

# Eye disorders in patients with multiple sclerosis: natural history and management

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**Abstract:** Multiple sclerosis (MS) is a demyelinating disease of the central nervous system and leading cause of disability in young adults. Vision impairment is a common component of disability for this population of patients. Injury to the optic nerve, brainstem, and cerebellum leads to characteristic syndromes affecting both the afferent and efferent visual pathways. The objective of this review is to summarize the spectrum of eye disorders in patients with MS, their natural history, and current strategies for diagnosis and management. We emphasize the most common disorders including optic neuritis and internuclear ophthalmoparesis and include new techniques, such as optical coherence tomography, which promise to better our understanding of MS and its effects on the visual system.

**Keywords:** optic neuritis, vision, internuclear ophthalmoparesis, nystagmus, diplopia

## Introduction

Approximately 300,000 individuals in the United States are affected by multiple sclerosis (MS).<sup>1-4</sup> The national economic burden of this disease has been estimated to be US \$6.8 billion yearly and the total lifetime cost per case to be US \$2.2 million.<sup>5</sup> Visual dysfunction is frequent and often irreversible. Afferent pregeniculate visual pathways (retina, optic nerves, chiasm, and tracts) are targets of inflammation, demyelination, and axonal degeneration (Panel 1). Nearly half of the MS patients develop optic neuritis (ON).<sup>6</sup> It is the heralding event in 15%–20% of patients.<sup>6</sup> However, patients without a clinical history of ON also exhibit poor visual function, including worse scores on low-contrast acuity and color-sensitivity testing, when compared with age-matched controls.<sup>7,8</sup> With the advent of newer technology, structural information about optic nerve disease is attainable, and MS patients with and without a history of ON demonstrate loss of axons in the retinal nerve fiber layer (RNFL).<sup>9-12</sup>

Injury is also common in the brainstem and cerebellum, generating efferent pathway deficits. Common ocular motor findings include internuclear ophthalmoparesis (INO), saccadic dysmetria, and nystagmus. Also found are skew deviation, abnormalities of smooth pursuit, and various nuclear and fascicular lesions. After careful bedside neuro-ophthalmologic examination, these disorders can be readily identified. Corresponding lesions are often visible on magnetic resonance imaging (MRI).

The principal objective of this review is to provide a framework for understanding both the afferent and efferent visual disorders in MS and outline the current strategies for management of these syndromes.

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**Panel I** Afferent neuro-ophthalmologic disorders in MS**Acute demyelinating optic neuritis**

Painful acute to subacute (hours to days) onset of visual loss typically characterized by central field deficit, dyschromatopsia, and recovery beginning within 2–4 weeks. Two-thirds will have normal fundoscopic exam.

**Subclinical visual loss in MS**

Functional loss as seen in low-contrast letter acuity testing; structural retinal nerve fiber loss as measured by techniques, such as OCT

**Chiasmal and postchiasmal visual field defects**

Homonymous field deficits are rare and are typically associated with large demyelinating lesions.

**Ocular inflammatory disorders**

Anterior uveitis (granulomatous, nongranulomatous)

Pars planitis (intermediate uveitis)

Retinal periphlebitis

**The afferent visual system in MS****Acute demyelinating ON****Clinical presentation**

ON refers to the inflammation of the optic nerve. Although the differential diagnosis is broad and includes infectious, ischemic, and autoimmune disorders, the most common form, acute demyelinating ON, is best known for its association with MS. It is more prevalent in young patients and in women.<sup>13</sup> The Optic Neuritis Treatment Trial (ONTT), the largest and most comprehensive study of this disease, followed an initial cohort of 457 patients for 10 years and provided important data on the natural history and visual outcomes of ON cases and the effects of high-dose steroids.<sup>14–19</sup>

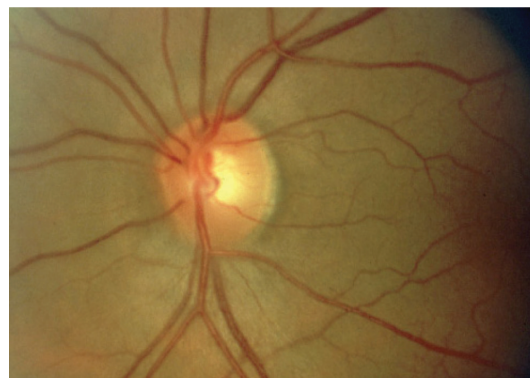
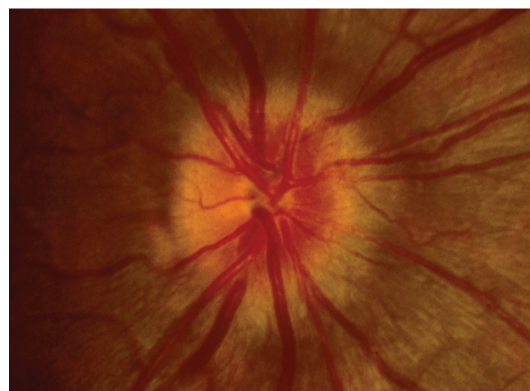
The diagnosis of ON is primarily clinical based on history and examination.<sup>20</sup> Patients report acute to subacute vision loss, color desaturation (in particular red color), and in the ONTT, 92% of patients reported pain with eye movements.<sup>13</sup> Vision loss is typically monocular and progresses over hours to days; worsening beyond 1–2 weeks is atypical and suggestive of other causes of optic neuropathy.<sup>15</sup> Similarly, it is expected that some recovery will occur within 1 month of symptom onset. Failure to see improvement in this time frame, the presence of no light perception at onset, and lack of eye pain suggest other diagnoses and are associated with lower risk for developing MS.<sup>21,22</sup> A single episode of ON with no history of other ophthalmologic or neurological events can be described as a clinically isolated syndrome (CIS).

