Sex-specific differences in retinal nerve fiber layer thinning after acute optic neuritis

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ABSTRACT

Objective: The primary objective of this study was to explore the potential influence of gender on recovery from optic neuritis (ON) by determining whether differences in retinal nerve fiber layer (RNFL) thickness can be detected between men and women 6 months after an ON event.

Methods: In this prospective cohort study, 39 men and 105 women with acute ON underwent repeat visual and optical coherence tomography (OCT) testing. The main outcome measures were change in RNFL measurements for male and female patients 6 months after ON.

Results: Men were older (mean age = 39 years) than women (35 years) ($p = 0.05$) in this study, and more men (62%) than women (41%) had a diagnosis of relapsing-remitting multiple sclerosis (MS) ($p = 0.02$). Because age and MS subtype were 2 significant covariates, both variables were controlled for in multiple regression analyses. Other covariates controlled for in the multivariate regression included disease duration (years), use of disease-modifying therapy (yes/no), and use of high-dose corticosteroids for acute ON (yes/no). After 6 months, mean RNFL values were lower in men (74 μm) than women (91 μm) ($p < 0.001$). Men showed more apparent change in RNFL thickness in their ON eyes from baseline to 6 months after ON than women ($p = 0.003$).

Conclusions: There may be differences in recovery between men and women after ON, which can be difficult to detect with conventional visual testing. Our findings raise interesting questions about the potential influence of gender in MS, which may be explored in future studies. *Neurology*®

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GLOSSARY

CIS = clinically isolated syndrome; **DMT** = disease-modifying therapy; **logMAR** = logarithm of the minimum angle of resolution; **MS** = multiple sclerosis; **OCT** = optical coherence tomography; **ON** = optic neuritis; **RNFL** = retinal nerve fiber layer; **RRMS** = relapsing-remitting multiple sclerosis; **VA** = visual acuity; **VF** = visual field.

Optic neuritis (ON) is an inflammatory injury of the optic nerve that represents the first clinical manifestation of multiple sclerosis (MS) in 20% of cases¹ and affects 30% to 70% of patients with MS during the course of their disease.² Visual deficits can be reliably quantified in ON, and the structural consequences of this diagnosis can be visualized as pallor of the optic nerve head, with corresponding defects in the retinal nerve fiber layer (RNFL).³ Recent optical coherence tomography (OCT) studies in patients with MS and ON have shown that lower RNFL values correlate with reduced visual acuity (VA), visual field (VF), and color vision measures,⁴⁻¹⁰ indicating a robust relationship between structure and function in the anterior visual pathway. Thus, OCT may be used in the ON model to study the acute and chronic consequences of CNS inflammation, and potentially help elucidate mechanisms of brain injury and repair in MS.

The Optic Neuritis Treatment Trial¹¹ demonstrated that the majority (77%) of patients with ON are young women, albeit the basis of the female predilection remains unclear. Women are at least twice as likely to develop MS compared with men,^{12,13} yet the latter have been reported to have worse clinical outcomes and faster disease progression.¹⁴⁻¹⁷ In this prospective cohort study, we aimed to explore the potential influence of sex in the ON model of

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Supplemental Data

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MS by determining whether men manifest more apparent change in RNFL thickness than women after an acute ON event.

METHODS Study design. This prospective cohort study included patients evaluated for acute ON in the Neuro-Ophthalmology Clinics at the Ottawa Hospital and the University of Calgary between January 2003 and June 2010.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethics committee at the Universities of Ottawa and Calgary, and all patients provided informed written consent.

Patient population. Patients with ON who underwent clinical evaluation within 30 days of symptom onset were included in the study. Criteria for the diagnosis of ON are outlined in appendix e-1 on the *Neurology*[®] Web site at www.neurology.org. Because the goal of the study was to explore the potential influence of gender on recovery from ON as a putative model of MS, we aimed to select patients with ON who carried, or would be at risk for, the diagnosis of MS. We excluded patients with atypical features of ON¹⁸ (appendix e-1). Despite detailed investigations, no other causes of ON were identified for either male or female patients, other than the diagnosis of MS. Patients with ON who did not meet radiologic or clinical criteria for the diagnosis of MS^{19–21} were identified as having a clinically isolated syndrome (CIS). To our knowledge, only patients with an isolated ON event either presenting as a CIS or in association with a radiologically proven¹⁹ or clinically confirmed diagnosis²⁰ of relapsing-remitting MS (RRMS)²¹ were included in the study. Patients with a history of recurrent ON in the same eye were excluded from the study.

