

Optic neuritis

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Acute optic neuritis is the most common optic neuropathy affecting young adults. Exciting developments have occurred over the past decade in understanding of optic neuritis pathophysiology, and these developments have been translated into treatment trials. In its typical form, optic neuritis presents as an inflammatory demyelinating disorder of the optic nerve, which can be associated with multiple sclerosis. Atypical forms of optic neuritis can occur, either in association with other inflammatory disorders or in isolation. Differential diagnosis includes various optic nerve and retinal disorders. Diagnostic investigations include MRI, visual evoked potentials, and CSF examination. Optical coherence tomography can show retinal axonal loss, which correlates with measures of persistent visual dysfunction. Treatment of typical forms with high-dose corticosteroids shortens the period of acute visual dysfunction but does not affect the final visual outcome. Atypical forms can necessitate prolonged immunosuppressive regimens. Optical coherence tomography and visual evoked potential measures are suitable for detection of neuroaxonal loss and myelin repair after optic neuritis. Clinical trials are underway to identify potential neuroprotective or remyelinating treatments for acutely symptomatic inflammatory demyelinating CNS lesions.

Introduction

Optic neuritis is an inflammation of the optic nerve (panel 1). It occurs throughout the world and has many causes. In temperate latitudes and white populations it is commonly associated with multiple sclerosis (MS). However, the differential diagnosis is extensive, and prognosis and treatment depend on the cause.

The incidence of unilateral optic neuritis around the world ranges from 0.94 to 2.18 per 100 000 per year.¹⁻⁴ Rates in Japan (1.6 per 100 000) are similar to those in Sweden (1.46 per 100 000) and the UK (1 per 100 000).^{5,6} Incidence studies universally show a female preponderance, although the ratio of men to women in the Japanese cohort (1:1.22) is greater than in northern European cohorts (1:3), suggesting that racial differences exist.⁵⁻⁷ Results of a meta-analysis of optic neuritis in the northern hemisphere showed rates to be greater at higher latitudes, during spring, and in people of north European ancestry.⁸ Similar findings have been reported in Australia.³ There is also an association between incidence rates and serological evidence of past Epstein-Barr virus infection, and an additive interaction with HLA-DRB1*1501 status,⁹ suggesting an association between risk factors for MS and cause of optic neuritis in areas of the world where MS is common. Conversely, in regions of low MS prevalence, optic neuritis is probably less frequently associated with MS and has different risk-factor profiles.

In adults the incidence of bilateral simultaneous optic neuritis in white populations is low¹⁰ and, as in all children with bilateral simultaneous optic neuritis, the risk of developing MS is low.¹¹ In recurrent optic neuritis, both visual recovery and neurological prognosis are more variable than in isolated occurrences. This variability is probably due to the broader differential diagnosis and the background population risk of these conditions.

Substantial developments have occurred in diagnostic work-up, understanding of pathophysiology, and treatment approaches in optic neuritis. In this Review we provide an update of these developments.

Optic neuritis and the risk of MS

Optic neuritis is the presenting symptom of MS in 25% of cases and occurs during the disease in about 70%, usually in the relapsing–remitting phase. Long-term follow-up studies before MRI reported conversion to clinically definite MS in 34–75% of patients presenting with optic neuritis in the UK¹² and USA.¹³ MRI studies in the same regions identified disseminated white-matter lesions suggestive of demyelination in 50%¹⁴ of patients in the USA and 61%¹⁵ in the UK. Clinically silent MRI lesions predispose to future clinical events, leading to clinically definite MS; in the North American Optic Neuritis Treatment Trial (ONTT),¹⁶ 72% of patients with an abnormal brain scan converted to MS after 15 years, compared with 25% with a normal scan. Brain MRI abnormalities in optic neuritis are less frequent in regions where MS is uncommon (eg, in Japan¹⁷), and, in these regions, optic neuritis is more likely to be associated with other disorders, such as neuromyelitis optica. MRI criteria have been developed that predict the conversion to clinically definite MS with high sensitivity and specificity in optic neuritis and other clinically isolated syndromes.^{18,19} MRI evidence of dissemination in space and time can now enable MS diagnosis at presentation in some patients with acute optic neuritis (panel 2).^{20,21}

Diagnosis, differential diagnosis, and investigations

Clinical features of typical optic neuritis

Typical optic neuritis presents with subacute monocular visual loss associated with pain during eye movement. Visual loss usually develops during hours or days.²² Most patients report diffuse blurring or fogging of vision. Severity varies widely and tends to reach its nadir within 2 weeks. Dyschromatopsia occurs early and has a variable spectral pattern. Investigators of the ONTT described mostly mixed defects (red–green and blue–yellow), but blue–yellow defects were slightly more common in the acute phase, and red–green more common at 6 months.^{23,24} Defect type was not associated with severity

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of visual loss. Other studies mostly show both red–green and blue–yellow colour defects with neither type dominating.^{25–27} Results of one study showed that greater foveal field depression was more likely to be associated

Panel 1: Terminology for optic neuritis

There is little consensus about a systematic nosology for optic neuritis. Research studies generally use different classification systems, which can lead to confusion in interpretation of their findings. Optic neuritis is traditionally divided on clinical grounds into typical and atypical forms, with the understanding that typical optic neuritis is generally associated with multiple sclerosis (MS) or is regarded as a demyelinating clinically isolated syndrome at risk of conversion to MS in white populations. An alternative method classifies optic neuritis by cause. On this basis, in this Review we describe immune-mediated optic neuritis, which itself can be subclassified into several types including MS-associated optic neuritis (MS-ON), optic neuritis associated with neuromyelitis optica (NMO-ON), optic neuritis associated with systemic disorders (connective tissue disease, granulomatous disease, infective conditions), and other idiopathic optic neuritis without systemic disease (recurrent isolated optic neuritis, chronic relapsing inflammatory optic neuropathy, solitary isolated optic neuritis). The term demyelinating optic neuritis has been also been used as a pathology-based definition, although this term is also not ideal because both MS-ON and NMO-ON cause demyelination and are managed differently. In this Review we tend to classify optic neuritis on clinical grounds—ie, as typical or atypical, for which typical optic neuritis is associated with MS and clinically isolated syndromes and atypical optic neuritis with non-MS immune-mediated causes (eg, neuromyelitis optica and systemic disorders, etc) because this is highly relevant for approach to clinical management. When appropriate—ie, when specific research has been undertaken—in relevant sections of this Review we allude to cause-based definitions (particularly MS-ON, NMO-ON).

Panel 2: Diagnosis of MS in MS-optic neuritis (2010 McDonald MRI criteria)²¹

Diagnosis requires dissemination in space and time

Dissemination in space

- At least one lesion visible on T2-weighted scan in at least two of four locations: juxtacortical, periventricular, infratentorial, and spinal cord

Dissemination in time

- A new T2 lesion or gadolinium-enhancing lesion visible on a follow-up MRI scan when compared with a previous scan (which is thought to be the baseline scan) obtained at any time after the onset of symptoms; or
- An MRI scan showing both gadolinium-enhancing and non-enhancing lesions that do not cause clinical signs (ie, asymptomatic lesions)

with red–green than with blue–yellow defects, but in patients with visual fields dominated by perifoveal defects the converse was recorded.²⁵ Periocular pain, exacerbated by eye movement, is usually mild but present in most patients and usually settles within days. It can precede or begin with the onset of visual dysfunction. Optic neuritis lesions posterior to the orbit are less likely to cause pain.²⁸ Other described symptoms include the presence of phosphenes,^{22,29} Uhthoff's phenomenon, and the Pulfrich effect (panel 3).