**Afferent neuro-ophthalmologic examination**

The afferent eye examination begins with acuity testing. Prescription lenses or pinhole correction are used to correct refractive error. Distance, near card, or both are measured for

normal contrast levels. As discussed below, further evaluation with low-contrast charts may reveal more subtle visual dysfunction. Visual fields are tested to confrontation for each eye separately and together. Static and dynamic finger recognition may be helpful. Red–green color desaturation is a common feature in ON and may be detected by the patient’s description of “washed out” appearance of red objects; however, it is usually formally tested with Ishihara pseudoisochromatic plates or Farnsworth–Munsell 100 hue test, as done in the ONTT.

Pupils are evaluated for shape, position, anisocoria, and reactivity. In addition, detection of a relative afferent pupillary defect (RAPD) is suggestive of an optic neuropathy. Absence of an RAPD in the setting of visual loss may reflect retinal disease or bilateral optic nerve disease. Fundoscopic examination reveals normal appearing discs in most of the cases; these patients are said to have retrobulbar ON. In the ONTT, optic disc swelling was present in 35.3% of the patients (Figure 1).<sup>13</sup> Marked swelling, retinal hemorrhages,

**A****B**

**Figure 1** The optic disc in acute demyelinating optic neuritis. Most patients have retrobulbar optic neuritis, and the optic disc appears normal (**A**). In one-third of the patients, disc swelling is present and is typically diffuse and mild (**B**).<sup>13</sup>

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and exudates are atypical, which suggest an alternative diagnosis and predict a lower risk of developing MS.<sup>21,22</sup>

### Differential diagnosis

Acute demyelinating ON must be differentiated from other causes of optic neuropathy. As described earlier, lack of eye pain, severe initial vision loss, marked swelling, and retinal hemorrhages may indicate an alternative diagnosis of anterior ischemic optic neuropathy (AION, Table 1).<sup>23</sup> AION usually occurs in older patients. Compared with ON, the vision loss is often sudden in onset, altitudinal, and more likely to persist, with longer time to recovery.<sup>24</sup> When vision loss progresses beyond 10–14 days, Leber hereditary optic neuropathy, a mitochondrial disorder leading to the degeneration of the optic nerve, may need to be considered, along with compressive optic neuropathy.

Bilateral ON or ON coupled with longitudinally extensive transverse myelitis (LETM) is suggestive of neuromyelitis optica (NMO), a disorder associated with aquaporin-4 (a water channel present in glial cells) antibodies.<sup>25–27</sup> Testing for NMO-IgG should be considered in those patients with the features described earlier, recurrent ON, or brain MRIs atypical for MS.<sup>27</sup> In 1 study, in which patients were identified by having been tested for NMO-IgG, seropositivity was shown to be 76% sensitive and 94% specific for NMO.<sup>28</sup> A prospective study of 114 patients with ON in various clinical contexts demonstrated that 56% of those with clinical NMO had positive serum antibodies.<sup>29</sup> In noncausations or while using different detection methods, the sensitivity of testing may vary, but specificity appears

to be robust across multiple testing contexts.<sup>30,31</sup> The revised criteria for diagnosing NMO are the presence of 2 of the following 3 findings – LETM (defined as  $\geq 3$  vertebral segments), onset brain MRI nondiagnostic for MS, or NMO-IgG seropositivity.<sup>28</sup> Antibody positivity may help determine the likelihood of recurrent disease and guide the decision to treat with immunosuppression following an episode of ON or recurrent ON.<sup>30,32–34</sup> Although large treatment trial data are not available, therapies studied and shown to have beneficial effects include plasma exchange, rituximab, and azothiaprime.<sup>35–39</sup>

Other causes of inflammatory or toxic metabolic optic neuropathy may mimic acute demyelinating disease.<sup>20</sup> Depending on the clinical assessment and presence of atypical features, serologic or cerebrospinal fluid (CSF) testing for sarcoidosis, systemic lupus and other vasculitides, thyroid disease, syphilis, nutritional deficiencies, Lyme disease, *Bartonella hensalae* infection (cat scratch neuroretinitis), and paraneoplastic disorders may be warranted. Consideration should also be given to the newly recognized entity, chronic relapsing inflammatory optic neuropathy (CRION), a granulomatous optic neuropathy.<sup>40</sup>

### Vision testing

Although the diagnosis of ON is made clinically, additional testing of vision function can be used to support the diagnosis and further characterize the patient's deficits. In the ONTT, visual outcome measures included formal visual field testing (Humphrey 30-2<sup>®</sup> program) and contrast sensitivity (Pelli-Robson<sup>®</sup> chart). Visual field deficits were found in 97.5% of patients.<sup>13</sup> Central scotomas were common but other patterns, including diffuse and focal defects, were seen. Contrast-sensitivity (minimum contrast level at which patients can see letter of single large size) abnormalities were seen in 98.2% of patients.<sup>41</sup>

Low-contrast letter acuity charts, which have a format similar to Early Treatment Diabetic Retinopathy Study (ETDRS) charts with light gray letters of progressively smaller size with varying contrast on white background, have also been used to detect visual dysfunction in patients with ON and MS.<sup>7–9,42</sup> Abnormalities can be detected even in those patients with 20/20 vision measured by standard Snellen<sup>®</sup> charts.

