REVIEW

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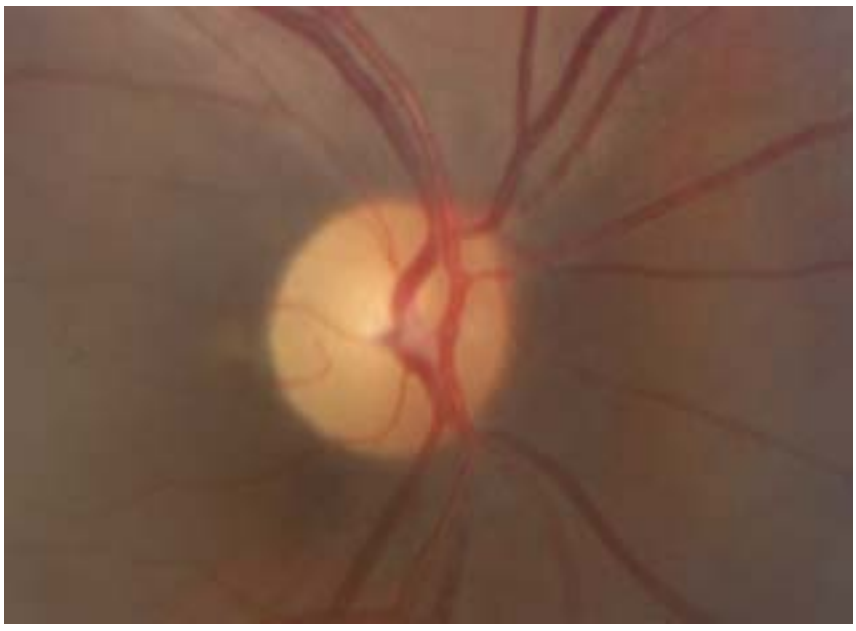

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INTRODUCTION

Neuro-ophthalmological involvement in multiple sclerosis (MS) is common, and often the initial manifestation. Increased understanding of both visual and ocular motor system demyelination has contributed significantly to advances in our knowledge of the prognosis, treatment, and pathogenesis of MS. Moreover, advances in neuroradiological techniques have improved correlation of brain demyelinating lesion burden with clinical disease activity, and their application to both optic nerve and ocular motility disorders has contributed to improved lesion localization, and prediction of disease course.

Approximately one-fifth of patients ultimately diagnosed with MS have initially presented with acute visual loss secondary to optic neuritis, and up to two-thirds of MS patients have an episode of acute optic neuritis at some stage during the course of their disease (Rodriguez *et al*. 1995). The propensity of MS to affect the optic nerves is further evidenced by the frequent occurrence of subclinical optic neuropathy, with eventual development of bilateral optic atrophy (Bashir & Whitaker 1999).

The most common eye movement disorder in MS is unilateral or bilateral internuclear ophthalmoplegia (Frohman *et al*. 2001). Other frequent ocular motility disorders include vari-

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ous forms of brainstem and cerebellar-mediated nystagmus and saccadic dysmetria. All these visual and eye movement disturbances are an important source of functional disability in MS.

Authors have stressed the importance of capturing generally unemphasized components of disability, such as chronic visual dysfunction, to improve the validity of disability outcome measures for research, and their accuracy (Frederiksen *et al.* 1997; Balcer 2001; Balcer *et al.* 2003). Indeed, this theme was central to the development of the Multiple Sclerosis Functional Composite (MSFC) as a measure of disability (Rudick *et al.* 2001), rather than the Kurtzke Expanded Disability Status Scale (EDSS) which is primarily a measure of walking and lower limb impairment (Kurtzke 1983). At present the MSFC yields a score based only on tests of upper and lower limb function, and cognition. Therefore, Balcer *et al.* (2001) have proposed that visual function measures, such as low contrast sensitivity testing, which are better able to detect chronic visual abnormalities in MS patients, be included as an additional component of the MSFC.

The aim of this review is to describe our approach to the diagnosis and management of optic neuritis and eye movement disorders in MS. This is particularly timely, following the July 2003 publication of the 10 year data from the Optic Neuritis Treatment Trial, the landmark study of treatment of idiopathic demyelinating optic neuritis (Optic Neuritis Study Group 2003).

OPTIC NEURITIS

Clinical picture and immediate outcome

Idiopathic demyelinating optic neuritis is the most common acute optic neuropathy in patients under the age of 40 (table). The typical presentation is with unilateral, acute to subacute, painful visual loss with decreased visual acuity, abnormal colour vision and contrast sensitivity, a visual field defect, and a relative afferent pupillary defect. Most visual field defects involve the central field and may be of any type: central scotomas, altitudinal defects, monocular hemianopic defects, etc. (Fig. 1). One third of patients have optic disc swelling (Optic Neuritis Study Group 1991). Optic nerve pallor develops after 4–6 weeks (Fig. 2). Asymptomatic visual field defects are present in the contralateral eye in up to two-thirds of patients, with peripheral rim and diffuse central defects being the most common (Keltner *et al.* 1993). About 90% of patients experience ocular pain, usually increased by eye movement (Optic Neuritis Study Group 1991). Initial visual acuity ranges from 20/20 to

Table 1 Common optic neuropathies.

