Active MS is associated with accelerated retinal ganglion cell/inner plexiform layer thinning

John N. Ratchford, MD*
Shiv Saidha, MRCPI*
Elias S. Sotirchos, MD
Jiwon A. Oh, MD, FRCPC
Michaela A. Seigo, ScB
Christopher Eckstein, MD
Mary K. Durbin, PhD
Jonathan D. Oakley, PhD
Scott A. Meyer, PhD
Amy Conger, COA
Teresa C. Frohman, BS
Scott D. Newsome, DO
Laura J. Balcer, MD, MSCE
Elliot M. Frohman, MD, PhD
Peter A. Calabresi, MD

Correspondence to Dr. Calabresi: calabresi@jhmi.edu

ABSTRACT

Objective: To determine the effect of clinical and radiologic disease activity on the rate of thinning of the ganglion cell/inner plexiform (GCIP) layer and the retinal nerve fiber layer in patients with multiple sclerosis (MS) using optical coherence tomography (OCT).

Methods: One hundred sixty-four patients with MS and 59 healthy controls underwent spectral-domain OCT scans every 6 months for a mean follow-up period of 21.1 months. Baseline and annual contrast-enhanced brain MRIs were performed. Patients who developed optic neuritis during follow-up were excluded from analysis.

Results: Patients with the following features of disease activity during follow-up had faster rates of annualized GCIP thinning: relapses (42% faster, $p = 0.007$), new gadolinium-enhancing lesions (54% faster, $p < 0.001$), and new T2 lesions (36% faster, $p = 0.02$). Annual GCIP thinning was 37% faster in those with disability progression during follow-up, and 43% faster in those with disease duration <5 years vs >5 years ($p = 0.003$). Annual rates of GCIP thinning were highest in patients exhibiting combinations of new gadolinium-enhancing lesions, new T2 lesions, and disease duration <5 years (70% faster in patients with vs without all 3 characteristics, $p < 0.001$).

Conclusions: MS patients with clinical and/or radiologic nonocular disease activity, particularly early in the disease course, exhibit accelerated GCIP thinning. Our findings suggest that retinal changes in MS reflect global CNS processes, and that OCT-derived GCIP thickness measures may have utility as an outcome measure for assessing neuroprotective agents, particularly in early, active MS. ***Neurology*® 2013;80:47–54**

GLOSSARY

CIS = clinically isolated syndrome; **EDSS** = Expanded Disability Status Scale; **GCIP** = ganglion cell/inner plexiform; **HC** = healthy control; **MSFC** = Multiple Sclerosis Functional Composite; **MS** = multiple sclerosis; **MSSS** = Multiple Sclerosis Severity Scale; **OCT** = optical coherence tomography; **ON** = optic neuritis; **PPMS** = primary progressive MS; **RNFL** = retinal nerve fiber layer; **RRMS** = relapsing-remitting MS; **SPMS** = secondary progressive MS.

The anterior visual pathway is frequently affected in multiple sclerosis (MS), with 94% to 99% of patients with MS demonstrating optic nerve lesions postmortem.[1,2] Transected and/or demyelinated optic nerve axons are thought to undergo retrograde degeneration.[3] Because these axons are derived from the retinal nerve fiber layer (RNFL), the RNFL atrophies.[4] In turn, the ganglion cell neurons from which these axons originate correspondingly degenerate.[5] Optical coherence tomography (OCT), a reproducible, noninvasive imaging technique, enables high-resolution quantification of retinal structures,[6–9] and demonstrates peripapillary RNFL thinning in MS eyes with and without a history of optic neuritis (ON).[10–14] Accordingly, OCT has been proposed as an outcome measure for assessing neuroprotection in MS.

The advent of OCT segmentation enables estimation of macular ganglion cell layer integrity by quantifying the composite thickness of the ganglion cell and inner plexiform (GCIP) layer (figure).[15–17] GCIP thinning also occurs in MS eyes with and without ON history, although

