Macular Volume Determined by Optical Coherence Tomography as a Measure of Neuronal Loss in Multiple Sclerosis

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Background: Inner (area adjacent to the fovea) and outer regions of the macula differ with respect to relative thicknesses of the ganglion cell layer (neurons) vs retinal nerve fiber layer (RNFL; axons).

Objective: To determine how inner vs outer macular volumes relate to peripapillary RNFL thickness and visual function in multiple sclerosis (MS) and to examine how these patterns differ among eyes with vs without a history of acute optic neuritis (ON).

Design: Study using cross-sectional optical coherence tomography.

Setting: Three academic tertiary care MS centers.

Participants: Patients with MS, diagnosed by standard criteria, and disease-free control participants.

Main Outcome Measures: Optical coherence tomography was used to measure macular volumes and RNFL thickness. Visual function was assessed using low-contrast letter acuity and high-contrast visual acuity (Early Treatment Diabetic Retinopathy Study charts).

Results: Among eyes of patients with MS (n=1058 eyes of 530 patients), reduced macular volumes were associated with peripapillary RNFL thinning; 10-µm differences in RNFL thickness (9.6% of thickness in control participants without disease) corresponded to 0.20-mm³ reductions in total macular volume (2.9% of volume in control participants without disease, \( P < .001 \)). This relation was similar for eyes of MS patients with and without a history of ON. Although peripapillary RNFL thinning was more strongly associated with decrements in outer compared with inner macular volumes, correlations with inner macular volume were significant \( (r=0.58, P < .001) \) and of slightly greater magnitude for eyes of MS patients with a history of ON vs eyes of MS patients without a history of ON \( (r=0.61 \text{ vs } r=0.50) \). Lower (worse) visual function scores were associated with reduced total, inner, and outer macular volumes. However, accounting for peripapillary RNFL thickness, the relation between vision and inner macular volume remained significant and unchanged in magnitude, suggesting that this region contains retinal structures separate from RNFL axons that are important to vision.

Conclusions: Analogous to studies of gray matter in MS, these data provide evidence that reductions of volume in the macula (approximately 34% neuronal cells by average thickness) accompany RNFL axonal loss. Peripapillary RNFL thinning and inner macular volume loss are less strongly linked in eyes of MS patients without a history of ON than in eyes of MS patients with a history of ON, suggesting alternative mechanisms for neuronal cell loss. Longitudinal studies with segmentation of retinal layers will further explore the relation and timing of ganglion cell degeneration and RNFL thinning in MS.


Multiple sclerosis (MS) is a complex neurodegenerative disorder that targets both white and gray matter elements of the central nervous system, which results in demyelination, gliosis, axonal dysfunction, and ultimately neuronal loss.1-3 The anterior visual pathways, which include the optic nerves, retinas, chiasm, and tracts, are frequent sites for inflammation and demyelination, and axonal degeneration within these structures is likely to be a final common pathway to permanent visual loss.4,5 Noninvasive ocular imaging, such as optical coherence tomography (OCT), has been increasingly recognized in MS as a marker for axonal loss.5-8 Retinal nerve fiber layer (RNFL) thinning measured by OCT in patients with MS occurs even in the absence of acute optic neuritis (ON) and is
associated with worse scores for low-contrast letter acuity and other vision tests. These important structure-function correlations make the anterior visual pathways an attractive model for the examination of therapeutic efficacy in MS clinical trials, particularly for the anticipated next generation of trials that will involve neuroprotective agents.

Scanning of the macula with OCT, which images the retinal ganglion cell layer (neurons), represents a potential method for capturing neuronal degeneration. Recent studies that used ultrahigh-resolution OCT have demonstrated that the inner retinal complex, a structure that comprises the ganglion cell layer and the much thinner inner plexiform and nuclear layers, comprises 34% of the total average macular thickness. Investigations of gray matter in patients with MS have demonstrated that cortical lesions and gray matter atrophy are associated with increasing disability and impairment across disease subtypes. These studies have also provided evidence that gray matter involvement in patients with MS does not occur exclusively as a consequence of inflammatory-demyelinating processes in the white matter.

