Management of acute optic neuritis

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Optic neuritis is a common condition that causes reversible loss of vision. It can be clinically isolated or can arise as one of the manifestations of multiple sclerosis. Occasional cases are due to other causes, and in these instances management can differ radically. The treatment of optic neuritis has been investigated in several trials, the results of which have shown that corticosteroids speed up the recovery of vision without affecting the final visual outcome. Other aspects of management, however, are controversial, and there is uncertainty about when to investigate and when to treat the condition. Here we review the diagnostic features of optic neuritis, its differential diagnosis, and give practical guidance about management of patients. The condition’s association with multiple sclerosis will be considered in the light of studies that define the risk for development of multiple sclerosis and with respect to results of trials of disease-modifying drugs in these individuals.

Optic neuritis is common, having an incidence of 1–5 per 100 000 per year.1 The incidence is highest in caucasians,4 in countries at high latitudes,2 and in spring.3 Orthostatic pain, which is often labelled retrobulbar neuritis. Retinal examination is usually unremarkable. However, in a series of 50 consecutive patients with optic neuritis,16 peripheral retinal periphlebitis (perivenous sheathing) was seen in six patients and fluorescein leakage in ten. The presence of other causes of visual loss that can mimic optic neuritis. We will also discuss ways of identifying cases that are not optic neuritis dependent and how to manage them. The association of optic neuritis with multiple sclerosis will be assessed, as will the role of investigations to define the risk of development of multiple sclerosis. The results of trials of disease-modifying drugs in those at risk of development of multiple sclerosis, and how to advise patients about that risk, will also be discussed.

Optic neuritis

Clinical features

Panel 1 shows the typical presenting symptoms and signs of optic neuritis.7 The condition usually presents as a painful subacute unilateral loss of vision, which progresses over a few days to 2 weeks.19 In 10% of individuals, no pain is reported and in the rest, the pain varies in severity, although typically does not interfere with sleep (G T Plant, unpublished). Light flashes (phosphenes or photopsias) might be seen by the patient on eye movement.20 Clearly, subclinical cases are frequent, since some patients present with Uhthoff’s phenomenon (visual deterioration on getting warm, or during exercise),21 and delayed visual evoked potentials are not uncommon in early multiple sclerosis, even without a previous history of optic neuritis.13 The maximum visual loss varies from minor blurring to no perception of light in the affected eye. Abnormal colour vision, reduced contrast sensitivity, visual field loss, and a relative afferent pupillary defect (RAPD) are usually present in the affected eye.4,10–14 The presence of an RAPD is a useful objective sign of a unilateral optic neuropathy, although it is not specific for optic neuritis. The absence of an RAPD can indicate mild clinical involvement in the affected eye, previous optic neuritis in the contralateral eye, or subclinical optic neuropathy in the contralateral eye.11

Slit lamp examination occasionally reveals cells in the anterior chamber or vitreous, but is usually normal.16 However, intermediate uveitis, pars planitis, panuveitis, and granulomatous uveitis are all associated with optic neuritis and multiple sclerosis. The uveitis can be present for some years before the onset of optic neuritis or multiple sclerosis.23,24 The optic disc appears swollen in 36–58% of patients at presentation (figure 1).4,6 Small flame-shaped haemorrhages or pronounced swelling of the optic disc with cotton wool spots on the disc are seen occasionally. In instances in which there is no disc swelling, the condition is often labelled retrobulbar neuritis. Retinal examination is usually unremarkable. However, in a series of 50 consecutive patients with optic neuritis,16 peripheral retinal periphlebitis (perivenous sheathing) was seen in six patients and fluorescein leakage in ten. The presence of

Search strategy

This review is based on reading of neuro-ophthalmology textbooks and on a search of PubMed for articles on “optic neuritis”. Treatment trials were identified by searching PubMed with the search terms: “treatment of”, “corticosteroids”, and “optic neuritis”. Articles on diseases mentioned as part of the differential diagnosis of optic neuritis were identified by searching PubMed for the appropriate condition. Only articles in English were used. The articles were selected to support the discussion and to present evidence-based features of our own practice.
initial period of recovery is rapid and probably relates to the resolution of acute inflammation, and the conduction block so caused, in the optic nerve. Further improvement in vision is seen up to a year after the acute episode. Remyelination and the proliferation of sodium channels in demyelinated segments of the nerve to restore conduction could be responsible for this recovery. Remyelination can continue for up to 2 years, as suggested by progressive shortening of initially prolonged visual evoked potential latencies, although after the first year, remyelination is not usually associated with functional improvement in vision. Reorganisation of cortical activation has also been reported after optic neuritis and could be involved in the recovery process. The mean visual acuity at 1 year after entry into the ONTT was better than 6/5 (Snellen equivalent), with less than 10% having a visual acuity worse than 6/12.  