	SEX	AGE	PAIN	LATERALITY	ONSET	COURSE	ACUITY	VISUAL FIELD	FUNDUS
Idiopathic optic neuritis	*F* › M	15–30	Yes	U	Acute/subacute	Spontaneous improvement	Any	Any central defect	Normal
Inflammatory optic neuritis	*F* › M	15–30	No	U or B	Acute/subacute	Spontaneous improvement less common	Any	Any central defect	Swollen optic nerve head, macular star
Acute ischaemic optic neuropathy	*F* = M	› 50	No	U	Acute	Improvement uncommon	20/20–20/80	Inferior altitudinal	Swollen optic nerve head
Compressive	*F* = M	Any	No	U	Chronic	Slowly progressive	Any	Any	Swollen or pale optic nerve head
Papilloedema	*F* = M	‹ 50	Yes*	B	Often incidental finding	Spontaneous improvement rare	20/20	Peripheral loss	Swollen optic nerve head

U, unilateral; B, bilateral.
*Usually in the form of headaches.

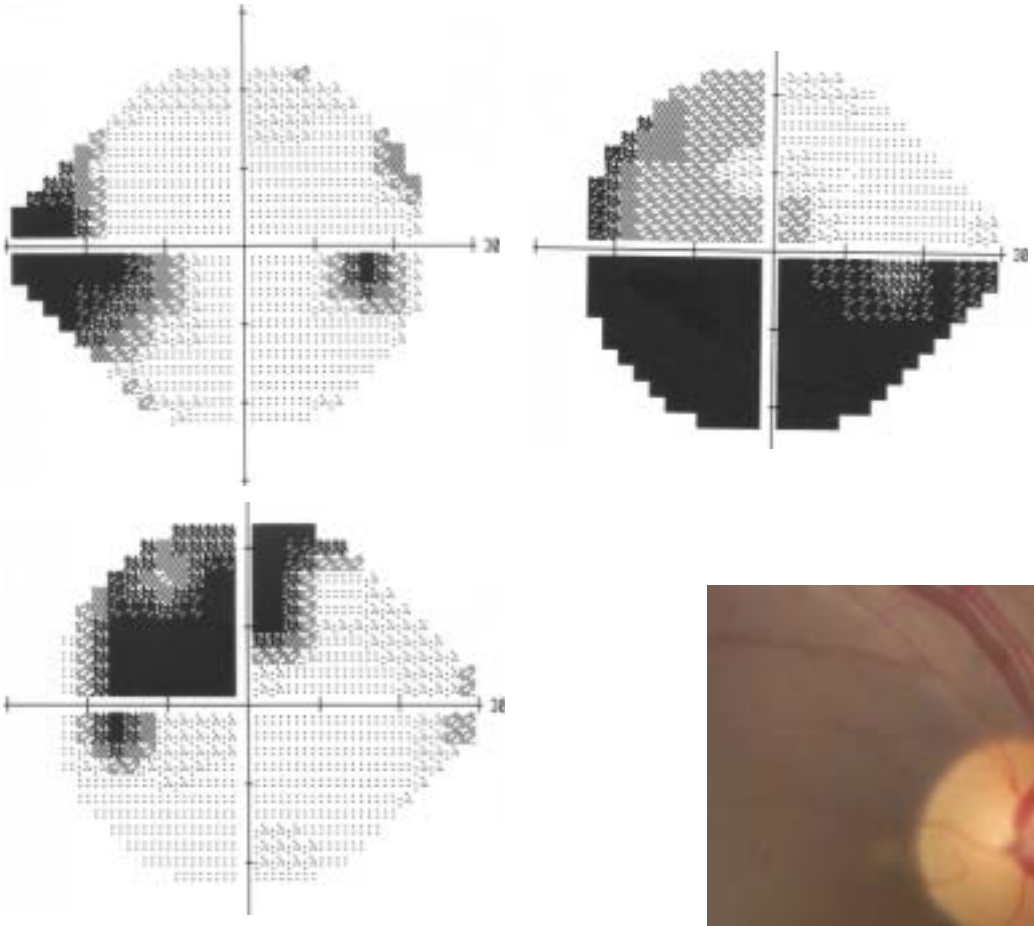

Figure 1 Examples of central visual field defects in acute optic neuritis.