Of particular interest in the anterior visual pathway, therefore, is whether volumes of the inner macula (ring-shaped area adjacent to the fovea) that contains a greater proportion of ganglion cells [neurons] than the outer region; Figure correlate well with peripapillary RNFL thickness (axons). Such a finding would suggest that retinal ganglion cell loss occurs concomitantly with RNFL thinning. We performed regional analyses to determine how inner and outer macular volumes relate to peripapillary RNFL thickness and visual function in MS patients and examined how these patterns differ among eyes with vs without a history of acute ON.

**METHODS**

**PATIENTS**

Participants were enrolled in an ongoing, prospective study of visual outcome measures in MS at the University of Pennsylvania School of Medicine, The University of Texas Southwestern Medical Center, and The Johns Hopkins University School of Medicine. Participants represented a convenience sample of patients willing to undergo OCT imaging and vision testing for research purposes and were not selected based on clinical features or extent of symptoms. Because macular scans were not performed during the first year of this study, results for RNFL thickness do not overlap with previously published reports of OCT in MS. Multiple sclerosis was diagnosed by standard criteria. Disease-specific therapies and MS disease subtypes were ascertained.

Patients with comorbid ocular conditions not related to MS were excluded by history, medical record review, and examination. A history (months to years prior to enrollment) of acute ON was determined by self-report and physician report and confirmed by record review. Patients with an acute attack of ON in either eye that was ongoing or had occurred within 3 months prior to testing were not included in this study to minimize potential optic disc swelling (and RNFL edema) associated with acute ON. Optic disc swelling was not noted among any participants.
Table 1. Clinical Characteristics of Patients With MS and Control Participants Without Disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients With MS (n=530 Patients; 1059 Eyes)</th>
<th>Control Participants Without Disease (n=111 Control Participants; 219 Eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>43 (11)</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Female</td>
<td>395 (75)</td>
<td>73 (66)</td>
</tr>
<tr>
<td>White&lt;sup&gt;b&lt;/sup&gt;</td>
<td>405 (85)</td>
<td>97 (87)</td>
</tr>
<tr>
<td>Relapsing-remitting MS</td>
<td>435 (82)</td>
<td>NA</td>
</tr>
<tr>
<td>Disease-modifying therapies</td>
<td>345 (65)</td>
<td>NA</td>
</tr>
<tr>
<td>History of ON prior to study, No. (%) of patients</td>
<td>250 (47)</td>
<td>NA</td>
</tr>
<tr>
<td>History of ON prior to study, No. (%) of eyes</td>
<td>328 (31)</td>
<td>NA</td>
</tr>
<tr>
<td>Visual acuity, median (range), Snellen equivalent from ETDRS charts</td>
<td>20/20 (20/12.5–20/250)</td>
<td>20/16 (20/12.5–20/20)</td>
</tr>
</tbody>
</table>

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; MS, multiple sclerosis; ON, optic neuritis.
<sup>a</sup>Age was lower among control participants without disease in this convenience sample (P<.001, t test); therefore, all statistical models that compare eyes of patients with MS vs those of control participants without disease accounted simultaneously for age.
<sup>b</sup>Ethnicity was ascertained from participant classification based on US Census categories; ethnicity was assessed in this study given ethnic differences in prevalence of MS and optical coherence tomography measures.

Control participants without disease who had no history of ocular or neurologic disease were recruited from among the medical staff and the family of patients. Control eyes were excluded if best-corrected high-contrast Snellen visual acuity equivalents were worse than 20/20 (minimum score of 60 on the Early Treatment Diabetic Retinopathy Study [ETDRS] chart).

Institutional review board approval was obtained for all study protocols, and each participant provided written informed consent. The study was conducted in accordance with Health Insurance Portability and Accountability Act guidelines.