Visual evoked potentials (VEPs) can be helpful in providing data to support the diagnosis of acute demyelinating disease, ON, or MS. Prolonged latencies are consistent with demyelinating disease and are present in over two-thirds of patients with ON.<sup>43–45</sup> Multifocal VEPs can be more sensitive

**Table 1** Clinical features and primary differential diagnosis of acute demyelinating optic neuritis

	Acute demyelinating optic neuritis	Anterior ischemic optic neuropathy
Age, y	20–50	>50
Pain	92%, exacerbated by eye movements <sup>a</sup>	Uncommon
Onset	Progression over hours to days	Sudden onset, often recognized upon awakening
Disc swelling	Present in only one-third of patients, remainder are retrobulbar <sup>a</sup>	Common, sectoral, often with hemorrhages
Field defect	Typically central, but variable	Typically altitudinal
Recovery	Begins within 2–4 weeks, overall good prognosis	Over months, in approximately 40% <sup>b</sup>

**Notes:** <sup>a</sup>From the optic neuritis treatment trial (ONTT);<sup>13</sup> <sup>b</sup>Ischemic optic neuropathy decompression trial.<sup>24</sup>

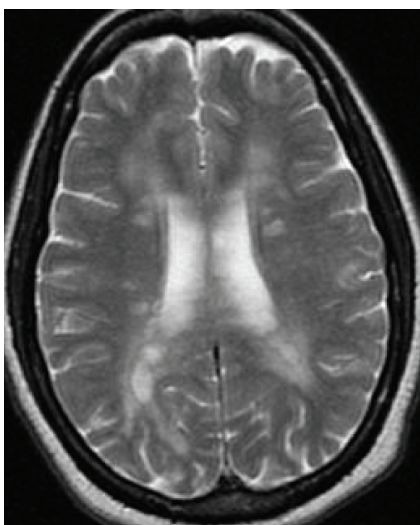
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and specific; they can be useful in distinguishing optic nerve and retinal disease or for detecting subclinical dysfunction, but are not widely available for clinical use.<sup>43,46,47</sup>

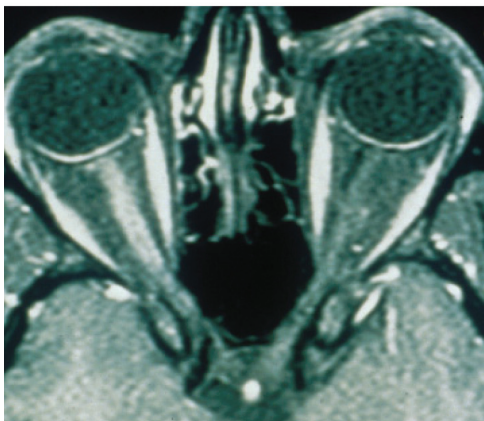
### Magnetic resonance imaging

MRI of the optic nerves is abnormal in approximately 90% of clinical cases (Figure 2B) and can be helpful in diagnosis under certain clinical circumstances, as in differentiating acute demyelinating ON and AION.<sup>48</sup> Gadolinium enhancement is frequent and has been shown to be associated with clinical findings such as decreased acuity, RAPD, and abnormal VEPs.<sup>49</sup>

**A**



**B**



**Figure 2** Magnetic resonance imaging (MRI) in multiple sclerosis (MS) and optic neuritis (ON). Multiple periventricular T<sub>2</sub>-hyperintense lesions are shown in a T<sub>2</sub>-weighted axial image of the brain in a patient with MS (**A**). T<sub>1</sub>-weighted gadolinium-enhanced axial image of the orbits demonstrates diffuse enhancement of the right optic nerve in a patient with acute demyelinating ON (**B**).

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It is recommended in every patient to pursue brain MRI (Figure 2A), as the presence of periventricular white matter lesions is associated with higher risk in first event cases of developing a second demyelinating event consistent with MS and may warrant early treatment as discussed below. In the ONTT follow-up at 10 years, 56% of ON patients with 1 or more T<sub>2</sub> lesions on MRI had developed MS compared with 22% of those with normal scans.<sup>21</sup> Brain lesions are common and are seen in 50%–70% of patients.<sup>50,51</sup> In 1 study, spinal cord T<sub>2</sub> lesions were seen in 27% of patients.<sup>50</sup>

Artifacts can limit MRI studies in ON and MS. Fat- and CSF-suppressed imaging, diffusion tensor and magnetization transfer imaging, and spectral presaturation inversion recovery–fluid-attenuated inversion recovery (SPIR–FLAIR) imaging promise more sensitivity and detailed structural information of not only ON but also of long-term atrophy and changes in the optic nerve.<sup>49,52,53</sup>

### Optical coherence tomography

New advances in optical coherence tomography (OCT) have also allowed for direct structural assessment of axonal loss associated with ON.<sup>10,54</sup> OCT, an optical analog of ultrasound B-mode imaging, provides cross-sectional or 3-dimensional images of the internal retinal structure.<sup>11,55,56</sup> Measurements of the thickness of RNFL, ganglion cell axons, can be readily obtained. Studies have demonstrated RNFL thinning in eyes with a history of ON; in 1 study, reductions in RNFL thickness occurred in 74% of patients, typically within 3–6 months of the acute episode.<sup>57,58</sup> Decreases in RNFL thickness have been correlated with measures of visual dysfunction, such as low-contrast acuity and with brain atrophy on MRI scans.<sup>9,59–61</sup> Although currently used primarily in the research setting, longitudinal OCT measurements have the potential to elucidate the natural history of axonal loss in ON and MS patients, as well as to provide a biomarker for the neuroprotective effects of current and future therapies. Studies of other methods for measuring the axonal layer, including scanning laser polarimetry, may also generate structural biomarkers for studying progression in MS.<sup>10,12</sup>

