ABSTRACT

Optic involvement in multiple sclerosis (MS) strongly suggests that the retina and optic nerve may serve as an important model system to examine disease progression. Optic neuritis is often the first acute episode leading to the diagnosis of MS. New low-contrast letter acuity tests have detected underlying functional vision deficits and neuroprotection in MS clinical trials. Optical coherence tomography (OCT) can measure optic structures with micrometer resolution and has allowed the correlation of retinal nerve fiber layer thickness and macular volume with clinical measures of disease and magnetic resonance imaging (MRI). The combination of low-contrast letter acuity testing, OCT, and MRI will assist clinicians in understanding the relationships between structural changes in the central nervous system and changes in function during disease progression. Additionally, visual system measures will serve as an accurate assessment of neuroprotection in clinical trials.

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MULTIPLE SCLEROSIS (MS) IS A DISABLING PROGRESSIVE NEURODEGENERATIVE DISEASE THAT OFTEN BEGINS WITH RELAPSING-REMITTING EPISODIC PATTERNS OF NEUROLOGIC DYSFUNCTION. MARKERS OF NEURODEGENERATION AND RECOVERY ARE NEEDED TO BE ABLE TO ASSESS DISEASE STATUS AND THE EFFICACY OF THERAPEUTIC INTERVENTION. HERE WE WILL CONSIDER THE RETINA AND OPTIC NERVE AS A UNIQUE MODEL SYSTEM IN WHICH MS CAN BE STUDIED.

THE NEED FOR DEVELOPING VISUAL OUTCOME MEASURES FOR MS

Ocular coherence tomography (OCT) is a technique that has grown in prominence, first within the retinal field, and now within the glaucoma field. Ocular imaging techniques will complement magnetic resonance imaging (MRI), because nowhere else in the central nervous system (CNS) can we look at unmyelinated axons as are present on the neural fiber layer. It is the one unique place in the CNS where we can correlate function (vision) directly with a specific structure.

There exist several observations that argue for considering the visual system as a model of MS-mediated CNS damage. Firstly, histologic studies from autopsy of patients who are optically asymptomatic clearly show evidence of axonal degeneration. Secondly, visual involvement in addition to optic neuritis (ON) is common in MS. However, we lack a good way to measure vision. The Snellen card is part of the Expanded Disability Status Scale (EDSS) but a sensitive visual test is absent from the MS functional composite. Nevertheless, although patients with MS recover their visual acuity after treatment for ON, they continue to comment on blurred or washed-out vision. These patients have persistent visual deficits, especially when measured by low-contrast vision tests.
VISUAL FUNCTION TESTING USING LOW-CONTRAST LETTER ACUITY

Although visual dysfunction is readily apparent during ON in patients with MS, measurement of visual dysfunction after recovery is more difficult. Low-contrast letter acuity has been invaluable in identifying and quantifying subtle visual deficiencies. Unlike the standard Snellen eye chart, which has black, high-contrast letters on a white background, the contrast sensitivity chart has light gray letters on a white background. Additionally, each line has 5 letters, allowing for a more equivalent jump in difficulty from line to line. Inter-rater reliability were found to be excellent with an interclass correlation coefficient of 0.86 to 0.95. Interestingly, at the lowest contrast levels, significant differences in performance were observed in different patients with MS compared with controls, whereas the Snellen eye chart showed no differences among groups. Low-contrast letter acuity testing has recently been used as a tertiary outcome in the Safety and Efficacy of Natalizumab in Combination with Interferon β-1a in Patients with Relapsing-Remitting MS (SENTINEL) and Natalizumab Safety and Efficacy in Relapsing-Remitting MS (AFFIRM) phase III trials. Though the Snellen eye chart was unable to discern any differences between the treatment groups for either trial, the low-contrast Sloan letter chart demonstrated a clear difference. The risk of loss of visual function was decreased by 35% in the AFFIRM trial (hazard ratio [HR] = 0.65; 95% confidence interval [CI], 0.47–0.90; \( P = 0.008 \)) and by 28% in the SENTINEL trial (HR = 0.72; 95% CI, 0.54–0.98; \( P = 0.038 \)). Contrast sensitivity tests also have been found to correlate with EDSS and MRI measures of lesion burden.

OCT

Optical coherence tomography allows noninvasive imaging of the retina and optic nerve. Whereas MRI can track damage to postgeniculate regions of the visual pathway, OCT can track damage in pregeniculate regions. Acute ON is, essentially, an MS lesion. However, as it involves the visual system, it is immediately detected, allowing precise knowledge of its appearance. Using OCT, this lesion can then be examined in extraordinary detail.

Optical coherence tomography is an inferometric measurement technique employing the echo time delay of back-scattered light. By using wide-bandwidth light sources, this technique can achieve submicrometer resolution. It is highly quantitative and reproducible. The 2 parameters of interest are the retinal nerve fiber layer (RNFL) thickness and the total macular volume that corresponds primarily to ganglion cell bodies. Conceptually, OCT resembles ultrasound imaging, using light instead of sound. Currently, the primary application of OCT is in the field of glaucoma. Here, RNFL thickness has been shown to correlate with visual field loss suggesting that OCT may have some ability to detect early glaucoma-induced visual changes.