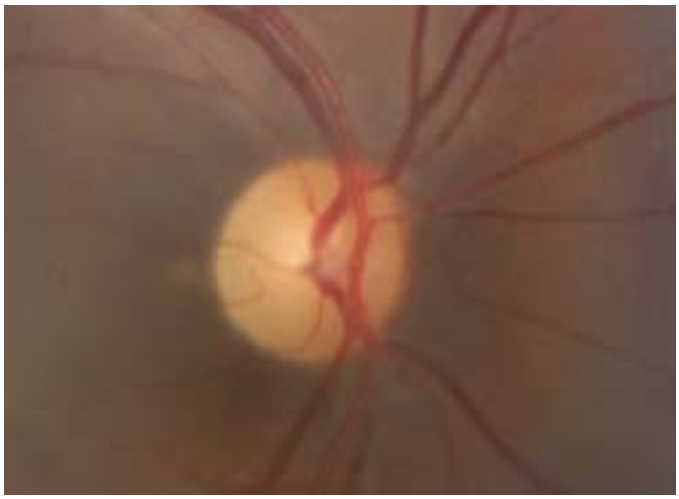

Figure 2 Atrophy of the right optic nerve after an episode of optic neuritis.

no light perception, with the majority of patients between 20/25 and 20/200. Acuity often worsens over several days, with a nadir typically within 1–7 days (Beck *et al*. 1994), followed by spontaneous improvement over several weeks. Most of the improvement is usually within 4–6 weeks, although there may be slow continuous improvement for up to one year.

Visual evoked potentials may confirm the presence of optic neuritis, but are rarely necessary because the clinical setting and examination findings (e.g. age of patient, temporal course of visual loss, presence of pain) are usually sufficient to make the diagnosis. Evoked potentials may be useful in identifying subclinical optic nerve demyelination but even here clinical exam is more sensitive.

Two interesting phenomena that occur in the setting of optic neuritis are Uhthoff's phenomenon and the Pulfrich effect. Uhthoff's phenomenon is the occurrence of decreased vision with exercise or heat exposure and this may occur either in the acute phase of optic neuritis or following recovery of the initial visual loss. The proposed mechanism is a reversible conduction block of the partially demyelinated optic nerve (Selhorst & Saul 1995). The Pulfrich effect is an illusion in which an object moving sinusoidally along a linear pathway (e.g. a pendulum swinging) appears to be moving in an elliptical pathway. The illusion is due to delayed neural conduction along one optic nerve relative to the other (Howard & Rogers 2002).

By 1 year, 95% of patients with optic neuritis have a visual acuity of 20/40 or better and only about 5% have a visual outcome of 20/50 or worse (Beck *et al*. 1993a). But, despite the good visual recovery in most patients, over half have persistent impairments and abnormalities on examination, particularly with contrast sensitivity testing (Beck *et al*. 1994; Frederiksen *et al*. 1997; Optic Neuritis Study Group 1997a).

Although most common in white patients, optic neuritis occurs in other racial groups, with black patients tending to have more severe visual loss, often bilateral, and with worse outcomes (Phillips *et al*. 1998; Pokrov *et al*. 2001).

Imaging the optic nerve

In optic neuritis, optic nerve enhancement and increased T2-weighted signal may be identified with MRI of the orbits with fat-suppression techniques (Figs 3 and 4). Long-echo time STIR (short tau inversion recovery) sequences appear to be the most sensitive method of identifying optic neuritis-related abnormalities (Onofrij *et al*. 1996) (Fig. 5). Optic nerve enhancement in the optic canal, or of a long segment of the nerve, correlates with worse initial visual dysfunction, but location and length of optic nerve enhancement are not predicative of visual recovery (Kupersmith *et al*. 2002).

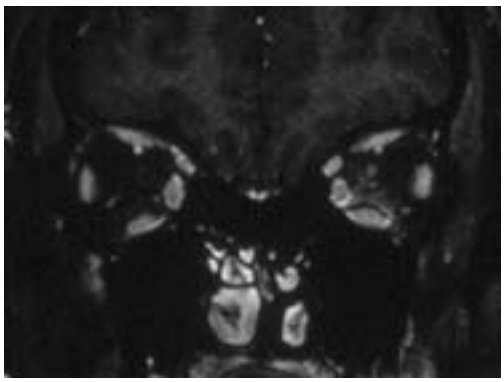

Figure 3 Coronal T1-weighted, gadolinium-enhanced MRI through the optic nerves, showing enhancement of the left optic nerve (arrow) in a patient with acute idiopathic, demyelinating optic neuritis.

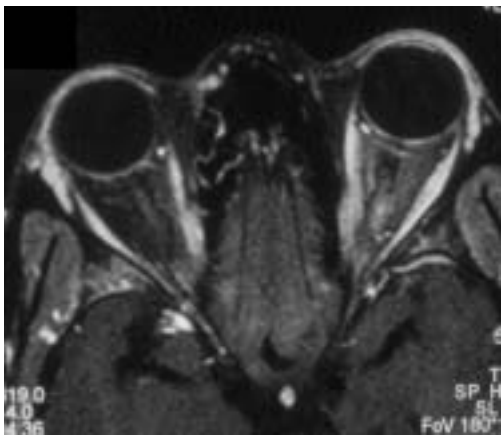

Figure 4 Axial T1-weighted, gadolinium-enhanced MRI, showing enhancement of the left optic nerve (arrow) in a patient with optic neuritis.