### Natural history

In cases of typical ON, visual recovery begins within 2–3 weeks. The natural history of the disease is likely best described by the course of patients in the placebo arm of the ONTT. With median baseline acuity of affected eyes measured to be 20/60, vision improved to 20/25 by day 15 and to 20/20 at 1 month of follow-up.<sup>62</sup> In the 10-year follow-up

of 319 patients from the ONTT, visual acuity (treated and untreated) in the affected eye was equal to or better than 20/20 in 74%, 20/25 to 20/40 in 18%, 20/50 to 20/200 in 5%, and 20/200 in 3%.<sup>19</sup> However, even with recovery of visual acuity, self-reported visual functioning as measured by the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) can remain affected. Evidence of optic atrophy can be seen weeks following the acute event.<sup>19</sup> Contrast sensitivity and visual fields were abnormal in 33% and 27% of affected eyes, respectively (compared with 98.2% and 97.5% at baseline as mentioned earlier), in the 10-year follow-up of the ONTT.<sup>19</sup>

Of interest in the natural history of ON is the rate of recurrent ON and the development of MS. Recurrence of ON in the 10-year follow-up of the ONTT was 31% for the placebo group (48% for those with MS and 24% of those without MS).<sup>19</sup> Risk for developing MS in the treatment and placebo arms followed for 10–13 years was 38%.<sup>22</sup> As discussed earlier, the risk was higher for those with brain MRI lesions and lower (close to zero) for those patients with atypical clinical features, such as severe optic disc swelling, peripapillary hemorrhages, and absence of eye pain.<sup>21,22</sup>

## Treatment

### Short-term therapy with corticosteroids

High-dose intravenous (IV) methylprednisolone hastens recovery of visual acuity and other visual function tests over a 2-year follow-up, but does not affect the long-term visual outcomes of patients with ON or their 10-year risk of developing MS. In the ONTT, patients were randomized within 8 days of onset of symptoms to 1 of 3 treatment groups: (1) IV methylprednisolone 250 mg every 6 hours for 3 days, followed by oral prednisone 1 mg/kg/d for 11 days with a 4-day taper, (2) oral prednisone 1 mg/kg/d for 14 days followed by 4-day taper, or (3) oral placebo.<sup>15</sup> Treatment with IV steroids was associated with a more rapid recovery of visual field deficits and contrast sensitivity, particularly within the first 15 days, and differences in recovery for these parameters remained significant at 6-month follow-up.<sup>15</sup> For visual acuity, there was no difference between treatment groups at 6 months. At 1 year of follow-up, there were no significant differences for any measure of visual function.<sup>17</sup>

The rate of development of MS, then defined as a second clinical demyelinating event, after 2 years of follow-up was 7.5% in the IV methylprednisolone group, 14.7% in the oral prednisone group, and 16.7% in the placebo arm. These data suggested an early protective effect in the development of

clinically definite MS (CDMS).<sup>63</sup> However, this effect did not persist in further follow-up evaluations.

Similar studies have also shown potential early but no significant long-term benefits for corticosteroid therapy in ON. A randomized study in Japan compared IV methylprednisolone with oral methylcobalamine and demonstrated quicker recovery of visual acuity, visual fields, contrast sensitivity, and color vision but no long-term effect on visual outcomes.<sup>64</sup> A meta-analysis of 12 randomized controlled trials in ON and MS also showed that corticosteroid use appeared to hasten recovery within 1 month of symptom onset, but significant benefits were not observed after 1 year of follow-up.<sup>65</sup>

Another outcome of the ONTT was an increased rate of recurrent ON in the oral prednisone group compared with the IV methylprednisolone and the placebo groups. At 5 years of follow-up, the oral prednisone group had a rate of recurrence of 41% compared with 25% for the IV methylprednisolone and placebo groups.<sup>66</sup> This increased risk did not persist at 10 years of follow-up.<sup>19</sup> This result has discouraged the use of oral prednisone for the acute treatment of ON. Higher doses of oral steroids (500 mg methylprednisolone daily for 5 days) in a small prospective trial did not show increased risk of recurrent ON within 1 year.<sup>67</sup>

### Long-term therapy with immunomodulatory agents

In patients with a first event of ON, early treatment with disease-modifying therapy (Table 2), interferon, or glatiramer acetate may delay the onset of a second clinical demyelinating event and the development of new T<sub>2</sub> lesions or gadolinium enhancement. Three randomized trials of patients with first demyelinating events, including ON, have shown benefit for early treatment with interferon  $\beta$ -1a and interferon  $\beta$ -1b. An additional trial recently showed similar results for glatiramer acetate.

The Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) was a double-blinded, randomized clinical trial that included 383 patients with acute ON or other first demyelinating event.<sup>68</sup> The patients were considered high risk for MS based on MRI criteria of 2 or more white matter lesions. All patients received 1 g of IV methylprednisolone daily followed by an oral prednisone taper. They were then randomly assigned within 27 days to receive weekly injections of 30  $\mu$ g intramuscular interferon  $\beta$ -1a (Avonex<sup>®</sup>) or placebo injections. The trial was stopped early after a preplanned efficacy analysis. The trial's 2 primary end points, development of CDMS and changes on MRI, demonstrated benefit for interferon

**Table 2** Treatment choices for optic neuritis or other first demyelinating event in patients at risk for multiple sclerosis