Editorial, page 19

Supplemental data at www.neurology.org

Supplemental Data

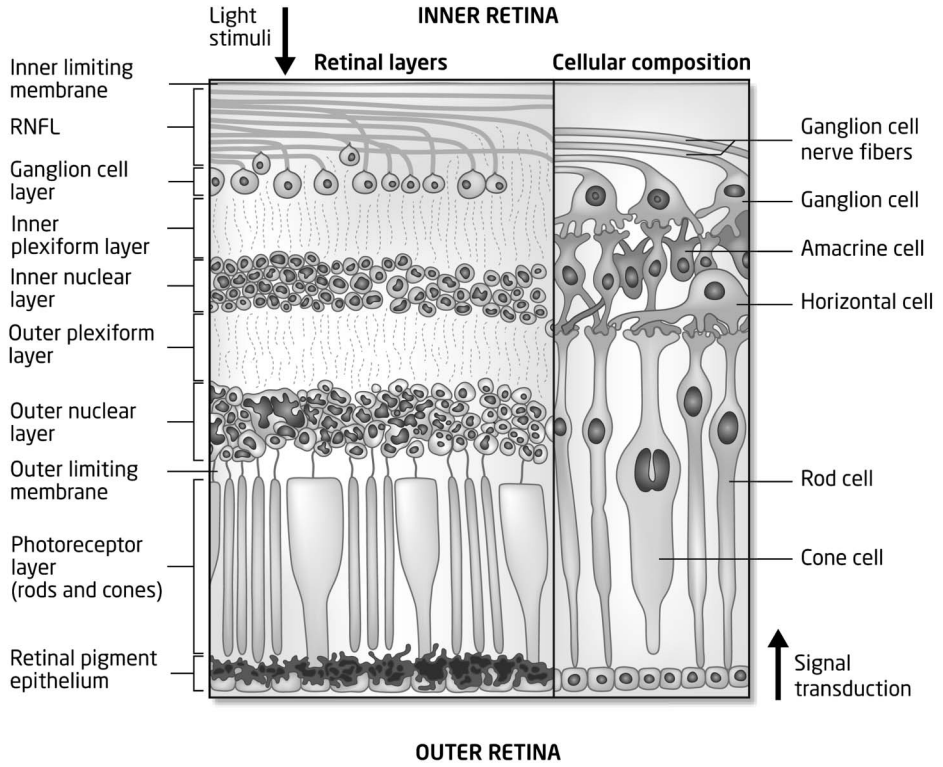
Podcast

*These authors contributed equally to the manuscript.

From the Department of Neurology (J.N.R., S.S., E.S.S., J.A.O., M.A.S., C.E., S.D.N., P.A.C.), Johns Hopkins University School of Medicine, Baltimore, MD; Department of Neurology (C.E.), University of South Alabama College of Medicine, Mobile; Carl Zeiss Meditec Inc. (M.K.D., J.D.O., S.A.M.), Dublin, CA; Voxeleron LLC (J.D.O.), San Francisco, CA; Department of Neurology and Ophthalmology (A.C., T.C.F., E.M.F.), University of Texas Southwestern, Dallas; and Department of Neurology and Ophthalmology (L.J.B.), University of Pennsylvania, Philadelphia.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure Illustration of the layers of the retina



RNFL: retinal nerve fiber layer.

Note that the retinal nerve fiber layer is composed of axons of the ganglion cells. Demyelination or transection of optic nerve axons (derived from the retinal nerve fiber layer) cause retrograde degeneration, resulting in atrophy of the retinal nerve fiber layer and ganglion cell body death. Reproduced from Saidha et al.[9] with permission from Remedica Medical Education and Publishing.

GCIP thickness measures may have better reproducibility and superior structure-function correlations with vision than RNFL thickness measures.[16,18] Although some studies have assessed longitudinal RNFL change in non-ON MS eyes,[19,20] the GCIP remains to be explored longitudinally. Moreover, the effect of MS disease activity on the rate of retinal neurodegeneration remains largely unexamined, an issue relevant for both the clinical utility of OCT and for the design of future trials utilizing OCT as an outcome. Our hypothesis was that patients with greater nonocular disease activity will have more neuroaxonal damage that will be measurable as more rapid thinning of the RNFL and GCIP layer.

METHODS

Patients. Patients with MS or clinically isolated syndromes (CIS) were enrolled from the Johns Hopkins MS Center. Participants underwent clinical evaluations and OCT every 6 months, as well as annual brain MRI scans. Patients with <6 months of clinical follow-up were excluded from analysis. MS diagnosis was based on 2005 McDonald criteria.[21] Patients with CIS had experienced an initial CNS inflammatory attack with MRI features compatible with MS, but did not fulfill MS diagnostic criteria. Patients with diabetes, glaucoma, refractive errors of ±6 diopters, or other ophthalmologic or neurologic disorders (other than MS) were excluded. Because acute swelling temporarily increases the RNFL thickness, patients with acute ON or evidence of optic disc swelling on fundoscopy within 3 months of baseline assessment, or during study follow-up, were excluded. Data from 9 patients were excluded for the following reasons: inadequate signal strength on baseline scan, glaucoma, diabetes, refractive error >6 diopters, revision of MS diagnosis, central serous chorioretinopathy (2 patients), and development of acute ON during the study (2 patients). Healthy controls (HCs) were recruited from among medical center staff. HCs were invited for OCT scans annually. HCs with <12 months of follow-up were excluded from analysis.

Standard protocol approvals, registrations, and patient consents. Johns Hopkins University and University of Texas Southwestern Medical Center Institutional Review Board approvals were obtained, and all participants provided written informed consent.

Clinical data. Patients were classified as having CIS, relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), or primary progressive MS (PPMS). Expanded Disability Status Scale (EDSS) scores were determined by a certified EDSS examiner at study visits.[22] Baseline disease duration and EDSS scores were used to determine subjects' baseline Multiple Sclerosis Severity Scale

(MSSS) scores.[23] EDSS progression was defined as a ≥1-point increase in EDSS score from baseline to final EDSS examination. Multiple Sclerosis Functional Composite (MSFC)[24] scores were available on a subset of MS/CIS patients (n = 95). Trial runs were performed to mitigate learning effects. MSFC progression was defined as worsening from baseline on scores of at least 1 MSFC component by 20% (MSFC progression-20), sustained for ≥3 months.[25] The occurrence of ON and non-ON relapses was recorded at study visits.

Magnetic resonance imaging. Contrast-enhanced brain MRI scans were performed on a 3-T Intera scanner (Philips Medical Systems, Best, The Netherlands). A reviewer blinded to the patients' clinical status assessed MRIs for the presence of contrast-enhancing lesions and the development of new T2-hyperintense lesions.