OPTICAL COHERENCE TOMOGRAPHY

We performed OCT for both eyes using the OCT-3 (Carl Zeiss Meditec Inc, Dublin, California). Fast RNFL thickness and fast macular thickness protocols were used. Trained technicians performed OCT after visual function testing. Scans were performed without flash photography to optimize patient comfort. If the pupils were large enough to permit adequate imaging (>5 mm), scanning was completed without the use of mydriatics. Dilation has little impact on OCT values and reproducibility, and previous studies of MS patients have been performed without uniform use of mydriatics. Pupils were dilated with tropicamide, 1%, when necessary. Internal fixation was used, and a patch was placed over the nontested eye. Good-quality scans were defined in accordance with specifications in the OCT-3 user manual; criteria included a signal strength of 7 or higher (maximum of 10), centering of the scan, and uniform brightness. These factors are important because RNFL thickness measurements may vary by signal strength. Values for average RNFL thickness and macular volume were recorded. Total macular volume represented the sum of the volumes of the neural retina in the central 6 mm of the macula. As outlined by recent investigations, outer and inner macular volumes were calculated as volumes for ring-shaped areas between the 1-mm-diameter and 3-mm-diameter circles for the inner macula (inner ring; Figure, B, red arrowheads) and between the 3-mm-diameter and 6-mm-diameter circles for the outer macula (outer ring; Figure, B, black arrows). These regions were examined separately because the inner macular volume, located adjacent to the fovea (Figure, B), has a greater proportion of ganglion cells vs RNFL axons. Borders for these areas were defined based on those provided by the OCT-3 printout as defined in the literature (Figure, A).

VISUAL FUNCTION TESTING

Low-contrast letter acuity testing was performed for each eye using retroilluminated low-contrast Sloan letter charts (1.25% contrast level at 2 m; Precision Vision, LaSalle, Illinois). High-contrast visual acuity was assessed using retroilluminated ETDRS charts at 3.2 m. Low-contrast Sloan letter and ETDRS charts have a similar standardized format with 5 letters per line. Numbers of letters identified (maximum of 70 per chart) were recorded for each eye. This scoring method provides a continuous scale that is equivalent to logMAR yet uses units that are more familiar to neurologists and have been used in recent MS trials. Testing was performed by trained technicians and physicians (M.J.L., E.B., A.C., C.W.) experienced in research examinations. Standardized protocols, such as written scripts and instructions, were followed. Snellen visual acuity equivalents were determined based on scores for the ETDRS charts.

Participants underwent detailed refractions to determine correlations with OCT that reflected best-corrected vision.

STATISTICAL ANALYSIS

Analyses were performed using Stata statistical software, version 10.0 (Stata Corp, College Station, Texas). Generalized estimating equation (GEE) models that account for age and adjust for within-patient, intereye correlations were used to examine the relation of reductions in macular volume to RNFL thinning in MS. These models were also used to assess the association between vision scores and macular volumes and to compare macular volume among MS vs control groups and between eyes of patients with MS with vs without a history of ON. In terms of univariate analyses, Pearson linear correlation coefficients were calculated. Type I error for significance was P<.05.

RESULTS

CLINICAL CHARACTERISTICS

Demographic and clinical data for patients (n=1058 eyes of 530 patients) and control participants without disease (n=219 eyes of 111 control participants) are...
summarized in Table 1. Characteristics of our patients were similar to the US population with MS for sex, age, and ethnicity. Analyses accounted for age differences between patients and control participants. The RNFL thickness and macular volumes were reduced in eyes of MS patients compared with those of control participants without disease (Table 2, P < .001 for all comparisons, GEE models, accounting for age and adjusting for within-patient, intereye correlations). Eyes of patients with MS with a history of acute ON also had significantly lower RNFL thickness and macular volumes than did eyes of patients with MS without a history of ON (P < .001 for all comparisons).