Trial evidence	Medication (standard dosage)	Contraindications/potential side effects	Potential benefits
<b>Short-term therapy</b>			
Optic neuritis treatment trial (ONTT, n = 457)	Intravenous methylprednisolone (250 mg every 6 h for 3 d) + oral taper	Contraindications: systemic infection, immune deficiency, severe hypertension, or diabetes mellitus; Side effects: insomnia, mood disturbance, gastric irritation, hyperglycemia, hypertension	<ol style="list-style-type: none"> <li>1. Faster recovery of visual function; long-term visual outcome not affected</li> <li>2. Reduced rate of MS development within the first 2 y</li> <li>3. Oral prednisone at dose of 1 mg/kg may increase the risk of recurrent optic neuritis and should be avoided.</li> </ol>
<b>Long-term therapy</b>			
Controlled high-risk subjects avonex MS prevention study (CHAMPS, n = 383)	Interferon $\beta$ -1a (Avonex, 30 $\mu$ g intramuscularly weekly)	Contraindications: pregnancy category C, hypersensitivity to interferon $\beta$ or human albumin; Side effects: flu-like symptoms (fever, myalgias), depression, anemia, hepatic dysfunction	<ol style="list-style-type: none"> <li>1. Reduction (44%, <math>P = 0.02</math>) in the 3-y risk of developing CDMS</li> <li>2. Fewer new and enhancing lesions on MRI</li> </ol>
Early treatment of MS study (ETOMS, n = 308)	Interferon $\beta$ -1a (Rebif, 22 $\mu$ g subcutaneously weekly) <sup>a</sup>	Contraindications: pregnancy category C, hypersensitivity to interferon $\beta$ or human albumin; Side effects: flu-like symptoms (fever, myalgias), depression, anemia, hepatic dysfunction	<ol style="list-style-type: none"> <li>1. Lower risk of developing CDMS over 2 y (34% vs 45% placebo, <math>P = 0.047</math>)</li> <li>2. Decreased annual relapse rate (0.33 vs 0.43, <math>P = 0.045</math>)</li> <li>3. Fewer lesions on MRI</li> </ol>
Betaferon/Betaseron in newly emerging MS for initial treatment (BENEFIT, n = 468)	Interferon $\beta$ -1b (Betaseron, 250 $\mu$ g subcutaneously every other day)	Contraindications: pregnancy category C, hypersensitivity to interferon $\beta$ or human albumin; Side effects: flu-like symptoms (fever, myalgias), depression, anemia, hepatic dysfunction	<ol style="list-style-type: none"> <li>1. Reduced 2-y risk of developing CDMS by the Poser (28% vs 45% placebo, <math>P &lt; 0.0001</math>) and McDonald (69% vs 85% placebo) criteria</li> <li>2. Fewer lesions on MRI</li> </ol>
Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis (PreCISE, n = 481)	Glatiramer acetate (Copaxone, 20 mg subcutaneously daily)	Contraindications: pregnancy category B; Side effects: injection site reaction, rash, vasodilation, dyspnea, chest pain	<ol style="list-style-type: none"> <li>1. Decreased risk of developing CDMS compared with placebo by 45% (<math>P &lt; 0.0005</math>)</li> <li>2. Fewer lesions on MRI</li> </ol>

**Notes:** <sup>a</sup>ETOMS used weekly 22  $\mu$ g Rebif, while standard therapy for MS is 22 or 44  $\mu$ g 3 times a week.

Adapted with permission from Burkholder et al.<sup>157</sup>

**Abbreviations:** MS, multiple sclerosis; CDMS, clinically definite multiple sclerosis; MRI, magnetic resonance imaging.

therapy. Patients receiving intramuscular interferon  $\beta$ -1a had a 44% reduction in the 3-year risk of CDMS ( $P = 0.02$ ) and fewer new and enhancing lesions on MRI.<sup>68</sup> In subgroup analyses, the beneficial effect was present for presentations of ON, as well as for brainstem–cerebellar and spinal cord syndromes.<sup>69,70</sup> The extension study, Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance (CHAMPIONS), demonstrated that patients who received the early interferon treatment (those initially randomized to the active treatment group) had persistently lower risk of developing MS at 5 years of follow-up (21%) compared with those who started therapy once efficacy was established at 2–3 years of follow-up in open-label extension (35%).<sup>71</sup>

The Early Treatment of Multiple Sclerosis (ETOMS) study also showed that interferon  $\beta$ -1a reduces risk of developing MS over 2 years after a first demyelinating event.<sup>72</sup>

In this trial, 308 patients were randomized to weekly 22  $\mu$ g subcutaneous interferon  $\beta$ -1a (Rebif<sup>®</sup>) or placebo within 3 months of symptom onset. Over one-third of patients had evidence of 2 or more white matter lesions on MRI at presentation, and most of the patients had received steroids before initiation of injections. Treated patients had a risk of 34% of developing MS in the 2-year period vs 45% for controls ( $P = 0.047$ ). Another marker for benefit, the time for 30% of each cohort to develop MS was 569 days in the interferon group and 252 in the placebo group ( $P = 0.034$ ). Annual relapse rate was also lower in the interferon group, 0.33 vs 0.43 per year ( $P = 0.045$ ), and disease burden by MRI was less.

The third trial, Betaferon/Betaseron in Newly emerging Multiple Sclerosis for Initial Treatment (BENEFIT) looked at another common injectable therapy for MS.<sup>73</sup> Patients with acute demyelinating events (487, 80 with ON) were

randomized to 250 µg of subcutaneous interferon β-1b (Betaseron®) or placebo. Development of CDMS by the Poser criteria was 28% in the treatment group vs 45% in the placebo group ( $P < 0.0001$ ) and by the newer McDonald criteria, including MRI parameters for lesions in time and space, was 69 vs 85%, respectively.<sup>73–75</sup> Patients on interferon also had significantly fewer lesions on brain MRI.

