

New developments in the treatment of optic neuritis

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Abstract: Acute optic neuritis (ON) has various etiologies. The most common presentation is inflammatory, demyelinating, idiopathic, or “typical” ON, which may be associated with multiple sclerosis. This must be differentiated from “atypical” causes of ON, which differ in their clinical presentation, natural history, management, and prognosis. Clinical “red flags” for an atypical cause of ON include absent or persistent pain, exudates and hemorrhages on fundoscopy, very severe, bilateral, or progressive visual loss, and failure to recover. In typical ON, steroids shorten the duration of the attack, but do not influence visual outcome. This is in contrast to atypical ON associated with conditions such as sarcoidosis and neuromyelitis optica, which require aggressive immunosuppression and sometimes plasma exchange. The visual prognosis of typical ON is generally good. The prognosis in atypical ON is more variable. New developments aimed at designing better treatments for patients who fail to recover are discussed, focusing on recent research elucidating mechanisms of damage and recovery in ON. Future therapeutic directions may include enhancing repair processes, such as remyelination or adaptive neuroplasticity, or alternative methods of immunomodulation. Pilot studies investigating the safety and proof-of-principle of stem cell treatment are currently underway.

Keywords: optic neuritis, multiple sclerosis, neuromyelitis optica, steroids, neuroplasticity, stem cells

Optic neuritis (ON) is defined as inflammation of the optic nerve. This general definition describes a common pathological phenotype, which may be caused by a wide range of heterogeneous conditions, varying greatly in their clinical features, natural history, treatment, and prognosis. The most commonly encountered syndrome is acute, inflammatory, demyelinating ON that may be associated with multiple sclerosis (MS). This will be referred to as typical ON in this review. Patients with typical ON generally make a good visual recovery and, although steroids are sometimes used to reduce the duration of the clinical attack, the overall visual recovery is unaffected by treatment. This is in contrast to some of the other, atypical, inflammatory, and infective causes of ON, in which the visual prognosis may be poor if left untreated. These types of ON differ in their clinical features from typical ON, and will be referred to collectively as atypical ON in this review. Atypical ON may be associated with non-MS inflammatory diseases of the central nervous system (CNS). In these patients, visual recovery is dependent on prompt immunosuppressive treatment, and delays in diagnosis can have serious consequences. Therefore, it is critical that these steroid-responsive, atypical optic neuritides are distinguished from typical ON, in order to select the group of patients who will benefit from immunosuppression.

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A minority of patients with typical ON fail to recover. At present, there are no effective treatments for these people. Recent research has elucidated the reasons underlying the mechanisms of damage and visual recovery in ON, which may lead to better therapies in the future.

In this review, we will outline the principles of diagnosis and management of ON. We will discuss the epidemiology, etiology, and common clinical presentation of typical ON. We will then discuss differential diagnosis, and emphasize the importance of identifying clinical “red flags” to help distinguish atypical ON. We will describe the differences in natural history, treatment, and prognosis of these two syndromes. Recent progress into understanding the pathophysiology of typical ON will then be reviewed, with a focus on future treatment directions for patients who fail to make a good visual recovery.

Epidemiology and etiology

The prevalence and incidence of ON varies across the world. Typical ON becomes more common with increasing latitude, in a similar manner to MS. A study based in the UK reported a lifetime prevalence of 0.6 per 1000 and an age and sex adjusted incidence of 1 per 100,000 per year.¹ A similar study based in the USA reported an age and sex-adjusted prevalence of 115 per 100,000 and an incidence rate

of 5 per 100,000 per year.² In Sweden researchers reported rather lower age-adjusted overall incidence rates of 1.40 per 100,000 per year (2.28 per 100,000 for females and 0.53 per 100,000 for males).³ This was somewhat surprising, given the high latitude of Scandinavia, but rates were still much higher than for people born outside of Nordic countries, for whom the rate was 0.28 per 100,000 per year.³ There is a seasonal pattern to the incidence, with rates highest in the spring.⁴

Typical ON most commonly affects young Caucasian women in their late 20s and early 30s. The mean age of onset is 31 to 32 years,^{5,6} although it is well recognized both in children and the elderly. The female to male ratio is approximately 3:1.⁵ Atypical optic neuritides are more variable in terms of demographics. Some types of atypical ON are more common in different ethnic groups, for example, sarcoidosis is more common in black people.

The cause of typical ON is unknown. As it is often associated with MS, it is thought that the two conditions share a common etiology. There are probably complex interactions between genetic predisposition and environmental triggers, that have yet to be identified but may include infectious agents and vitamin D deficiency.^{7,8} Atypical ON may be caused by infections, or be related to other inflammatory and autoimmune diseases (Table 1).

