Optic neuritis: the eye as a window to the brain

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Abstract

Purpose of review: Acute optic neuritis (ON) is a common clinical problem, requiring a structured assessment to guide management and prevent visual loss. The optic nerve is the most accessible part of the central nervous system (CNS), so ON also represents an important paradigm to help decipher mechanisms of damage and recovery in the CNS. Important developments include the advent of optical coherence tomography (OCT) as a biomarker of CNS axonal loss, the discovery of new pathological antibodies, notably against aquaporin-4 and, more recently, myelin oligodendrocyte protein, and emerging evidence for sodium channel blockade as a novel therapeutic approach to address energy failure in neuroinflammatory disease.

Recent findings: We will present a practical approach to assessment of ON, highlighting the role of OCT, when to test for new antibodies and the results of recent trials of sodium channel blockers.

Summary: ON remains a clinical diagnosis; increasingly OCT is a key ancillary investigation. Patients with "typical" ON, commonly a first presentation of multiple sclerosis, must be distinguished from "atypical" ON, who require testing for new pathological antibodies and require more aggressive targeted treatment. Sodium channel blockade is an emerging and novel potential therapeutic pathway in neuroinflammatory disease.

Introduction

Acute optic neuritis (ON) is relatively common with an estimated lifetime prevalence of 0.6/1000 [1], and age- and sex-adjusted incidence of 1-5/100 000 [1, 2]. ON most frequently affects young Caucasian women; the mean age of onset is 31-32 years [3, 4]. Patients may present to ophthalmologists, neurologists, emergency physicians or general practitioners, so knowledge of the condition is necessary for a wide range of clinicians. The presenting symptoms are readily recognisable and diagnosis is essentially clinical. In most patients, the pathology is demyelination of the optic nerve, which may reflect a first relapse of multiple sclerosis (MS), if there is additional clinical or radiological evidence of brain lesions fulfilling diagnostic criteria [5], or a clinically isolated syndrome suggestive of MS, if no evidence of intracranial involvement is present. In these patients with "typical" demyelinating ON (T-ON), spontaneous visual recovery is expected, and visual prognosis is good in 90-95% of cases [6]. In a smaller proportion of patients, ON occurs with a cause other than typical demyelination, usually an alternative inflammatory or infective disease. These patients exhibit "red flags" for an more aggressive aetiology, generally do not recover without directed treatment and are termed atypical ON (A-ON) in this review. Distinguishing T-ON from A-ON is critical to prevent permanent visual loss. In this review, we will describe a structured approach to the assessment of a patient with ON with a focus on recent developments, including the expanding role of optical coherence tomography (OCT), identification of new pathogenic antibodies implicated in cases of A-ON, and the insights that ON has provided into pathology of central nervous system (CNS) disorders including an emerging role for energy failure in neuroinflammatory disease and sodium channel blockade as a potential new therapeutic strategy.

Clinical features of T-ON

An attack of ON generally begins with periocular pain characteristically as worse on eye movements. Concurrent with pain onset, or following within a few days, visual loss occurs, ranging from mild blurring to loss of perception of light. There is usually dyschromatopsia. Associated positive visual phenomena, such as flashes of light on eye movements (termed phosphenes or photopsia) have been described. The presence of a relative afferent pupillary defect is a key clinical finding; patients with subclinical demyelination in the fellow eye or ipsilateral mild optic neuritis may not exhibit this sign. The optic disc is usually normal but is swollen in a third of patients [3] (termed papillitis rather than papilloedema); haemorrhages and exudates are unusual in T-ON but are more commonly seen in A-ON. In patients with subtle visual loss, acuities may be preserved but deficits of colour vision or low contrast acuity are evident in the vast majority [3]. Seventy nine percent of patients with T-ON begin to improve by three weeks and 93% by five weeks [7]. Vision returns to near normal, in terms of measured acuity [7], but patients often report their eyesight is not quite as good as before [8]; colours often appear washed out and residual visual problems may still impact on quality of life [9]. Uhthoff's and Pulfrich's phenomena may be noted around the time of visual recovery (respectively, transient worsening of vision with elevation of body temperature, for example, after a hot bath or exercise [10], and difficulty judging the trajectory of a moving object, for example, a tennis ball, despite good visual acuity [11]).