Early clinical signs include reduced visual and contrast acuities. Findings from the ONTT showed variable visual field deficits with static perimetry (panel 3) that included focal and diffuse deficits; central, centrocaecal, altitudinal, arcuate, and nasal step defects; and even hemianopic defects.³⁰ Central defects were more common than peripheral ones.³¹ Results of other studies using kinetic or higher resolution static perimetry have shown central scotomas to be prevalent,^{32,33} the discordance in findings from the ONTT potentially explained by methodological differences—eg, a diffuse defect assigned in the ONTT (testing the central 30 degrees of vision) could actually have been a large central scotomas if tested with larger field perimetry. A relative afferent pupillary defect is usually seen, although involvement of the other optic nerve might mask it. Diffuse optic disc swelling is present in a third of cases but the optic disc is normal in two-thirds (retrobulbar optic neuritis).²² Retinal periphlebitis (perivenous sheathing) is occasionally observed and could indicate a greater risk of conversion to MS.³⁴

Asymptomatic concomitant visual dysfunction can occur in the other eye.^{22,35} In the ONTT, these abnormalities were not associated with a previous MS history or brain MRI lesion load, but did take several months to recover, suggesting that subclinical acute contralateral optic nerve demyelination could be the cause.³⁵

Recovery from typical optic neuritis usually begins within the first few weeks of symptom onset. An initial rapid recovery is followed by a slow improvement that can continue for up to a year after onset, with more than 90% of patients making a good visual recovery (20/40 acuity or better).^{36,37} After a final 15 year ONTT analysis of 294 patients (65% of the original cohort), investigators reported that 72% of patients had acuities of 20/20 or better whereas 8.7% had acuities of 20/40 or worse in the affected eye. Six patients (2%) had a visual acuity of 20/40 or worse and only three (1%) had a visual acuity of 20/200 or worse in both eyes.³⁸ Visual improvement is slightly correlated with initial degree of visual loss,²² although patients with severe visual loss can still recover well. In the ONTT, 64% of patients with perception of light only or worse recovered to acuity of 20/40 or better.³⁶ Poor acuity (20/200 or worse), contrast sensitivity (<1.0 log units), or visual mean deviation (≤ -15 dB) at 1 month, but not baseline, can predict poor vision at 6 months.³⁹

Although recovery is usually good, persistent residual deficits can include disturbances of visual acuity

(15–30%), contrast sensitivity (63–100%), colour vision (33–100%), visual field (62–100%), stereopsis (89%), pupillary reaction (55–92%), and visual evoked potentials (VEPs) (63–100%).⁴⁰ Results of psychophysical studies have shown variable contributions of parvocellular and magnocellular pathway damage to visual deficit,^{41,42} and persistent deficits in motion perception.⁴³ Optic disc pallor, especially involving the temporal aspect, often develops even when recovery is excellent.

Differential diagnosis

Diagnosis of optic neuritis can be made clinically. Patient history and neuro-ophthalmic examination can be used to look for other causes of acute monocular visual loss (table 1). After diagnosis of optic neuritis, a clinical distinction should be made between typical and atypical forms (table 2). Patients with atypical optic

neuritis can be classified into those with systemic disease and those without (table 3). Optic neuritis without systemic disease includes patients with neuromyelitis optica-optic neuritis (NMO-ON) (panel 4), and corticosteroid-dependent chronic relapsing inflammatory optic neuropathy.⁴⁶ Systemic disorders associated with atypical optic neuritis include sarcoidosis, connective tissue diseases (eg, lupus), and vasculitis (eg, Wegener's granulomatosis). Many patients who are not corticosteroid-dependent could have isolated optic neuritis without systemic or neurological disease. These patients are diagnosed retrospectively, after extended follow-up, with solitary optic neuritis or recurrent optic neuritis.⁴⁷ Solitary optic neuritis is rarely associated with neuromyelitis optica seropositivity (about 5%) and tends to be a common retrospective diagnosis when brain MRI is normal.⁴⁸

Panel 3: Visual phenomena and measurements in optic neuritis

- Phosphenes are bright, fleeting flashes of light that, in optic neuritis, tend to be connected to eye movement. The symptom of phosphenes should be clinically distinguished from a scintillating scotomas, which are usually associated with visual aura of migraine. This aura tends to appear as a blind region surrounded by a margin of sparkling lights that can change shape or move over a period of time, typically 15–30 min.
- Uhthoff's phenomenon is a worsening of vision provoked by small increases in body temperature, typically attributed to exercise, hot baths or showers, or hot weather conditions.
- The Pulfrich effect describes anomalous stereoscopic perception of objects in motion due to asymmetrical conduction between optic nerves.
- Visual acuity measures the spatial resolution ability of the visual system. Traditionally it is measured with Snellen charts and expressed in fractional notation, with the numerator denoting the actual distance (20 feet or 6 m) from the chart and the denominator denoting the distance at which a person with normal eyesight can see the line of letters—eg, an acuity of 20/40 means that a person viewing the chart at 20 feet can read letters that normal eyesight can distinguish at 40 feet. 20/20 or 6/6 vision is normal; 20/200 or its equivalent 6/60 signifies very poor vision. Research studies such as the North American Optic Neuritis Treatment Trial (ONTT) tend to use logMAR scores, requiring a retro-illuminated Early Treatment Diabetic Retinopathy Study (ETDRS) chart. A standard ETDRS chart measures the logarithmic (base 10) minimum angle of resolution at 4 m and provides a linearly continuous variable amenable to parametric statistics. LogMAR scores can be converted to Snellen equivalent scores, and vice versa.
- Low-contrast acuity charts are more sensitive than standard-contrast acuity charts at detection of visual dysfunction in optic neuritis. Several types of chart exist, but the Pelli-Robson chart has been commonly used in research studies (including the ONTT). This chart comprises eight lines of six letters, each arranged in two triplets per line. With each successive triplet, the contrast decreases in logarithmic steps by 0.15 log units. The patient is asked to read along and down the chart until the detection limit is reached, scored from 0 to about 2 log units. High scores indicate better contrast sensitivity, measured at the peak of the contrast sensitivity function (about one to two cycles per degree).
- Colour vision is conventionally measured in clinical practice with Ishihara pseudoisochromatic plates. The patient is asked to distinguish different coloured numbers, but this test is designed for deficiencies of the red–green axis. In research, the Farnsworth-Munsell 100-hue test provides a comprehensive assessment (used in the ONTT). The patient is asked to grade 85 coloured caps according to perceived hue, from which an error score is established. The resulting data are amenable to parametric statistics and indicate the type of spectral deficiency.
- Visual fields can be measured with static or dynamic perimetry. The ONTT used the Humphrey field perimetry (static), which can test different field sizes in an automated fashion but typically tests the central 30 degrees of vision. The patient has to acknowledge luminant stimuli briefly presented in different locations. The stimuli are randomly repeated at various luminances to assess reliability and luminance threshold. The output can be quantitatively summarised as a score ranging usually from 0 to –30 decibels, where 0 is normal vision and –30 is severe visual-field loss. Goldmann perimetry is dynamic and relies on the patient detecting a luminant stimulus moving in from the peripheral field. The test is done by a trained operator who uses targets of different luminances and sizes to create a field map. Its advantages over Humphrey perimetry are that patient compliance can be assessed and the whole visual field can be mapped; however, its output is more qualitative and scotomas can be missed if not properly assessed.

Clinical clues

Optic nerve

Ischaemic optic neuropathy	Non-arteritic: painless, acute, disc swelling invariably during acute episode, altitudinal field defect, poor recovery, vascular risk factors Arteritic (usually associated with giant-cell arteritis): high erythrocyte sedimentation rate, painless, acute disc swelling, altitudinal field loss, severe visual loss, could be bilateral if untreated, systemic symptoms of myalgia, fatigue, temporal headache, jaw claudication
Optic nerve compression	Progressive symptoms, usually painless (except aneurysms, mucocoele)
Leber's hereditary optic neuropathy	Usually men, bilateral simultaneous or sequential optic neuropathy, painless
Toxic optic neuropathy	Methanol poisoning (sometimes seen in alcohol-dependent patients), tobacco or alcohol amblyopia, bilateral involvement
Nutritional optic neuropathy	B12 deficiency, risks for malabsorption
Drug-induced	Ethambutol in treatment of tuberculosis
Diabetic papillopathy	Painless acute disc swelling with signs of diabetic retinopathy and mild visual loss, usually good recovery
Infectious	Lyme disease: tick exposure, erythema chronicum migrans, radiculoneuropathy, neuroretinitis, vitritis, meningeal involvement, retinopathy, CSF cells Syphilis: risk factors, genital ulcers, rash, neuroretinitis, vitritis, dorsal-column involvement Viral (HIV, Epstein-Barr virus, cytomegalovirus): viral prodrome, vitritis, CSF cells Tuberculosis: history of exposure, vitritis, abnormal chest radiograph Toxoplasmosis: active chorioretinitis with retinal oedema, disc swelling, HIV positive Toxocariasis: neuroretinitis, eosinophilia Bartonella: history of cat scratch, neuroretinitis, lymphadenopathy
Post-infectious	Bilateral, post-viral, more common in children than in adults
Traumatic optic neuropathy	History of trauma, facial or intracranial injury