Table 1 Causes of atypical optic neuritis

| Etiology | Cause of ON | Clinical clues |
|----------------|---|--|
| INFLAMMATORY | Neuromyelitis optica | Longitudinally extensive myelitis, positive anti-aquaporin-4 antibodies, CSF cells but negative OCBs |
| | Sarcoidosis | Respiratory involvement, hilar lymphadenopathy, sometimes neuroretinitis, vitritis, uveitis (although uveitis may be seen in typical ON too ²⁹), meningeal enhancement on MRI, CSF cells |
| | SLE | Rash, arthritis, multiorgan involvement, positive ANA, and dsDNA, CSF cells |
| | Behçet's | Mouth and genital ulcers, CSF cells, positive skin pathergy test |
| | Chronic relapsing inflammatory optic neuropathy (CRION) | Relapses off steroids, no other inflammatory cause found, normal brain MRI, optic sheath enhancement, negative CSF OCBs, (term implies granulomatous pathology) |
| | Autoimmune ON | Relapses off steroids, similar to CRION but implies an autoimmune, nongranulomatous pathology |
| INFECTIOUS | Acute disseminated encephalomyelitis (ADEM) | Bilateral, additional neurology, multiple lesions on MRI all enhancing |
| | Lyme | History of exposure, erythema chronicum migrans, radiculo-neuropathy, heart and joints involved, neuroretinitis, vitritis, CSF cells |
| | Syphilis | Risk factors, genital ulcers, rash, involvement of other neurological systems (cord especially dorsal columns, cortex), neuroretinitis, vitritis |
| | Viral (EBV, CMV, HIV, others) | Prodrome, risk factors, polysystem involvement, vitritis, CSF cells |
| | Tuberculosis | History of exposure, vitritis, abnormal CXR |
| | Toxoplasmosis | Retinal or papillary lesion usually visible on fundoscopy |
| POSTINFECTIOUS | Toxocariasis | Neuroretinitis, eosinophilia |
| | Bartonella (cat scratch) | History of exposure, respiratory involvement, neuroretinitis |
| | Histoplasmosis | Respiratory symptoms, neuroretinitis |
| | | Commonly children, bilateral |

Note: The term “CSF cells” refers to an increased number of white cells in the cerebrospinal fluid (the normal reference range in most laboratories is <5 white cells per mm³).
Abbreviations: ANA, antinuclear antibodies; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CXR, chest radiograph; dsDNA, double stranded deoxyribonucleic acid; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; OCB, oligoclonal bands.

Typical ON may present as an isolated event, be a recurrent problem, or be followed later in life by inflammatory events elsewhere in the CNS. The occurrence of multiple events, disseminated in time and space within the CNS, defines MS.^{9,10} Subsequent events that are restricted to the optic nerves and spinal cord can be caused by neuromyelitis optica (NMO).¹¹ ON associated with NMO is often particularly severe and other atypical features may be present. The recent discovery of a pathogenic autoantibody has resulted in a realization that the clinical phenotype is wider than previously thought, and may include some patients with recurrent ON, without spinal cord involvement.¹²

The risk of recurrence of ON depends on the cause and length of follow-up, and was found to be 28%¹³ and 35%¹⁴ for typical ON, at five and ten years, respectively.

Clinical features

Typical ON usually presents with subacute painful loss of vision in one eye. The pain is sometimes ill defined at first, but then usually localizes in or around one eye. It is commonly worse with eye movements. The severity of the pain varies, but it is unusual for it to disturb sleep, or last longer than a few days.

This is concurrent with, or followed by, a reduction of vision in the same eye. Affected patients' reports of the early stages of visual loss are: "like looking through frosted glass" or "as if there is a smear of grease on my eye". The severity of visual loss is very variable, ranging from minimal blurring to inability to perceive light. Flashes of light on eye movements, called phosphenes or photopsias, may be reported. Visual loss usually progresses over a few days to two weeks, remains at a nadir for a period of days, and then begins to improve. Sometimes, during this period of recovery, patients notice that vision temporarily worsens with a rise in body temperature, for example, after a hot shower or exercise, termed Uhthoff's symptom.¹⁵ This can also occasionally be the presenting symptom. Pulfrich's phenomenon, an anomalous depth perception sensitive to objects in motion, may also be reported.¹⁶ Patients may describe persistent difficulties in certain sporting activities, for example, difficulty judging the trajectory of a tennis ball, despite near normal visual acuity.