Severity of the initial visual loss does seem to be related to final visual outcome, but most patients recover well. Of 187 patients with visual acuity worse than 6/60 on admission to ONTT, only 6% had this level of acuity or worse at 6 months. Of 28 patients in whom visual acuity was down to light perception, or worse, 64% recovered to 6/12 or better. In another group, of 12 patients who presented with no light perception in the affected eye, five recovered to 6/6 or better, three to 6/12 or better, and four had peripheral recovery but dense central scotomata and visual acuities of less than 3/60.  

Other visual parameters tend to improve in parallel with the improvement in visual acuity, but subjective residual deficits are frequent. In one study of 58 patients, 59% reported that their vision had not returned to normal 1 year after untreated optic neuritis, although only five (8%) had a visual acuity in the affected eye worse than 6/9. Vision after optic neuritis can vary greatly during the day and from one day to the next, and might deteriorate in specific situations—eg, Uhthoff’s phenomenon, and fatigue or fading of vision. Pullrich’s phenomenon (misperception of the trajectory of moving objects) is occasionally noted.  

The optic disc of patients usually becomes pale, either diffusely or usually in the temporal region, despite improvements in vision. The RAPD might disappear on recovery, although, especially in instances in which there is poor recovery, it can be persistent.  

### Differential diagnosis

Panel 2 shows the differential diagnoses of optic neuritis and appropriate tests. Misdagnosis of optic neuritis has been reported in clinical trials. Of 457 patients enrolled in the ONTT, three were subsequently diagnosed as having anterior ischaemic optic neuropathy, two had compressive lesions (one ophthalmic artery aneurysm and one pituitary tumour), and two had connective tissue diseases in addition to optic neuritis. In a later study, of 102 patients enrolled, 17 were later excluded due to misdiagnosis. The final diagnoses in these patients included rhinogenic optic neuroophathy (sinus mucocoele), brain tumour, ischaemic optic neuropathy, Leber’s hereditary optic neuropathy, nutritional optic neuropathy, and age-related macular degeneration.  

Presentation with severe pain that restricts ocular movements or wakes the patient from sleep should alert to the possibility of posterior scleritis or an infective or granulomatous optic neuropathy, such as sarcoidosis or chronic relapsing inflammatory optic neuropathy (CRION). Visual loss in infective and granulomatous optic neuropathy is usually more severe than in typical
optic neuritis and does not spontaneously improve. In instances of optic neuropathy due to sarcoidosis, there are usually systemic features of the disease that can be detected, although the condition might be restricted, at least initially, to the optic nerve.42

Children or adults can present with a typical history for optic neuritis, but on fundus examination swelling of the optic disc and a macular star is seen, leading to the diagnosis of neuroretinitis. This condition is usually idiopathic, but can be associated with cat-scratch disease, Lyme disease, syphilis, toxocariasis, toxoplasmosis, and histoplasmosis.12 Prognosis for recovery is good and there is no risk of development of multiple sclerosis.9 Sarcoïd optic neuropathy, if it affects the anterior optic nerve, can cause disc swelling and a macular star,11 but spontaneous recovery is unusual in sarcoidosis.

