Assessing Visual Changes in Multiple Sclerosis: How Vision Captures Disease

Salim Chahin, MD, MSCE
University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

Abstract
Visual and oculomotor pathway dysfunction is a frequent manifestation of multiple sclerosis (MS). Adequate assessment of visual symptoms leads to better lesion localization and faster diagnosis and treatment. During the joint 28th Annual Meeting of the Consortium of MS Centers (CMSC) and the 19th Annual Meeting of the Americas Committee for Treatment and Research in MS (ACTRIMS), specialists discussed how best to capture the common visual symptoms of MS and presented the latest advances in visual outcome measures. Diplopia and optic neuritis are common manifestations of the disease. The visual system provides a unique opportunity to reliably study structure-function correlations, and it may reflect global measures of neurologic impairment and fatigue.

Visual dysfunction is a common occurrence among patients with multiple sclerosis (MS). Clinically, MS affects the visual system in multiple ways. Patients may experience visual symptoms related to optic neuritis, or, when the oculomotor system is affected, they may have diplopia and nystagmus. During the joint 28th Annual Meeting of the Consortium of MS Centers (CMSC) and the 19th Annual Meeting of the Americas Committee for Treatment and Research in MS (ACTRIMS), a course on visual dysfunction in MS patients provided lessons vision can teach us about global disease metrics.

Visual Symptoms and Findings in MS: Clues and Management

Based on a presentation by Teresa C. Frohman, PA-C, Clinical Research Manager, Department of Neurology, Division of Multiple Sclerosis, The University of Texas Southwestern Medical Center, Dallas, Texas.

When evaluating patients with visual complaints including optic neuritis, diplopia, and nystagmus, clinicians must consider the latest findings and diagnostic tools. Visual problems in MS patients may involve a visual pathway (optic nerve) or the oculomotor system.

Differential Diagnosis
The use of a diagnostic algorithm may facilitate the workup of visual complaints and identify the source of the ophthalmic problem (Figure 1). When evaluating visual dysfunction, the physician first must rule out etiologies that are not related to MS. For example, when a patient presents with a complaint of blurry vision, symptoms may be corrected with refraction. In such cases, if the patient has no other complaints, the etiology is most likely due to a refractive error (Figure 1A). Of note, pinhole refraction is a rapid and efficient way to diagnose refractive errors at the bedside. However, best-corrected visual acuity with pinhole refraction is usually not more than 20/30 and rarely 20/20.

Because of the length and complexity of the visual and oculomotor pathways, visual symptoms are common in MS and can involve different parts of the central nervous system (CNS).

Diplopia
Diplopia (double vision) is the experience of seeing two images of the same object. It is caused by weakening or incoordination of the eye muscles and often results from oculomotor dysfunction.

After ruling out refractive errors, physicians then must identify the source of the symptoms. If the patient is seeing double, or if the complaint is not typical of visual symptoms commonly seen in the context of optic neuritis, the physician should evaluate for diplopia. Often, the patient’s complaint of double vision is obvious; at other times, however, diplopia can be more subtle and nuanced.

Diplopia can be monocular or binocular. Monocular diplopia, which doesn’t disappear when the unaffected eye is closed, results from eye-specific issues involving the cornea, lens, a refractive problem, or dry eyes. In contrast, binocular diplopia only is apparent when both eyes are open; it results from CNS dysfunction and is the type of diplopia seen in MS (Figure 1C). Even in binocular diplopia, however, other etiologies need to be carefully evaluated and ruled out, especially when the presentation is atypical of MS.

Dr. Chahin is a Multiple Sclerosis Fellow in the Department of Neurology at the University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania.
The nature of diplopia and accompanying symptoms can provide clues about the source and etiology of double vision. Diplopia can be horizontal or vertical, depending upon the etiology: Diplopia from intranuclear ophthalmoplegia or sixth-nerve palsy is horizontal, whereas diplopia due to fourth-nerve palsy is usually vertical.

The most common causes of diplopia in MS include, in descending order, intranuclear ophthalmoplegia, sixth-nerve palsy, third-nerve palsy, fourth-nerve palsy, and skew deviation.