Clinical signs in the acute stage include reduced monocular visual acuity in 90% of cases.⁵ Tests of low contrast acuity are sensitive at detecting deficits in the minority of people who have mild visual loss and are abnormal in 98%. Color vision is characteristically affected, sometimes more than other aspects of vision, and abnormalities on testing are

detectable in 94% of patients in the acute stage. The spectral location of color deficits varies between patients and no consistent pattern is seen.¹⁷

Visual field defects are detectable in 97% of people.¹⁸ Due to the patchy nature of the underlying pathology, a wide variety of defects are possible. The most commonly encountered is a diffuse pattern of visual loss, seen in 48% of cases.¹⁹ Central field abnormality is seen more commonly than peripheral deficit, and peripheral defects may improve more rapidly.¹⁸ Isolated central and centrocecal scotomas occur in 8%.¹⁹ Altitudinal defects are seen in 20% and various other types make up 23%. Chiasmal and retrochiasmal defects are less frequent, seen in only 3% of people. Incidental abnormalities of the unaffected eye are common.^{19,20} Recovery of visual field function is generally good and does not differ between diffuse and localized field defects.²¹

Nearly all patients with unilateral ON have a relative afferent pupillary defect (RAPD),²² and this was an inclusion criterion in the North American Optic Neuritis Treatment Trial (ONTT),⁵ the largest clinical study of ON, from which the symptom prevalences, cited above, were derived. Fundoscopy reveals a diffusely swollen disc in 35%, or may be normal, particularly if inflammation solely affects the posterior part of the nerve (retrobulbar ON). The retina is typically normal, except for perivenous sheathing (retinal periphlebitis), which is occasionally seen, and is associated with a higher risk of MS.²³ After around six weeks, the optic disc may become pale due to atrophy of the optic nerve.

There are some ethnic differences in the clinical profile. Acute disc swelling is more common in Japanese patients than Americans, and pain was less frequent in a Japanese cohort, compared to the patients in the ONTT.²⁴

Recovery usually begins within the first month. In the ONTT, 79% of people had started to improve by three weeks and 93% by five weeks.²⁵ Improvements may continue after this, especially in patients who have been severely affected and those in whom recovery is slower, and significant improvement may continue for up to six months. Subtle improvement may still be detectable a year or more after the acute attack, although by this time the patients do not tend to notice changes relevant to function. Most patients make a good functional visual recovery, improving to a Snellen acuity of 20/40 or better, but around 5%–10% of people fail to recover.²⁶ Many more complain of residual symptoms and deficits of acuity, fields, color vision, and, especially, low contrast acuity may be detectable for years afterwards.^{13,27}

Atypical presentations occur and, whilst these may be seen in typical ON, they can be a marker of a more unusual alternative etiology of ON (Table 1), or in other conditions mimicking ON (Table 2). Atypical features include absence of pain, which is seen in only 8% of people with typical ON,⁵ marked swelling of the nerve with retinal exudates and peripapillary hemorrhages, evidence of neuroretinitis, such as a macular star, severe visual loss to no light perception, progression of visual loss or pain for more than two weeks, and lack of recovery after three weeks.^{28–30} Bilateral ON may occur, either simultaneously or sequentially,³¹ which would also be an unusual feature in typical ON.²⁹ These “red flags” should prompt consideration of an atypical cause of ON, or an alternative diagnosis, and are summarized in Table 3.

Diagnosis and association with multiple sclerosis

The diagnosis of typical ON is essentially clinical, based upon a characteristic clinical presentation, with consistent physical signs, in an appropriate demographic group. A careful history and physical examination should be performed to identify any previous neurological episodes, and to look for involvement of other neurological systems, which may indicate an underlying diagnosis of MS. In typical ON with recovery, further confirmatory investigations are not mandatory. Patients are informed of the association with MS. Magnetic resonance

imaging (MRI) of the brain helps to stratify the risk of future inflammatory events, and is generally discussed with patients. If MRI shows radiological evidence of asymptomatic demyelination in the brain (Figure 1), which has been reported in 59% of patients presenting with isolated ON,³² and 70% of clinically isolated syndromes in general,³³ then the risk of developing MS is higher. Visual recovery should be assessed one month after the acute episode.