| Panel 2: Differential diagnosis of optic neuritis9,30–42 |
|---------------------------------|-------------------------------------------------|---------------------------------|
| **Diagnosis**                     | **Usual clinical features in each category**                | **Tests to consider in each category**               |
| **Corticosteroid-responsive optic neuropathies** |                                                                                         |
| Sarcoidosis                      | Progressive severe visual loss; may be very painful; often bilateral (simultaneous or sequential); isolated or as part of a multisystem disorder; more frequent in Africans or Afro-Caribbeans (sarcoidosis); relapse when corticosteroids withdrawn | MRI, orbits and brain with contrast Lumbar puncture ANA Serum ACE Chest radiograph Gallium scan Biopsy of accessible tissue (sarcoid) |
| Systemic lupus erythematosus     | Bilateral and simultaneous; isolated or at presentation of systemic lupus erythematosus | MRI, orbits and brain with contrast Lumbar puncture |
| Autoimmune optic neuritis        | Swollen optic disc and macular star; spontaneous recovery | Bartonella, borrelia, and syphilis serology |
| Chronic relapsing inflammatory optic neuropathy |                                                                                         |
| Optic perineuritis               |                                                                                         |
| Behçet’s disease                 |                                                                                         |
| Neumyelitis optica (Devic’s disease) |                                                                                         |
| **Other inflammatory optic neuropathies** |                                                                                         |
| Post-infectious                  |                                                                                         |
| Post-vaccination                 |                                                                                         |
| Acute disseminated encephalomyelitis |                                                                                         |
| Neuroretinitis                   | Painless (rarely painful—eg, aneurysms and mucocoeles); progressive visual loss; optic atrophy at presentation; past history of, or evidence for, primary tumour (metastases) | CT or MRI, orbits and brain with contrast Biopsy if appropriate |
| **Compressive optic neuropathies** |                                                                                         |
| Primary tumours—eg, meningiomas, gliomas, and pituitary tumours |                                                                                         |
| Metastases                       |                                                                                         |
| Tuberculomas                     |                                                                                         |
| Thyroid ophthalmopathy           |                                                                                         |
| Arterial aneurysms               |                                                                                         |
| Sinus mucocoeles                 |                                                                                         |
| **Infectious optic neuropathies** |                                                                                         |
| Syphilis                         | Progressive visual loss with exposure to infectious agent; severe optic disc oedema cellular reaction in vitreous | Appropriate serology Lumbar puncture Chest radiograph Tuberculin test |
| Tuberculosis                     |                                                                                         |
| Lyme disease                     |                                                                                         |
| Viral optic neuritis             |                                                                                         |
| **Ischaemic optic neuropathies** |                                                                                         |
| Anterior ischaemic optic neuropathy | Usually older age group; sudden onset; painless (except GCA); swollen optic disc (except PION); altitudinal field defect | Erythrocyte sedimentation rate |
| Posterior ischaemic optic neuropathy (PION) |                                                                                         |
| Giant cell arteritis (GCA)       |                                                                                         |
| Diabetic papillopathy            |                                                                                         |
| **Toxic and nutritional optic neuropathies** |                                                                                         |
| Vitamin B12 deficiency           | Bilateral and symmetrical; painless; poor prognosis | Serum vitamin B12 |
| Tobacco-alcohol amblyopia        |                                                                                         |
| Methanol intoxication            |                                                                                         |
| Ethambutol toxicity              |                                                                                         |
| Cuban and Tanzanian epidemic optic neuropathies |                                                                                         |
| **Inherited optic neuropathies** |                                                                                         |
| Leber’s hereditary optic neuropathy | Family history; sequential (or simultaneous) bilateral painless; visual loss | Genetic testing for Leber’s mutation |
| **Ocular causes**                |                                                                                         |
| Posterior scleritis              | Severe pain; less visual symptoms | B-mode ultrasound of orbits |
| Maculopathies and retinopathies, including central serous retinopathy | Painless; metamorphopsia; preserved colour vision | Electroretinogram Fluorescein angiogram |
| Big blind spot syndrome and acute zonal occult outer retinopathy | Visual field loss and photopsias; normal fundus; preserved colour vision | Electrocardiogram |

ACE=angiotensin converting enzyme. ANA=antinuclear antibodies. Metamorphopsia=distorted vision.
Panel 3: Warning signs in the presentation of optic neuritis that should prompt further investigation to rule out alternative diagnoses

Optic atrophy on presentation without previous optic neuritis or multiple sclerosis
Severe optic disc oedema with vitreous reaction
Optic disc haemorrhage
Bilateral loss of vision
Previous history of neoplasia
African or Afro-Caribbean patients with vision <6/12 and no early recovery
Loss of vision to no perception of light with no early recovery
Painless loss of vision to <6/60 with no early recovery
Severe or persistent pain for >2 weeks since onset
Visual loss progressing for >2 weeks since onset of visual symptoms
Absence of recovery > 3 weeks after onset of visual symptoms
Deterioration of vision after withdrawal of corticosteroids