Optical coherence tomography. Retinal imaging was performed using Cirrus HD-OCT (model 4000) with software version 5.0 (Carl Zeiss Meditec, Dublin, CA), as described in detail elsewhere.[26] Peripapillary data were obtained with the Optic Disc Cube 200 × 200 protocol. Macular data were obtained using the Macular Cube 512 × 128 protocol. OCT scanning was performed by 3 trained technicians who monitored scans to ensure reliable fixation. Scans with signal strength <7/10 or with artifact were excluded from analysis. Macular Cube scans were further analyzed in a blinded manner using segmentation software, as previously described by our group.[16,17] The interrater reproducibility of the GCIP measurement was previously found to be very high in both MS patients and HCs (intraclass correlation 0.99 for both groups).[15]

Visual function. Standardized visual function testing was performed with retro-illuminated eye charts of constant light source in a darkened room. High-contrast Early Treatment of Diabetic Retinopathy Study charts (at 4 m) and low-contrast Sloan letter charts (2.5% and 1.25% contrast at 2 m) were used. Testing was performed monocularly, with subjects using their habitual distance spectacles or contact lenses as needed for corrected vision. High-contrast visual loss was defined as a decrease of ≥5 letters during follow-up, and low-contrast (both 2.5% and 1.25%) visual loss was defined as a decrease of ≥7 letters during follow-up, in accordance with previously published data.[19,27,28] Eyes with baseline high-contrast letter-acuity scores of <5 letters, or baseline 2.5%- or 1.25%-contrast letter-acuity scores of <7 letters were excluded from visual loss analyses, because these eyes could not fulfill visual loss criteria.

Statistical analyses. Statistical analysis was completed on STATA version 11 (StataCorp, College Station, TX). Analyses included both eyes of participants. Mixed-effects linear regression adjusting for age and sex, accounting for within-subject intereye correlations, was used to assess differences between baseline OCT measures and visual function between patients with MS and HCs. Age and sex were used as covariates because prior studies have found them to be significantly associated with OCT measures.[29] Using time-to-visit from baseline as a continuous variable, annual rates of change in OCT measures were determined using mixed-effects linear regression adjusting for age and sex, accounting for within-subject intereye correlations. Interaction terms with time were used to determine differences in the annual rates of change in OCT measures according to the following characteristics: disease duration <5 years and <10 years, prior ON, baseline MSSS and EDSS scores, disability progression, baseline gadolinium-enhancing lesions, MSFC progression-20, non-ON relapses, new gadolinium-enhancing lesions, new T2 lesions, or visual loss (high-contrast or low-contrast) during follow-up. Type I error for significance was defined as $p = 0.05$.

RESULTS A total of 164 MS/CIS patients (116 RRMS, 24 SPMS, 16 PPMS, and 8 CIS) and 59 HCs were followed, with a mean follow-up duration of 21.1 months for both groups. Ninety percent of the patients with RRMS and CIS and 53% of the patients with SPMS and PPMS received treatment with

Table 1 Baseline demographics and disease characteristics

	All MS/CIS	RRMS	SPMS	PPMS	CIS	HCs
No. (eyes)	164 (328)	116 (232)	24 (48)	16 (32)	8 (16)	59 (118)
Age, y (SD)	43.5 (11.9)	40.1 (10.5)	55.7 (5.4)	55.8 (6.6)	31.6 (9.2)	36.8 (9.8)
Female (%)	117 (71)	86 (74)	16 (67)	9 (56)	6 (75)	39 (66)
Mean follow-up time, mo (SD)	21.1 (7.7)	20.4 (7.9)	23.7 (6.2)	23.2 (6.6)	18.8 (8.9)	21.1 (11.5)
Mean disease duration, y (SD)	11.1 (9.0)	8.8 (6.7)	21.5 (8.2)	11.9 (8.8)	1.0 (0.8)	—
ON eyes (%)	95 (29)	78 (34)	10 (21)	0 (0)	7 (44)	—
Mean EDSS score (SD)	3.2 (2.1)	2.5 (1.6)	5.9 (1.3)	5.4 (1.4)	1.2 (1.2)	—
Mean MSSS score (SD)	4.1 (2.5)	3.5 (2.3)	5.7 (2.0)	6.4 (2.1)	3.4 (3.0)	—
Letter acuity, 100% contrast (SD)	58.5 (10.1)	59.4 (10.7)	57.3 (6.6)	55.0 (8.8)	57.7 (11.8)	61.5 (6.2)
Letter acuity, 2.5% contrast (SD)	27.4 (12.3)	28.5 (12.3)	26.8 (9.1)	23.5 (12.6)	22.5 (16.3)	33.7 (7.8)
Letter acuity, 1.25% contrast (SD)	13.1 (11.4)	14.3 (11.9)	10.4 (8.3)	8.1 (9.3)	14.9 (12.9)	20.0 (8.4)
Mean RNFL thickness, μm (SD)	84.7 (12.5)	85.0 (12.4)	79.5 (12)	87.9 (11.2)	87.7 (13.3)	92.0 (10.2)
Mean GCIP thickness, μm (SD)	71.6 (9.8)	71.9 (9.9)	68.5 (10.3)	73.7 (7.1)	72.7 (10.1)	81.3 (6.5)
Patients with gadolinium-enhancing lesion at baseline (%)	15/112 (13.4)	15/76 (20)	0/18 (0)	0/14 (0)	0/4 (0)	—

Abbreviations: CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; GCIP = ganglion cell/inner plexiform; HC = healthy control; MS = multiple sclerosis; MSSS = Multiple Sclerosis Severity Scale; PPMS = primary progressive MS; RNFL = retinal nerve fiber layer; RRMS = relapsing-remitting MS; SPMS = secondary progressive MS.