If atypical features are present, urgent further investigations are indicated to exclude the differential diagnoses listed in Tables 1 and 2. The choice of investigations depends upon the exact clinical picture, but should include MRI of the optic nerves, especially to rule out compressive causes of optic neuropathy, and also to assess for signal change within the nerves (Figure 2). Computerized tomography (CT) of the orbits is sometimes helpful in delineating bony orbital lesions. Cerebrospinal fluid examination is required to detect cells (in infective and atypical inflammatory causes), elevated protein, and oligoclonal bands. Blood tests and other paraclinical investigations may be indicated if atypical infective or inflammatory ON is suspected (Table 4). If other specific differential diagnoses are considered likely, further specialized tests may be necessary (eg, toxin screens, serum B12, mitochondrial genetics for Leber’s hereditary optic neuropathy, orbital ultrasound for posterior scleritis, optical coherence tomography, fluorescein angiography, and electroretinography for retinal disease).

Table 2 Mimics of optic neuritis: Other causes of optic neuropathy, retinal, scleral, and orbital disease

| Anatomical region | Condition | Clinical clues |
|-------------------|--|--|
| Retina | Central serous retinopathy (CSR) | Painless central blurring and photopsia, usually good recovery, macular abnormalities on fundoscopy |
| | Big blind spot syndrome/acute zonal occult outer retinopathy (AZOOR) | Painless enlargement of the blind spot, usually self-limiting, sometimes associated with disc swelling, color vision preserved |
| Sclera | Posterior scleritis | Severe pain wakes patient from sleep, visual symptoms not prominent, proptosis, disc swelling |
| Optic nerve | Ischemic optic neuropathy (may be related to giant cell arteritis – in which case may be painful – or diabetic papillitis) | Painless, acute, disc swelling invariably present during the acute episode, altitudinal field defect, poor recovery |
| | Optic nerve compression | Progressive symptoms, usually painless (except aneurysms, mucocele) |
| | 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, history of exposure Tobacco/alcohol amblyopia: painless, bilateral B12 deficiency: risks for malabsorption, painless, bilateral Ethambutol in treatment of TB |
| Orbit | Orbital cellulitis | Proptosis, other cranial nerve involvement |
| Other | Functional | Variability, no objective signs such as RAPD, normal VEPs |

Abbreviations: RAPD, relative afferent papillary defect; TB, tuberculosis; VEP, visual evoked potentials.

Table 3 “Red flags” in the diagnosis of optic neuritis, leading to consideration of atypical causes or mimics

| Feature | Red flag | Consider |
|----------------------|--|--|
| Demographic | African or Asian ethnicity Children Older people | Sarcoidosis, lupus, TB Postinfectious ON Ischemic optic neuropathy |
| Past medical history | History of cancer (especially breast, lymphoma) | Metastatic optic nerve compression |
| Family history | Positive FH | Leber’s hereditary optic neuropathy |
| Symptoms | Absence of pain Severe pain waking from sleep Bilateral ON Severe visual loss | Ischemic ON, most causes of optic nerve compression, CSR Posterior scleritis, atypical inflammatory especially CRION and sarcoidosis, infections Atypical inflammatory, infections, Leber’s, postinfectious/postvaccine, ADEM Atypical ON |
| Signs | Severe hemorrhages and exudates on fundoscopy Vitritis Neuroretinitis | Atypical inflammatory causes eg, sarcoidosis, SLE. Infections Sarcoid, infections CSR, Lyme, syphilis, viruses, cat scratch disease, toxocarasis, histoplasmosis, sarcoid |
| Progress | Persistent pain >2 weeks Progressive visual loss >2 weeks Relapses on withdrawal of steroids | Aneurysmal or mucocele compression, posterior scleritis, atypical inflammation, infections Compression, atypical inflammatory causes Atypical inflammatory causes, CRION |
| Recovery | No improvement at 3 weeks | Compression, atypical inflammatory ON |

Abbreviations: ADEM, acute disseminated encephalomyelitis; CRION, chronic relapsing inflammatory optic neuritis; CSR, central serous retinopathy; SLE, systemic lupus erythematosus; TB, tuberculosis.