Diagnostic tests
Generally, optic neuritis can be diagnosed on clinical grounds (panel 1). However, if any warning signs or atypical features for optic neuritis arise, which are suggestive of an alternative diagnosis (panel 3), further investigations should be done promptly. The best management of some conditions—e.g., optic nerve compression by a sinus mucocoele, or a tuberculous or granulomatous optic neuropathy—requires appropriate treatment to be administered within days of presentation; delay can result in a much worse visual outcome. Thus, an expectant approach must not be adopted if clinical features are atypical. Combined ophthalmological and neurological services are helpful in improving diagnostic accuracy, and early review is important to ensure that visual recovery, either subjectively or objectively, has begun since, if not, optic neuritis is an unlikely diagnosis.

Investigations should be guided by the clinical presentation (panel 2). Ready access to imaging facilities is important. Contrast-enhanced high-resolution CT with fine cuts through the orbits will show up most compressive lesions. Short tau inversion recovery or fat-saturated fast spin-echo MRI is preferable in that it does not involve ionising radiation and can also show any intrinsic optic nerve lesions, as arise in optic neuritis (figure 2). Visual evoked potentials might not be helpful in differentiating between different causes of optic neuropathies in the acute phase, although the combination of visual evoked potentials with pattern electroretinogram (PERG) can be useful in differentiating macular from optic nerve disorders. In retinal disorders, both the P50 (early) and N95 (late) components of the PERG are abnormal, whereas in disorders of the optic nerve only the N95 component is abnormal. In acute optic neuritis, however, the P50 can also be reduced in the acute phase, which normalises during recovery. In clinical practice, the presence of a delayed but well preserved P100 wave of the visual evoked potential is most useful in confirming a diagnosis of optic neuritis if the presentation is delayed, or in supporting a diagnosis of multiple sclerosis, by showing dissemination in space in appropriately selected patients.

If a corticosteroid-responsive optic neuropathy is suspected, both conventional and gadolinium-enhanced MRI of the orbits and brain should be done. In sarcoidosis, CRION, and optic perineuritis, enhancement of the optic nerve sheath is typical. Additionally, in sarcoidosis, basal meningeal enhancement and enhancing cerebral lesions might be seen. White-matter lesions on both T2-weighted and gadolinium-enhanced MRI are usually seen in the context of multiple sclerosis, however, the finding can be non-specific. The importance of small T2 abnormalities alone requires a consideration of the site and shape of the lesions and the age of the patient, recognising that age-related changes due to small-vessel disease should not be misinterpreted as evidence for demyelination.

Serological and other evidence for sarcoidosis, vasculitis, and syphilis should be sought, and tuberculosis considered in appropriate patients. In instances of suspected infectious or corticosteroid-responsive optic neuropathy, a lumbar puncture should also be done. Results of examination of the cerebrospinal fluid can be used to look for infections, hypercellularity, a raised protein concentration, and local or systemic production of oligoclonal bands of immunoglobulins to try to help differentiate between demyelinating optic neuritis and other causes of inflammatory optic neuritis. In optic neuritis there might be no oligoclonal bands or local intrathecal synthesis of immunoglobulins (unmatched bands compared with serum). In CRION, sarcoidosis, vasculitis, or acute disseminated encephalomyelitis there might be no oligoclonal bands or systemic production of immunoglobulins (matched oligoclonal bands in both cerebrospinal fluid and serum).

Treatment
Several trials have been done to attempt to improve the prognosis of typical optic neuritis with respect to visual outcome. Findings of early, observational studies suggested that corticosteroids might be effective, although this view was controversial. Subsequent placebo-controlled trials of corticosteroids have been done and are summarised in panel 4. A meta-analysis of these trials showed that corticosteroids reduced the number of patients without clinical improvement at 30 days (odds ratio 0·60, range 0·42–0·85), but did not result in long-term improvement in visual outcome (0·96, 0·71–1·31). When the presenting visual acuity was 6/12 or better, corticosteroids conferred no benefit in the ONTT. There has been a suggestion that the absence of a long-term beneficial effect in the trials might be because the corticosteroids were given too late to provide neuroprotection. Treatment trials in the hyperacute phase are required to address this issue.