Intranuclear ophthalmoplegia, the most common cause of double vision in MS patients, is present in up to 40% of patients. Intranuclear ophthalmoplegia is caused by lesions on the ipsilateral medial longitudinal fasciculus. In this disorder of the conjugate lateral gaze, the affected eye demonstrates slowing or limitation of adduction. When an attempt is made to gaze contralaterally (relative to the affected eye), the affected eye adducts minimally or doesn’t adduct at all (Figure 2).

Intranuclear ophthalmoplegia can be unilateral or bilateral. Interestingly, patients with clinically isolated syndrome (CIS) who have bilateral intranuclear ophthalmoplegia are at increased risk of developing MS.

Sixth-nerve palsy. The second most common cause of diplopia in MS is sixth-nerve palsy, which manifests as impaired abduction of the affected eye.

Other causes of diplopia. Although relatively uncommon, third- or fourth-nerve palsies and skew deviation can cause diplopia in MS patients. Again, it is imperative that physicians rule out other, more common underlying etiologies when patients complain of double vision.

Nystagmus

Nystagmus is a frequent ocular motor deficit in MS that may occur with diplopia or be an isolated symptom. Nystagmus is an involuntary, often jerking, movement of the eyes that can be horizontal (as seen in intranuclear ophthalmoplegia), vertical, pendular, or gaze-evoked. Nystagmus most often can be seen clinically on examination, but special techniques may be used to evaluate for nystagmus at the bedside if it is not clinically evident.

Optic Neuritis and Visual Pathway Involvement

Optic neuritis, one of the most common clinical presentations of MS, results from inflammation of the optic nerve. If the patient’s complaint of blurry vision is not corrected with refraction and is not due to double vision, or if the patient complains of looking through “frosted glass” or having dark spots in the visual field, a workup for optic neuritis is warranted (Figure 1B).

Optic neuritis often presents as subacute, painful loss of vision. Symptoms can include blurred vision (“looking
through frosted glass”), reduced color perception, and loss of visual fields (most commonly, central scotomas). Severe, complete monocular vision loss can occur. In almost all cases, symptoms are accompanied by pain that is worsened with eye movements.

Assessment of optic neuritis. Several clinical tools are available to assess optic neuritis. In addition, paraclinical testing, including magnetic resonance imaging (MRI) and visual evoked potentials (VEPs), can further help with the diagnosis. Novel methods, such as low-contrast visual acuity (LCVA) testing and optical coherence tomography (OCT), are also sensitive to visual dysfunction in MS.

In the clinic, the cranial nerve II commonly is assessed by testing visual acuity, visual fields, and the pupillary light reflex and by performing a fundoscopic examination.

Visual acuity is commonly assessed using handheld or wall-mounted Snellen charts. These tools represent traditional, high-contrast visual acuity (HCVA) and may not capture all elements of visual dysfunction. LCVA, on the other hand, is a sensitive and useful measure of visual dysfunction in MS.

Visual field testing is commonly accomplished by confrontation field testing at the bedside. The superior, temporal, inferior, and nasal fields are assessed using confrontational testing. This method is not always accurate and is insensitive to small scotomas. If suspicion of a visual field defect is high, automated neuro-opthalmic tools can be used to more accurately assess the visual fields.

The pattern of visual field loss depends on the location of the lesion within the visual pathway. In optic neuritis, the abnormality is commonly a central scotoma or, when severe, complete visual loss in the affected eye. Lesions of the optic chiasm will result in bitemporal hemianopia, whereas lesions in the posterior visual pathway result in homonymous hemianopia or quadrantopia depending upon the exact location of the lesion.

Fundoscopy. A fundoscopic examination may not show any abnormalities in the context of acute optic neuritis but can demonstrate optic disk pallor in eyes with a history of optic neuritis. This pallor is a reflection of axonal loss in the retinal and optic disk due to optic neuritis. Pallor can sometimes be seen in eyes with no prior clinical history of optic neuritis and usually reflects subclinical involvement of those eyes in the context of MS.

Pupillary light reflex. When assessing the pupillary light reflex, a relative afferent pupillary defect is a sensitive measure of optic nerve dysfunction. Damage to the optic nerve will result in less light perception in the affected eye, as well as less pupillary constriction bilaterally when the light is shone onto the affected eye, as compared with the unaffected eye.