Table 2. Mean (SD) Visual Function, RNFL Thickness, and Macular Volume

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Eyes of Patients With MS (n=1058 Eyes of 530 Patients)</th>
<th>Eyes of Patients With MS With ON a (n=328 Eyes of 164 Patients)</th>
<th>Eyes of Patients With MS Without ON a (n=730 Eyes of 366 Patients)</th>
<th>Eyes of Control Participants Without Disease (n=219 Eyes of 111 Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-contrast visual acuity, no. of letters on ETDRS charts (maximum score, 70)</td>
<td>57 (12)</td>
<td>53 (17)</td>
<td>59 (9)</td>
<td>66 (3)</td>
</tr>
<tr>
<td>Low-contrast (1.25%) acuity, no. of letters on ETDRS charts (maximum score, 70)</td>
<td>13 (11)</td>
<td>9 (10)</td>
<td>15 (11)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>RNFL thickness, average for 360° around optic disc, µm</td>
<td>92.5 (16.7)b</td>
<td>85.7 (19.0)</td>
<td>95.6 (14.5)</td>
<td>104.5 (10.7)</td>
</tr>
<tr>
<td>Total macular volume, mm3</td>
<td>6.54 (0.51)b</td>
<td>6.36 (0.53)</td>
<td>6.63 (0.48)</td>
<td>6.84 (0.36)</td>
</tr>
<tr>
<td>Outer macular volume, mm3</td>
<td>4.79 (0.39)b</td>
<td>4.67 (0.40)</td>
<td>4.85 (0.37)</td>
<td>4.98 (0.35)</td>
</tr>
<tr>
<td>Inner macular volume, mm3</td>
<td>1.60 (0.13)b</td>
<td>1.56 (0.14)</td>
<td>1.63 (0.13)</td>
<td>1.68 (0.12)</td>
</tr>
</tbody>
</table>

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; MS, multiple sclerosis; OCT, optical coherence tomography; ON, optic neuritis; RNFL, retinal nerve fiber layer.

a ON indicates eyes with a history of acute ON prior to study enrollment (patients with acute ON within 3 months prior to study enrollment were excluded).
b Measurements of average overall RNFL thickness and macular volumes were significantly reduced in eyes of patients with MS compared with those from control participants without disease (P < .001 for all comparisons, generalized estimating equation models, accounting for age and adjusting for within-patient, intereye correlations). Eyes of patients with MS with a history of ON also had significantly lower RNFL thickness and macular volumes than did eyes of patients with MS without a history of ON (P < .001 for all comparisons).
c Total macular volume represented the sum of the volume of the neural retina in the central 6 mm of the macula; outer and inner macular volumes were calculated as the sum of volumes between the 1-mm-diameter and 3-mm-diameter circles for inner macula (inner ring, Figure, B) and between the 3-mm-diameter and 6-mm-diameter circles for outer macula (outer ring).

Table 3. Linear Correlations of Inner vs Outer Macular Volumes to Peripapillary RNFL Thickness a

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total Macular Volume, r</th>
<th>Outer Macular Volume, r</th>
<th>Inner Macular Volume, r</th>
</tr>
</thead>
<tbody>
<tr>
<td>All eyes of patients with MS (n=1058)</td>
<td>0.67</td>
<td>0.67</td>
<td>0.58</td>
</tr>
<tr>
<td>Eyes of patients with MS with history of ON (n=328) b</td>
<td>0.68</td>
<td>0.68</td>
<td>0.61</td>
</tr>
<tr>
<td>Eyes of patients with MS without history of ON (n=730)</td>
<td>0.62</td>
<td>0.63</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Abbreviations: MS, multiple sclerosis; ON, optic neuritis; RNFL, retinal nerve fiber layer.
a P < .001 for all comparisons.
b ON indicates eyes with a history of acute ON prior to study enrollment (patients with acute ON within 3 months prior to study enrollment were excluded).

