NMO was associated with a thinner RNFL than MS after adjusting for visual outcome (acuity or CS), compatible with more axon loss with ON in NMO. The study also found that the superior and inferior quadrants were affected to a greater magnitude in NMO than MS, whereas the temporal quadrants were not demonstrably different.

In this study, findings in unaffected eyes in subjects with MS were consistent with published litera-

Figure 2 Retinal nerve fiber layer quadrant thickness in multiple sclerosis vs neuromyelitis optica controlled for visual acuity

Interquartile box plots demonstrate that the adjusted superior ($p < 0.01$) and inferior ($p = 0.03$) retinal nerve fiber layer is thinner in neuromyelitis optica for those eyes previously affected by optic neuritis. MS = multiple sclerosis; NMO = neuromyelitis optica; VA = visual acuity.

Figure 3 Average retinal nerve fiber layer thickness in multiple sclerosis vs neuromyelitis optica controlled for contrast sensitivity

Interquartile box plots demonstrate that median retinal nerve fiber layer is thinner in neuromyelitis optica for those eyes previously affected by optic neuritis ($p = 0.02$).

ture. The average RNFL thickness in MS has been previously noted to be 92 μm in unaffected eyes, a mean of 85 μm in eyes affected by a prior clinical episode of ON, and 105 μm in healthy controls.²⁴ In the present study, the lower RNFL in the affected MS eyes is likely due to preferred selection of indi-

viduals with poor visual outcomes to match NMO subjects. In this cohort, the mean RNFL thickness for the unaffected NMO eyes was greater than the unaffected MS eyes ($p < 0.05$). The reason for this is not clear. This may be due to a relatively small sample of unaffected eyes (14 unaffected NMO vs 29 unaffected MS) with relatively short disease duration (4 years for NMO vs 27 years for MS) in NMO. Some additional hypothetical explanations may include more common occurrence of subclinical optic neuritis in MS than in NMO; axonal attrition in MS, independent of ON; or increased predilection for MS lesions in the optic chiasm or tracts, leading to bilateral RNFL involvement.

The present NMO cohort had a thinner average RNFL than the unadjusted 78 μm previously reported.³² In the latter published study, blind subjects were excluded, thus eliminating subjects likely to have the thinnest RNFLs. The present NMO group included all identified cases within our institution's patient population. We observed that this cohort of subjects with NMO tended to have very thin RNFL, with 39% of NMO eyes compared to 10% of MS eyes having thickness $\leq 50 \mu\text{m}$. In either group, having a RNFL thickness $\leq 50 \mu\text{m}$ conferred 50% odds of having vision $\leq 20/100$. Another study in NMO reported an unadjusted RNFL of 65 μm , which included both affected and unaffected eyes.³³ This is similar to the 71 μm in the present study, as reported in the table.

Histopathologic studies of NMO have revealed necrotizing lesions with cavitation, involving both

Figure 4 Retinal nerve fiber layer quadrant thickness in multiple sclerosis vs neuromyelitis optica controlled for contrast sensitivity

Interquartile box plots demonstrate that the adjusted superior ($p < 0.01$), inferior ($p = 0.03$), and nasal ($p = 0.03$) retinal nerve fiber layer is thinner in neuromyelitis optica for those eyes previously affected by optic neuritis. MS = multiple sclerosis; NMO = neuromyelitis optica; CS = contrast sensitivity.

gray and white matter of the spinal cord. There may be a component of ischemia from thickened blood vessel walls.⁵ The intense inflammatory response can result in prominent axonal involvement.⁷ MS is characterized by demyelination with relative axonal preservation, as originally described by Charcot.³⁴ Thus, we hypothesized that if thinned RNFL measured by OCT reflects axon loss, the RNFL would be thinner in NMO than in MS. The data herein lend credence to the concept that OCT can be used to identify axon destruction in the optic nerve using RNFL thickness as a surrogate marker for axon loss.³⁵

Some caveats of this study should be mentioned. First, the clinical outcome used was central vision, chosen due to its functional relevance. The temporal retinal quadrant serves central vision, and was not different between the two conditions. Whether NMO, at a given level of central acuity, is associated with more severe peripheral vision loss compared to MS is unknown. Second, postgeniculate lesion load within the visual system was not assessed. Lesions there might have accounted for some of the visual acuity decrease, particularly in patients with MS, without necessarily causing alterations detected by OCT.³⁶ Third, our inclusion criteria for the NMO group included five subjects who would be classified as NMO spectrum disorders. The adjusted analyses only included those eyes affected by clinical ON, meaning that these individuals did not contribute to the adjusted analyses.

At each level of visual function there was considerable overlap in OCT measures, limiting the role of OCT to differentiate the two conditions on an individual basis. Thus, OCT alone is unlikely to serve as a diagnostic test. Nonetheless, if an individual has ON with poor recovery, an RNFL thickness less than 50 μm , or involvement of the superior and inferior quadrants, the possibility of NMO should be strongly considered. Other forms of optic neuropathy, such as ischemia and glaucoma, were not evaluated in this study, so the specificity of the test remains unknown. The optic disc and retina can have increased RNFL thickness in acute ON, and may take up to 6 months to resolve. Hence, the role for OCT in predicting prognosis based on findings in the acute situation is also unclear.

Measuring RNFL thickness deserves further research effort, particularly in longitudinal studies to assess its prognostic utility, to assess the effect of therapeutics, and in evaluating other imaging modalities. Furthermore, OCT has potential to yield insights into pathogenetic mechanisms.

AUTHOR CONTRIBUTIONS

Dr. Trinkaus performed the statistical analyses.

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