Clinical assessment. Study participants underwent visual testing within 30 days of symptom onset, 3 months (optional), and 6 months after initial presentation with ON. For the purposes of this study, best-corrected Early Treatment Diabetic Retinopathy Study VA was expressed as the logarithm of the minimum angle of resolution (logMAR).²² VF analysis was obtained with Humphrey perimetry (Carl Zeiss Meditec, Dublin, CA), using the Central 30–2, full-threshold strategy. VF test results were used if the false-positive and false-negative errors measured less than 33% and fixation losses measured less than 20% for each eye tested.

Optical coherence tomography. The OCT (Stratus version 3, software 4.0; Zeiss Meditec) testing protocol used in this study has been previously described.⁸ A trained ophthalmic technologist at each site performed all OCT testing, and only studies with good fixation, a circular scan centered on the nerve head, and a signal strength ≥ 7 (of a possible 10) were included.

Clinical follow-up. Patients were evaluated within 30 days of symptom onset (baseline), and 6 months after ON, because this time interval has been shown to represent the window during which significant RNFL thinning manifests after ON in patients with CIS and MS.^{5,6,23}

Main outcome measures. The main outcome measures were change in average and quadrant RNFL measurements (μm) for male and female patients from baseline to 6 months after ON. Secondary outcomes included logMAR VA and VF mean deviation (measured in decibels [dB]) scores at baseline and 6 months after ON.

Statistical analysis. The primary variable of interest was RNFL thickness (μm). Secondary outcomes included VF and VA. All measurements were obtained at baseline and 6 months after ON. Data analysis was performed using STATA version 9.02 (StataCorp, College Station, TX), and level of significance was set at 0.05. Only 1 eye was picked randomly to be included in the data analysis in patients with bilateral acute ON. Variables were first checked for normality before performing any analytical statistics. Continuous variables were summarized by mean with SD, and 95% confidence interval. Median values were used for continuous variables with a non-Gaussian distribution. Depending on the distribution attributes of the variables, Student *t* test, χ^2 test, Fisher exact test, or Wilcoxon rank sum test was used to test the difference in demographic and clinical variables at baseline between men and women. Significance of change in RNFL thickness, VF, and VA over time (baseline to 6 months) was tested by repeated-measures analysis of variance for both men and women. Results of preliminary analyses were used to suggest potential covariates that needed to be controlled for in subsequent linear regression analysis. Linearity of independent variables was determined using scatterplots and further by Pearson correlation. The Pearson correlation test was also used to determine the relationships between the recovery indices. Multiple linear regression analysis was performed using gender to predict changes in RNFL thickness, VF, and VA. Age, disease duration, use of disease-modifying therapy (DMT), use of high-dose corticosteroids for acute ON (equivalent to 5 daily doses of 1,000 mg of IV methylprednisolone), and MS subtype (CIS vs RRMS) were 5 predetermined covariates to be included in the regression

Table 1 Patient demographics and clinical characteristics at baseline

Characteristics	Women	Men	p Value
No. of patients	105	39	—
Mean age (SD), y	35.2 (9.7)	39.0 (11.0)	0.05 ^a
CIS:MS	62:43	15:24	0.02 ^b
Eyes affected, OD:OS:OU	45:54:6	15:23:1	0.65 ^c
Disease duration, y ^e	5.0 (4.4)	6.6 (7.2)	0.27 ^a
Median EDSS score (95% CI)	3 (1–3.2)	3 (2–6)	0.41 ^d
MRI lesions, n (%)	72/103 (70)	33/39 (85)	0.09 ^c
Steroids, n (%) ^f	38/105 (36)	10/39 (26)	0.22 ^b
DMT, n (%)	23/105 (22)	9/39 (23)	0.49 ^b

Abbreviations: CI = confidence interval; CIS:MS = ratio of patients with optic neuritis as a clinically isolated syndrome vs relapsing-remitting multiple sclerosis; DMT = patients with relapsing-remitting multiple sclerosis or CIS using disease-modifying drug therapy (interferon or glatiramer acetate) at time of acute optic neuritis event; EDSS = Expanded Disability Status Scale; MRI (%) = patients with evidence of disseminated CNS inflammation³⁵ on baseline MRI; OD = right eye; OS = left eye; OU = both eyes.

^a Unpaired Student *t* test.