Figure 2: Fat-saturated proton-density fast spin-echo MRI of left-sided acute optic neuritis
Arrow points to affected optic nerve.
Corticosteroids can cause side-effects. Frequent minor side-effects reported include insomnia, mild mood changes, stomach upsets, facial flushing, acne, oedema, and weight gain. More serious side-effects seen in the intravenous methylprednisolone group of the ONTT (n=151) include one patient developing psychotic depression and another developing pancreatitis. There have also been reports of avascular necrosis (osteonecrosis) of the femoral head and deaths in children due to chickenpox after short-term corticosteroid therapy. There are currently no other treatment options for acute demyelinating optic neuritis.

**Panel 4: Randomised controlled trials of corticosteroids in acute unilateral optic neuritis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Entry criteria</th>
<th>Treatment groups</th>
<th>Visual outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rawson et al, 1966</td>
<td>Treatment to commence within 10 days of onset of symptoms</td>
<td>1) IM ACTH 40 units/day for 30 days (n=25)  2) IM placebo for 30 days (n=25)</td>
<td>Faster recovery of VA in treatment group (p=0.01 at 30 days) but no effect at 1 year</td>
<td>All treated patients pain-free by 2 days</td>
</tr>
<tr>
<td>Bowden et al, 1974</td>
<td>Any patient irrespective of delay to initiation of treatment</td>
<td>1) IM ACTH 40 units/day for 30 days (n=27)  2) IM placebo for 30 days (n=27)</td>
<td>No significant treatment effect for any visual variable at any time up to 2 years</td>
<td>Placebo group pain-free by 2 weeks</td>
</tr>
<tr>
<td>Gould et al, 1977</td>
<td>Treatment to commence within 10 days. VA &lt;6/9, abnormal colour vision, RAPD, and central scotoma</td>
<td>1) Retrobulbar triamcinolone 40 mg (n=31)  2) No injection (n=30)</td>
<td>Faster rate of recovery of VA in treatment group (p=0.01 at 1 week)</td>
<td>Mean delay to treatment of 16-7 days (ACTH group) and 18-5 days (controls)</td>
</tr>
<tr>
<td>Liversedge, 1969</td>
<td>Randomisation within 21 days and before recovery RAPD and more than two of: abnormal VA; central scotoma; abnormal VEP or flicker test, or both</td>
<td>1) Oral prednisolone 1 mg/kg per day for 14 days (n=156)  2) IV MP 250 mg QDS for 3 days then 1 mg/kg per day prednisolone for 11 days (n=151)  3) 3 days of dose tapering in both treatment groups  3) Oral placebo for 14 days (n=150)</td>
<td>Median VA 6/7-5 by day 4 in IV MP group compared with day 15 in other two groups</td>
<td>Single blind</td>
</tr>
<tr>
<td>Bowden et al, 1974</td>
<td>Any patient irrespective of delay to initiation of treatment</td>
<td>1) Oral prednisolone 1 mg/kg per day for 3 days with no tapering dose (n=33)  2) IV saline for 3 days (n=33)</td>
<td>Trend for increased rate of recovery of VA after IV MP in all patients and in those with long lesions</td>
<td>No benefit shown for prednisolone</td>
</tr>
<tr>
<td>Gould et al, 1974</td>
<td>Treatment to commence within 8 days of onset of symptoms RAPD and abnormal visual field in affected eye</td>
<td>1) Oral prednisolone 1 mg/kg per day for 14 days (n=156)  2) IV MP 250 mg QDS for 3 days then 1 mg/kg per day prednisolone for 11 days (n=151)  3) 3 days of dose tapering in both treatment groups  3) Oral placebo for 14 days (n=150)</td>
<td>Median VA 6/7-5 by day 4 in IV MP group compared with day 15 in other two groups</td>
<td>Increased risk of recurrence of ON after prednisolone at 5 years (p=0.003 vs IV MP, p=0.004 vs placebo) Decreased 2-year (ARR 0.34, 95% CI 0.16-0.74) but not 3-year rate of CDMS after IV MP</td>
</tr>
<tr>
<td>Kapoor et al, 1998</td>
<td>Randomisation within 30 days VA &lt;6/9 Optic nerve lesions classified as long (&gt;15 mm) or short on STIR MRI</td>
<td>1) IV MP 1 g per day for 3 days with no tapering dose (n=33)  2) IV saline for 3 days (n=33)</td>
<td>Trend for increased rate of recovery of VA after IV MP in all patients and in those with long lesions</td>
<td>No IV placebo group</td>
</tr>
<tr>
<td>Sellebjerg et al, 1999</td>
<td>Treatment to commence within 28 days of onset of symptoms VA &lt;0.7</td>
<td>1) Oral MP 500 mg per day for 5 days with a tapering dose for 10 days (n=30)  2) Oral placebo for 15 days (n=30)</td>
<td>Improved spatial vision at 3 weeks in treatment group (p=0.03)</td>
<td>No benefit after 8 weeks and 1 year</td>
</tr>
<tr>
<td>Wakakura et al, 1999</td>
<td>Treatment to commence within 14 days of onset of symptoms RAPD in affected eye</td>
<td>1) IV MP 1 g per day for 3 days then oral taper for 7-10 days (n=33)  2) IV mecobalamin 500 µg per day for 3 days then orally for 7 days (n=33)</td>
<td>Faster visual recovery for all variables tested after IV MP but no treatment effect seen after 12 weeks and 1 year</td>
<td>Mecobalamin treatment used for comparison as placebo treatment considered unethical in Japan</td>
</tr>
</tbody>
</table>