The inner macular volume, represented by the 3-mm-diameter ring-shaped area adjacent to the fovea (Figure), contains a greater proportion of retinal ganglion cells per unit volume compared with the outer macular volume (6-mm-diameter ring-shaped area farthest from the fovea). As such, the outer macular volume is likely to have stronger correlations with peripapillary measurements of RNFL thickness given the greater proportion of RNFL (and therefore redundancy of structures) in the

**RELATION OF TOTAL MACULAR VOLUME TO PERIPAPILLARY RNFL THICKNESS**

Among eyes of patients with MS, peripapillary RNFL thinning was associated with reductions in macular volume. Linear correlations of RNFL thickness vs total macular volume were moderate and significant and slightly higher for eyes of patients with MS with ON (r=0.68, P < .001) compared with eyes of patients with MS without ON (r=0.62, P < .001, Table 3). On average, 10-µm differences in RNFL thickness (approximately 9.6% of the mean thickness of the control group) were associated with 0.20-mm³ reductions in total macular volume (2.9% of the mean volume of the control group, P < .001, GEE models). Eyes of both patients with MS with and without ON showed similar degrees of total macular volume reduction per 10 µm of RNFL thinning (0.19 vs 0.20 mm³, P < .001 for both groups). Total macular volumes also differed between MS disease subtypes, with lower values seen in secondary progressive MS (n=101 eyes; mean [SD], 6.25 [0.52] mm³) than in primary progressive MS (n=89 eyes; mean [SD], 6.57 [0.50] mm³).

**INNER VS OUTER MACULAR VOLUMES**

The inner macular volume, represented by the 3-mm-diameter ring-shaped area adjacent to the fovea (Figure), contains a greater proportion of retinal ganglion cells per unit volume compared with the outer macular volume (6-mm-diameter ring-shaped area farthest from the fovea). As such, the outer macular volume is likely to have stronger correlations with peripapillary measurements of RNFL thickness given the greater proportion of RNFL (and therefore redundancy of structures) in the
Changes in low- and high-contrast acuity were associated with substantial reductions in total macular volume (0.16 mm³; 95% confidence interval, 0.12–0.19; for low-contrast acuity; 0.11 mm³; 95% confidence interval, 0.08–0.14; for high-contrast acuity; P < .001, GEE models). Linear correlations for total macular volume vs vision were r = 0.31 for low-contrast and r = 0.32 for high-contrast acuity (P < .001). Reductions of both inner and outer macular volumes were significantly associated with worse visual function. The inner macular volume remained a significant predictor of visual function when we account for peripapillary RNFL in eyes of patients with MS and ON and eyes of patients with MS without ON (P < .001 for low-contrast acuity and P = .03 for high-contrast acuity, GEE models). This finding might suggest that neuronal loss is also associated with impaired visual function.

**COMMENT**

Analogous to studies21–25 of gray matter in MS, these data provide evidence that reductions of volume in the macula, which comprises a large component of neuronal cells, accompany RNFL axonal loss. Peripapillary RNFL thinning and inner macular volume loss are less tightly linked in eyes of patients with MS without a history of ON than in eyes of patients with MS with a history of ON, which suggests alternative mechanisms for neuronal loss. Longitudinal studies with segmentation of retinal layers and ultrahigh-resolution OCT will further explore the relation and timing of ganglion cell (neuronal) degeneration and RNFL thinning. When we account for peripapillary RNFL thickness, the relation between visual function and volumes for the inner macula remained significant and unchanged in magnitude, which suggests that this region contains retinal structures separate from RNFL axons that are important to vision.

Findings of our cross-sectional investigation of the macula and RNFL are relevant in the context of recent magnetic resonance imaging (MRI) studies21–25 of gray matter in MS. In our study, reduced macular volumes were associated with worse visual function, even when we account for peripapillary RNFL thickness; similarly, cortical lesion volumes or numbers and gray matter atrophy by MRI have correlated with increasing levels of disability. Our observation that inner macular volume reductions were less strongly associated with peripapillary RNFL thinning in eyes of patients with MS without ON (vs eyes of patients with MS with ON) may be analogous to MRI findings indicating that MS gray matter damage does not occur exclusively as a consequence of white matter disease. The MRI studies have demonstrated that gray matter damage is of particular importance in progressive MS, particularly primary progressive MS.21 In our study, macular volumes correlated well with low-contrast acuity in eyes of patients with primary progressive MS (n = 89, r = 0.27, P = .009), and macular volumes were reduced compared with controls in primary progressive MS and secondary progressive MS.