Treatment of acute typical ON

At present, no therapy has been shown to improve long-term visual outcome in typical ON. Corticosteroids shorten the duration of the attack, but the consensus of several studies and a meta-analysis is that they do not appear to change the long-term outcome.^{34–39} Steroids have a risk of side effects, even if used

short-term, including mood change, weight gain, insomnia, pancreatitis, avascular osteonecrosis, and psychosis.²⁹ In the UK, corticosteroids tend to be reserved for patients with atypical features, coincident problems in the fellow eye, if pain is particularly severe, or at the patient’s request, although practice varies in different countries. Intravenous methylprednisolone

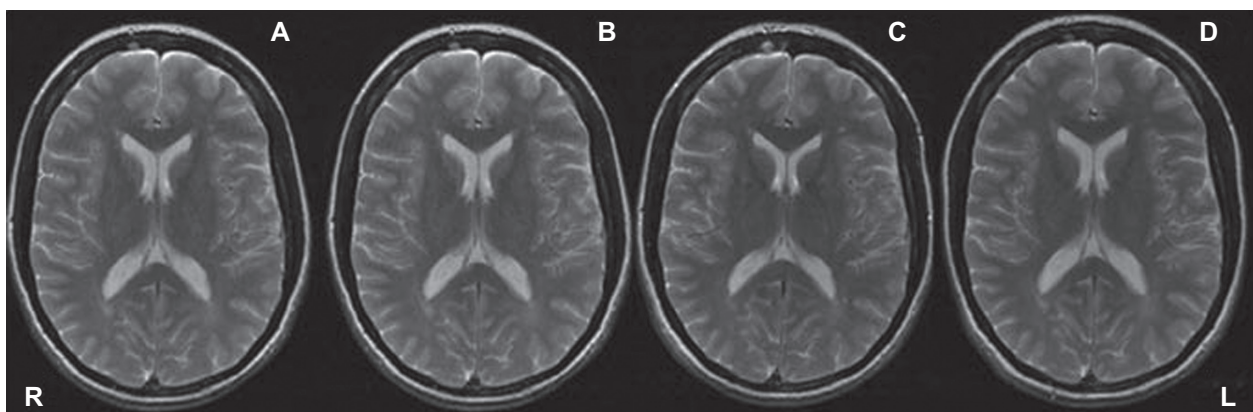


Figure 1 Serial axial brain MRI from a young woman with clinically isolated ON, taken over a 12 month period, demonstrating subtle demyelinating lesions. The presence of brain lesions is associated with a higher risk of MS after an isolated attack of typical ON, if the lesions are in a typical distribution for demyelinating disease, and excessive for the patient’s age. T2-weighted high signal abnormalities are seen in the white matter of the brain at the time of presentation with ON (A), and new lesions develop over the course of the year at three months (B), six months (C), and 12 months (D). At presentation, periventricular lesions are seen on the right, adjacent to the frontal and occipital horns. In addition, there is ill-defined signal change adjacent to the occipital horn of the left lateral ventricle. A more peripheral left frontal lesion is seen. New lesions are seen at six months, with the appearance of a right frontal juxtacortical lesion, and a new discrete lesion adjacent to the occipital horn of the left lateral ventricle. At 12 months, the left frontal lesion appears less conspicuous.

Abbreviations: R, right; L, left.



Figure 2 Coronal post-triple dose gadolinium T1-weighted MRI demonstrating left optic nerve enhancement (arrow).

Abbreviations: R, right; L, left.

tends to be preferred³⁴ (typically 1 g a day intravenously for three days without an oral taper). A prospective small trial showed that oral methylprednisolone 500 mg a day for five days (with an oral taper) hastened visual recovery but did not affect outcome, so this may be a viable alternative.⁴⁰

Beta-interferon and glatiramer acetate are established disease-modifying therapies in MS, which are known to reduce the rate of relapses by around a third over two years.^{41–43} The indications for their use following a single neurological episode suggestive of MS, such as ON, is still debated. In the USA, disease-modifying drugs are often prescribed after clinically isolated ON if the brain MRI is abnormal, indicating a higher risk of MS.⁴⁴ There is evidence that this delays the onset of the disease,^{45–49} which is consistent with their known efficacy in preventing a proportion of relapses in established MS. Some authorities argue that early treatment to prevent relapses may help prevent subsequent axonal damage. There may be an effect on short-term disability,⁵⁰ but any long-term benefits have yet to be reliably proven. In addition, in a significant proportion of patients with ON, no further clinical symptoms emerge for many years, and not all patients with an abnormal brain MRI subsequently develop MS, even after 30 years of follow up.⁵¹

In the UK, disease-modifying therapies are not used routinely following clinically isolated ON, and two clinical relapses are generally required before institution of treatment. The other treatments licensed in MS, mitoxantrone^{52,53} and natalizumab,^{54,55} are reserved for patients with severe, aggressive disease because of the risk of serious side effects, and do not have a role in the management of clinically isolated ON.

Treatment with steroids does not influence the subsequent long-term risk of MS. Although two year follow-up data from the ONTT initially suggested that intravenous methylprednisolone might delay the second, MS-defining relapse in comparison with oral prednisolone or placebo,⁵⁶ this was not sustained at three years, or fifteen years,⁵⁷ and therefore steroids are not used for this purpose.