VEPs can confirm the presence of optic neuritis if the clinical presentation is atypical; it also can detect evidence of prior optic neuritis. A unilateral delay in the P100 waveform strongly suggests anterior visual pathway demyelination in the context of MS.

MRI. In acute optic neuritis, an MRI scan of the brain or dedicated MRI of the orbits can show T2 signal changes, swelling, and contrast enhancement in the optic nerve. MRI also can show optic nerve atrophy in chronic, or longstanding, optic nerve involvement.

NEW MEASURES OF VISUAL PATHWAY STRUCTURE AND FUNCTION

Based on a presentation by Laura Balcer, MD, MSCE, Adjunct Professor of Biostatistics and Epidemiology, Chief, Multiple Sclerosis Division, Department of Neurology, and Senior Scholar, Clinical Epidemiology Unit, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

In addition to the traditional clinical and paraclinical tools used to evaluate the visual pathway (with our without a history of optic neuritis), new methods (eg, LCVA, OCT) have provided eloquent and unique measures of structure and function correlations.

As mentioned previously, LCVA is a sensitive measure that captures elements of visual dysfunction not captured by traditional HCVA testing. Low-contrast vision and OCT have become recognized, important outcome measures in MS.

LCVA

Optic neuritis and resultant decreased visual acuity and visual field abnormalities typically progress over a few weeks and then gradually improve, with or without treatment. Despite the fact that 95% of eyes recover to 20/40 visual acuity or better on Snellen charts, patients often continue to complain of visual symptoms and report reduced quality of life (QOL) years after the initial optic neuritis episode. In addition, patients without a history of acute optic neuritis who have 20/20 vision on conventional HCVA testing often have visual symptoms and show axonal loss on pathology and structural retinal imaging.

Over the past decade, LCVA has emerged as a measure that is more sensitive than HCVA, able to distinguish MS patients from healthy controls, more reflective of real-world tasks, and sensitive to treatment effect. Using charts that are similar to Early Treatment Diabetic Retinopathy Study (ETDRS) charts, retro-illuminated low-contrast Sloan charts were developed. These charts consist of five letters per line and use gray letters on a white background. In its early testing in MS patients, LCVA was better at distinguishing affected individuals from...
Assessing Visual Changes in Multiple Sclerosis: How Vision Captures Disease

Salim Chahin, MD, MSCE

How Vision Captures Disease in MS

Based on a presentation by Salim Chahin, MD, MSCE.

The development of tools such as LCVA and OCT has made the visual pathway an attractive model for the study of structure-function correlations in MS.1 Visual dysfunction is a common occurrence in MS patients.1–3,7,8 Up to 50% of these individuals develop optic neuritis during the course of their disease, and up to 80% have subclinical involvement of the visual system.2,7,8 The eye now is being evaluated as a potential window to the brain, and visual dysfunction and subsequent evaluation of the visual system may serve as a surrogate for overall disease dysfunction and severity. To that extent, visual outcomes measures are now routinely included in clinical trials and are gaining traction in clinical practice.

VFT

Traditionally, VFT was performed using HCV charts included in the Expanded Disability Status Scale (EDSS).1,10,16,19 However, HCV testing may not capture all the elements of visual dysfunction that LCVA can capture in MS.10 LCVA is more sensitive to visual dysfunction and more reflective of real-world tasks, such as driving or facial recognition.9,10

Structure/function correlations in the visual system. LCVA is strongly associated with structural measures such as the RNFL, which, as mentioned previously, represents axons and white-matter lesion burden on MRI.20 LCVA also is associated with other visual functional measures as captured by VEPs.21

Low-contrast vision captures treatment effect. LCVA, which now is routinely included in clinical trials as a secondary outcomes measure, has captured treatment effect in several trials. For example, in the pivotal AFFIRM and SENTINEL trials, patients in the natalizumab treatment arm had less sustained visual loss than did those in the placebo arm.14 The treatment arm also showed greater sustained visual improvement.22 The proportion of patients with visual improvement in terms of LCVA at a majority of study visits was significantly greater in the natalizumab group, whereas no difference in HCV was observed at these visits.22

Similar results were seen in the alemtuzumab trial, where patients on alemtuzumab were significantly more likely to experience visual improvement than were those taking interferon β-1a.23