Because axonal loss in the anterior and postgeniculate visual pathways likely contributes to visual dysfunction in MS, OCT may be a useful complement to MRI in the assessment of how visual loss reflects disease activity. Studies9,11,29 of ON, glaucoma, and optic nerve band atrophy (pattern of RNFL thinning associated with lesions at the optic chiasm) have begun to explore total macular volume as a measure that may reflect neuronal loss in the anterior visual pathways but have not thus far emphasized regional analyses.

Macular volumes, as determined by OCT-3, include all neural retinal tissue (full thickness of the retina) and thus capture the retinal ganglion cell layer as well as the RNFL (Figure, B). Given the need to quantify the relation of retinal ganglion cell loss to RNFL thinning and visual loss in other ocular disorders, such as glaucoma, recent studies10 have used ultrahigh-resolution OCT to measure retinal layers. On the basis of calculations of macular thickness, the inner retinal complex, which includes the ganglion cell layer and the thinner inner plexiform and nuclear layers (currently difficult to separate from the ganglion cell layer by OCT), comprises 34% of the total mean (SD) macular thickness in healthy eyes (90.7 [4.2] µm for inner retinal complex vs 265.3 [8.3] µm for total macular thickness).19,20 The relative thicknesses of the ganglion cell layer vs macular RNFL vary, however, based on distance from the fovea. As illustrated in Figure, B, the outer macula contains a greater proportion of RNFL axons vs ganglion cells compared with the inner macular region. These differences allow for interesting observations with regard to the relation between RNFL thinning and losses of non-RNFL retinal structures.

Our study examined the relation between visual dysfunction and macular volumes by means of low-contrast letter acuity, an emerging visual outcome that has been incorporated successfully into MS clinical trials.28 Reductions in total macular volumes were associated with worse scores for low- and high-contrast acuity. Previous OCT studies10,11 have shown that RNFL thinning correlates well with low-contrast acuity loss, which suggests that axonal degeneration is a likely cause of visual dysfunction in MS. Pathophysiologic changes in MS involve immune-mediated axon transection with subse-
quent wallerian degeneration. As suggested by animal models, neuronal loss may occur secondary to myelin and axon damage, possibly because of loss of Na\textsuperscript{+}, K\textsuperscript{+}-adenosinetriphosphatase.\textsuperscript{30} Although axonal and neuronal losses that manifest as RNFL and macular thinning likely occur in part, on the basis of the dying back of optic nerve axons, our findings and those of others support a role for neuronal loss that occurs independently from white matter pathology.

Although the results of our investigation highlight regional abnormalities of macular volume in MS, studies of eyes with acute ON have also demonstrated losses of total macular volume. In a cross-sectional study\textsuperscript{9} of ON eyes, all of which experienced incomplete visual recovery after ON, decreases in RNFL thickness in affected eyes were accompanied by losses in macular volume when compared with fellow and disease-free control eyes. This study also compared the relation between RNFL axonal loss and loss of macular volume. It demonstrated that 1 µm of RNFL thinning in the temporal quadrant was associated with a 0.019-mm\textsuperscript{2} reduction in macular volume (P < .001).\textsuperscript{9} This result is in agreement with the findings from our cohort, namely, that 10 µm of RNFL thinning was associated with a 0.2-mm\textsuperscript{2} reduction of total macular volume (P < .001).

Ongoing longitudinal studies will incorporate ultra-high-resolution OCT techniques and measurements of specific retinal layers. These investigations will allow us to more precisely characterize the relation between ganglion cell layer and RNFL thinning over time in MS and will thereby provide insight into temporal patterns of axonal and neuronal degeneration.

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