^b χ^2 test.

^c Fisher exact test.

^d Wilcoxon rank sum test.

^e Mean duration³⁴ for the diagnosis of relapsing-remitting multiple sclerosis or CIS.

^f Patients treated with high-dose corticosteroid therapy for acute ON (equivalent to 1,000 mg methylprednisolone daily for 5 days) initiated within the first 2 weeks of therapy.

model for their clinical significance. In addition, interaction terms were created for variables that displayed statistical correlations or clinical associations and fitted in the multivariate models. Further subanalyses by the use of DMT and steroids indicated statistical insignificance regarding differences between men and women.

RESULTS Patient demographics and clinical features are documented in table 1. Men were slightly older ($n = 39$; mean age = 39 years) than women ($n = 105$; 35 years) ($p = 0.05$) in this study, and more men (62%) than women (41%) had a confirmed diagnosis of RRMS ($p = 0.02$) (table 1). Thirty-six percent of women (38 of 105) and 26% of men (10 of 39) were treated with high-dose corticosteroids for acute ON. On average, both groups were treated 6 days after the initial onset of symptoms.

Clinical characteristics. At presentation, 92% of men ($n = 36$) and 94% of women ($n = 99$) reported pain. Eight men (21%) and 23 of 105 women (22%) had mild to moderate optic nerve head swelling. One man and 2 women had a history of ON in their contralateral eye; therefore, OCT measurements and visual data from the remotely affected fellow eyes for these 3 patients were excluded from the analyses. Three women presented with bilateral simultaneous ON, and 1 woman developed bilateral sequential ON during the study period. For these patients, only OCT and visual data from a single randomly selected

eye were included the ON eyes group. No patients experienced recurrent ON in the same eye during the course of the study. There were 105 ON eyes and 99 non-ON eyes in the female patient group, and 39 ON eyes and 38 non-ON eyes in the male patient group.

RNFL values. At baseline, mean RNFL values in ON eyes did not differ between men (115 μm) and women (111 μm) ($p = 0.44$) (table 2, figure 1). For both genders, RNFL values in ON eyes were significantly higher at baseline relative to recovery after 6 months (table 2, figure 1). Men had higher RNFL values in their ON eyes at baseline relative to their non-ON eyes (intereye RNFL difference = 13 μm) as compared with women (5 μm), but differences were not significant between genders ($p = 0.22$). There was greater intereye asymmetry in mean RNFL values (paired differences between ON eyes and non-ON eyes) for male patients after 6 months ($-27 \mu\text{m}$; SD = 16.3) relative to female patients ($-13 \mu\text{m}$; SD = 14.0) ($p < 0.0001$). The intereye asymmetry in mean RNFL thickness after 6 months was $-18 \mu\text{m}$ between ON eyes (86 μm) vs non-ON eyes (104 μm) when the data for men and women were analyzed as one group. After 6 months, mean RNFL values were lower in men (74 μm) than in women (91 μm) ($p < 0.001$) (table 2, figure 1), and men ($-38 \mu\text{m}$ [SD = 27.7]) showed greater change in RNFL thickness in their ON eyes from baseline to 6 months after ON than women ($-20 \mu\text{m}$ [SD = 33.2]) ($p = 0.003$) (figure 2). Multivariate regression (adjusted for age, disease duration, MS subtype, DMT, and corticosteroid use) showed that RNFL values were lower in male ON eyes in the superior ($p < 0.0001$), inferior ($p < 0.0001$), temporal ($p < 0.0001$), and nasal quadrants ($p = 0.03$) relative to female ON eyes 6 months after ON (table 3). The change in RNFL thickness from baseline to 6 months was worse in the ON eyes of men in the superior ($p = 0.001$), inferior ($p < 0.0001$), and temporal ($p < 0.0001$) quadrants, but RNFL changes in the nasal quadrant from baseline to 6 months after ON did not differ significantly between genders ($p = 0.10$) (table 3, figure 2).