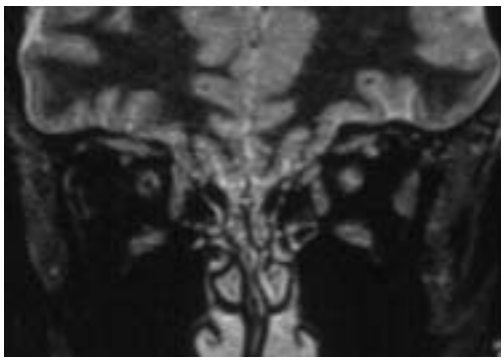

Figure 5 Coronal T2-weighted MRI with STIR (short tau inversion recovery) fat suppression technique for optimal optic nerve imaging. Increased signal in the left optic nerve (arrow) signifies acute optic neuritis.

Lepore (1991) postulated that the pain in optic neuritis is due to traction of the origins of the superior and medial recti muscles on the optic nerve sheath at the orbital apex, and MRI enhancement in the orbital segment of the optic nerve does correlate with the presence of pain (Fazzone *et al*. 2003a).

The typical MRI findings in idiopathic demyelinating optic neuritis differentiate it from other optic neuropathies. For example, a retrospective study of optic nerve gadolinium-enhanced and STIR MRI sequences in 32 optic neuritis and 32 anterior ischaemic optic neuropathy patients revealed that all those with optic neuritis had abnormal optic nerve signal, most with both increased T2 signal and enhancement along an extensive portion of the optic nerve. In contrast, most patients with anterior ischaemic optic neuropathy had normal optic nerve signal; only five of 32 had increased T2 signal and just two of them enhanced, but along a short nerve segment (Rizzo *et al*. 2002).

Just as brain atrophy is neuroradiographically evident early in the course of MS, optic nerve atrophy is present on MRI after even a single episode of unilateral optic neuritis (Hickman *et al*. 2001). Progression of such atrophy over time correlates with progressive visual deterioration and decreasing visual evoked potentials (Hickman *et al*. 2002). The lack of long-term benefit of corticosteroid treatment on visual function (see below) may be because it cannot prevent this optic nerve atrophy (Hickman *et al*. 2003).

Functional MRI demonstrates that following recovery of a unilateral episode of optic neuritis, activation in the primary visual cortex is reduced. However, there is extensive increase in activation in extra-occipital areas during stimulation of the involved eye (Langkilde *et al*. 2002; Toosy *et al*. 2002), indicating that the brain is capable of adapting to abnormal afferent visual information.

Treatment of the acute attack with corticosteroids

Much of current practice is a result of the Optic Neuritis Treatment Trial (ONTT) (Beck *et al*. 1992). This was a multicentre trial in which 448 patients with acute, isolated, unilateral optic neuritis (onset in the previous eight days and without an existing diagnosis of MS) were randomized into three treatment groups:

- IV methylprednisolone 1 g/day for three days, followed by oral prednisone 1 mg/kg/day for 11 days;
- oral prednisone 1 mg/kg/day for 14 days;
- oral placebo for 14 days.

The results led to a major change of practice, at least in the US (Trobe *et al*. 1999). The first outcome assessments were at 6 months, with follow-up data published at 1, 2, 5 and 10 year intervals (Beck *et al*. 1993a; Beck *et al*. 1993b; Optic Neuritis Study Group 1997a; Optic Neuritis Study Group 2003).

At 6 months, the IV methylprednisolone group experienced faster recovery of visual function and slightly better contrast sensitivity, colour vision and visual fields compared to the placebo and oral prednisone groups, but the beneficial effect on visual function was not sustained at 1 year (Beck *et al*. 1993a). The oral prednisone group not only had no benefit, but the surprising increased risk of recurrent optic neuritis led to the conclusion that there was no role for standard dose oral prednisone in acute optic neuritis.

The ONTT, and other studies, confirmed the short-term beneficial effect of steroid treatment on vision (Brusaferri & Candelize 2000). But the optimal dose and method of administration are controversial. The ONTT finding of the ineffectiveness of oral prednisone may have been because of the relatively low dose. A trial of 60 patients randomized to a higher dose (oral methylprednisolone, 500 mg/day for 5 days followed by a 10 day taper) vs. placebo failed to identify any increased risk of visual relapse in the steroid group over 1 year of follow-up (Sellebjerg *et al*. 1999); and the oral steroid group showed a beneficial effect on visual function at 1 week follow-up, but there was no difference between the two groups at 8 weeks. Controversy over the most effective steroid dosing regimen prompted the Quality Standards Subcommittee of the American Academy of Neurology to publish practice parameters (Kaufman *et al*. 2000). These concluded that 'Oral prednisone in doses of 1 mg/kg/day has no demonstrated efficacy in the recovery of visual function in acute monosymptomatic optic neuritis, and therefore is of no proven value in treating this disorder.' The committee further stated that high dose oral or intravenous steroid therapy may hasten visual recovery and that treatment decisions should be made, not with regard to visual outcome, but rather with regard to patient quality of life and present visual disability related to the patients' need for rapid recovery.