Low-contrast vision and neurologic impairment. LCVA is correlated with the EDSS and the MS functional composite (MSFC).21 However, the relationship between LCVA and the EDSS is complex. LCVA may capture elements of dysfunction not captured by the EDSS, and worsening of LCVA can occur independently from EDSS progression. As an example of this complex relationship, in the natalizumab trial, a substantial number of patients had worsening LCVA, even without EDSS progression, and no significant differences in LCVA were seen between patients with and without EDSS progression. Furthermore, a composite measure of LCVA and EDSS showed sensitivity to treatment effect.24,25

OCT

As mentioned previously, OCT is a reliable tool to obtain retinal axonal and neuronal layer thickness, as represented by the RNFL, GCL, and TMV.11

Natural history. The thickness of the RNFL and GCL is reduced over time in the eyes of MS patients.16–18 This thinning is more pronounced in the context of a history of optic neuritis, but it also occurs in eyes without a history of MS.1,16–18 Table 1 shows average RNFL, GCL, and TMV thickness in the eyes of MS patients.1,16,17 There was loss in RNFL and GCL thickness and macular volume, even in patients without optic neuritis as compared with controls.

OCT and disease course. Interestingly, retinal pathology, as represented by RNFL thickness and TMV, can occur early in the MS disease course and can be seen as early as the initial relapse or CIS.26 Oberwahrenbrock et al26 showed that CIS patients with optic neuritis exhibited significant RNFL and TMV loss when compared with matched healthy controls. Furthermore, when compared with controls, there was significant RNFL loss in CIS eyes with subclinical visual pathway involvement (as captured by VEP) and significant TMV loss in CIS eyes with no visual involvement.26

Balk et al27 showed that patients with

Healthy controls than were other visual functional tests.1,10

HCV and LCVA are often referred to collectively as visual function testing (VFT). These tests can be monocular (performed for each eye separately) or binocular (performed for both eyes at the same time).1 Monocular VFT often is used when evaluating eye-specific outcomes, whereas binocular VFT may be more appropriate for person-specific outcomes. Binocular VFT also has several advantages—It reflects real-world experience; is simpler and easier to undergo for patients; and, when one eye is more severely affected, can provide additional, useful information because of binocular summation (improved vision under binocular viewing when compared with either eye individually because of compensation from the better eye) and binocular inhibition (worse binocular vision when compared with the better eye alone).15

OCT

OCT is a reliable, noninvasive imaging method that uses near-infrared light to generate high-resolution cross-sectional images of the retina.3,11 Images of the peripapillary and macular regions are segmented, and the thickness of individual retinal layers is obtained. The retinal nerve fiber layer (RNFL) contains axons and represents white matter; the ganglion cell layer (GCL) contains neurons and represents gray matter.11 Importantly, total macular volume (TMV) can serve as a surrogate to gray matter volume, because the GCL comprises 34% of the TMV.11 Retinal neuronal and axonal thickness, as captured by OCT, is reduced over time in MS patients.1,9,10,16–18

Table 1: RNFL, GCL, and TMV Thickness in MS Patients

<table>
<thead>
<tr>
<th>Layer</th>
<th>Mean Thickness (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNFL</td>
<td>90 ± 10</td>
</tr>
<tr>
<td>GCL</td>
<td>125 ± 15</td>
</tr>
<tr>
<td>TMV</td>
<td>1,500 ± 100</td>
</tr>
</tbody>
</table>

Notes: RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; TMV, total macular volume; MS, multiple sclerosis.

Structure/function correlations in the visual system. LCVA is strongly associated with structural measures such as the RNFL, which, as mentioned previously, represents axons and white-matter lesion burden on MRI.20 LCVA also is associated with other visual functional measures as captured by VEPs.21

Low-contrast vision captures treatment effect. LCVA, which now is routinely included in clinical trials as a secondary outcomes measure, has captured treatment effect in several trials. For example, in the pivotal AFFIRM and SENTINEL trials, patients in the natalizumab treatment arm had less sustained visual loss than did those in the placebo arm.14 The treatment arm also showed greater sustained visual improvement.22 The proportion of patients with visual improvement in terms of LCVA at a majority of study visits was significantly greater in the natalizumab group, whereas no difference in HCV was observed at these visits.22