Two interaction terms were created: MS subtype and age, because it was suspected that older age may be associated with a greater risk of having the diagnosis of RRMS. These 2 interaction terms were fitted into the model with sex, and the 5 predetermined clinical covariates. The resulting model indicated insignificance of these 2 interaction terms ($p > 0.5$). Because their inclusion did not affect the model statistics significantly, they were not removed from the final model. In fact, sex remained the only independent variable that significantly predicted RNFL

Table 2 Comparing retinal nerve fiber layer measurements between men and women with acute optic neuritis

	Retinal nerve fiber layer, mean (SD), μm			
	Baseline ^a	3 mo	6 mo	p Value ^b
ON eyes				
Female	111.4 (26.2)	97.6 (18.1)	90.8 (16.9)	0.0001
Male	115.1 (19.2)	87.5 (17.8)	73.5 (14.0)	0.0001
p Value ^c	0.44	0.17	0.0001	—
p Value ^d	—	—	0.001	—
Non-ON eyes^e				
Female	106.8 (12.9)	103.3 (10.4)	103.4 (14.0)	0.1849
Male	102.5 (11.5)	104.4 (9.9)	100.1 (13.8)	0.4744
p Value ^c	0.08	0.79	0.3731	—
p Value ^d	—	—	0.913	—

Abbreviation: ON = optic neuritis.

^a Initial mean retinal nerve fiber layer measurement documented within 30 days of the acute optic neuritis event.

^b Repeated-measures analysis of variance statistical comparison.

^c Unpaired t test (a 2-sample [pooled or unequal variance] t test was used to compare men vs women).

^d Multivariate regression: effect of sex on retinal structural change at 6 months from baseline (adjusted for age, disease duration, use of disease-modifying therapy, use of high-dose corticosteroids for acute ON, and multiple sclerosis subtype [clinically isolated syndrome vs relapsing-remitting multiple sclerosis]).

^e Unaffected eyes of patients with optic neuritis.

Figure 1 Retinal nerve fiber layer (RNFL) measurements (in μm) at baseline and 6 months after optic neuritis (ON)

Baseline = RNFL measurements within 30 days of acute ON; recovery = RNFL measurements 6 months after acute ON; average = mean global RNFL measurement; superior = superior RNFL quadrant; inferior = inferior RNFL quadrant; nasal = nasal RNFL quadrant; temporal = temporal RNFL quadrant.

thickness after ON; the other 5 covariates were only included in the final model to control for patient clinical characteristics.

To determine whether the age at onset of ON may have affected recovered RNFL thickness in our study, we performed subgroup analyses: RNFL measures were compared between genders for patients aged 18 to 24 years, 25 to 40 years, and older than 40 years (appendix e-2). RNFL measurements in ON eyes decreased with increased age at onset for both genders, and were significantly lower after 6 months in men relative to women, except in the 18- to 24-year-old age group, in which there were only 3 male patients (appendix e-2).

Visual recovery after ON. In ON eyes, there were no differences in VA between men (1.2 [1.1]) and women (0.9 [0.9]) at presentation (table e-1). Six months after ON, 97 of 103 women (94%) and 32 of 39 men (82%) achieved a Snellen VA equivalent

of 20/40 or better, and 94 of 103 women (91%) and 29 of 39 men (74%) had recovered VA of 20/25 or better. Both female ($p < 0.0001$) and male ($p = 0.0004$) ON patient groups demonstrated significant improvement in VF after ON (table e-1). At baseline, mean VF values were worse in ON eyes of men (-17.4 dB [10.8]) than women (-12.2 dB [9.6]), but after 6 months, multivariate regression analysis showed no differences ($p = 0.24$) between genders (table e-1). The crude magnitude of VF recovery (from baseline to 6 months after ON) was greater in men than in women (median: men = 7.19 dB [$-5, 0$] vs women = 4.59 dB [$-4, 2$]) ($p = 0.06$), but the analysis did not reach statistical significance.

Relationships between visual recovery outcome measures. Regardless of gender, VA and VF values were related ($r = -0.82, p < 0.0001$), such that worse (higher LogMAR values) VA correlated with reduced VF scores. The same degree and level of significance remained when men ($r = -0.82, p < 0.0001$) and women ($r = -0.82, p < 0.0001$) were analyzed separately.

Retention/withdrawals/dropout. Six-month follow-up data were obtained for all 39 male participants and 103 of 105 women in the study. Two female patients (Calgary) were lost to follow-up because they relocated before their 6-month follow-up visits.