Applications for OCT to MS are just beginning to be made. An example of RNFL data derived from this procedure is shown in the Figure. A near-infrared light travels around the optic disc several times to create a map of the thickness of RNFL. This thickness is compared to a range of thicknesses observed for a normal population. It can be expressed as a linear graph as shown on the left or as a pie chart as shown on the right. Whereas the eyes from a healthy individual clearly fall within the normal thickness observed, the eyes from a patient with MS with bilateral optic nerve disease show significantly decreased thickness in many places surrounding the optic disc. At present, the most useful parameter from these measures is the average thickness of the RNFL. Macular volumes are obtained by performing line scans through the optic disc rather than circles around the disc. Again, patients with MS with optic nerve disease have been found to have decreased macular volumes compared with healthy patients. Using this technique, one can show that eyes from patients with ON have reduced RNFL thickness as compared to healthy controls. Importantly, when one examines patients with MS with no history of ON, the RNFL is still reduced in thickness, consistent with the concept of MS as a neurodegenerative disease.

Several studies characterizing axonal and macular degeneration in ON have recently been reported. In one study, 25 patients who had experienced a single episode of ON were compared with 15 healthy controls. The goals of the researchers were to measure neurodegeneration and to determine if it correlated with clinical measures of residual visual dysfunction. Eleven of the 25 patients with ON were diagnosed with MS. As shown in the Table, there were significant reductions in RNFL thickness and macular volume in
the affected eyes as compared to control eyes or to unaffected patient eyes. Furthermore, this group found significant correlations with RNFL thickness changes and changes in visual acuity, visual field, color vision, and visual-evoked potential amplitude.

Another study examined 54 patients who had experienced single episodes of ON.10 These patients underwent repeated measures of RNFL thickness by OCT in combination with standardized ophthalmic testing. Axonal loss occurred within 3 to 6 months of ON. Affected eyes showed an average RNFL thickness of 78 µm compared with 100 µm for unaffected eyes. Interestingly, the authors identified a threshold RNFL thickness of 75 µm. Above 75 µm, the authors saw little change in the visual field. However, below 75 µm, there was a clear correlation between loss of RNFL thickness and visual dysfunction. These data show an excellent correlation between OCT measures of RNFL thickness, macular volume, and disease progression as measured by visual dysfunction. Given the close association of ON episodes with a diagnosis of MS, these measures provide important information concerning disease progression. RNFL thickness measures are emerging as a viable biomarker for assessing disease in this patient population.

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<tr>
<th align="left">Table. OCT Results in Control, Unaffected Patient, and Affected Patient Eyes</th>
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<tr>
<td align="left"><strong>RNFL Thickness</strong></td>
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*P* values represent comparisons of control eyes and patient eyes.
OCT = optical coherence tomography; RNFL = retinal nerve fiber layer.

**Correlations Between MRI and OCT Measures of Disease**

Magnetic resonance imaging has been the premier imaging tool for MS. It is sensitive to changes over time; however, the pathophysiologic correlates are not always clear. It is especially difficult to distinguish between demyelinating events and early stages of axon-
al degeneration. Because MRI has been used to study ON, these measures could serve as a means to establish whether MRI measures of ON correlate with OCT measures. To this end, one group compared MRI measurements of optic nerve cross-sectional area and OCT measures of RNFL thickness in patients who had undergone a single episode of ON compared with healthy controls. The correlation was quite good—30% decrease in optic nerve cross-sectional area compared with 33% decrease in RNFL thickness. These data confirmed that axonal loss in the RNFL reflect MRI measures of the optic nerve.

**CONCLUSIONS**

There is good evidence to support the contention that the optic nerve is an important model for MS. Visual function can be assessed and optic structures visualized with great accuracy. The combination of new sensitive visual tests with OCT and MRI is likely to provide important new data in neuroprotective clinical trials.

**DISCUSSION**

**Q:** Are the low-contrast eye charts more sensitive than the old Ishihara plates, or are they just better quantitated?

**Dr Balcer:** The Ishihara plates are a test of color vision and the low-contrast acuity charts capture ability to perceive low-contrast (gray on white) targets. Both are of interest and are important aspects of vision in MS. More formal tests of color vision are sensitive for visual dysfunction in MS but are more involved to administer.

**Q:** Steroids often are used to treat ON. Have you looked at any steroid effects on the unaffected eye or the affected eye in terms of OCT?

**Dr Balcer:** We have not examined the potential role of corticosteroids on OCT outcomes in ON or MS, but future trials may incorporate ocular imaging techniques to assess losses of axons.

**Q:** You showed some nice data comparing OCT values from center to center. Do we now have any absolute values such as 100% is normal? As a second question, besides glaucoma, what other conditions can also impair these values as measured by OCT?

**Dr Balcer:** It will be helpful to continue to collect data from several centers on patients with MS as well as disease-free volunteers. These values can then be compared and perhaps combined to form a reference dataset. Patients with any form of optic neuropathy or anterior visual pathway lesions (those anterior to the lateral geniculate nucleus—optic nerve, optic chiasm, or tracts) may have axonal loss, and thus, reduced values for RNFL thickness by OCT.

**REFERENCES**