Clinical features of A-ON

Many of the initial features of A-ON are the same as T-ON but painless or very painful onset is more common (absence of pain was only seen in 8% of people with T-ON in the pivotal Optic Neuritis Treatment Trial [3]). Severe visual loss with haemorrhages and exudates on fundoscopy are red flags for A-ON, especially in non-Caucasian patients, in whom alternative inflammatory disorders such as sarcoidosis and lupus erythematosis (SLE) have a higher prevalence. Progression of visual loss beyond three weeks of onset, or failure of significant recovery at six weeks, suggest A-ON. The clinical features that help identify patients with A-ON are summarised in Table 1, together with some of the more common alternative causes to consider. Atypical inflammatory causes include neuromyelitis optica spectrum disorder with anti-aquaporin-4 (AQ4) or anti-myelin oligodendrocyte glycoprotein (MOG) antibodies, sarcoidosis, SLE, Behcet's disease or granulomatosis with polyangiitis (GPA formerly known as Wegener's granulomatosis), and are important to identify because early and aggressive immunosuppression, initially with steroids, can prevent permanent visual loss. Optic atrophy evident before six weeks can suggest optic nerve compression, metabolic or hereditary disorders (Leber's hereditary optic neuropathy (LHON) or autosomal dominant optic atrophy). There are a number of infective causes that also require targeted treatment (for example, human immunodeficiency virus (HIV), tuberculosis (TB), syphilis and Bartonella henselae "cat scratch disease";

look for a macular star of associated neuroretinitis). Nutritional causes of optic neuropathy include tobacco-alcohol amblyopia, but the history is often slower than T-ON and painless. Ischaemic optic neuropathy tends to occur in patients with hypermetropic discs; this is usually painless (unless there is associated temporal arteritis), optic nerve swelling is universal during the acute phase and an altitudinal visual field defect is typical (but can also occur in T-ON).

Investigations

T-ON is a clinical diagnosis and ancillary investigations are not mandatory if there are no red flags to suggest A-ON. OCT is emerging as a useful ancillary investigation and assessment of retinal nerve fibre layer (RNFL) thickness, with a peripapillary ring scan, and macular volume, were advocated in a recent expert consensus review [12]. OCT has identified additional pathological features, such as macular cystic changes in some patients [13]; the significance and nature of their pathophysiology is debated and a topic of further research. Cranial magnetic resonance imaging (MRI) is helpful to stratify risk of subsequent MS in clinically isolated T-ON- if the patient wishes to know- and to confirm the diagnosis of MS in people with a history of previous neurological episodes. High signal and contrast enhancement in the optic nerves are commonly seen on these scans in acute T-ON [14, 15]. In patients with isolated T-ON, subsequent risk of MS is dependent on length of follow-up and is approximately 25% at 15 years with a normal baseline cranial MRI and 72% if even a single demyelinating brain lesion was present [16]; risk rises with number of intracranial lesions. Risk rises with presence of oligoclonal bands in the cerebrospinal fluid too [17], but this is not routinely performed in T-ON.

The situation is different in A-ON. If any red flags are present to indicate A-ON, patients require early and more extensive investigation, described in Table 2.

Management

In many patients with T-ON, no treatment is usually required. Early follow-up is important to ensure visual recovery. Methylprednisolone reduces the duration of an attack of T-ON but does not appear to improve visual outcome [18]. Prednisone was ineffective and, surprisingly, increased recurrence risk in the Optic Neuritis Treatment Trial (ONTT), the pivotal study that also yielded much of the natural history data reported above [18]. The benefits and risks of steroids versus no treatment may be discussed with patients with T-ON; patients with severe pain or visual loss, or coexistent fellow eye pathology, may have most to gain. Short-term side effects of steroids include insomnia, mood disturbance and, rarely, aseptic necrosis of the femoral head. If a patient opts for steroids, clinical practice is extrapolated from MS studies showing equivalence of using intravenous or oral steroids in MS relapses [19]; either oral methylprednisolone 500mg for 5 days or intravenous methylprednisolone 1g for 3 days may be used depending on local preference [20]. There is at present no available treatment for patients with T-ON who fail to recover. Biomarkers to identify these patients early are required; cerebrospinal fluid neurofilament light chains have been proposed [21], and research in this area is ongoing.

Patients with A-ON require targeted treatment to prevent visual loss. In particular, people with an inflammatory cause of A-ON require prolonged courses of steroids; initial intravenous methylprednisolone induction is followed by oral prednisolone tapered over several months. The duration of therapy and use of alternative steroid-sparing agents depends on subsequent clinical course and the underlying cause. Plasma exchange has been used in cases with severe visual loss unresponsive to steroids of varying aetiologies [22].