The effect of glatiramer acetate (Copaxone®) on the development of second demyelinating events after a CIS was addressed by the PreCISe trial. Patients with CIS and 2 or more T<sub>2</sub>-weighted brain lesions were assigned to 20 mg subcutaneous glatiramer acetate daily vs placebo for 36 months.<sup>76</sup> Use of the drug reduced the risk of developing CDMS by 45% compared with placebo.<sup>76</sup>

### Summary

In patients with ON and high risk of MS, defined as 2 or more white matter lesions on brain MRI and lack of atypical clinical features, we recommend treatment in the acute setting with IV methylprednisolone followed by disease modifying therapy. Discussion with the patient about his or her risk of MS is important in this setting. Even in those patients without the evidence of other MRI lesions, it is appropriate to follow them with MRI scans for future development of white matter lesions. IV steroids may also be recommended in this group to expedite recovery of visual function.

### Visual loss in absence of acute clinical ON

Even in patients without history of acute clinical ON, MS is associated with visual dysfunction. Low-contrast letter acuity charts have been used to detect clinically subtle visual dysfunction in MS, even among patients with 20/20 or better high-contrast visual acuity and no history of acute ON.<sup>7,8</sup> Use of low-contrast letter acuity charts and the Pelli-Robson contrast-sensitivity chart can distinguish MS eyes from controls to a degree better than high-contrast visual acuity testing.<sup>42</sup> OCT studies demonstrate subclinical RNFL thinning in MS eyes, even among those without a history of acute ON. While the greatest reductions in RNFL thickness are seen in eyes with history of ON, non-ON eyes of MS patients show decreases in RNFL thickness compared with disease-free controls.<sup>9,77</sup> RNFL thinning in MS has been shown to correlate with MRI measures of lesion volume and normalized brain volumes, for example, T<sub>1</sub>- and T<sub>2</sub>-lesion volume and normalized gray matter volume (relationship to normalized white matter

volume is less clear) and with losses of low-contrast acuity over time.<sup>60,78–80</sup>

### Other afferent disorders in MS

Disorders of the afferent visual system in MS may encompass structures beyond the optic nerve, including chiasmal and postchiasmal visual field deficits, or may involve diseases of ocular inflammation (Panel 1). Symptomatic homonymous field deficits are rare, but with screening, unrecognized defects may be found.<sup>81</sup> In the ONTT, 13.2% of patients had evidence of a chiasmal or retrochiasmal deficit upon serial screening, 5.1% of which were bitemporal and 8.9% were homonymous.<sup>82</sup> In 1 study of 18 patients with retrochiasmal field deficits, lesions were found on MRI in the posterior optic radiations, the optic tract, lateral geniculate nucleus, and the posterior limb of the internal capsule; all of the lesions were unusually large, a characteristic feature considered necessary to observe a homonymous deficit in this disease.<sup>83</sup>

Ocular inflammation may be seen in patients with MS. Types include anterior uveitis, pars planitis (intermediate uveitis), and retinal periphlebitis. Uveitis is 10 times more common in MS patients than in the general population, but it is a rare complication and often unrecognized.<sup>84,85</sup> In a study of 16 MS patients with uveitis, Zein et al<sup>86</sup> reported that 94% of those cases were bilateral and 81% were pars planitis. Half of the cases were previously diagnosed with MS; in 25% of the cases, the diagnosis of uveitis preceded the diagnosis of MS; and in 19% of the cases, the diagnoses were made concomitantly.<sup>86</sup>

Anterior uveitis, including granulomatous and non-granulomatous forms, arises uncommonly in patients with known MS, but may manifest before diagnosis.<sup>85</sup> In cases of granulomatous disease, other etiologies must be excluded, including sarcoidosis, tuberculosis, syphilis, Lyme disease, rheumatologic disorders, Behcet's disease, and Vogt–Koyanagi–Harada syndrome. Despite the rarity of isolated anterior uveitis in MS, it is worth considering that the agents used in other inflammatory processes, such as tumor necrosis factor α, may be ineffective or detrimental in demyelinating disease.<sup>87–89</sup>

Pars planitis, an idiopathic form of intermediate uveitis, is characterized by intravitreal inflammation and pars plana and peripheral retinal exudates.<sup>90</sup> It may have no symptoms or be associated with vision loss from complications, including cataracts, epiretinal membrane formation, or macular edema. In a prospective study of 21 patients with pars planitis, 47.6% were found to have demyelinating lesions on MRI, and relapsing remitting MS was diagnosed in

33.3%.<sup>90</sup> Another small study found MS in 16% of patients with pars planitis and found an association between human leukocyte antigen-DR15 (HLA-DR15) and this form of uveitis (odds ratio [OR] = 2.86; 95% confidence interval [CI], 1.42–5.78,  $P = 0.004$ ).<sup>91</sup> The latter association between pars planitis and HLA-DR2 allelic subtypes has been observed by other groups as well.<sup>92,93</sup> Overall visual prognosis is generally good with most affected eyes retaining better than 20/40 visual acuity.<sup>90,91</sup> Treatment options include steroids, nonsteroidal anti-inflammatory agents, immunosuppressant therapy, cryotherapy, or vitrectomy.<sup>90</sup> In pars planitis patients not previously diagnosed with MS, MRI studies should be considered to rule out demyelinating disease.