Predicting the risk of developing MS

In the ONTT at 2 years follow-up, the IV methylprednisolone group had a lower rate of MS development but this was not sustained (Beck *et al*. 1993b). At 5 years, 30% of patients had developed MS, with no significant risk difference between the three groups. The intense predictive power of MRI T2-weighted hyperintense brain lesions at the onset, in determining future MS risk, was established by the 5-year ONTT data (Optic Neuritis Study Group 1997b). With a normal MRI, the 5-year risk of MS development was 16%. With one or two brain lesions at least 3 mm in size, the 5-year risk was 37%. With three or more brain lesions, the 5-year risk was 51%. Independent of MRI appearance, nonspecific neurological symptoms, such as transient numbness, also predicted increased future MS risk.

The 10-year ONTT data (Optic Neuritis Study Group 2003) have confirmed the 5-year finding that MRI brain lesions are the single most important factor in predicting future MS risk. However, in contrast to the 5-year results, there was no significant difference in MS development between patients with one brain lesion and those with more than one lesion. The ONTT had extremely good 10-year follow-up, with data available on 87% of the original 388 patient cohort. Overall, regardless of initial treatment randomization, MS had developed in 38% of patients by 10 years. The median time to MS development after the episode of optic neuritis was 3 years, with most patients developing it within 5 years. With a single MRI brain lesion, the 10-year MS risk was 56%; with a normal MRI, the risk was 22%. That even a single brain lesion on MRI predicts a higher risk of MS should be important in developing future trials of immunomodulatory therapies after clinically isolated demyelinating events.

Earlier studies support the predictive role of concomitant MRI lesions. In a 5-year follow-up of 89 patients with acute clinically isolated optic neuritis, transverse myelitis or brainstem demyelination, 85% of patients with four or more brain lesions, 54% with one to three lesions, and only 3% with a normal brain MRI developed MS. At 14 years, more than 85% of those with one or more brain lesions developed MS, compared with only 19% of those with a normal brain MRI (Frohman *et al*. 2003). Both the smaller sample size and lower proportion followed-up may explain the differences between this study and the ONTT. Additional studies of clinically isolated demyelinating syndromes have found correlations not only of brain lesion number, but also lesion localization (periventricular and juxtacortical), gadolinium enhancement, and development of new brain lesions with future MS risk and increased disability (Frohman *et al*. 2003; Simon & Thompson 2003).

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No other factors correlated with future MS risk in the ONTT patients with an *abnormal* brain MRI – demographic data and clinical characteristics are not helpful in determining which patients with abnormal scans should receive immunomodulatory therapy. Factors that carried a decreased risk of future MS in patients with a *normal* initial brain MRI included male sex, optic disc swelling or haemorrhage, no perception of light, the absence of pain, and the presence of retinal exudates (Optic Neuritis Study Group 2003). But all of these characteristics are atypical for demyelinating optic neuritis.

A recent development that may be useful in risk prediction is detecting serum antibodies to myelin basic protein (MBP) and myelin-oligodendrocyte glycoprotein (MOG) in patients with the triad of a clinically isolated demyelinating event, CSF oligoclonal bands and MRI white matter lesions (Berger *et al*. 2003). During 4-year follow-up, 95% of patients with antibodies to both MBP and MOG, and 83% of patients with antibodies to MOG, developed MS, compared with only 23% of antibody-

negative patients. Another potentially useful tool in determining future MS risk after isolated optic neuritis is spinal MRI, although in a recent analysis in 115 patients this rarely contributed to diagnosis (Dalton *et al*. 2003).

Interestingly, ultimate MS disability may not be as profound in patients presenting initially with optic neuritis, compared to those with other presentations (Weinshenker *et al*. 1991; Sorenson *et al*. 1999). Poor prognostic factors for disability include older age at onset, male sex, cerebellar involvement, and insidious onset of a motor deficit as the presenting symptom (Weinshenker *et al*. 1991).

Other strategies for preventing permanent visual loss

The lack of long-term steroid benefit, the frequent persistent subjective and contrast visual disability, and the progression to optic atrophy, have all stimulated the search for preventative neuroprotective agents. For example, blockade of sodium or calcium channels might improve axonal conduction (Kapoor *et al*. 2003; Waxman 2003). Intravenous verapamil in eight MS patients with abnormal visual or brainstem auditory-evoked potentials shortened the prolonged latencies toward normal, suggesting that calcium blockade may facilitate conduction along demyelinated axons (Gilmore *et al*. 1985). But 3,4 diaminopyridine and 4-aminopyridine, which block potassium channels and improve axonal conduction, yielded only minor visual benefit (Bever *et al*. 1994; Polman *et al*. 1994). Despite enhancement of remyelination by intravenous immunoglobulin in animal models of MS, a randomized trial in 55 patients with persistent acuity loss following optic neuritis produced no significant improvement (Noseworthy *et al*. 2001).