Table 2 Differences in OCT and visual measures at baseline between patients and healthy controls[a]

	All MS/CIS vs HCs	RRMS vs HCs	SPMS vs HCs	PPMS vs HCs	CIS vs HCs
RNFL difference, μm (*p* value)	−7.26 (<0.001)	−7.50 (<0.001)	−9.05 (0.01)	−2.16 (0.58)	−2.31 (0.57)
GCIP difference, μm (*p* value)	−9.97 (<0.001)	−9.90 (<0.001)	−12.82 (<0.001)	−7.05 (0.006)	−6.93 (0.006)
Letter acuity difference, 100% contrast (*p* value)	−2.15 (0.12)	−1.77 (0.24)	−2.17 (0.25)	−4.10 (0.07)	−1.56 (0.42)
Letter acuity difference, 2.5% contrast (*p* value)	−5.32 (0.002)	−4.81 (0.007)	−2.31 (0.42)	−5.83 (0.08)	−9.92 (0.002)
Letter acuity difference, 1.25% contrast (*p* value)	−5.70 (<0.001)	−5.12 (0.004)	−4.76 (0.09)	−6.25 (0.04)	−5.48 (0.10)

Abbreviations: CIS = clinically isolated syndrome; GCIP = ganglion cell/inner plexiform; HC = healthy control; MS = multiple sclerosis; OCT = optical coherence tomography; PPMS = primary progressive MS; RNFL = retinal nerve fiber layer; RRMS = relapsing-remitting MS; SPMS = secondary progressive MS.
[a] All analyses are adjusted for age, sex, and within-subject intereye correlations.

an MS disease-modifying therapy for the duration of this study. Baseline demographics are shown in table 1.

Baseline analyses. At baseline, peripapillary RNFL thinning was greatest in patients with SPMS (79.5 ± 12.0 μm), followed by RRMS (85.0 ± 12.4 μm), CIS (87.7 ± 13.3 μm), and PPMS (87.7 ± 13.3 μm), relative to HCs (92.0 ± 10.2 μm). A similar pattern was observed for macular-GCIP thinning: SPMS (68.5 ± 10.3 μm), RRMS (71.9 ± 9.9 μm), CIS (72.7 ± 10.1 μm), and PPMS (73.7 ± 7.1 μm) vs HCs (81.3 ± 6.5 μm). Patients with MS and CIS had lower values on all OCT and visual acuity measures relative to HCs at baseline (table 2). Differences in GCIP thickness were significant for all MS subtypes and CIS (table 2). Although RNFL thickness was significantly lower in the total MS/CIS cohort, the RRMS subgroup, and the SPMS subgroup relative to HCs, RNFL thickness was not significantly different between PPMS or CIS and HCs at baseline. For visual acuity, 1.25% low-contrast letter acuity provided the greatest ability to discriminate between all MS/CIS patients and HCs (table 2).

A multivariate linear regression model was used to assess factors influencing baseline OCT measures in the MS/CIS cohort. Disease duration and prior ON in eyes were found to be most strongly associated with baseline OCT values in this model. Disease duration was associated with a thinner baseline RNFL (β: −0.35 μm/year, $p < 0.001$) and GCIP layer (β: −0.26 μm/year, $p < 0.001$). Eyes with ON history had on average 9.5 μm lower RNFL thicknesses and 8.4 μm lower GCIP thicknesses than eyes without ON history ($p < 0.001$ for both). Age or baseline MSSS score was not significantly associated with baseline RNFL or GCIP thicknesses in this cohort. Although RNFL and GCIP thicknesses differed by MS subtype at baseline, these differences were not significant after adjusting for disease duration.

Longitudinal analyses. Clinical and radiologic changes during the study are summarized in table 3, and

Table 3 Summary of clinical and radiologic changes during the study

	RRMS	SPMS	PPMS	CIS	HCs
Worsening vision, 100% contrast (%)	98/218 (45)	13/46 (28)	12/32 (38)	5/16 (31)	18/78 (23)
Worsening vision, 2.5% contrast (%)	63/199 (32)	16/45 (36)	12/28 (43)	3/11 (27)	24/76 (32)
Worsening vision, 1.25% contrast (%)	44/147 (30)	10/27 (37)	4/13 (31)	2/10 (20)	21/74 (28)
1-point EDSS worsening (%)	31/114 (27)	3/24 (13)	1/15 (7)	3/8 (38)	—
Sustained 1-point EDSS worsening (%)	21/100 (21)	5/23 (22)	0/15 (0)	3/8 (38)	—
MSFC progression-20 (%)	47/56 (16)	2/20 (10)	4/12 (33)	0/7 (0)	—
Relapse during the study period (%)	29/116 (25)	0/24 (0)	0/16 (0)	5/8 (62)	—
New gadolinium-enhancing lesion (%)	20/114 (18)	1/23 (4)	2/14 (14)	2/8 (25)	—
New T2-hyperintense lesion (%)	36/113 (32)	3/23 (13)	1/14 (7)	4/8 (50)	—