Cuffing of retinal veins by inflammatory cells causing whitish exudates, or retinal periphlebitis, is found in 5%–36% of patients with MS.<sup>94–97</sup> Its presence is thought to be more common in active stages of the disease and its pathogenesis may share commonalities with perivenular inflammation in typical MS plaques.<sup>95,96,98,99</sup> Retinal periphlebitis in MS is typically mild and may not have any clinical manifestations; more severe cases may be seen in disorders such as sarcoid, syphilis, toxoplasmosis, Eale disease, and idiopathic uveitis.<sup>100</sup>

## The efferent visual system in MS

Discrete lesions in the ocular motor pathway result in classic efferent syndromes (Table 3). The most common of these are INO, saccadic dysmetria, nystagmus, and suppression of the vestibulo-ocular reflex (VOR).<sup>101,102</sup> MRI studies, particularly proton density and  $T_2$  images, often show these lesions in the corresponding areas of the brainstem and cerebellum.<sup>103</sup>

## The ocular motor examination

Careful bedside examination can reveal the common efferent disorders associated with MS.<sup>104</sup> Components of the examination should include assessment of ocular alignment and motility. Alignment in the primary and the cardinal directions of gaze should be evaluated, and the presence of tropias, phorias, and head tilt determined. Ductions (monocular motility) and versions (binocular motility) as well as Maddox rod measurements or other assessment of diplopia should be performed. Saccades, brief eye movements from one point of fixation to another, should be assessed for latency, velocity, and accuracy and may reveal INO and ocular dysmetria due to cerebellar dysfunction, nystagmus, or gaze palsy. Smooth pursuit can be affected by inattention or broken into saccadic movements. Saccadic intrusions visible by external or funduscopy examination are also seen in MS and include square-wave jerks,

oscillations, and ocular flutter or opsoclonus. Various types of nystagmus and vestibular disorders are often observed, with the most common types summarized below. Evaluations, such as observation during eye movements, VOR testing, and head thrust, can help distinguish between the neuroanatomic possibilities.

## Internuclear ophthalmoparesis

INO, characterized by limited or slow adduction of the ipsilateral eye on horizontal saccadic eye movements and usually accompanied by horizontal nystagmus in the contralateral eye, INO is commonly associated with MS, and when seen in young undiagnosed patients, an INO should prompt a workup for demyelinating disease.<sup>102,105–107</sup> Lesions of the medial longitudinal fasciculus (MLF), located in the dorsomedial pontine or midbrain tegmentum, cause INO. In a study of 58 patients with MS and INO, all had evidence of lesions in the MLF by proton density imaging.<sup>103</sup> Etiologies of INO in a retrospective study of 65 patients included vascular (36.9%), MS (32.3%), and infectious disease (13.8%).<sup>105</sup> In half of these patients, the INO persisted after 1 year of follow-up. In 2005, Keane<sup>106</sup> summarized 33 years of his clinical experience with INO and also noted approximately one-third of cases to be from stroke and one-third from MS. Although 87% of the stroke cases were unilateral, bilateral disease was more suggestive of MS.

About one-quarter of MS patients suffer from clinically diagnosed unilateral or bilateral INO.<sup>102,107</sup> Symptoms may include blurred vision, diplopia, oscillopsia, loss of stereopsis, and reading fatigue. Convergence typically remains intact. Physician detection of INO is accurate in severe cases with decreased range of adduction, but in mild to moderate cases, only the velocity of adduction may be affected, and the diagnosis is often missed.<sup>108</sup> In these patients, the use of infrared oculography may reveal the adduction deficit.<sup>108–110</sup> Thus, the prevalence of INO in MS patients is likely underestimated.

Nystagmus of the contralateral eye may be an adaptive process to compensate for the break in binocular fusion with the weak or slow adduction of the ipsilateral eye.<sup>111–113</sup> Other findings which may be associated with an INO include slowing of abduction, disturbance in vertical eye movement, and skew deviation.<sup>113</sup> Slowing of abduction in the ipsilateral eye has been reported, particularly in cases of significant ophthalmoparesis and large MRI lesions, and it is thought to be related to defective relaxation of the dysfunctioning antagonist medial rectus.<sup>104,113–115</sup> Vertical eye movement disorders are associated with bilateral INO. The MLF carries the



**Table 3** Common efferent neuro-ophthalmologic disorders in MS

Abnormality	Frequency <sup>a</sup>	Localization	Features	Treatment	References
INO	60%–68%	MLF (Dorsomedial pontine or midbrain tegmentum)	Limited or slow adduction in ipsilateral eye on horizontal saccadic eye movements; horizontal nystagmus in contralateral eye	Steroids acutely	88, 103–118
Saccadic dysmetria	80%–91%	Cerebellum, brainstem	Overshoots, undershoots, directional dysmetria, ipsipulsion, contrapulsion	Steroids acutely	102–103, 105, 119
Nystagmus	36%–65% (gaze-evoked) 10%–18% (pendular and downbeat in central position)	Cerebellum, brainstem, vestibular apparatus	Gaze-evoked, pendular, upbeat, downbeat, multidirectional, rebound, vestibular, periodic alternating, occult (with ophthalmoscopy)	Gabapentin, memantine, baclofen, clonazepam, 3,4-diaminopyridine, prisms, surgery	102–103, 124–143
Saccadic intrusions	n/a	Brainstem (pause cell neurons), cerebellum	Inappropriate saccades including square-wave jerks, macro square-wave jerks, macrosaccadic oscillations, ocular flutter, opsoclonus, and microsaccadic flutter	Baclofen, anticonvulsants, memantine?	88, 105, 120–123
Smooth pursuit impairment	31%–75%	Higher cortical pursuit system (parietal-occipital-temporal junction)	Inability to maintain conjugate fixation on a moving target	None	102–103, 145
VOR impairment	36%–55% (75%) <sup>b</sup>	Flocculus	Inability to suppress the VOR; characteristic catch-up saccades when trying to fixate on a target moving with the head	None	102–103, 105, 146, 147

**Notes:** <sup>a</sup>In MS patients with abnormal eye movements;<sup>102,103</sup> <sup>b</sup>In a study of 20 patients with MS.<sup>146</sup>

**Abbreviations:** MS, multiple sclerosis; MLF, medial longitudinal fasciculus; INO, internuclear ophthalmoparesis; VOR, vestibular ocular reflex.