Intravenous immunoglobulin has been tried in patients with persistent visual loss, but this did not result in any clinically significant benefits in randomized placebo-controlled trials. Both an American Phase II study of 55 patients⁵⁸ and a Danish placebo-controlled trial of 68 patients⁵⁹ used visual outcome at six months as an outcome measure and found no benefit.

Treatment of atypical ON

Treatment of atypical ON depends on the cause, and a detailed discussion of the management of systemic inflammatory and autoimmune conditions is outside the scope of this review. Infective ON requires appropriate antimicrobials. Atypical inflammatory causes require large doses of steroids (typically 1 g per day of intravenous methylprednisolone is used), and immunosuppressants targeted towards the underlying disease process, for example, cyclophosphamide for lupus,^{60,61} or azathioprine, mycophenolate, or rituximab for

Table 4 Specific tests to consider in atypical ON, in addition to MRI of the optic nerves and brain and cerebrospinal fluid analysis

| Suspected condition | Investigations to consider |
|----------------------|---|
| Neuromyelitis optica | Anti-aquaporin-4 antibodies |
| Sarcoidosis | Serum ACE, CXR [±] CT chest, (lymph node or other tissue biopsy) |
| Lupus erythematosus | Serum antinuclear antibodies, extractable nuclear antigens, anti-dsDNA antibodies, serum complement |
| Behçets | Skin pathergy test |
| CRION/Autoimmune ON | No specific tests – usually have negative CSF OCBs and antibodies. Defined by relapses when off steroids. |
| Lyme | Borrelia serology, ECG |
| Syphilis | Treponemal serology (eg, VDRL) |
| Viral | Specific serology, CD4 count if HIV positive |
| Tuberculosis | CXR, CSF for TB culture |
| Toxoplasmosis | Serology |
| Cat scratch disease | Bartonella serology |

Abbreviations: ACE, angiotensin converting enzyme; CSF, cerebrospinal fluid; CT, computerized tomogram; CXR, chest radiograph; dsDNA, double stranded deoxyribonucleic acid; ECG, electrocardiogram; FH, family history; HIV, human immunodeficiency virus; OCB, oligoclonal bands; TB, tuberculosis; VDRL, venereal diseases research laboratory.

neuromyelitis optica.⁶² The administration of intravenous steroids should be supplemented with a prolonged oral tail. If high dose steroids are ineffective at restoring vision during the acute episode, then plasma exchange may be used.⁶³ There is a lack of randomized trial evidence, and further studies are needed.

There can be difficulties in the management of recurrent inflammatory ON. In a proportion of patients ancillary investigations do not identify any specific underlying diagnosis. If steroid withdrawal results in further relapses, this syndrome is termed chronic relapsing inflammatory optic neuropathy (CRION),⁶⁴ or autoimmune ON, depending on whether a granulomatous or nongranulomatous autoimmune etiology is thought most likely. A proportion of patients with recurrent ON subsequently develop NMO, with a conversion rate of 21% reported in one study after six years of follow up.⁶⁵ In another study, 20% of patients with recurrent ON were seropositive for anti-aquaporin-4 antibodies, and 50% of these seropositive patients developed NMO within the next nine years.⁶⁶ This illustrates an increasing appreciation of the phenotypic spectrum of NMO, following the discovery of the anti-aquaporin-4 antibody.^{11,67-69} It appears that limited forms of NMO exist, and that the presence of antibodies is also associated with visual prognosis.^{12,66} Therefore, early diagnosis of NMO presenting as ON has become increasingly important, in order to institute appropriate treatment, such as rituximab.⁷⁰

Visual prognosis

The majority of people with typical ON make a good visual recovery, even if visual loss is initially severe.^{25,71} Improvement usually begins in the first month. Outcome at six months is associated with the degree of initial visual loss,²⁵ and with vision at one month.⁷² One year later, 95% of people have improved to Snellen 20/40 or better.²⁶ After five years, 28% of people in the ONTT had had a further attack, but 87% still had acuities of 20/25 or better, 94% 20/40 or better, and 97% 20/200 or better.¹³ Ten years later, 74% had a visual acuity of 20/20 or better, and 92% and 97% still had acuities of 20/40 and 20/200 or better, respectively.¹⁴ Recently, the 15 year final follow-up results were reported, and 72% of patients still had acuities of 20/20 or better.⁷³ However, many patients who are able to score well on the Snellen chart still have residual deficits of low contrast acuity, impaired color vision, and visual field defects.⁷⁴ Most patients report that their vision is not quite as good as it was before,⁷⁵ and this may impact on quality of life.⁷⁶ No associations have been found between the degree of visual recovery and age, gender,

ethnicity, abnormalities on brain MRI,²⁵ visual evoked potential (VEP) parameters during the acute stage,⁷⁷ or optic nerve MRI measures of myelination.⁷⁸