Retina

Central serous retinopathy	Painless central blurring and photopsia, macular abnormalities on fundoscopy, usually good recovery
Cystoid macular oedema	Painless, central blurring; risk factors include cataract operation, retinal artery/vein occlusion, diabetes, intraocular inflammation; macular oedema observed
Big blind spot syndrome/acute zonal occult outer retinopathy (AZOOR)	Poorly understood painless enlargement of blind spot, photopsias, sometimes associated with disc swelling, usually self-limiting
Retinal detachment	Floater or flashing lights then peripheral field loss (shadow) progressing centrally, abnormal red reflex, retinal separation visible; might have relative afferent pupillary defect
Central retinal artery occlusion	Painless, sudden severe visual loss, retinal oedema, cherry red spot, retinal emboli
Central retinal vein occlusion	Variable central visual blurring, disc swelling, tortuous vessels, multiple retinal haemorrhages, cotton-wool spots

Uveal membrane

Uveitis	Anterior: painful blurring of vision with reddening of eye and photophobia, dilated ciliary vessels, keratic precipitates, cells in anterior chamber Posterior: floaters, blurred vision, vitreous cells, chorioretinitis seen on examination
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Vitreous

Vitreous haemorrhage	Painless visual loss, no red reflex, pre-existing proliferative retinopathy or retinal vein occlusion
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Cornea

Acute closed-angle glaucoma	Blurred vision and haloes, painful red eye, photophobia, nausea, fixed pupil, corneal oedema, high intraocular pressure, shallow anterior chamber
Herpes simplex keratitis	Visual blurring, visible ulcer on fluorescein staining, history of corneal injury, contact lens use, herpetic V1 rash

Sclera

Posterior scleritis	Severe pain wakes patient from sleep, proptosis, disc swelling
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Orbit

Orbital cellulitis	Proptosis, other cranial nerve involvement
Optic perineuritis	A type of orbital inflammatory disease, older age, central vision sparing, severe pain, associated with connective tissue, autoimmune disease or infection (eg, syphilis, Lyme), good response to steroids

Other

Functional	Variability, no objective signs such as relative afferent pupillary defect, normal visual evoked potentials
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Adapted from Jenkins and Toosy.⁴⁴

Table 1: Examples of causes of acute monocular visual loss other than immune-mediated optic neuritis, by anatomical region and condition

20–30% of patients with recurrent optic neuritis develop seropositivity for neuromyelitis optica over variable follow-up periods up to 12 years.^{49,50} Investigators of a retrospective case analysis reported findings from 74 patients with recurrent or bilateral optic neuritis. For the recurrent unilateral group (n=47), final diagnoses were MS in 29, chronic relapsing inflammatory optic neuropathy in 11, neuromyelitis optica in four, and

thyroid eye disease in three.⁵¹ Bilateral optic neuritis (n=23) was divided into recurrent (n=15) and non-recurrent (n=8) types. Final diagnoses for the recurrent group were vasculitis or connective tissue disease in 13 (including lupus, Sjögren's syndrome, and polyarteritis nodosa) and MS in two, and for the non-recurrent group were post-infectious in four, sarcoid in two, and MS in two.⁵¹

Investigations

For typical optic neuritis, basic investigations such as erythrocyte sedimentation rate (or C-reactive protein), syphilis serology, and chest radiograph can be considered.⁵² Optic nerve MRI with gadolinium, although usually not necessary for diagnosis, shows the intrinsic optic neuritis lesion in 95% of patients.⁵³ T2-weighted optic nerve signal change on MRI is also noted. Brain MRI in typical optic neuritis can help to stratify the future risk of conversion to MS. Visual evoked potentials can be used to diagnose optic nerve involvement but do not robustly distinguish between different acute optic neuropathies, although a delayed but well preserved P100 waveform is characteristic of demyelination.^{54–56} Visual evoked potentials with pattern electroretinograms can distinguish between optic nerve and macular pathology. Optical coherence tomography is used to exclude macular pathology in appropriate cases.

For atypical optic neuritis, additional investigations are done, including MRI of the orbits or optic nerves with gadolinium (figures 1 and 2) and usually a lumbar puncture. MRI can show compressive lesions, nerve-sheath enhancement in granulomatous disorders, orbital inflammation, meningeal or brain parenchymal enhancement (eg, with sarcoid), and can assess the degree of optic nerve involvement. In NMO-ON, white matter lesions can be seen but are atypical for MS. Periaqueductal grey matter and hypothalamic abnormalities have also been described, corresponding with sites of high aquaporin-4 (AQ4) antibody expression.^{55,57}

Lumbar puncture can show CSF pleocytosis, raised protein concentrations, and sometimes low glucose concentrations in atypical inflammatory infectious or infiltrative disorders. CSF serology can detect some infectious causes. Matched oligoclonal bands in CSF and serum can indicate a systemic disorder (although the absence of CSF oligoclonal bands does not exclude this diagnosis). A relatively high CSF pleocytosis is very unusual in MS-associated optic neuritis (MS-ON) and would reinforce the likelihood of an atypical cause.

Other investigations include chest radiograph and blood tests, such as full blood count, erythrocyte sedimentation rate (or C-reactive protein), renal function, liver function, bone profile, vitamin B12, folate, serum angiotensin converting enzyme, autoantibodies (anti-nuclear double-stranded DNA, anti-neutrophil cytoplasmic antibodies), syphilis serology, tuberculosis quantiferon testing, and AQ4 antibody.^{58,59} AQ4 antibody has high sensitivity (68–91%) and high specificity (85–99%) for neuromyelitis optica,^{58,60} and is positive in about 5–6% of cases of unilateral optic neuritis.^{47,48} Its presence probably indicates a more severe relapsing disease course and clinical conversion to neuromyelitis optica.^{48,61,62} Myelin-oligodendrocyte glycoprotein antibodies in patients with AQ4 antibody-negative neuromyelitis optica spectrum disorder have been identified in a small study,⁶³ but further research is

	Typical	Atypical
Age	Young adult	Age >50 years or <12 years
Ethnic origin	White	African, Asian, or Polynesian descent
Laterality	Unilateral symptoms	Bilateral simultaneous or rapidly sequential
Pain	Mild periocular pain; worse on eye movement	Severe periocular pain waking patient from sleep, painless visual loss, pain persisting longer than 2 weeks
Vision	Mild to moderate unocular visual loss followed by spontaneous improvement	Severe visual loss (worse than 6/60 or 20/200), no recovery starting within 3 weeks of onset, progression of visual loss for more than 2 weeks
Appearance	Normal or swollen optic disc	Severe optic disc swelling, macular star (neuroretinitis), optic disc haemorrhages, anterior–posterior segment inflammation, marked retinal exudates
Other	Uhthoff's phenomenon, Pulfrich effect, previous self-limiting neurological episodes	Family history, neoplastic history

Table 2: Features of typical and atypical optic neuritis

needed to elucidate their clinical value. Other specialised tests might depend on the particular diagnosis being sought, but include genetic testing for Leber's hereditary optic neuropathy, or viral or atypical infection serological screening. A body PET scan can show avid localised soft tissue uptake amenable to biopsy (figure 2). After early investigations, appropriate treatment can be started.

Pathophysiology

The pathophysiology of MS-ON has been studied in human beings and in animal models.^{64,65} The optic nerve lesion is pathologically very similar to MS brain lesions. In the acute phase, inflammatory demyelination occurs,⁶⁶ resulting in varying degrees of conduction block⁶⁷ and visual loss. Predominant T-cell activation occurs in the acute phase, with release of pro-inflammatory cytokines,⁶⁸ although there could also be B-cell involvement⁶⁹ and microglial activation.⁷⁰

Resolution of inflammation and visual recovery occur over the next few weeks.^{67,71,72} Remyelination occurs,⁷³ although it is usually incomplete,⁷⁴ and sodium channels are redistributed over demyelinated segments. This redistribution improves conduction but can make surviving axons vulnerable to damage.⁷⁵ Visual recovery can be incomplete, probably because of the effects of persistent demyelination⁷⁶ and axonal loss. Advances in optical coherence tomography, visual evoked potentials, and MRI have provided insight into the pathophysiological processes and clinical correlations for optic neuritis.