Immunomodulatory therapies

Over the past decade, the advances in predicting MS risk and future disability after clinically isolated optic neuritis have developed alongside advances in immunomodulatory therapies. Furthermore, recognition of neurodegenerative axonal injury causing brain atrophy, even early in the course of MS, has encouraged early and aggressive therapeutic intervention (DeStefano *et al*. 2003; Filippi *et al*. 2003). And, not surprisingly, the beneficial effect of immunomodulatory therapies on disability progression, relapse rate and MRI lesion development in established MS has prompted consideration of whether these therapies might also reduce the risk of MS *development* in clinically isolated demyelinating syndromes, such as optic neuritis.

The Controlled High Risk Avonex Multiple Sclerosis Trial (CHAMPS) was designed to address this question (Jacobs *et al*. 2000). 383 patients with a first, clinically isolated demyelinating event (involving optic nerve, spinal cord, brainstem or cerebellum) and at least two clinically silent MRI brain lesions >3 mm in diameter, were randomized to either interferon beta-1a (Avonex) 30 micrograms intramuscular weekly, or matched placebo for three years. All patients initially received a 1 gram single daily dose of IV methyprednisolone for 3 days, followed by prednisone 1 mg/kg/day for 11 days and a short taper. During the 3-year follow-up, the cumulative probability of developing MS was significantly lower in the interferon treated group (35%) compared with the placebo group (50%). In addition, the treated group had fewer new or enlarging brain lesions and fewer gadolinium-enhancing lesions. Subgroup analysis confirmed that there were benefits of treatment regardless of the presenting manifestation (Beck *et al*. 2002).

A second study, of interferon beta-1a (Rebif), 22 g subcutaneously per week, showed similar benefit when initiated within 3 months of the initial demyelinating event (Comi *et al*. 2001). Although both these studies were too short to assess any long-term effect on disability, they do suggest that treatment should be initiated after a clinically isolated demyelinating event, in the setting of more than two lesions on MRI. Longer-term data from the CHAMPS study will soon be forthcoming, as the Controlled High Risk Avonex Multiple Sclerosis Prevention Surveillance (CHAMPIONS) study ended in May 2003 when the last patient reached the 5-year mark after enrollment (Galetta 2001).

Given the ONTT 10-year finding that patients with only one MRI brain lesion have the same MS risk as patients with more lesions, future studies will need to determine the potential benefit of immunomodulatory therapy in patients with just a single brain lesion. Presently, we suggest initiation of interferon beta-1a (either Avonex or Rebif) following a single episode of idiopathic demyelinating optic neuritis in the setting of two or more brain lesions on MRI, with at least one lesion in a characteristic location for demyelination (e.g. corpus callosum or perpendicular to the ventricles) (Fig. 6).

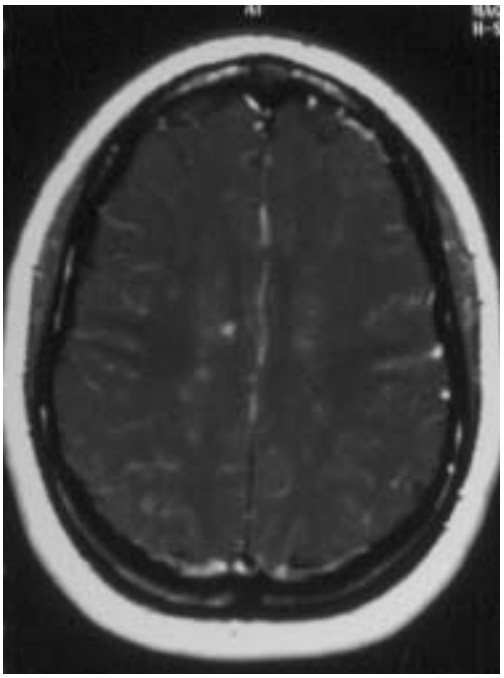

Figure 6 Axial T1-weighted, gadolinium enhanced brain MRI showing several enhancing white matter lesions characteristic of demyelination.

NEUROMYELITIS OPTICA

When idiopathic demyelination affects only the spinal cord and both optic nerves, the term Devic's disease, or neuromyelitis optica, is often applied. Whether this disease pattern represents a form of MS or a distinct disease has been resolved by histopathological, clinical and paraclinical evidence that proves neuromyelitic optica is, in fact, a distinct disease. The original descriptions were of a monophasic illness with rapid, successive, bilateral optic neuritis and transverse myelitis. But more recent literature emphasizes that over half the patients may have a relapsing course (Weinshenker 2003). Bilateral sequential optic neuritis is more common than bilateral simultaneous optic neuritis and episodes involving both optic nerves and the spinal cord usually occur within 3 months of each other, but can be separated by years (Cree *et al*. 2002). The neuromyelitis optica disease pattern, usually in the relapsing form, is common in Japan, where it is called the pure optic-spinal form of multiple sclerosis, and it may also be more common in black populations (Phillips *et al*. 1998; Kira 2003).