**ACTH=adrenocorticotropic hormone (corticotropin); ARR=adjusted rate ratio; CDMS=clinically definite multiple sclerosis; IM=intramuscular; IV=intravenous; MP=methylprednisolone; ON=optic neuritis; QDS=4 times per day; RAPD=relative afferent pupillary defect; STIR=short tau inversion recovery; VA=visual acuity; VEP=visual evoked potential.**
Recommendations for management
Optic neuritis

In 2000, the Quality Standards Subcommittee of the American Academy of Neurology72 stated that “oral prednisolone 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. Higher dose oral or parenteral methylprednisolone or adrenocorticotropic hormone [corticotropic] may hasten the speed and degree of recovery of visual function in persons with acute monosymptomatic optic neuritis. There is, however, no evidence of long-term benefit for visual function. The decision to use these medications to speed recovery but not to improve ultimate visual outcome should therefore be based on other non-evidence-based factors such as quality of life, risk to the patient, visual function in the fellow eye, or other factors that the clinician deems appropriate.”

When treatment is instigated, 1 g per day intravenous methylprednisolone for 3 days has become the preferred option.7 This option tends to be given as a single daily dose, which enables outpatient treatment. In the USA, an oral taper of prednisolone after this regimen remains popular, although it is less often used in the UK and Europe.73 The rationale for the use of an oral taper is to suppression of the hypothalamic-pituitary-adrenal axis, although with the short treatment regimens used fast recovery of the axis is seen and the oral taper should not normally be needed.74 Another concern is that after cessation of intravenous methylprednisolone symptoms can deteriorate with recrudescence of inflammation, as has been suggested by results of studies on the brain with serial gadolinium-enhanced MRI in patients with multiple sclerosis.75 However, there were no reports of recovery followed by deterioration of vision in the one study that did not use an oral taper.76 Furthermore, we have not noticed worsening of vision after cessation of intravenous methylprednisolone in our patients, except in instances proven to have another cause—eg, granulomatous optic neuropathy.

Because of the lack of evidence of long-term benefit and because of the potential for side-effects from corticosteroids, we do not routinely treat typical optic neuritis with corticosteroids. However, if there is pre-existing poor vision in the contralateral eye, we offer corticosteroids to shorten the period of functional impairment. We give 1 g per day intravenous methylprednisolone for 3 days without an oral taper, but review early to ensure that vision does not deteriorate after cessation of treatment. Appropriate precautions are taken before starting treatment, and we warn all patients of possible side-effects.77

If a corticosteroid-responsive optic neuropathy is suspected, we start treatment with intravenous methylprednisolone 1 g per day for 3 days followed by 1 mg/kg per day oral prednisolone. This dose is then slowly reduced over 8–12 weeks. If a relapse occurs on reducing the dose, high-dose treatment is reinstigated and a corticosteroid-sparing agent such as azathioprine started before reducing the dose again. That patients are instructed to report immediately if deterioration in vision is noticed, is of utmost importance. Protocols for osteoporosis prophylaxis are followed. In optic neuritis associated with vasculitis—eg, in systemic lupus erythematosus—the visual outcome may be improved if cyclophosphamide is given at an early stage, but there are no published data to support this course of action.