The data regarding the influence of steroids on recurrence of ON are somewhat confusing. Surprisingly, in the ONTT, a weak effect was found suggesting that oral prednisolone was associated with a higher risk of recurrence of ON, compared to intravenous methylprednisolone or placebo. This is difficult to explain at the neurobiological level, and the statistical significance of this finding disappeared over time.¹⁴ Therefore, interpretation remains difficult. Low dose oral prednisolone is avoided by some clinicians for this reason. When steroids are prescribed to shorten the duration of ON, methylprednisolone tends to be preferred.

Neurological prognosis

The risk of developing MS after typical ON depends predominantly on the length of follow-up, and whether the brain MRI at the time of presentation was normal. Five years after an attack of typical ON, 16% of people with a normal brain MRI had developed MS, compared with 51% of people who had three lesions or more.⁷⁹ Ten years after onset, in the same cohort, the risk was reported as 22% if the initial MRI was normal, increasing to 56% if it was abnormal.²⁸ Female gender, absence of optic disc swelling, and absence of atypical features were all associated with a higher risk profile. Other researchers have reported retinal vascular abnormalities,²³ HLA-DR2 genotype,⁸⁰ and the presence of oligoclonal bands in the cerebrospinal fluid⁸¹ as additional risk factors. Fifteen year follow up of the ONTT cohort subsequently reported conversion rates of 25% with a normal MRI, and 72% with an abnormal MRI.⁵⁷ The longest reported follow-up is located in a Swedish study, in which an overall 40% conversion rate was found after 31 years.⁵¹

In a different study people with a variety of clinically isolated syndromes were assessed, 14 years after the acute attack.³³ More than half of the patients had presented with ON, and the remainder had transverse myelitis or brainstem syndromes. The authors reported conversion rates of 19% in people who had a normal MRI at baseline, increasing to 88% if the scan was abnormal.

If MS does subsequently develop, it is said to generally follow a more benign course if typical ON is the presenting symptom, rather than pyramidal or cerebellar symptoms.⁸² In the ONTT, 65% of people had an Expanded Disability Status Score (EDSS) of 3.0 or less ten years later,⁸³ and 14% had severe disability (EDSS of 6 or more, corresponding to needing a stick to walk 100 m).

Therefore, the majority of people have a favorable visual and neurological prognosis following typical ON. However, for the minority who fail to recover, treatment options are limited. It also remains somewhat unclear when it is optimal to intervene with disease modifying therapy after a single attack of typical ON. This is because the relationships between inflammation, demyelination, and neuroaxonal loss are incompletely understood. Recent researchers have focused on elucidating the mechanisms underlying damage and recovery in ON, with a view to devising better therapies in the future.

Investigating damage and recovery in ON

In recent years, much progress has been made in elucidating mechanisms of damage and recovery in typical ON. Our current level of understanding has been achieved by combining the results of pathological studies in humans, extrapolating data from work in MS, experimental allergic encephalomyelitis work in animals, and *in vivo* studies in patients with ON, using MRI, electrophysiology, and optical coherence tomography. During the acute stage, inflammation,^{84–86} which is predominantly T-cell mediated, and demyelination^{87–89} occur. These two distinct, but linked, processes have detrimental effects on neural conduction, which may lead to acute conduction blocks in the optic nerve,⁹⁰ manifested clinically as visual loss. Inflammation is associated with edema.⁹¹ After a few weeks, inflammation, edema, and conduction block resolve and vision begins to recover. Redistribution of sodium channels also occurs.⁹² Subsequently, there is persistent demyelination, neuroaxonal loss,^{88,93–98} and probably gliosis. There are secondary effects on the rest of the visual pathway, which are incompletely understood, but may involve retrograde, Wallerian, and trans-synaptic degeneration.^{77,97,99–102} Atrophy is detectable in the optic nerve^{91,96,103} and dynamic changes in MRI diffusion parameters occur, which reflect changes in myelin and axonal damage.^{104–107} Neuroaxonal loss occurs in the retinal nerve fiber layer and macula.^{97,98,103} Despite this, most patients make a good clinical recovery, which may reflect neuroaxonal redundancy,¹⁰⁸ or an influence of repair mechanisms, such as remyelination^{78,109,110} or adaptive changes in the gray matter, known as neuroplasticity.^{103,111,112} Recently, it has been hypothesized that aggressive early immunosuppression in demyelinating disease may prevent the subsequent neuroaxonal loss thought to underpin later neurodegeneration,¹¹³ although further work is needed to support or refute this hypothesis.