Abbreviations: CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; HC = healthy control; MSFC progression-20 = Multiple Sclerosis Functional Composite 20% progression; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Table 4 Effect of clinical and radiologic characteristics on the rate of change in GCIP and RNFL thicknesses in patients with MS and CIS[a]

	GCIP	RNFL
Disease duration <5 y	−0.23 (0.003)[b]	−0.34 (0.08)
Disease duration <10 y	−0.01 (0.82)	0.14 (0.41)
Age, y	0.004 (0.12)	−0.006 (0.42)
Non-ON relapses	−0.23 (0.007)[b]	−0.01 (0.92)
Enhancing lesion on baseline MRI	−0.17 (0.21)	−0.34 (0.30)
New enhancing lesion	−0.34 (<0.001)[b]	−0.18 (0.38)
New T2 lesion	−0.18 (0.02)[b]	−0.007 (0.96)
Baseline MSSS score	−0.009 (0.51)	−0.03 (0.37)
Baseline EDSS score	−0.01 (0.33)	0.02 (0.60)
1-point EDSS score increase	−0.19 (0.01)[b]	−0.10 (0.61)
6-mo sustained EDSS score progression	−0.0004 (0.99)	0.27 (0.19)
MSFC progression	0.20 (0.09)	−0.06 (0.81)
Worsening vision, 100% contrast	−0.01 (0.86)	0.09 (0.53)
Worsening vision, 2.5% contrast	−0.05 (0.37)	−0.04 (0.78)
Worsening vision, 1.25% contrast	0.08 (0.27)	0.41 (0.03)[b]
New T2 and enhancing lesions	−0.41 (<0.001)[b]	−0.22 (0.37)
New enhancing lesion and disease duration <5 y	−0.60 (<0.001)[b]	0.26 (0.46)
New T2 lesion and disease duration <5 y	−0.60 (<0.001)[b]	−0.28 (0.43)
New T2 and enhancing lesions, disease duration <5 y	−0.76 (<0.001)[b]	0.09 (0.81)
1-point EDSS score increase and disease duration <5 y	−0.48 (0.001)[b]	0.13 (0.71)

Abbreviations: CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; GCIP = ganglion cell/inner plexiform; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSSS = Multiple Sclerosis Severity Scale; ON = optic neuritis; RNFL = retinal nerve fiber layer.

[a] Values are β coefficients from the regression model indicating the difference in the rate of GCIP or RNFL change between those with and without the covariate, measured in μm/year (*p* value) (except age in which the β coefficient is the difference in rate of change per year of baseline age and EDSS and MSFC scores in which the value represents the rate difference associated with a difference of 1 point on the EDSS or MSSS). All analyses are adjusted for age and sex.

[b] Statistically significant association.

differences in OCT and vision outcomes between baseline and end-of-study visits are summarized in table e-1 on the *Neurology*® Web site at www.neurology.org (unlike the results reported below, results in table e-1 do not account for OCT or vision measures during the intervening visits between the baseline and end-of-study visits). Among patients with RRMS and CIS, 27% experienced a nonocular relapse during the study, and 33% developed new T2-hyperintense MRI lesions. Correcting for age and sex, the overall rate of change in the MS/CIS cohort was −0.21 μm/year for RNFL thickness ($p = 0.01$) and −0.37 μm/year for GCIP thickness ($p < 0.001$). In HCs, the rate of change was −0.25 μm/year ($p = 0.04$) for RNFL thickness and −0.20 μm/year ($p < 0.001$) for GCIP thickness. The rate of GCIP thinning was 46% faster in patients with MS/CIS than HCs ($p = 0.008$), whereas there was no significant difference in the rate of RNFL thinning between patients with MS/CIS and HCs.

Several clinical and radiologic characteristics were assessed to determine whether they were associated with more rapid RNFL or GCIP thinning in MS/CIS (table 4). This was done using mixed-effects linear regression models adjusting for age and sex. Several markers of disease activity during follow-up were associated with greater rates of GCIP thinning in patients, as compared with those without these features: nonocular relapses (42% faster; −0.55 vs −0.32 μm/year, $p = 0.007$), new gadolinium-enhancing lesions (54% faster; −0.63 vs −0.29 μm/year, $p < 0.001$), and new T2 lesions (36% faster; −0.50 vs −0.32 μm/year, $p = 0.02$). Rates of GCIP thinning were faster in patients exhibiting disability progression (≥1-point increase in EDSS score during follow-up) than in patients without disability progression during follow-up (37% faster; −0.52 vs −0.33 μm/year, $p = 0.01$). GCIP thinning was also faster in those with disease duration <5 years vs >5 years (43% faster; −0.54 vs −0.31 μm/year, $p = 0.003$). Rates of GCIP thinning were highest in patients exhibiting combinations of new gadolinium-enhancing lesions, new T2 lesions, or disease durations <5 years (table 4).

New gadolinium-enhancing lesions during follow-up in patients with disease duration <5 years were associated with 67% faster rate of GCIP thinning compared with patients with disease duration <5 years without new gadolinium-enhancing lesions (−0.89 vs −0.29 μm/year, $p < 0.001$). Similarly, new T2 lesions during follow-up in those with disease durations <5 years were associated with 70% faster rates of GCIP thinning vs those with disease duration <5 years without new T2 lesions (−0.86 vs −0.26 μm/year, $p < 0.001$).