At present there is no treatment that can reverse established poor visual outcome after typical optic neuritis. An early report78 suggested that intravenous immuno-
Panel 5: McDonald diagnostic criteria for multiple sclerosis after optic neuritis

MRI dissemination in space, consisting of three out of four of the following:
- One gadolinium-enhancing lesion or nine T2 hyperintense lesions if no enhancing lesions
- At least one infratentorial lesion
- At least one juxtacortical lesion
- At least three periventricular lesions

(One spinal cord lesion can be substituted for one brain lesion)

or

Two or more MRI-detected lesions consistent with multiple sclerosis plus positive cerebrospinal fluid (oligoclonal bands different from any such bands in the serum, or the presence of raised IgG index, or both)

and

MRI dissemination in time
- First MRI 3 or more months after the clinical event
  1. A gadolinium-enhancing lesion (not at the site implicated in the first clinical event) is sufficient evidence to indicate dissemination in time
  2. If there are no gadolinium-enhancing lesions a second scan is required more than 3 months later.
- A new T2 or gadolinium-enhancing lesion is sufficient evidence for dissemination in time
  1. First MRI less than 3 months after the clinical event
  2. If no enhancing lesion is seen on this MRI, a further scan done not less than 3 months after the first scan that shows a new T2 or enhancing lesion will suffice

or

A second clinical attack

spinal cord and brain stem syndromes—ten of 21 (48%) patients with abnormal brain and spinal cord imaging developed multiple sclerosis at 1 year compared with three of 17 (18%) with brain lesions alone. The risk of multiple sclerosis within 1 year also increased if new brain lesions were detected on repeat brain imaging after 3 months. Multiple sclerosis arose in 12 of 21 (57%) patients with new lesions on T2-weighted imaging and seven of 11 (64%) patients with new gadolinium-enhancing lesions, but in only one of 20 (5%) patients who had abnormal baseline imaging and no new lesions at 3 months. The International Panel on Multiple Sclerosis Diagnosis has published diagnostic criteria for multiple sclerosis (McDonald criteria), which suggest that MRI evidence of dissemination of lesions of the central nervous system in time and space is sufficient for the diagnosis of multiple sclerosis even before clinical dissemination has occurred (panel 5; figure 3). These criteria clarify the role of MRI in clinical practice but have not been without controversy, principally with respect to the reliance on imaging data when the findings on MRI can be non-specific. However, when applied to a cohort of CIS patients, the criteria using repeat imaging after 3 months, had a specificity of 93% and a positive predictive value of 83% for the development of clinically definite multiple sclerosis at 3 years.

Even if multiple sclerosis does develop after optic neuritis, the prognosis for disability is usually good, being associated with a benign course of the disease (odds ratio 1.73, 95% CI 1.27–2.35). After 5 years, only 17 of 105 patients who developed clinically definite multiple sclerosis (4% of the entire cohort) in the ONTT had an expanded disability status scale (EDSS) score of three or more, and only five had an EDSS score of six or more, although this finding did include one patient who died from multiple sclerosis. As well as predicting an increased risk for the development of multiple sclerosis, brain MRI lesion load can also help to predict the probability of development of disability after a CIS. In a cohort of patients followed up for 14 years after a CIS, EDSS correlated with both baseline lesion volume ($r=0.48$) and change in lesion volume in the first 5 years ($r=0.61$), suggesting that early inflammatory activity in multiple sclerosis is related to the later development of disability.