Similar results were seen in the alemtuzumab trial, where patients on alemtuzumab were significantly more likely to experience visual improvement than were those taking interferon β-1a.23 Similarly, patients on alemtuzumab were significantly less likely to experience sustained visual worsening than were those using interferon β-1a.23

Low-contrast vision and neurologic impairment. LCVA is correlated with the EDSS and the MS functional composite (MSFC).21 However, the relationship between LCVA and the EDSS is complex. LCVA may capture elements of dysfunction not captured by the EDSS, and worsening of LCVA can occur independently from EDSS progression. As an example of this complex relationship, in the natalizumab trial, a substantial number of patients had worsening LCVA, even without EDSS progression, and no significant differences in LCVA were seen between patients with and without EDSS progression. Furthermore, a composite measure of LCVA and EDSS showed sensitivity to treatment effect.24,25

OCT

As mentioned previously, OCT is a reliable tool to obtain retinal axonal and neuronal layer thickness, as represented by the RNFL, GCL, and TMV.11

Natural history. The thickness of the RNFL and GCL is reduced over time in the eyes of MS patients.16–18 This thinning is more pronounced in the context of a history of optic neuritis, but it also occurs in eyes without a history of MS.1,16–18 Table 1 shows average RNFL, GCL, and TMV thickness in the eyes of MS patients.1,16,17 There was loss in RNFL and GCL thickness and macular volume, even in patients without optic neuritis as compared with controls.

OCT and disease course. Interestingly, retinal pathology, as represented by RNFL thickness and TMV, can occur early in the MS disease course and can be seen as early as the initial relapse or CIS.26 Oberwahrenbrock et al26 showed that CIS patients with optic neuritis exhibited significant RNFL and TMV loss when compared with matched healthy controls. Furthermore, when compared with controls, there was significant RNFL loss in CIS eyes with subclinical visual pathway involvement (as captured by VEP) and significant TMV loss in CIS eyes with no visual involvement.26

Balk et al27 showed that patients with...
Fatigue and the Visual System

Fatigue is a common and often disabling syndrome experienced by patients with MS.\(^{36,37}\) Fatigue in MS is complex with poorly understood mechanisms. It can be primary (related to disease mechanisms such as brain dysfunction or increased inflammation) or secondary to medications, sleep problems, or depression; in addition, it can manifest itself as either central fatigue or peripheral muscle fatigue. Physical fatigue is related to tiredness when performing tasks, cognitive fatigue is related to impaired attention and concentration, and lassitude is a subjective feeling of fatigue and exhaustion.\(^{36–38}\) Fatigue has inconsistent associations with MRI findings.\(^{36,39,40}\) Although central fatigue in MS is associated with axonal loss on MRI, it failed to demonstrate consistent relationships with lesion load or location.\(^{36,39,40}\) Furthermore, the presence of fatigue in the first 2 years was predictive of brain atrophy up to 6 years later.\(^{41}\)

Fatigue can precede MS symptoms and diagnosis by months\(^{42}\) and can worsen during a relapse.\(^{43}\) Given the reliability of VFT as a measure that can capture impairment beyond the visual system and the associations seen between retinal neuronal and axonal loss and global structural and functional outcomes in MS, Chahin and others\(^{44–46}\) investigated whether the visual system can be used to better understand fatigue in MS.

**VFT and Fatigue**

The research showed that worsened LCVA and HCVA are associated with increased levels of fatigue in MS patients. Stronger associations with LCVA were seen for patients with more physical fatigue than cognitive fatigue scores \(r = –0.26, P = 0.003\) for physical and \(r = –0.19, P = 0.02\) for cognitive fatigue and low contrast vision, respectively. Additionally, patients classified as having fatigue

**TABLE 1**

Mean Reference Values for RNFL and GCL Thickness and TMV

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control patients</th>
<th>MS patients</th>
<th>MS patients without optic neuritis</th>
<th>MS patients with optic neuritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripapillary RNFL thickness using SD-OCT, μm</td>
<td>92.9 ± 10.0</td>
<td>84.3 ± 12.8</td>
<td>87.6 ± 11.1</td>
<td>78.4 ± 13.6</td>
</tr>
<tr>
<td>GCL thickness using SD-OCT, μm</td>
<td>88.9 ± 6.9</td>
<td>84.1 ± 8.4</td>
<td>87.0 ± 6.6</td>
<td>79.9 ± 9.2</td>
</tr>
<tr>
<td>TMV using TD-OCT, mm(^3)</td>
<td>6.84 ± 0.36</td>
<td>6.54 ± 0.51</td>
<td>6.63 ± 0.48</td>
<td>6.36 ± 0.53</td>
</tr>
</tbody>
</table>