Patients with both new gadolinium-enhancing and new T2 lesions during follow-up, regardless of disease duration, had 57% faster rates of GCIP thinning (−0.72 vs −0.31 μm/year in those without both during follow-up, $p < 0.001$). The combination of both new T2 lesions and new gadolinium-enhancing lesions in those with disease duration <5 years was associated with 70% faster rates of GCIP thinning (−1.09 vs −0.33 μm/year in those with disease durations <5 years without both new gadolinium-enhancing and new T2 lesions during follow-up, $p < 0.001$). Disease duration dichotomized at 10 years, baseline MSSS score, baseline EDSS score, MSFC progression-20, MS subtype, prior ON, and high-contrast or low-contrast visual loss were not significantly associated with rates of GCIP thinning.

Clinical and radiologic markers of MS disease activity were not associated with RNFL thinning, unlike GCIP thinning, although prior ON in eyes was associated with a trend toward a greater rate of RNFL thinning (78% faster; −0.41 vs −0.09 μm/year in eyes without prior ON, $p = 0.07$).

DISCUSSION In this study, we demonstrate that MS-related subclinical optic neuropathy, and the neurodegeneration associated with this process, occurs more significantly in patients exhibiting classic evidence of clinical and/or radiologic disease activity. This suggests that clinical trials enriched with patients with active MS may have better power to detect neuroprotective effects of novel therapeutic agents. Moreover, our findings suggest that the basis for subclinical optic neuropathy/subclinical optic nerve neurodegeneration may at least be partially related to microscopic optic nerve inflammatory disease. GCIP thinning was accelerated in patients exhibiting evidence of disease activity such as non-ON relapses, new T2 lesions, and new gadolinium-enhancing lesions. Patients exhibiting disability progression also were found to have faster rates of GCIP thinning. Furthermore, rates of GCIP thinning were faster in those with disease duration <5 years, which may reflect a greater availability of retinal ganglion cells for neurodegeneration earlier in the disease course, or a greater tendency for inflammatory disease activity earlier in the disease course. Rates of GCIP thinning were also augmented when these independent factors were present in combination. For example, patients with new T2 lesions, new enhancing lesions, and disease durations <5 years exhibited 70% faster rates of GCIP thinning. These results provide evidence that longitudinal GCIP changes in MS may be clinically meaningful and associated with more aggressive inflammatory disease. In addition, GCIP thinning was observed in all MS subtypes, suggesting GCIP neurodegeneration occurs throughout the disease course, perhaps related to microscopic inflammation. Although overall rates of GCIP thinning were significantly greater in patients with MS than in HCs, the rate of GCIP thinning observed in patients with MS is relatively modest. However, the mean duration of this study was short and presented results are expressed as annualized rates of thinning, rather than total thickness reduction between study beginning and study end.

Although baseline RNFL results in this study are consistent with prior studies,[10–14] the rate of RNFL thinning in this study (−0.21 μm/year) was lower than that observed in some other studies, and was not significantly different from HCs. In one study, the rate of RNFL thinning in MS was −2.0 μm/year,[19] and in another it was −2.7 μm/year.[20] In the latter study, a rate of RNFL thinning of −1.4 μm/year was also observed in HCs. Our results, however, are more in line with 2 other studies in which no significant decrease was observed in RNFL thickness during follow-up.[30,31] Discrepancies in RNFL change across studies may relate to differences in cohort characteristics. Our results raise the possibility that rates of RNFL thinning may be greater in cohorts with larger proportions of patients with prior ON. Also, another source of potential difference is that the rates we report control for several disease characteristics, whereas some other studies have reported unadjusted rates. Differences in the use of disease-modifying medication could also account for different results. Although all studies excluded patients who developed ON during follow-up, an important factor still bearing consideration is the differential effect of optic nerve inflammation on RNFL and GCIP thicknesses.[17]

Our finding that rates of GCIP thinning are accelerated in those with nonocular disease activity suggests that retinal changes in MS may be reflective of more global CNS processes, consistent with cross-sectional observations.[32,33] However, the mechanism by which retinal changes may reflect global CNS processes is unclear. One plausible explanation is that disruption of the blood-brain barrier in one part of the CNS (reflected for example by an enhancing lesion) may represent a susceptibility for the blood-brain barrier to become disrupted elsewhere, such as in the optic nerves (even though it may be subclinical). If this was the case, it could imply that microinflammatory processes may be occurring within the optic nerves of patients with MS. Because optic nerve inflammation is associated with RNFL swelling but not GCIP swelling,[17] these processes could result in the pseudonormalization or swelling of the RNFL, thus underestimating the true rates of RNFL thinning. The absence of GCIP swelling during optic nerve inflammation, as well as the absence of astroglial influence on GCIP thickness measures (the retinal astrocytes are predominantly located in the RNFL),[16,34] may help explain the superiority of GCIP thickness measures over RNFL thickness measures, cross-sectionally and longitudinally. These factors may contribute toward the better reproducibility and lower variance of GCIP over RNFL thickness measures.[16]

It was surprising in this study that expected associations between worsening vision and changes in OCT measures were not observed, because these measures correlate well cross-sectionally.[8,9] However, changes in visual acuity can have multiple causes in MS (e.g., posterior visual pathway lesions, refractive changes, temporary changes due to Uhthoff phenomenon), potentially weakening the association between changes in OCT and changes in vision in a cohort. Also, much of the change in vision that correlates with change in OCT measures comes from ON episodes. Because data after acute ON episodes were excluded in this study, this likely also weakened the ability to identify an association between change in low-contrast vision and change in OCT. Although patients with other known ocular diseases were excluded, the patients in this cohort were not systematically examined by an ophthalmologist, which limits our ability to correlate the OCT findings with aspects of visual function other than high- and low-contrast vision.