Imaging of pre-geniculate visual pathways

Retinal nerve fibres

Optical coherence tomography relies on interferometry of near-infrared light to construct very high-resolution images of the retinal layers. The most visible layer is the retinal nerve fibre layer, comprising unmyelinated axons in a supportive connective-tissue framework. The retinal nerve fibre layer axons originate from retinal ganglion cell bodies, and continue through the optic nerve, chiasm, and tract (where they are myelinated), to synapse in the lateral

Features	
No systemic disease	
Multiple sclerosis-associated optic neuritis	Typical symptoms of optic neuritis, usually disseminated white-matter brain lesions suggestive of demyelination, CSF-positive oligoclonal bands (unmatched); if first episode can be called demyelinating clinically isolated syndrome
Solitary isolated optic neuritis	Diagnosed after extended follow-up; normal brain MRI, isolated optic neuritis
Neuromyelitis optica-associated optic neuritis	Positive antibodies to aquaporin 4 or myelin-oligodendrocytes, longitudinally extensive cord lesion (myelitis), CSF pleocytosis, negative oligoclonal bands, normal MRI brain or abnormalities atypical for MS (hypothalamus, third ventricle, medulla)
Chronic relapsing inflammatory optic neuropathy	Tendency to relapse when off steroids, normal MRI brain, optic nerve sheath enhancement, might become bilateral, needs chronic immunosuppression
Recurrent isolated optic neuritis	Diagnosed after extended follow-up; normal brain MRI, no other neurological sequelae
Acute disseminated encephalomyelitis	Enhancing brain lesions, severe bilateral optic neuritis, more common in children than in adults
Systemic disease	
Sarcoid	Other signs of intraocular inflammation, optic nerve sheath enhancement, white matter brain lesions, meningeal enhancement, respiratory symptoms, abnormal chest radiograph, CSF pleocytosis, matched oligoclonal bands
Connective tissue disease (eg, lupus)	Skin rash, arthritis, alopecia, positive autoantibodies (double-stranded DNA for lupus), raised inflammatory markers
Vasculitis (eg, polyarteritis nodosa, Wegener's granulomatosis)	Ischaemic presentation if pure vasculitic; compressive presentation if sino-nasal disease Positive anti-neutrophil cytoplasmic antibodies

Table 3: Main causes of immune-mediated optic neuritis

Panel 4: Neuromyelitis optica spectrum

- Neuromyelitis optica
- Some forms of neuromyelitis optica
 - Idiopathic single or recurrent events of longitudinally extensive myelitis (≥three vertebral segment spinal cord lesions seen on MRI)
 - Optic neuritis: recurrent or simultaneous bilateral
- Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease
- Optic neuritis or myelitis associated with brain lesions typical of neuromyelitis optica (hypothalamic, corpus callosal, periventricular, or brainstem)

Modified from Wingerchuk and colleagues.⁴⁵

geniculate bodies. The retinal nerve fibre layer measurements using optical coherence tomography are typically made from a circular arc through the retinal nerve fibre layer 3–4 mm from the centre of the optic disc. In acute optic neuritis, retinal nerve fibre layer thickness increases occur with optic nerve swelling.⁷⁷ Subsequent reductions in retinal nerve fibre layer thickness indicate significant axonal loss after acute optic neuritis (figure 3).^{78,79} Investigators of two serial optical coherence tomography studies identified a median 20% decrease in retinal nerve fibre layer thickness after 6 months in two cohorts of 54 and 23 patients with optic neuritis, respectively,^{79,80} although retinal nerve fibre layer loss varied greatly between patients (0–50%).⁸⁰ Consistent with these findings, results of a study of 90 patients with MS showed a mean 20% decrease in retinal nerve fibre layer thickness in eyes previously affected by optic neuritis.⁸¹ Retinal nerve fibre layer thinning correlates with visual dysfunction,^{78,79,82} optic nerve MRI-detected atrophy,⁸³ and radial diffusivity (water

diffusivity perpendicular to the main axis of diffusion along the nerve).⁸⁴ Impaired colour vision is particularly correlated with thinning of the retinal nerve fibre layer in both cross-sectional and prospective cohorts.^{85,86}

Supported by data (obtained in an animal model of optic neuritis) showing an association between visual evoked potential latency and demyelination,⁵⁶ clinical studies have acquired both visual evoked potential and optical coherence tomography measures to investigate the association between myelination and axonal loss. Both visual evoked potential amplitude and latency were correlated with optical coherence tomography measures of axonal loss in a clinical cross-sectional study of post-acute optic neuritis.⁸⁷ In another clinical study,⁸⁸ sectoral retinal nerve fibre layer thickness correlated with the multifocal visual evoked potential amplitude from the corresponding part of the visual field, suggestive of a structural–functional association, whereby the largest reductions in retinal nerve fibre layer thickness affected the temporal disc and the largest reductions in multifocal visual evoked potential amplitude affected the central field.⁸⁸ Results of a longitudinal clinical study showed that the improvement in latency delay in acute optic neuritis tends to be greatest in the first 6 months.⁷³ From 1 to 3 years an ongoing small reduction in retinal nerve fibre layer thickness did not correlate with the change in multifocal visual evoked potential latency, suggesting no association between optic nerve demyelination and ongoing axonal loss.⁸⁸

Clinical optical coherence tomography studies have used intraretinal layer segmentation to examine the retinal ganglion cell and inner plexiform layers. Measurements of retinal ganglion cell layer (or retinal ganglion cell and inner plexiform layers combined, because the two layers are difficult to discriminate) are not affected by disc swelling and should be more specific to axonal pathology. Thin retinal ganglion cell and inner

plexiform layers have been recorded in patients with MS, particularly those affected by previous optic neuritis, and the depths of the layers are associated with visual function.⁸⁹ Such thinning has also been recorded in longitudinal studies of optic neuritis.⁹⁰

Greater retinal nerve fibre layer thinning is seen in NMO-ON eyes than in MS-ON eyes,^{91,92} with the greatest thinning in the superior and inferior retinal nerve fibre layer quadrants.^{92,93} Results of one study suggested that retinal nerve fibre layer thickness loss greater than 15 μm in patients without MS should prompt investigations for neuromyelitis optica spectrum disorder.⁹¹ Early administration of high-dose steroids preserved retinal nerve fibre layer thickness in an uncontrolled, retrospective study.⁹² Longitudinal reductions in retinal ganglion cell and inner plexiform layer thickness have also been recorded in NMO-ON eyes.⁹⁰ Thickness of the inner nuclear layer could be increased in neuromyelitis optica,^{94,95} although in-vivo quantification of the inner nuclear layer has also included the outer plexiform layer; thus the specificity of the observation for the inner nuclear layer itself is uncertain. A qualitative abnormality called microcystic macular oedema has been observed in the inner neuronal layer of the retina in 20% of patients with neuromyelitis optica⁹⁶ and about 5% of those with MS.^{95,97} Microcystic macular oedema has been defined as cystic, lacunar areas of hyporeflexivity with clear boundaries, evident on at least two contiguous B scans, or visible in a comparable region on at least two separate acquisitions, and has been associated with more severe MS.⁹⁸ Microcystic macular oedema might be indicative of a greater degree of neuroinflammation, rather than being more specific to neuromyelitis optica. An alternative mechanism for the cystic spaces might be tissue loss due to neurodegeneration.

Optic nerves

The acute inflammatory lesion is detectable on MRI with gadolinium enhancement.^{53,67,99} Optic nerve atrophy often develops and has been associated with disease duration and visual function (figure 3),^{83,100} thinner retinal nerve fibre layer, and lower visual evoked potential amplitude.⁸³ Results of two studies showed that the NMO-ON lesion is most likely to affect the posterior optic nerve, including the chiasm,^{101,102} although the distinction is not absolute, and chiasmal involvement can be seen in MS-ON.