DISCUSSION In this study, we compared RNFL values over a 6-month period to determine whether there were sex-specific differences after acute ON. Mean RNFL values were significantly lower in ON eyes of men ($74 \mu\text{m}$) relative to women ($91 \mu\text{m}$), and men ($-38 \mu\text{m}$) manifested more apparent change in RNFL thickness from baseline to 6 months relative to women ($-20 \mu\text{m}$) ($p < 0.003$). When ON eyes and non-ON eyes were compared 6

Figure 2 Change in retinal nerve fiber layer (RNFL) thickness 6 months after optic neuritis (ON)

Change in RNFL = change in RNFL thickness (μm) from baseline to 6 months after acute ON; average = mean global RNFL measurement; superior = superior RNFL quadrant; inferior = inferior RNFL quadrant; nasal = nasal RNFL quadrant; temporal = temporal RNFL quadrant.

Table 3 Comparing quadrant retinal nerve fiber layer measurements in optic neuritis eyes between men and women

RNFL quadrant	Retinal nerve fiber layer, mean (SD), μm			
	Baseline ^a	3 mo	6 mo	p Value ^b
Superior				
Male	145.1 (28.2)	113.5 (23.9)	93.3 (21.8)	0.0001
Female	141.9 (41.2)	123.6 (29.9)	117.1 (25.9)	0.0001
p Value ^c	0.66	0.39	0.0001	
p Value ^d			0.001	
Inferior				
Male	144.3 (26.1)	107.0 (21.3)	90.7 (23.2)	0.0001
Female	139.8 (34.1)	122.4 (23.4)	113.0 (23.2)	0.0001
p Value ^c	0.47	0.11	0.0001	
p Value ^d			0.0001	
Nasal				
Male	96.4 (26.0)	79.9 (19.1)	65.4 (16.4)	0.0001
Female	92.0 (31.4)	83.0 (17.5)	73.2 (19.6)	0.0001
p Value ^c	0.46	0.66	0.03	
p Value ^d			0.10	
Temporal				
Male	74.2 (13.9)	48.8 (12.6)	43.5 (10.4)	0.0001
Female	71.2 (20.0)	61.1 (15.8)	59.3 (18.2)	0.0001
p Value ^c	0.40	0.05	0.0001	
p Value ^d			0.0001	

Abbreviation: RNFL = retinal nerve fiber layer.

^a Initial RNFL measurements documented within 30 days of the acute optic neuritis event.

^b Repeated-measures analysis of variance statistical comparison.

^c Unpaired t test (a 2-sample [pooled or unequal variance] t test was used to compare men vs women).

^d Multivariate regression: effect of sex on visual structural change at 6 months from baseline (adjusted for age, disease duration, use of disease-modifying therapy, use of steroids and multiple sclerosis subtype [clinically isolated syndrome vs relapsing-remitting multiple sclerosis]).

months after ON, men had more intereye asymmetry in RNFL thickness ($-27 \mu\text{m}$) compared with women ($-13 \mu\text{m}$) ($p < 0.0001$). However, when we considered the cohort as a whole, the intereye RNFL difference at 6 months ($-18 \mu\text{m}$) was similar to the findings of a recent meta-analysis of time domain OCT studies ($-15 \mu\text{m}$) in patients with MS.²³ The results of our study suggest that men may have worse RNFL thinning than women after ON, and that the influence of gender may need to be further explored in the ON model of MS.

Previous MS studies have shown that men tend to have worse clinical outcomes, faster disease progression, and higher burden of destructive lesions on MRI studies relative to women.^{14–17} Several factors have been proposed to account for gender differences in MS including sex hormones, genetics, immune biases, and environmental influences.¹² As a sex hormone, estrogen has reduced the severity of experi-

mental autoimmune encephalomyelitis in animal models of CNS inflammation,^{24–26} and in the clinical setting, treatment with estrogen derivatives has been associated with decreased MRI-measured gadolinium-enhancing lesions in women with RRMS.²⁷ Estrogen has also been shown to increase retinal blood flow and protect the RNFL in animal and clinical models of optic nerve injury.²⁸ In an experimental model of Leber hereditary optic neuropathy, 17β -estradiol activated mitochondrial biogenesis and improved energetic competence, prompting the authors to postulate that the protective effects of estrogen may explain the higher prevalence of Leber hereditary optic neuropathy in men relative to women.²⁹ Although it is plausible that the neuroprotective benefits of estrogen may have contributed to the relatively well-preserved RNFL values in women relative to men observed in this study, we did not specifically evaluate sex hormones and therefore cannot draw any conclusions in this regard.