Given the potentially slow rate of change in OCT measures in non-ON MS eyes and nonactive MS, it is possible that a long timeframe may be needed to identify a neuroprotective therapeutic effect in a clinical trial using OCT as an outcome measure (such as in progressive MS). Nonetheless, if used as a secondary outcome, a finding of slower OCT change in treated relative to untreated patients may provide compelling evidence for neuroprotection. OCT has already shown promise as an outcome measure in acute ON, whereby a 10% to 20% change in RNFL thickness occurs within months.[14] As discussed above, GCIP thickness may be a more sensitive measure to detect clinical change in MS than RNFL thickness. Because patients exhibiting active MS in this study, particularly early on in their disease course, had greater rates of GCIP thinning, a clinical trial using OCT as an outcome measure could potentially be enriched by the recruitment of patients with early, active MS. Our results suggest that researchers planning future trials incorporating OCT should consider the inclusion of macular-GCIP thickness measures (which will be commercially available soon), in addition to conventional peripapillary RNFL thickness measures.

AUTHOR CONTRIBUTIONS

Conceptualization of the study: Dr. Ratchford, Dr. Saidha, Dr. Balcer, Dr. E.M. Frohman, and Dr. Calabresi. Drafting/revising the manuscript: Dr. Ratchford, Dr. Saidha, Dr. Sotirchos, Dr. Oh, M.A. Seigo, Dr. Eckstein, Dr. Durbin, Dr. Oakley, Dr. Meyer, A. Conger, T.C. Frohman, Dr. Newsome, Dr. Balcer, Dr. E.M. Frohman, and Dr. Calabresi. Analysis of the data: Dr. Ratchford, Dr. Saidha, and Dr. Sotirchos. Interpretation of the data: Dr. Ratchford, Dr. Saidha, Dr. Sotirchos, Dr. Balcer, Dr. E.M. Frohman, and Dr. Calabresi.

STUDY FUNDING

National Multiple Sclerosis Society (TR 3760-A-3 to P.A.C. and RG 4212-A-4 to L.J.B. subcontracted to P.A.C.), National Eye Institute (R01 EY 014993 and R01 EY 019473 to L.J.B. subcontracted to P.A.C.), and Braxton Debbie Angela Dillon and Skip (DADS) Donor Advisor Fund (to P.A.C. and E.M.F).

DISCLOSURE

J. Ratchford consulted for Bristol-Myers Squibb and DioGenix, received a speaking honorarium from Teva, and receives research funding for clinical trials from Novartis and Biogen Idec. S. Saidha received consulting fees from Medical Logix for the development of continuing medical education programs in neurology, and has received educational grant support from Teva Neurosciences. E. Sotirchos, J. Oh, M. Seigo, and C. Eckstein report no disclosures. M. Durbin is employed by Carl Zeiss Meditec Inc. J. Oakley is a cofounder and employee of Voxeleron. He was previously employed by Carl Zeiss Meditec Inc. S. Meyer is employed by Carl Zeiss Meditec Inc. A. Conger and T. Frohman report no disclosures. S. Newsome received consulting fees from Biogen Idec, Teva, and Novartis and speaking honoraria from Biogen Idec and Teva. L. Balcer received speaking and consulting honoraria from Biogen Idec, Bayer, and Novartis. E. Frohman received speaking honoraria and consulting fees from Biogen Idec, Teva, and Athena. He received consulting fees from Abbott Laboratories. P. Calabresi has provided consultation services to Novartis, Teva, Biogen Idec, Vertex, Vaccinex, and Genentech, and has received grant support from EMD-Serono, Teva, Biogen Idec, Genentech, Bayer, Abbott, and Vertex. Go to Neurology.org for full disclosures.

Received March 28, 2012. Accepted in final form August 21, 2012.