The distinctive features of neuromyelitis optica include bilateral optic neuritis and myelitis (often one after the other and separated by months) with a normal brain MRI, but a gadolinium-enhancing lesion extending over at least three vertebral segments on spinal MRI. CSF pleocytosis (> 50 WBC/mm^3) without oligoclonal bands is characteristic (Cree *et al*. 2002; Weinshenker 2003). Acute attacks tend to be more severe than in classic MS and to recover less completely, if at all. In the relapsing form, attacks tend to occur with a higher frequency than in MS. As a result of poor recovery from subsequent attacks, patients generally have a poor prognosis, with visual and motor disability within a few years of disease onset, which is in contrast to the usual minor disability in the first 10–15 years of relapsing–remitting MS. Neuromyelitis optica also has a higher case fatality than MS, primarily because of respiratory arrest from cervical myelitis.

The diagnosis was once based purely on clinical and paraclincal evidence but Lennon *et al*. (2003) from the Mayo Clinic have identified a serological marker. This is a novel autoantibody called NMO-IgG, found to have a sensitivity of 70% and a specificity of 100% (Lennon *et al*. 2003).

Given the poor prognosis of relapsing neuromyelitis optica, there is considerable interest in identifying the factors that might predict it. The Mayo group found that a relapsing course was predicted with 82% accuracy in patients with a longer interattack interval between the first two clinical events, older age at onset, female sex, and less severe motor impairment after resolution of the initial myelitis (Wingerchuk & Weinshenker 2003). The five-year survival for relapsing patients was 68%. Factors associated with increased mortality included a history of other autoimmune diseases, higher attack frequency during the first two years of disease, and better motor recovery after the initial myelitis. The seemingly paradoxical situation where good motor recovery predicts a relapsing course and increased mortality is unexplained.

The most direct evidence that neuromyelitis optica is a disease process distinct from classic MS is histopathological. Lucchinetti *et al*. (2002) analysed 82 lesions from nine autopsy cases, and identified many histopathological features that were atypical for MS – prominent perivascular immunoglobulins, activation of the complement cascade, and eosinophilic infiltrates in all early demyelinating plaques, suggesting a role for humoral autoimmunity. This may provide therapeutic targets in neuromyelitis optica distinct from those in MS, where humoral mechanisms may be less prominent. Steroids may be appropriately tried as initial therapy and plasmapheresis may be effective in patients with neuromyelitis optica who do not

respond to steroids (Weinshenker 2003). There have been no randomized controlled trials evaluating the most effective long-term treatment, but a small uncontrolled, prospective study suggested that azathioprine and prednisone might improve disability and protect against further attacks (Mandler *et al*. 1998). The value of standard MS immunomodulatory therapy is uncertain. Although anecdotal reports suggest a beneficial effect of glatiramer acetate (Bergamaschi 2003), there is a theoretical possibility that this could be harmful because it augments humoral immune mechanisms (Gold & Linington 2003).

VISUAL LOSS AND INTRACRANIAL LESIONS

Not all complaints of visual loss in MS patients are due to optic nerve involvement. Although rare, demyelination may affect the optic chiasm or retrochiasmal pathways, causing bitemporal or homonymous hemianopias, respectively (Newman *et al*. 1991; Fazzone *et al*. 2003b). Visuoperceptual impairments secondary to slowed visual information processing from parietal or temporal lobe demyelination may also occur (Vleugels *et al*. 2001).

Uveitis is more frequent in MS patients than in the general population, and visual loss secondary to cataracts or glaucoma, possibly attributable to repeated steroid treatment, must also be considered (Biousse *et al*. 1999; Polman *et al*. 2003).

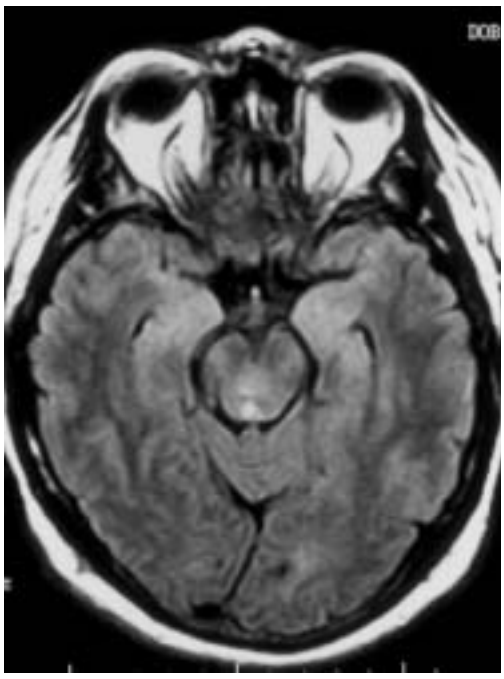

Figure 7 Axial FLAIR MRI through the caudal midbrain in a patient with a right internuclear ophthalmoplegia. A demyelinating lesion in the right medial longitudinal fasciculus (arrow) is seen.

OCULAR MOTILITY IN MULTIPLE SCLEROSIS

Eye movement abnormalities are very common in MS, reflecting posterior fossa lesions, and may be a bedside method of predicting disability (Weinshenker *et al*. 1991; Downey *et al*. 2002). The most frequently encountered sign is internuclear ophthalmoplegia (INO), due to a lesion in the medial longitudinal fasciculus (MLF) in the rostral pons and caudal midbrain (Fig. 7). Other motility abnormalities include pendular and jerk nystagmus, horizontal gaze palsies, Parinaud's syndrome, vestibular ocular reflex dysfunction, ocular dysmetria and flutter, and saccadic intrusions such as square wave jerks (Matsumoto *et al*. 2001; Barton *et al*. 1999; Milea *et al*. 2001; Schon *et al*. 2001; Lee *et al*. 2003).