Optic-nerve diffusion tensor imaging measures water diffusion to provide microstructural information.¹⁰³ Diffusion tensor imaging markers of tissue disruption are present in the affected optic nerves after optic neuritis and are associated with visual function and visual evoked potentials.^{104,105} Low axial diffusivities in the acute phase (suggesting greater axonal damage) are associated with worse vision at 6 months.¹⁰⁶

Magnetisation transfer imaging distinguishes between free and macromolecular bound protons, and the magnetisation transfer ratio is affected by myelination and axonal loss and is altered from normal in optic

neuritis^{107–109} and MS, decreasing in the initial post-acute phase.¹¹⁰ A time-dependent association between visual evoked potential latency and magnetisation transfer ratio

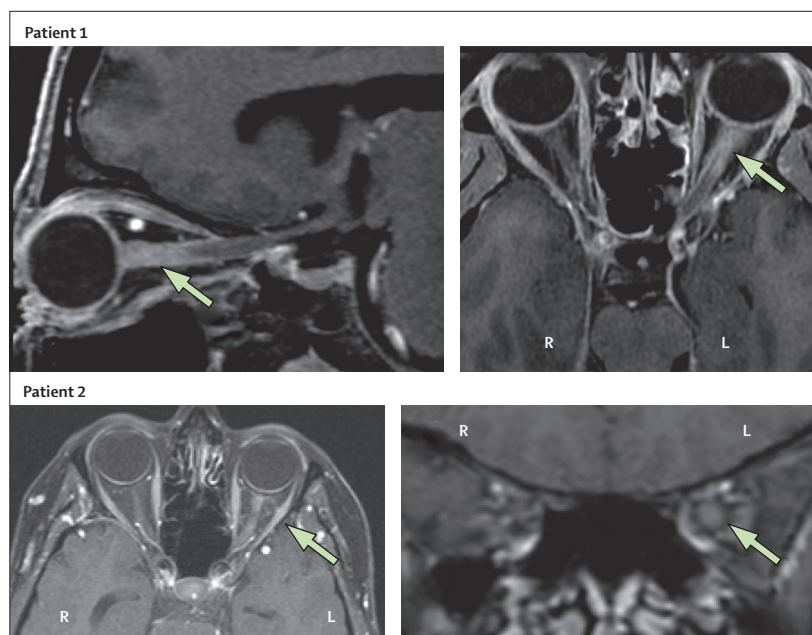


Figure 1: Examples of neuromyelitis optica-optic neuritis in two patients showing left optic nerve enhancement on post-contrast T1-weighted MRI scans

Patient 1 images reproduced with permission from Dr Lynette Masters (Brain and Mind Research Institute, University of Sydney, Sydney, Australia).

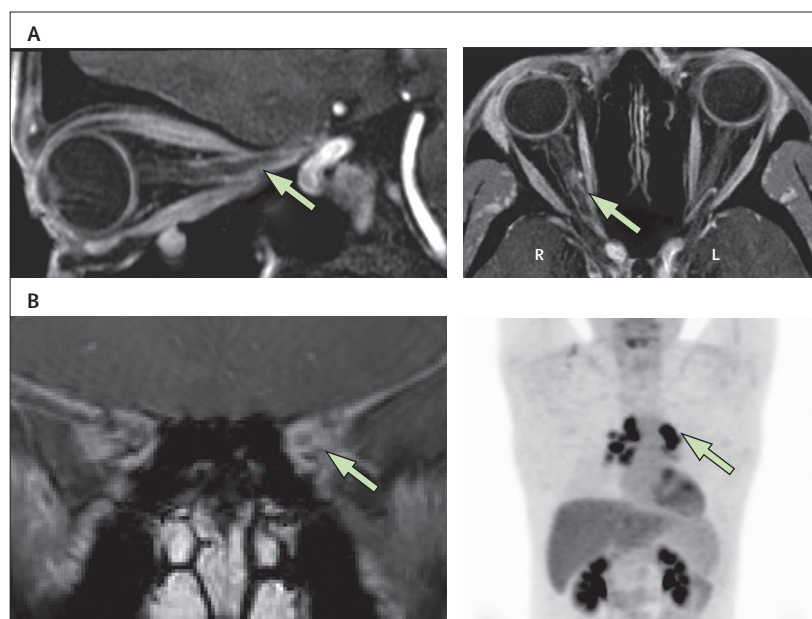


Figure 2: Two cases of sarcoid-related optic neuropathy

(A) Right optic nerve sheath enhancement (indicated by arrows) from a granulomatous optic neuropathy. (B) Patient who presented with an acute right optic neuritis. MRI showed optic nerve sheath enhancement. FDG-PET scan showed hilar/mediastinal avid nodes. Lymph node biopsy showed non-caseating granulomata. Arrows indicate FDG-avid hilar/mediastinal lymph nodes in the right-hand figure, and to enhancing optic nerve sheath in the left-hand figure. Figure 2A reproduced with permission from Dr Lynette Masters (Brain and Mind Research Institute, University of Sydney, Sydney, Australia).

suggests the potential for the lesional magnetisation transfer ratio to be indicative of remyelination after optic neuritis,¹⁰⁹ and results of post-mortem pathology–MRI studies have shown higher magnetisation transfer ratio in remyelinated than in demyelinated lesions.^{111,112}

Imaging of post-geniculate visual pathways

Optic radiations

Diffusion tensor imaging metrics have identified abnormalities in the optic radiations in post-acute optic neuritis.¹¹³ A reported significant association between a

multifocal visual evoked potential measure of anterior visual axonal dysfunction (reduced amplitude) and reduced optic radiation axial diffusivity (which correlates with axonal injury in animal studies¹¹⁴) suggests possible anterograde trans-synaptic axonal degeneration—ie, degeneration of retrogeniculate fibres secondary to primary degeneration of anterior visual pathway axons.¹¹³

Visual cortex

Audoin and colleagues¹¹⁵ noted a lower grey matter magnetisation transfer ratio within the visual cortices