REFERENCES

1. Ikuta F, Zimmerman HM. Distribution of plaques in seventy autopsy cases of multiple sclerosis in the United States. Neurology 1976;26:26–28.
2. Toussaint D, Perier O, Verstappen A, Bervoets S. Clinicopathological study of the visual pathways, eyes, and cerebral hemispheres in 32 cases of disseminated sclerosis. J Clin Neuroophthalmol 1983;3:211–220.
3. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L. Axonal transection in the lesions of multiple sclerosis. N Engl J Med 1998;338:278–285.
4. Naismith RT, Xu J, Tutlam NT, Trinkaus K, Cross AH, Song SK. Radial diffusivity in remote optic neuritis discriminates visual outcomes. Neurology 2010;74:1702–1710.
5. Shindler KS, Ventura E, Dutt M, Rostami A. Inflammatory demyelination induces axonal injury and retinal ganglion cell apoptosis in experimental optic neuritis. Exp Eye Res 2008;87:208–213.
6. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. Science 1991;254:1178–1181.
7. Hrynchak P, Simpson T. Optical coherence tomography: an introduction to the technique and its use. Optom Vis Sci 2000;77:347–356.
8. Frohman EM, Fujimoto JG, Frohman TC, Calabresi PA, Cutter G, Balcer LJ. Optical coherence tomography: a window into the mechanisms of multiple sclerosis. Nat Clin Pract Neurol 2008;4:664–675.
9. Saidha S, Eckstein C, Ratchford JN. Optical coherence tomography as a marker of axonal damage in multiple sclerosis. Mult Scler 2010;2:33–43.
10. Parisi V, Manni G, Spadaro M, et al. Correlation between morphological and functional retinal impairment in multiple sclerosis patients. Invest Ophthalmol Vis Sci 1999; 40:2520–2527.
11. Trip SA, Schlottmann PG, Jones SJ, et al. Retinal nerve fiber layer axonal loss and visual dysfunction in optic neuritis. Ann Neurol 2005;58:383–391.
12. Costello F, Coupland S, Hodge W, et al. Quantifying axonal loss after optic neuritis with optical coherence tomography. Ann Neurol 2006;59:963–969.
13. Fisher JB, Jacobs DA, Markowitz CE, et al. Relation of visual function to retinal nerve fiber layer thickness in multiple sclerosis. Ophthalmology 2006;113:324–332.
14. Petzold A, de Boer JF, Schippling S, et al. Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurol 2010;9:921–932.
15. Saidha S, Syc SB, Ibrahim MA, et al. Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography. Brain 2011;134:518–533.
16. Saidha S, Syc SB, Durbin MK, et al. Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness. Mult Scler 2011;17:1449–1463.
17. Syc SB, Saidha S, Newsome SD, et al. Optical coherence tomography segmentation reveals ganglion cell layer pathology after optic neuritis. Brain 2012;135:521–533.
18. Seigo MA, Sotirchos ES, Newsome S, et al. In vivo assessment of retinal neuronal layers in multiple sclerosis with

manual and automated optical coherence tomography segmentation techniques. J Neurol 2012;259:2119–2130.
19. Talman LS, Bisker ER, Sackel DJ, et al. Longitudinal study of vision and retinal nerve fiber layer thickness in multiple sclerosis. Ann Neurol 2010;67:749–760.
20. Garcia-Martin E, Pueyo V, Almarcegui C, et al. Risk factors for progressive axonal degeneration of the retinal nerve fibre layer in multiple sclerosis patients. Br J Ophthalmol 2011; 95:1577–1582.
21. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald criteria." Ann Neurol 2005;58:840–846.
22. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.
23. Roxburgh RH, Seaman SR, Masterman T, et al. Multiple sclerosis severity score: using disability and disease duration to rate disease severity. Neurology 2005;64:1144–1151.
24. Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999;122:871–882.
25. Rudick RA, Polman CH, Cohen JA, et al. Assessing disability progression with the multiple sclerosis functional composite. Mult Scler 2009;15:984–997.
26. Warner CV, Syc SB, Stankiewicz AM, et al. The impact of utilizing different optical coherence tomography devices for clinical purposes and in multiple sclerosis trials. PLoS One 2011;6:e22947.
27. Balcer LJ, Baier ML, Pelak VS, et al. New low-contrast vision charts: reliability and test characteristics in patients with multiple sclerosis. Mult Scler 2000;6:163–171.
28. Beck RW, Maguire MG, Bressler NM, Glassman AR, Lindblad AS, Ferris FL. Visual acuity as an outcome measure in clinical trials of retinal diseases. Ophthalmology 2007;114:1804–1809.
29. Kashani AH, Zimmer-Galler IE, Shah SM, et al. Retinal thickness analysis by race, gender, and age using Stratus OCT. Am J Ophthalmol 2010;149:496–502.
30. Henderson AP, Trip SA, Schlottmann PG, et al. A preliminary longitudinal study of the retinal nerve fiber layer in progressive multiple sclerosis. J Neurol 2010;257:1083–1091.
31. Serbecic N, Aboul-Enein F, Beutelspacher SC, et al. High resolution spectral domain optical coherence tomography (SD-OCT) in multiple sclerosis: the first follow up study over two years. PLoS One 2011;6:e19843.
32. Sepulcre J, Murie-Fernandez M, Salinas-Alaman A, Garcia-Layana A, Bejarano B, Villoslada P. Diagnostic accuracy of retinal abnormalities in predicting disease activity in MS. Neurology 2007;68:1488–1494.
33. Gordon-Lipkin E, Chodkowski B, Reich DS, et al. Retinal nerve fiber layer is associated with brain atrophy in multiple sclerosis. Neurology 2007;69:1603–1609.
34. Green AJ, McQuaid S, Hauser SL, Allen IV, Lyness R. Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration. Brain 2010; 133:1591–1601.

This Week's *Neurology*® Podcast

Active MS is associated with accelerated retinal ganglion cell/ inner plexiform layer thinning (See p. 47)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the January 1, 2013, issue of Neurology. In the second segment, Dr. Michelle Johansen talks with Dr. Jack Ratchford about his paper on active multiple sclerosis. Dr. Jennifer Fugate then reads e-Pearl of the week about nummular headache. In the next part of the podcast, Dr. Jennifer Bickel focuses her interview with Dr. Gretchen Tietjen about the topic of women and migraine. Disclosures can be found at www.neurology.org.

At www.neurology.org, click on the "Download Latest Issue" link or "Subscribe Now" to subscribe to the RSS Feed.

CME Opportunity: Listen to this week's Neurology® Podcast and earn 0.5 AMA PRA Category 1 CME Credits™ by answering the multiple-choice questions in the online Podcast quiz.