INO occurs in about one-quarter of patients with MS, it may be the initial isolated demyelinating event, and it is often bilateral (Frohman *et al*. 2001). The MLF carries signals from the abducens nucleus to the contralateral oculomotor nucleus to allow conjugate horizontal gaze with cocontraction of the ipsilateral lateral rectus and contralateral medial rectus muscles. Examination in a unilateral INO discloses impaired adduction of the eye ipsilateral to the MLF lesion, and dissociated nystagmus of the contralateral abducting eye. However, adduction of the affected ipsilateral eye is often evident with convergence eye movements. Saccades seem specifically impaired because the demyelinated MLF axons are poorly equipped to carry the high-frequency discharges required for these rapid eye movements (Leigh & Zee 1999). With bilateral MLF lesions, an exotropia may develop, referred to as a WEBINO or 'wall-eyed bilateral INO' (Leigh & Zee 1999). Patients with INO may be asymptomatic, or they may experience diplopia or oscillopsia (see below).

Bilateral INO is common because the brainstem periventricular location of the MLF is a region that is particularly vulnerable to demyelination (Frohman *et al*. 2001). 58 patients with infrared oculographic-proven INO underwent proton density, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) MRI. Proton density imaging proved to be the most sensitive method of detecting the demyelinating plaque responsible (Frohman *et al*. 2001); 93% of

patients had MLF lesions in the pons, 66% in the midbrain, and 59% had both pons and midbrain involvement. Only 48% of lesions identified with proton density imaging were seen on FLAIR images. This study also demonstrated the disconnection between clinical disability and MRI lesion burden in MS.

The exquisite neuroanatomical localization of ocular motility deficits emphasizes the importance of their role in defining the clinical use of MRI (Leigh & Wolinsky 2001). The Frohman *et al*. (2001) study also underscores the ability of quantitative ocular movement recordings to detect subclinical INO, because several patients with oculographic evidence of INO did not have an INO detected on clinical examination. Thus quantitative eye movement recordings provide an additional way of detecting a subclinical demyelinating lesion, which may confirm the diagnosis of MS in patients with a clinically isolated demyelinating event.

The typical visual symptom of nystagmus is oscillopsia, which can be disconcerting for patients. Therefore, improved nystagmus treatment would be useful (Leigh & Tomsak 2003). But, at present, most of the therapeutic suggestions for nystagmus are based on single case reports or small case series. Suggested treatments for demyelinating pendular nystagmus include gabapentin, memantine, clonazapam, trihexphenidyl, scopolamine, cannabis and alcohol. Upbeat and periodic alternating nystagmus may respond to baclofen (Leigh & Tomsak 2003). Downbeat nystagmus treatments include clonazepam, baclofen, trihexphenidyl, and 3,4-diaminopyridine (Leigh & Tomsak 2003; Leigh 2003; Strupp *et al*. 2003).

The ocular motility examination can provide information about disability that is not readily captured by the standard Kurzke EDSS, or the MSFC. A study comparing disability between two groups of MS patients, 22 with ocular motility deficits and 28 without, found those with motility problems were more disabled both on initial examination and following an interval of 2 years (Downey *et al*. 2002; Derwenskus *et al*. 2003).

CONCLUSIONS

Neuro-ophthalmological involvement in MS is a frequent cause of disability. Advances in understanding of both afferent and efferent neuro-ophthalmic manifestations have contributed significantly to diagnostic accuracy, therapeutic intervention, and patient counselling in MS.

SUMMARY

- Optic neuritis and eye movement disorders, particularly internuclear ophthalmoplegia, are a common cause of disability in patients with multiple sclerosis.
- Optic neuritis causes acute, unilateral, painful visual loss which progresses over days to weeks and spontaneously recovers over weeks to months. Initially, the optic nerve head looks normal in two-thirds of cases.
- Persistent subjective complaints of abnormal vision are common after optic neuritis and are often explained by defects in contrast sensitivity.
- Optic atrophy may occur after a single episode of optic neuritis, supporting the argument for early therapeutic intervention.
- Short tau inversion recovery (STIR) MRI sequences are best at showing optic nerve abnormalities.
- Optic neuritis does not require acute intervention, but may appropriately be treated with high dose steroids.
- There is no role for standard dose (1 mg/kg/day) oral prednisone in the treatment of optic neuritis.
- Brain MRI lesions identified at the time of an initial episode of optic neuritis are highly predictive of future MS risk.
- Initiation of immunomodulatory therapy in the setting of optic neuritis and at least two MRI brain lesions should be considered.
- Proton density MRI is the most sensitive method for detecting a medial longitudinal fasciculus lesion in the setting of internuclear ophthalmoplegia.

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