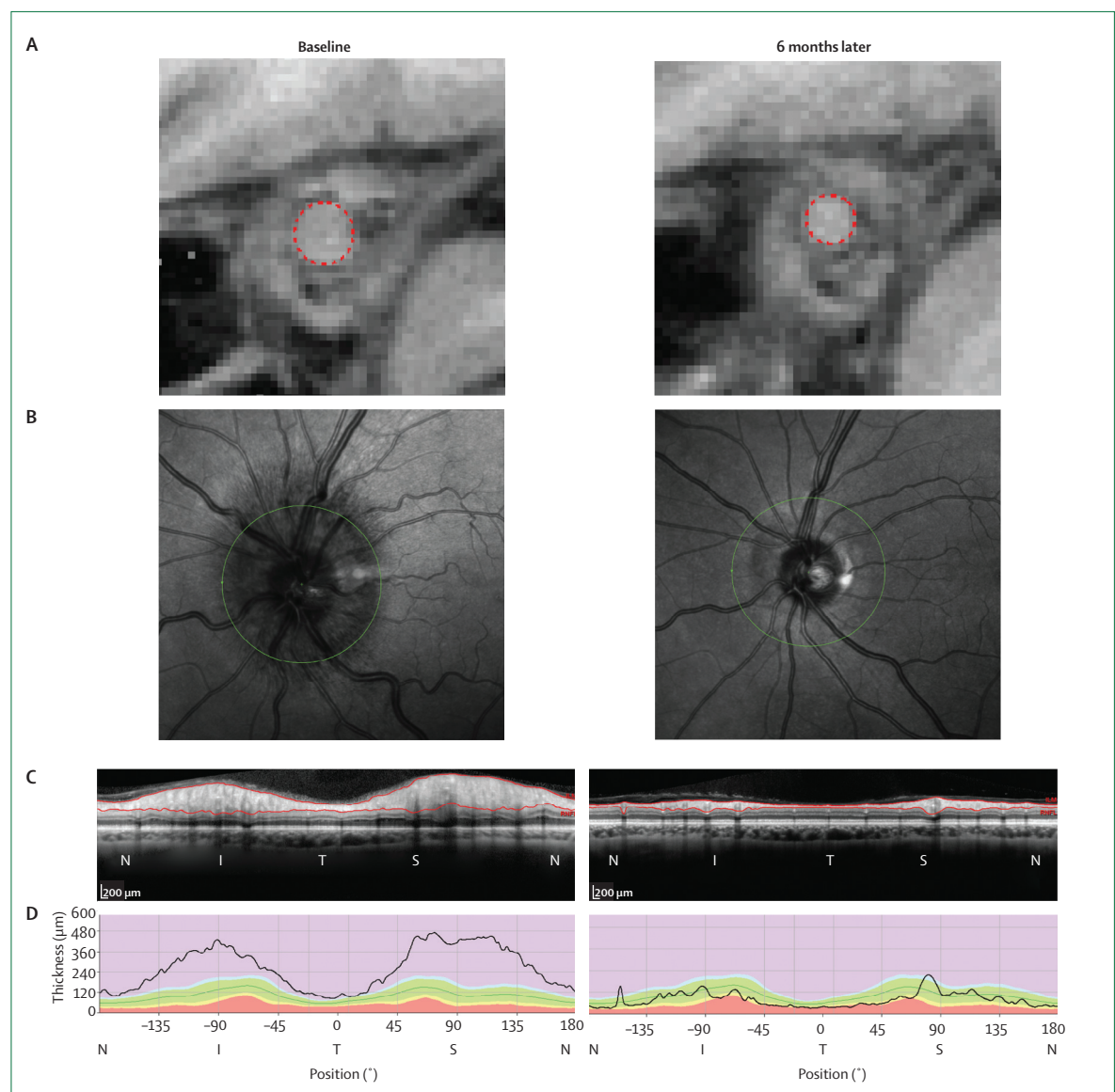


Figure 3: Left optic neuritis at baseline and after 6 months

(A) T1-weighted MRI optic nerve showing acute swelling at baseline and some atrophy 6 months later. The nerve is outlined in red. B–D show outputs from optical coherence tomography. (B) Peripapillary optic nerve circular scan with disc swelling at baseline. (C and D) Profile of retinal nerve fibre layer along circular scan from nasal (N) to inferior (I) to temporal (T) and to superior (S) fibres. Respective swelling and atrophy are shown at baseline and 6 months. OCT images reproduced with permission from Dr Rhian Saftopoulos, University College London Institute of Neurology, University College London, London, UK.

after optic neuritis compared with healthy controls, suggesting cortical structural changes. Results of a longitudinal study showed that early pericalcarine atrophy predicts later conversion to MS at 1 year after acute optic neuritis.¹¹⁶

Results of functional MRI studies have shown reduced visual cortex activation after optic neuritis that is sometimes associated with visual dysfunction¹¹⁷ and with retinal nerve fibre layer thickness.¹¹⁸ Findings from longitudinal studies have implicated several brain regions that might help visual recovery, including the lateral occipital complexes,^{119,120} cuneus,¹²¹ and lateral geniculate nuclei.¹²² Some degree of neuroplasticity might help to explain the discordance between good visual recovery and persistent structural optic nerve damage after acute optic neuritis.¹²³

Acute treatment options for optic neuritis

Corticosteroids

Several studies have assessed acute corticosteroid treatment for optic neuritis, providing level 1¹²⁴ evidence.^{125–127} Results of the ONTT showed no improvement in visual acuity ($p=0.66$) at 6 months after 3 days of high-dose (1 g per day) intravenous methylprednisolone followed by 11 days of low-dose oral prednisolone versus placebo, although visual recovery was faster.^{125,128} Mild benefits were noted for some secondary outcomes—visual fields ($p=0.054$), contrast sensitivity ($p=0.026$), and colour vision ($p=0.033$). Patients taking standard-dose (1 mg per kg) oral prednisolone did not differ from those taking placebo in visual outcomes but there was an unexpected increased risk of optic neuritis recurrence for reasons that are unclear. Intravenous methylprednisolone also delayed the onset of clinically definite MS at 2 years,¹²⁹ but this difference abated over time.¹⁶ In a Cochrane review,¹³⁰ no long-term benefit was reported for corticosteroid treatment for visual acuity, visual fields, or contrast sensitivity.¹³⁰ Most participants in these studies were likely to have typical optic neuritis, and the poor efficacy of corticosteroids is concordant with studies investigating their effects on non-optic neuritis MS relapses—ie, hastening recovery but not affecting final outcome.

Results of some studies suggest that timing of corticosteroid administration might be important, but more research is warranted. In the rat model of MS, corticosteroids given before induction of experimental allergic encephalomyelitis reduced the incidence of optic neuritis and preserved the retinal ganglion cells after optic neuritis.¹³¹ In human beings, poor evidence for the efficacy of corticosteroids exists, and only results of uncontrolled studies examining very early treatment (within days of symptoms) have been published. In a case series, steroids administered hyperacutely to eight patients with previous optic neuritis (including MS, chronic relapsing inflammatory optic neuropathy, and neuromyelitis optica) who reported a relapse of their

pain, resulted in no visual loss and in resolution of their pain.¹³² MRI was done in five patients and confirmed optic neuritis in all. A retrospective analysis of neuromyelitis optica cases reported that earlier administration (within 3 days) of intravenous methylprednisolone for optic neuritis relapse was associated with more preservation of retinal nerve fibre layer thickness.⁹² Oral high-dose methylprednisolone could be an alternative to the intravenous form. A randomised controlled trial ($n=60$) showed that 500 mg per day oral methylprednisolone was superior to placebo at 1 and 3 weeks, although final visual outcome was unaltered after optic neuritis.¹²⁷

Randomised controlled trials on atypical optic neuritis are scarce, and evidence is observational or retrospective (mainly level 4).¹²⁴ NMO-ON seems to respond to intravenous methylprednisolone, particularly if administered early.^{92,132} Similarly, for sarcoid-related optic neuritis, high-dose corticosteroids are indicated, although visual recovery might be hard to induce.^{133,134} Lupus-associated optic neuritis is also thought to respond to steroids,¹³⁵ although cyclophosphamide in combination with, or as an alternative, might be more effective.¹³⁶ Vasculitic optic neuritis is very rare but some patients might respond to corticosteroids.¹³⁷ High-dose corticosteroid treatment for atypical optic neuritis is usually followed by an oral weaning dose. Patients with chronic relapsing inflammatory optic neuropathy might have a granulomatous optic neuropathy, which is very steroid-sensitive but also steroid-dependent, and can relapse on weaning.⁴⁶

Plasmapheresis

Plasmapheresis has been tested in patients with steroid-unresponsive demyelinating optic neuritis in observational cohort studies. Early treatment, within weeks, is more likely to be beneficial.^{138,139} In a case series of 23 patients (ten with relapsing–remitting MS, one with neuromyelitis optica, and 12 with isolated optic neuritis), 70% improved with plasmapheresis, given after two cycles of intravenous methylprednisolone.¹⁴⁰ In another case series of 20 patients with MS, 13 of 17 (76%) with affected optic nerves reported benefit.¹³⁸ A pooled review of plasmapheresis in neuromyelitis optica, together with the authors' data for steroid-refractory optic neuritis with severe visual loss, analysed 39 eyes.^{139,141} People who improved received plasmapheresis a median of 19 days after onset, compared with 41 days for those who did not improve. Finally, patients with NMO-ON who were given plasmapheresis with corticosteroids had better visual outcome than did those given corticosteroids alone.¹⁴² Plasma exchange might be considered a viable option in demyelination of optic neuritis that is unresponsive to steroids.

Intravenous immunoglobulins

Studies with intravenous immunoglobulins have produced mixed results. Results of an open-label, non-randomised, prospective study¹⁴³ showed a good

improvement in visual acuity in 18 of 23 steroid-refractory patients with MS-ON who had treatment, compared with three of 24 patients who did not. However, findings from two earlier randomised, double-blinded, placebo-controlled studies recruiting a total of 123 patients with acute optic neuritis showed no significant beneficial effect.^{144,145} Overall, evidence for a beneficial effect is weak.

Recommendations

For typical optic neuritis, the affected patient is counselled about the benefits, limitations, and potential side-effects of corticosteroids, and is offered treatment if visual loss is functionally disabling or if the patient has pre-existing visual impairment of the other eye. We tend to prescribe high-dose methylprednisolone (either 500 mg per day orally for 5 days or 1 g per day intravenously for 3 days) with no oral tail, and patients are followed up clinically, irrespective of treatment, within the next few weeks to check recovery. If atypical features develop or recovery does not begin, the atypical pathway for investigations and treatment is immediately followed. The patient is also counselled about the future potential of conversion to MS and is offered brain MRI for risk stratification.

For atypical optic neuritis, after appropriate and urgent investigations, treatment is instigated in our regimen with intravenous methylprednisolone (1 g per day for 3–5 days) followed by a prolonged oral tail, with weaning over 4–6 months. If patients relapse after initial treatment, the dose of oral corticosteroids can be increased, or a further course of intravenous methylprednisolone can be given and a steroid-sparing immunosuppressant considered (panel 5). If initial high-dose steroids do not effectively improve vision and the cause is demyelination, plasmapheresis can be considered. For lupus-related optic neuritis, cyclophosphamide can be considered.