Future directions

Remyelination

There is evidence that remyelination improves clinical function from experimental models of demyelination in rats.¹¹⁴ However, remyelination after ON in people occurs slowly, months to years after the initial insult,^{109,110,115} by which time most of the clinical improvement has already occurred. Recently, evidence has emerged that remyelination may also prevent subsequent degeneration of the axon,¹¹⁶ which has led to interest in remyelination as a therapeutic strategy to prevent neurodegeneration.

In both health and disease, maintenance of the myelin sheath is a dynamic process. Following demyelination, remyelination may occur spontaneously,¹¹⁷ through the action of oligodendrocytes recruited from precursor cells, expressing platelet-derived growth factor.¹¹⁸ The recruitment and differentiation of oligodendrocytes from these precursors appears to be critical for successful remyelination to occur. Sometimes remyelination fails, and this is either because oligodendrocytes are not present or, if present, are inactive. The reasons for this are incompletely understood, but animal work suggests that differentiation, rather than recruitment, of oligodendrocytes from precursors is the main problem in demyelinating disease.¹¹⁹ The migration of precursors to the demyelinated lesion appears to be impaired, perhaps through dysregulation of cellular signalling molecules,¹²⁰ or aberrant clearance of myelin debris.¹²¹ At present, it remains unclear how these insights can be translated into facilitating remyelination in patients.

One potential therapeutic avenue is through the use of exogenous stem cells. Although remyelination is usually dependent on oligodendrocyte function in the CNS, it is also possible using a variety of other different cell types, such as exogenous Schwann cells,¹²² olfactory ensheathing cells,¹²³ and neural stem cells, derived from bone marrow.¹²⁴ This led to the idea of using exogenous stem cells as a therapeutic strategy, which is discussed further in later sections.

Adaptive plasticity

It is likely that gray matter responses to an abnormal afferent input are associated with the degree of visual recovery. Several regions have been implicated. Results of early studies showed widely distributed changes in functional MRI responses to visual stimulation in extra-occipital cortex.^{125,126} More recently, researchers have implicated specific regions early after the acute episode as being crucial for visual recovery: the lateral occipital complexes,^{103,111} cuneus,¹²⁷

and lateral geniculate nuclei.¹¹² Therapeutic manipulation of the mechanisms underpinning adaptive plasticity may be possible in the future, and provide a novel target for future treatments. This could be through rehabilitation approaches, such as visual restitution therapy, which has been successfully applied to patients with visual field defects¹²⁸ or by using drugs to enhance adaptive neuroplastic responses, or perhaps prevent maladaptive responses in patients who fail to recover.

Stem cells

The initial hope was that stem cells would enhance neural repair, perhaps through a mechanism of remyelination, and it has been hypothesized that remyelination may prevent future axonal damage. In practice, results from animal models are proving that the mechanism of action of stem cells is much more complex. It appears that therapeutic effects are exerted through several mechanisms, and that immunomodulatory effects may be more influential than actual cell replacement.^{129,130} More work is needed to decipher the complex cell biology, but there remains great optimism in the research community about the potential of stem cells. Preliminary pilot studies to investigate safety and proof-of-principle are underway in patients with MS-associated ON.¹³¹

Conclusion

ON is essentially a clinical diagnosis, and a careful history and examination is critical in differentiating the common phenotype of typical ON from rarer, atypical, steroid-responsive, and infective causes. Typical ON is usually self-limiting and the majority of patients recover without treatment, although steroids are considered in patients who stand to benefit from a more rapid recovery. MRI is useful in stratifying the subsequent risk of MS in typical ON. Atypical ON requires urgent investigation and a more aggressive therapeutic approach, using high dose steroids, immunosuppression, and sometimes plasma exchange. For the minority of patients with typical ON who fail to recover, there are at present no effective treatments. Research insights into the pathophysiology of ON may help develop more effective therapies in the future, perhaps by exploiting reparative processes, such as remyelination and neuroplasticity, or through new methods of immunomodulation. Investigations into the potential utility of stem cells are underway.

Disclosure

The authors report no conflicts of interest in this work.

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