Despite the observation that men manifested worse RNFL loss after ON, we did not detect significant differences in visual recovery between genders. One of the reasons for the apparent discordance between structure and function in the ON model in this study may be that high-contrast acuity testing is a relatively insensitive means of capturing visual dysfunction in patients with MS.¹⁰ Had we used low-contrast letter acuity,¹⁰ contrast sensitivity,¹⁰ or color vision testing^{7,30} as outcome measures, we may have been better equipped to detect differences between genders 6 months after ON. In a previous study, we demonstrated that $75 \mu\text{m}$ represents the threshold of RNFL thickness that determines the extent of visual recovery after ON.⁸ Although RNFL values were lower in ON eyes of men 6 months after ON, the group en masse may have reached, but not breached, the $75\text{-}\mu\text{m}$ threshold to the extent that significant differences emerged in group comparisons of visual outcomes between genders.

Our study had a number of limitations, and therefore our findings should be interpreted with caution. Our patient population was small, particularly with respect to men. We attempted to control for all variables that could potentially influence RNFL values, but given the inherent heterogeneity of MS cohorts, there may remain differences between the male and female subgroups in our study, which may have affected our results. Mean RNFL values are lower in patients with MS relative to healthy control subjects,¹⁰ and decreased in eyes affected by recurrent ON relative to a single ON event.³¹ Therefore, given the higher proportion of male patients with the diagnosis of RRMS in this study it is possible that these patients were more vulnerable to RNFL thinning for

reasons that were difficult to control for in a multivariate regression model. An additional potential weakness of our study is that we did not stratify CIS patients into low- and high-risk groups for conversion to MS³² based on initial MRI characteristics, because we did not have a standardized MRI protocol. If we had included serial MRI studies, we may have detected additional patients with a radiologically confirmed diagnosis of MS, which could have affected the subtype ratios for both genders. In a recent study, RNFL thickness was associated with MRI measures of abnormality along the optic radiations,³³ indicating that transsynaptic retrograde degeneration is a plausible mechanism of axonal loss in MS. Therefore, another limitation of our study was that we did not account for the potential contribution of retrogeniculate visual pathway lesions to both RNFL measures and visual outcomes in our patients.

Our findings raise interesting questions about the potential influence of gender in the ON model of MS, particularly if OCT-measured RNFL thickness is to be used as an outcome measure for proof-of-concept trials of acute neuroprotection.⁵ Many of the issues that hamper small observational studies can be better addressed as secondary analyses in large-scale clinical trials, in which the randomization process will help equalize the effects of potential confounders including disease duration, MS subtype, DMT treatment, baseline MRI features, and as our findings suggest, the age of the patient at the time of ON onset. Thus, as our knowledge of factors that impact the ON model continues to evolve, the potential influence of gender on mechanisms of injury and repair in MS may be better understood.

AUTHOR CONTRIBUTIONS

Dr. Costello has drafted and revised the manuscript for content, contributed to the study concept or design, and analyzed and interpreted the data. Dr. Hodge has drafted and revised the manuscript for content, contributed to the study concept or design, and analyzed and interpreted the data. Y. Irene Pan has drafted and revised the manuscript for content, contributed to the study concept or design, performed the statistical analyses, and analyzed and interpreted the data. Dr. Burton has drafted and revised the manuscript for content, contributed to the study concept or design, and analyzed and interpreted the data. Dr. Freedman has drafted and revised the manuscript for content, contributed to the study concept or design, and analyzed and interpreted the data. Dr. Stys has drafted and revised the manuscript for content, contributed to the study concept or design, and analyzed and interpreted the data. Dr. Kardon has drafted and revised the manuscript for content, contributed to the study concept or design, and analyzed and interpreted the data.

DISCLOSURE

F. Costello served on a scientific advisory board or similar group for Celgene, Roche, and Biogen Idec, and received research support from the Canadian National Institute for the Blind and the Multiple Sclerosis Society of Canada. W. Hodge and Y.I. Pan report no disclosures. J. Burton served on a scientific advisory board or similar group for Novartis and

Biogen Idec. M. Freedman received research or educational grants from Bayer HealthCare and Genzyme; received honoraria or consultation fees from Bayer Healthcare, Biogen Idec, EMD Canada, Novartis, Sanofi-Aventis, and Teva Canada Innovation; and served as a member of a company advisory board, board of directors, or other similar group for Bayer Healthcare, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, and Celgene. P. Stys received an honorarium for presenting at an education meeting sponsored by Teva Pharmaceuticals. J. Trufyn reports no disclosures. R. Kardon served on a scientific advisory board for Novartis. **Go to Neurology.org for full disclosures.**

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