Long-term management of typical optic neuritis

Consideration of disease-modifying treatments used in MS

Several placebo-controlled trials of the MS disease-modifying drugs beta interferon and glatiramer acetate have enrolled patients with clinically isolated syndrome (CIS) (including those with isolated optic neuritis) with MRI scans positive for demyelinating lesions.^{149–152} The results of all these trials showed delay of subsequent relapse and conversion to clinically definite MS. A follow-up study of one of the trial cohorts treated with beta interferon showed that this delaying effect persisted for up to 5 years, although long-term disability between early and late treatment groups did not differ.¹⁵³ Findings from a 10 year follow-up of another beta interferon trial cohort recorded similar effects.¹⁵⁴ Despite the modest long-term clinical efficacy, advocates for early versus delayed treatment of patients with clinically isolated syndromes argue that many will otherwise accumulate new MRI lesions, which could increase the chances of future disability.

Recommendations

Patients with typical, isolated optic neuritis are usually monitored. They are counselled about the risk of MS conversion, based on their brain MRI result, if possible. Although the most recent prescribing guidelines¹⁵⁵ from the Association of British Neurologists suggest that disease-modifying drugs can be considered for patients with clinically isolated syndromes who have demyelination on brain scans, funding for this treatment can be, in practice, problematic to secure in the UK, and the potential long-term benefits are still uncertain. If the patient converts to MS, with a further relapse within 2 years, then disease-modifying drugs are often prescribed. MRI done at intervals during monitoring might enable an earlier diagnosis of MS to be made.

Long-term management of atypical optic neuritis

NMO-ON relapse prevention

Atypical optic neuritis often needs long-term immunosuppression, particularly if the risk of relapse is high or if relapses have occurred. The specific choice of immunosuppressant might be affected by the underlying causes.^{59,156}

Maintenance of remission is crucial, because the accumulation of disability is associated with relapses. Several drugs have been studied retrospectively and observationally in neuromyelitis optica, its limited forms, and spectrum disorders, providing mainly level 4 evidence.^{124,147}

Results of a small prospective study of seven patients with neuromyelitis optica reported a relapse-free follow-up of 18 months with treatment with azathioprine plus prednisolone.¹⁵⁷ Findings from two retrospective studies of patients with neuromyelitis optica spectrum disorder^{158,159} showed that azathioprine, with or without prednisolone, reduced the annualised relapse rate by about three-quarters. Doses larger than 2 mg per kg and increases in mean corpuscular volumes were possibly associated with greater reductions in relapse rate.¹⁵⁸ Beneficial effects on disability scores and visual acuities have also been recorded.^{158,159} A target dose of 2.5–3.0 mg/kg per day is recommended, and the first few months of treatment should be in combination with oral prednisolone while treatment takes effect. This regimen is followed by a slow steroid wean. Some patients might need low steroid maintenance doses.¹⁴⁸

Methotrexate can be considered as an alternative first-line drug, especially in those who are intolerant to azathioprine. A report described 14 patients on long-term methotrexate and recorded an 85% reduction in annualised relapse rate (from 1.39 to 0.18, $p < 0.005$), with disability improvement or stabilisation in 11 patients (79%).¹⁶⁰

Although the European Federation of Neurological Societies Guidelines suggest rituximab as a potential first-line treatment,¹⁴⁷ in practice it is usually second line.¹⁴⁸

Panel 5: Considerations for immunosuppressant use in atypical optic neuritis

For the immunosuppressants listed here, the treatment advice is not definitive and the reader is encouraged to refer to local guidelines for more details about monitoring and use. Most patients will also need pre-treatment screening investigations.

- Corticosteroids can be started at 0.75–1 mg/kg per day (after intravenous doses given in an acute relapse) and then tapered slowly over about 6 months, with close clinical monitoring for atypical optic neuritis. Many side-effects are associated with corticosteroid use. The main ones include mood disturbances, glucose intolerance or diabetes, osteoporosis, proximal myopathy, Cushing's syndrome, adrenal suppression, increased risk of infections (eg, varicella zoster, tuberculosis reactivation), hypertension, glaucoma, cataracts, electrolyte imbalance, neutrophilia, lymphopenia, peptic ulceration, and avascular necrosis. Patients on long-term corticosteroids in the UK should carry a steroid treatment card (providing information about reduction of risk and dose details) and should not discontinue treatment abruptly because of the risk of acute adrenal insufficiency. Local guidelines should be implemented for the prevention and treatment of osteoporosis, and patients should be monitored for diabetes and hypertension.
- Azathioprine treatment usually has a maintenance dose of 2.5–3.0 mg/kg per day, assuming that thiopurine methyltransferase concentrations are normal. It can be commenced at 25 mg daily and increased in 50 mg steps every week as an outpatient. Side-effects include bone-marrow suppression, hypersensitivity reactions, gastrointestinal reactions (nausea and vomiting), liver dysfunction, increased infection risk, and, rarely, pancreatitis. Full blood count and liver function tests should be monitored

frequently during early treatment while dose changes are occurring, and less frequently after reaching maintenance dose. A high mean corpuscular volume or lymphopenia tends to suggest a treatment effect.

- Mycophenolate treatment typically starts at 500 mg daily, increasing every week in 500 mg steps to a maintenance dose of 1 g twice daily. Main side-effects include hypersensitivity reactions, bone-marrow suppression, gastrointestinal reactions, liver dysfunction, renal dysfunction, potential risk of lymphoma and skin malignancy. Blood-test monitoring should include full blood count, urea and electrolytes, and liver function, and should be done frequently during the early treatment phase.
- Methotrexate treatment can aim for a maintenance dose of initially 15 mg once weekly. Doses start at 7.5 mg weekly (with folate supplementation) and then slowly increase in 2.5 mg steps each week. Side-effects include bone-marrow suppression, liver toxicity, pulmonary fibrosis, gastrointestinal symptoms, hypersensitivity reactions, and increased infection risk. Blood-test monitoring is mandatory (usually full blood count and liver function tests). Yearly chest radiographs are advised.
- Rituximab treatment is usually 1 g intravenously on days 1 and 14, repeated every 6 months or when the CD19 count (which is measured monthly) begins to rise.¹⁴⁶ Side-effects include allergic reactions, hypotension, and exacerbation of cardiac disease. Infections can occur in 30% of rituximab-treated patients and are severe in 1–2%.¹⁴⁷ Pre-infusion blood tests are recommended (full blood count, urea and electrolytes, and liver function).

Modified from Palace and colleagues.¹⁴⁸

It is an anti-CD20 chimeric monoclonal antibody administered by intermittent infusion, while the CD19 count is monitored.^{157,148} The three largest retrospective studies (recruiting 23, 35, and 30 patients, respectively)^{161–163} all described reductions in median annualised relapse rate by at least 90%, and stabilisation or improvement of disability in at least 80% of cases.

Mycophenolate is gaining favour as an effective immunosuppressant, despite the scarcity of evidence in neuromyelitis optica.¹⁴⁷ The authors of a retrospective analysis of 24 patients reported an improvement in median annualised relapse rate of 93% (1.3 before treatment; 0.09 after treatment, $p < 0.001$) and stabilisation or improvement of disability in 91% of cases.¹⁶⁴

Ecuzumab has shown promising results, albeit in a small open-label pilot study.¹⁶⁵ Median annualised relapse rate fell from 3 (range 2–4) to 0 (range 0–1) after a year's treatment in 14 patients ($p < 0.001$). Median Expanded Disability Status Scale score improved from 4.3 to 3.5 ($p = 0.0078$). Further studies are warranted.