RNFL = retinal nerve fiber layer; GCL = ganglion cell layer; TMV = total macular volume; SD-OCT = spectral-domain optical coherence tomography; TD-OCT = time-domain optical coherence tomography

Sources: Sakai et al\(^{16}\); Talman et al\(^{45}\); Walter et al\(^{47}\)

Fatigue has inconsistent associations with MRI findings.\(^{36,39,40}\) Although central
Fatigue and a 6-µm loss in GCL thickness. Optic neuritis caused a 1-µm loss in GCL thickness (Figure 3). The combined effect of fatigue and optic neuritis resulted in a 7.4-µm loss in GCL thickness.Investigators used a generalized estimating equations model and accounted for age, duration, subtype, and within-patient inter-eye correlations. Adapted, with permission, from Chahin et al.46

FIGURE 4 The effect of optic neuritis on ganglion cell layer (GCL) thickness in fatigued and nonfatigued multiple sclerosis patients. A history of optic neuritis resulted in a 1.3-µm loss in GCL thickness in nonfatigued patients and a 5.7-µm loss in GCL thickness in fatigued patients. The combined effect of fatigue and optic neuritis resulted in a 7.4-µm loss in GCL thickness. Investigators used a generalized estimating equations model and accounted for age, duration, subtype, and within-patient inter-eye correlations. Adapted, with permission, from Chahin et al.46

FIGURE 5 The effect of optic neuritis on retinal nerve fiber layer (RNFL) thickness in fatigued and nonfatigued multiple sclerosis patients. A history of optic neuritis resulted in a 4.8-µm loss in RNFL thickness in nonfatigued patients and a 9.8-µm loss in RNFL thickness in fatigued patients. The combined effect of fatigue and optic neuritis resulted in a 11.2-µm loss in RNFL thickness. Investigators used a generalized estimating equations model and accounted for age, duration, subtype, and within-patient inter-eye correlations. Adapted, with permission, from Chahin et al.46

had worse overall LCVA scores than nonfatigued patients and healthy controls (Figure 3).44,45

OCT and Fatigue

Loss of gray matter in the retina was associated with increased levels of fatigue, and a complex relationship was seen among fatigue, optic neuritis, and retinal neuronal and axonal loss.46

Interestingly, the effect of optic neuritis on GCL thinning differed between patients with and without fatigue (Figure 4).46 Optic neuritis caused a 1-µm loss in GCL thickness (P = 0.426) in patients without fatigue and a 6-µm loss in GCL thickness (P < 0.001) in patients with fatigue. The difference in the effect of optic neuritis on GCL thickness between fatigue and nonfatigued patients was 4.5 µm (P = 0.026).46

Similarly, optic neuritis was responsible for a 5-µm loss in RNFL thickness in nonfatigued patients (P = 0.006) and a 10-µm loss in fatigue patients—a difference of 5 µm (Figure 5).46 When compared with the baseline group, which had neither optic neuritis nor fatigue, patients with both optic neuritis and fatigue had a 7.4-µm loss in GCL thickness (P < 0.001) and a 11.2-µm loss in RNFL thickness (P < 0.001).46

Summary

This research shows that reduced vision in patients with MS is highly associated with fatigue and that the relationship is stronger for physical, as compared with cognitive, fatigue. VFT scores confirmed that physical fatigue may occur separately from cognitive fatigue and should be evaluated and treated separately. Additionally, there was significantly more neuronal loss due to optic neuritis in the context of fatigue, and the combination of fatigue and optic neuritis resulted in the most neuronal and axonal loss in the retina.

Longitudinal studies that incorporate MRI and OCT are needed to further explore the relationship between fatigue and the visual system. The presence of fatigue in MS may reflect disease susceptibility and overall gray matter injury, and visual dysfunction may contribute to and partially explain fatigue in MS patients.

REFERENCES

11. Galetta KM, Calabresi PA, Frohman EM, Balcer LJ. Optical coherence tomography: imaging