myelinated fibers of the vertical pursuit, vertical vestibular, and otolithic-mediated ocular movement pathways. Patients with bilateral INO present with vertical and torsional nystagmus, characteristic of vertical gaze-holding and vertical VOR abnormalities, and altered optokinetic and pursuit responses.<sup>104,116,117</sup> Skew deviation and supranuclear vertical ocular misalignment with binocular torsional deficits can occur with an INO. The higher eye is usually on the side of the MLF lesion.<sup>87,104,113</sup>

## Disorders of fixation

Saccadic dysmetria, saccadic intrusions, and nystagmus are disorders of fixation seen in MS patients. Saccadic dysmetria is present in most of the MS patients with abnormal eye movements.<sup>101,102</sup> Patients may exhibit overshoots (hypermetria), undershoots (hypometria), or directional dysmetria (vertical movements in a horizontal saccade). Lesions in the cerebellar vermis and posterior fastigial nuclei affect sac-

cadic accuracy. Hypometria may occur if the vermis alone is affected, and hypermetria may occur if deep nuclei are involved.<sup>104,118</sup>

Saccadic intrusions include square-wave jerks, inappropriate sudden movements away from and back to a point of fixation. There is an intersaccadic latency between these events. Macro square-wave jerks are similar to and from intrusions but are larger in amplitude. Ocular flutter and opsoclonus are saccadic intrusions without interval latency. The former is characterized by back to back horizontal saccades, and the latter involves horizontal, vertical, and torsional saccades.<sup>119</sup> Microsaccadic flutter similarly has no intersaccadic latency, and when patients may report shimmering or wavy vision, ophthalmoscopy or eye-movement recordings are often required to make this rare diagnosis.<sup>120</sup> Saccadic intrusions result from lesions in the cerebellum and brainstem; pause cell (located in the pontine raphe) dysfunction has been implicated, and these disorders may

respond to anticonvulsants or baclofen.<sup>87,104,120</sup> For various etiologies, a number of other agents have been tried, including methylphenidate, IV immunoglobulin, and clonazepam.<sup>121</sup> Memantine has also been used to improve saccadic intrusion frequency in 2 patients with hereditary ataxia.<sup>122</sup>

Dysfunction of gaze-holding mechanisms in the brainstem and cerebellum may lead to the drifting of the eyes away from a target followed by involuntary corrective saccades, defined as nystagmus. When symptomatic, the patient often experiences visual dysfunction and oscillopsia, a skipping of the visual environment. Many types of nystagmus may be seen in MS. Gaze-evoked nystagmus is seen in roughly one-third of MS patients and may be caused by lesions in the medial vestibular nucleus, nucleus prepositus hypoglossi, and flocculus.<sup>101,102,123</sup> Pendular nystagmus, oscillations in which there is equal velocity in both directions, also occurs often relatively and can interfere with visual function.<sup>101,102,123–127</sup> Other forms of nystagmus reported in MS include upbeat, downbeat, rebound, multidirectional, periodic alternating, see-saw, dissociated, and vestibular.<sup>101,102,104,128–131</sup> Small studies have demonstrated successful treatment for nystagmus with baclofen, gabapentin, memantine, clonazepam, 3,4-diaminopyridine, fampridine, prisms, and surgery.<sup>104,121,128,132–143</sup>

## Other efferent disorders in MS

A variety of other efferent syndromes may be present in MS patients depending on the location of demyelinating lesions. Impairment of smooth pursuit is common and likely related to the disruption of higher cortical centers, including the parieto-occipital-temporal junction.<sup>101,102,144</sup> Patients with abnormal smooth pursuit also often demonstrate abnormal suppression of the VOR.<sup>104,145</sup> They exhibit catch-up saccades on head impulse testing.<sup>104,146</sup> Lesions in the abducens nucleus or the pontine paramedian reticular formation (PPRF) and the ipsilateral MLF cause one-and-a-half syndrome, in which there is an ipsilateral horizontal gaze palsy and an INO.<sup>144,147</sup> Abduction of the contralateral eye is the only remaining horizontal eye movement.

Skew deviation is a vertical ocular misalignment and results from lesions in the pathways connecting the vestibular nuclei in the medulla to the third and fourth nuclei in the midbrain.<sup>144</sup> If the lesion is in the lower brainstem, the contralateral eye is hypertropic. Lesions in the pons and midbrain cause ipsilateral hypertropia. Patients will report vertical diplopia. The ocular tilt reaction is a skew deviation combined with head tilt (away from hypertropic eye) and conjugate ocular torsion.

The dorsal midbrain (Parinaud) syndrome and nuclear and fascicular cranial nerve lesions can occur in MS. In the former, lesions to the posterior midbrain cause supranuclear upgaze paresis, pupillary light-near dissociation, convergence-retraction nystagmus, and eyelid retraction.<sup>144,148,149</sup> Of the cranial nerve syndromes, sixth nerve paresis is the most common.<sup>150–152</sup> Nuclear lesions produce an ipsilateral gaze paresis, whereas fascicular lesions cause an ipsilateral lateral rectus palsy. Various presentations of third nerve palsies including partial fascicular, upper or lower division, have been reported,<sup>150,153,154</sup> whereas rare, isolated trochlear (fourth) nerve paresis has been described in MS.<sup>155</sup>

## Summary

Demyelinating lesions in MS cause characteristic afferent and efferent visual syndromes. Detection of these syndromes during ophthalmologic evaluation may lead to early diagnosis and treatment and potentially better outcomes for these patients. Vision loss and ocular motility deficits are associated with overall disability, and these disorders may be an indication of disease severity.

Careful attention to the neuro-ophthalmologic findings in MS not only reveals information about current disease burden, but also offers discrete measures of structure and function in an accessible part of the nervous system amenable to research and the testing of current and future therapies for this disabling disease.

## Disclosure

The authors report no conflicts of interest in this work.

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