Low-dose maintenance corticosteroids could have a role in maintenance of remission.¹⁶⁶ Evidence is scarce or mixed for other treatments used in relapse prevention, including mitoxantrone,¹⁶⁷ cyclophosphamide,¹⁶⁸ pulsed plasmapheresis,¹⁶⁹ cyclosporin A,¹⁷⁰ tacrolimus,¹⁴⁸ intravenous immunoglobulins,¹⁷¹ and tocilizumab.¹⁷²

Use of interferon beta, fingolimod, and natalizumab should be avoided in neuromyelitis optica and neuromyelitis optica spectrum disorders because some evidence suggests that clinical disease does not improve or can worsen with these treatments.^{173–177}

Optic neuritis with systemic disease or chronic relapsing inflammatory optic neuropathy

Most immunosuppressants used to maintain clinical remission in systemic inflammatory disease (eg, sarcoid, connective tissue disorder, or vasculitis) are the same as those described for neuromyelitis optica. Specific treatments should be tailored towards the underlying disorder, individual clinical course, and the

degree of multiorgan involvement. Available evidence is usually level 4.¹²⁴

In a retrospective analysis together with a literature review, Myers and colleagues¹⁷⁸ reported 48 patients with corticosteroid-dependent atypical optic neuritis. 17 had lupus, 12 had sarcoid, three had other conditions, and 16 had no identifiable systemic disease. About 80% of patients showed clinical benefit with various immunosuppressive drugs.

Lupus-associated optic neuritis is reported rarely, but some case reviews suggest that it responds to cyclophosphamide,^{138,179} azathioprine, or low-dose maintenance corticosteroids.¹³⁵ Sarcoid-associated optic neuritis has a variable clinical course (including acute mono-symptomatic, relapsing–remitting, and progressive)¹⁸⁰ and might improve with azathioprine,¹⁸¹ methotrexate,¹⁸² cyclosporin,¹⁸³ mycophenolate, and infliximab.^{133,184} Chronic relapsing inflammatory optic neuropathy could respond to low-maintenance-dose corticosteroids, azathioprine, and methotrexate.⁴⁶

Recommendations

For neuromyelitis optica, guidelines have been published that suggest steroid-sparing drugs for first-line and second-line treatment, with dosing and monitoring regimens.¹⁴⁸ This guide could be applied to management of relapsing NMO-ON. First-line treatments would therefore include azathioprine, methotrexate, or mycophenolate (panel 5). A relapse during treatment of sufficient dose and duration would indicate treatment failure. Monitoring of AQ4 antibody titres, if available, could be helpful.¹⁸⁵ Second-line treatment would be rituximab followed by other options, including mitoxantrone.

For non-NMO-ON (systemic disorders or chronic relapsing inflammatory optic neuropathy), similar first-line drugs can be considered—ie, azathioprine, methotrexate, or perhaps mycophenolate. Treatment

should be disease-oriented, although overlap with second-line drugs will also occur—eg, cyclophosphamide might be useful in lupus optic neuritis or infliximab in sarcoid optic neuritis.

Experimental neuroprotection and remyelination trials

After optic neuritis the degree of neuroaxonal loss correlates with quantitative measures of visual dysfunction.⁷⁸ Corticosteroids do not prevent axonal loss¹⁸⁶ or improve visual outcome. Therefore a key area of therapeutic research is to identify neuroprotective drugs that can prevent long-term axonal loss and hopefully lead to better visual outcomes.

The development of effective neuroprotection in optic neuritis also has implications for treatment of MS. Acute CNS inflammatory demyelination leads to axonal transection,¹⁸⁷ and effective neuroprotectants should reduce axonal loss in all CNS lesions, not only in those of the optic nerve. Optic neuritis is a suitable clinical model for neuroprotection studies. First, visual function can be measured with quantitative methods, including low-contrast acuity, visual fields, and colour discrimination. Second, optical coherence tomography provides an in-vivo measure of axonal loss secondary to optic neuritis—because axons in the retina are not myelinated, a decrease in retinal nerve fibre layer thickness is direct evidence for axonal loss, and sample-size calculations indicate that retinal nerve fibre layer loss is a sensitive outcome measure for proof-of-concept trials of neuroprotection after optic neuritis.⁸⁰ Third, visual evoked potentials can measure optic nerve conduction. A well preserved P100 wave form with prolonged latency provides evidence for demyelination, and subsequent shortening of latency is expected with remyelination.⁷³ Remyelination is also an important therapeutic aim—it might enhance conduction, thereby improving visual function, and could be neuroprotective

	Clinical group	Mechanisms	Trial design	Clinical outcome	Paraclinical outcome
Erythropoietin	Optic neuritis	Neurotrophism	Placebo-controlled	Borderline improvement in vision	Reduced loss of RNFL thickness
Simvastatin	Optic neuritis	Neuroprotection	Placebo-controlled	Borderline improvement in vision	Reduced VEP latency; increased VEP amplitude
Autologous mesenchymal stem cells	Secondary progressive MS	Neuroprotection; repair	Baseline crossover	Improved visual acuity	Reduced VEP latency; increased optic nerve area
Phenytoin	Optic neuritis	Neuroprotection (sodium channel blockade)	Placebo-controlled	In progress	In progress (primary outcome: reduction in OCT-measured RNFL loss)
Amiloride	Optic neuritis	Neuroprotection (acid sensing channel blockade)	Placebo-controlled	In progress	In progress (primary outcome: reduction in OCT-measured RNFL loss)
Anti-LINGO antibody	Optic neuritis	Remyelination	Placebo-controlled	In progress	In progress (primary outcome measure: reduction in VEP latency)

RNFL= retinal nerve fibre layer. VEP=visual evoked potential. OCT=optical coherence tomography.

Table 4: Trials of neuroprotection and repair in optic neuritis or the anterior visual pathway in multiple sclerosis

Search strategy and selection criteria

We searched PubMed for articles published in English from 1970 to July, 2013, with the general search term “optic neuritis” combined with more specific search terms related to the subheadings—eg, “optical coherence tomography”, “corticosteroid”, “plasmapheresis”, and “magnetic resonance imaging”. References from identified studies were checked and included if deemed appropriate, relevant, and scientifically important. We considered articles in other languages if referenced in a selected English article. We also searched references from our own files. We preferentially selected articles published within the past 10 years, although we also included older references that were important.

by reducing the vulnerability of axons to adverse effects associated with inflammation and demyelination.⁸⁶

Some trials have investigated neuroprotection or remyelination in the anterior visual pathway in optic neuritis and MS (table 4). Results of a placebo-controlled trial of erythropoietin showed smaller decreases in retinal nerve fibre layer thickness in the affected nerve with erythropoietin when compared with placebo,¹⁸⁸ but were complicated by retinal nerve fibre layer swelling during the acute phase of optic neuritis. Swelling indicates acute inflammation, and the decrease in retinal nerve fibre layer thickness is a combination of axonal loss and resolution of inflammation. More specific evidence for axonal protection should be obtained by comparison of the final thickness of the affected optic nerve with that of the unaffected nerve.⁸⁰ Another randomised controlled trial investigated simvastatin in acute optic neuritis.¹⁸⁹ Significant benefits were noted with visual evoked potential amplitude ($p=0.01$) and latency ($p=0.01$), and borderline effects for contrast sensitivity ($p=0.06$). A small baseline crossover trial of autologous stem cells in secondary progressive MS identified shortening of visual evoked potential latency and increase in optic nerve area after treatment, which could indicate remyelination.¹⁹⁰

Conclusions

To clinically distinguish typical optic neuritis from atypical forms in the acute phase is crucial; this distinction will then guide further management. The most common form is typical optic neuritis, probably demyelinating and closely associated with MS, although sometimes occurring in isolation. Typical optic neuritis resolves spontaneously, and provides researchers with a useful in-vivo model with which to study mechanisms of localised damage and recovery due to inflammatory demyelination in the CNS, including the study of neuroprotective and remyelination strategies. If untreated, atypical optic neuritis can lead to irreversible visual loss, and often needs urgent treatment with corticosteroids, with slow wean and, sometimes, chronic immunosuppression.

Contributors

ATT, DFM, and DHM were involved in planning, writing, critical reviewing, and revision of the Review. DHM was involved in conception of the manuscript.

Conflicts of interest

ATT has received honoraria from Sereno Symposia International Foundation and Bayer. DHM has received honoraria through payments to his employer, UCL Institute of Neurology, for Advisory Committee or consultancy advice in MS studies from Biogen Idec, GlaxoSmithKline, Novartis, Merck, Chugai, Mitsubishi Pharma Europe, and Bayer Schering Pharma. He has also received compensation through payments to his employer for doing central MRI analysis of MS trials from GlaxoSmithKline, Biogen Idec, Novartis, and Merck. DFM has received honoraria from Biogen.

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