**Treatments to delay onset of multiple sclerosis**

Are there any treatments that alter the risk for development of multiple sclerosis after clinically isolated

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**Figure 3: MRI evidence of dissemination of central nervous system lesions in time and space**

Baseline proton-density weighted fast spin-echo MRI of a 37-year-old woman with optic neuritis (left), showing asymptomatic brain lesions (arrows), and gadolinium-enhanced T1-weighted spin-echo image taken 3 months later (right), showing two new enhancing lesions (arrows) sufficient to give a diagnosis of multiple sclerosis based on the McDonald criteria.
optic neuritis? Results of a post hoc analysis from the ONTT suggested that there was a decreased risk for the development of clinically definite multiple sclerosis in patients who received intravenous methylprednisolone (n=10, 7.5%) compared with the risk in those who received prednisolone (n=19, 14.7%) or placebo (n=21, 16.7%), after a follow-up of 2 years in patients with clinically isolated optic neuritis. In the study (n=389), the adjusted rate ratio for the development of clinically definite multiple sclerosis in the group on intravenous methylprednisolone was 0.34 (95% CI 0.16-0.74) compared with placebo. Most of the treatment effect was seen in patients with an abnormal brain MRI on entry to the trial. The findings, however, were based on a retrospective analysis, using an open-label treatment (there was no intravenous placebo arm) with only small numbers developing multiple sclerosis. Also, data were not available for 50 of the patients, which could have had a confounding effect. The beneficial effect was lost by 3 years, with a cumulative incidence of clinically definite multiple sclerosis of 17.3% in the methylprednisolone group, 24.7% in the prednisolone group, and 21.3% in the placebo group. The importance of these findings remains uncertain. If intravenous methylprednisolone delays the onset of clinically definite multiple sclerosis, the effect is short-lived and does not affect either the eventual risk of clinically definite multiple sclerosis or the development of disability. In our opinion, intravenous methylprednisolone should not be given in instances in which the sole aim is to protect against multiple sclerosis; treatment should be guided by the other factors outlined in this Review.

Two trials have addressed whether β interferon can slow down the progression from CIS to clinically definite multiple sclerosis. 383 patients were recruited to the CHAMPS study after their first demyelinating event (192 with optic neuritis) who, in addition, had two or more clinically silent brain lesions on MRI. Half the patients received intramuscular interferon β-1a 30 μg once a week and half placebo. The trial was stopped early after an interim analysis since the cumulative probability of the development of clinically definite multiple sclerosis during 3-years’ follow-up was significantly lower in the interferon group than in the placebo group (rate ratio 0.56; 95% CI 0.38-0.81; p=0.002). There was also a relative reduction in new lesion activity on MRI in the interferon group (p<0.001). A similar group of patients (n=309, 98 with optic neuritis) was enrolled to the ETOMS study, but four asymptomatic white matter lesions (or three if one was vascular origin) were given interferon β-1a on the erroneous assumption that the cause of visual loss was optic neuritis.

Because the risk of multiple sclerosis after optic neuritis is much lower in children than in adults, and since disease-modifying drugs are not licensed for use in children, we do not recommend routine brain imaging after either unilateral or bilateral optic neuritis in this population unless required for initial diagnosis.

What to tell the patient
There has been understandable reluctance to discuss the link between optic neuritis and multiple sclerosis with patients. An awareness of their risk of development of multiple sclerosis can cause much anxiety, despite the fact that many will not develop the disease. A previous diagnosis of optic neuritis can, however, affect future insurance policy applications, and many patients have discovered that they are at risk of developing multiple sclerosis only when they have had insurance applications refused. There is also a wealth of information available on the internet, linking optic neuritis with multiple sclerosis. Our policy is to discuss the risks fully with all patients, emphasising that they might never develop multiple sclerosis but that if they do the prognosis can be good. The decision of whether to organise initial or follow-up MRI should be guided by the availability of disease-modifying drugs and by discussion with the patients as to whether definitive diagnosis and risk stratification is important to them.
Conclusion
Optic neuritis is a self-limiting condition that can usually avoid affecting the long-term prognosis for visual function. An expectant approach to management is therefore reasonable, although if there is suspicion of a different diagnosis or deviation from the expected clinical course then urgent investigations are called for to rule out, in particular, a compressive lesion or a corticosteroidresponsive optic neuropathy. Furthermore, optic neuritis can be the first manifestation of multiple sclerosis. An increased risk of multiple sclerosis exists if there are asymptomatic brain lesions on MRI. Serial MRI can provide an early diagnosis of multiple sclerosis in some patients. Although interferons can delay the time to a second relapse, their long-term effect on disability is unknown.

Contributors
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Conflict of interest statement
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