Recent developments and future directions: the eye as a window to the brain

The optic nerve represents the most accessible part of the CNS, may be viewed directly using the ophthalmoscope and, now, the RNFL axons can be measured accurately using OCT. This accessibility and the fact that visual function can be measured objectively make ON an important model for research into CNS inflammatory disease. Study of patients with ON has led to advances in understanding of the pathophysiology of CNS inflammatory disease, for example, blood-brain barrier changes in association with conversion from ON to MS [23], trans-synaptic degeneration [24], relationships between demyelination and deficits in specific visual modalities [25] and the role of cortical plasticity in recovery [26, 27]. OCT measures such as RNFL thickness are now recommended as a surrogate marker for axonal loss in clinical trials in MS [28, 29] and appear to correlate with brain atrophy, especially within grey matter [30]. A recent multi-centre study showed that RNFL thinning correlated with disability in MS [31], implying that the axonal loss measurable with OCT is clinically relevant, and validating its role as a surrogate marker of the pathology underpinning MS progression. Interestingly, RNFL thinning appears to progress in MS but not NMO [32], another fascinating difference between these contrasting neuroinflammatory diseases. The importance of OCT is likely to continue to grow because, despite rapid advances in relapsing-remitting MS therapeutics, treatment for the progressive phase remains the greatest challenge in the field. ON research therefore remains at the front line in the battle against neurodegenerative disease.

Blockade of sodium channels has been proposed as a novel therapeutic strategy to address axonal loss in secondary progressive MS. A hypothesis of energy failure was developed from animal models of experimental allergic encephalomyelitis [33, 34]; subsequent intra-axonal sodium accumulation is thought to lead to reversal of the sodium-calcium exchange pump and result in lethal accumulation of intra-axonal calcium [35, 36]. Phenytoin, a sodium channel blocker, reduced RNFL loss by 30% in a recent trial in ON patients [37], supporting proof of principle, although no effect on visual acuity was detectable. Similar results were obtained from a previous trial of memantine [38]. Alternative strategies of ion channel blockade using amiloride are also under investigation [39]. A differing approach is based upon a proposed neurotrophic role for erythropoietin; one phase II trial was encouraging [40] but another was negative [41]. A further trial of erythropoietin is underway [42]; The role of vitamin D in neuroinflammatory disease is debated; dynamic associations with RNFL thickness have been observed [43] but a recent study showed no association with disease severity [44].

Another key development has been the widening spectrum of antibody-mediated neuroinflammatory disease affecting the optic nerve, starting with the discovery of AQ4 antibodies [45, 46] in neuromyelitis optica (NMO). NMO restricted to the optic nerve is now a well established disease phenotype [47-49] and requires early and aggressive immunosuppression. The discovery of the AQ4 antibody was followed by the identification of antibodies to myelin oligodendrocyte protein (MOG) [50], found in 25-33% of AQ4 negative patients. These patients have a similar NMO phenotype [51, 52] but also some important differences to AQ4 patients, such as a higher frequency in children [53], a male preponderance, a monophasic course with fewer relapses [52] and more frequent involvement of the anterior, rather than posterior, visual pathways [54]. It appears likely that discovery of other antibodies will follow and the spectrum of A-ON will continue to expand, with important consequences for our understanding of CNS inflammatory disease.

Conclusion

In summary, accurate diagnosis of ON is important, especially the recognition of any atypical features, in order to guide management and optimise visual prognosis. Moreover, ON offers a window into CNS pathophysiology that is starting to be exploited to address key therapeutic challenges in areas such as progressive MS.

Key points

- ON is a clinical diagnosis; in typical cases, no diagnostic investigations are routinely required although MRI is offered to help stratify the risk of future conversion to MS.
- The most important aspect of assessment is to identify any atypical features; these patients require further investigation and targeted management.
- ON offers a window into the pathophysiology of neuroinflammatory disease.

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Table 1 Red flags that can indicate a case of A-ON and possible alternative diagnoses

Clinical feature	**Comments**	**Possible alternative diagnoses**
History:		
Lack of pain	Seen in 8% of patients with T-ON	Optic nerve compression, hereditary (e.g. LHON), nutritional, maculopathies
Severe or prolonged pain	Wakes the patient up at night	Inflammatory or granulomatous causes e.g. AQ4, sarcoid
Severe visual loss in non-Caucasian	<6/60	SLE, sarcoid, Behcet's disease,
Prolonged deterioration >2-3 weeks		Infectious (e.g. HIV, syphilis, Lyme, Bartonella, TB), nutritional, compression, alternative inflammatory (AQ4, MOG, SLE, sarcoid, Behcet's, GPA), CRION
Bilateral simultaneous ON		AQ4, MOG, infectious
History of cancer		Compression, paraneoplastic retinopathy
Examination:		
Visual acuity	<6/60	Alternative inflammatory, infectious

Fundoscopy: optic atrophy at presentation		Compression, metabolic
Fundoscopy: retinal abnormalities	Macular star and papillitis	Neuroretinitis (Bartonella, Lyme, syphilis)
Follow-up:		
Lack of recovery at 6 weeks	Beware ON in an amblyopic eye as an alternative cause of apparent poor recovery	Compression, LHON, nutritional, atypical inflammatory (AQ4, MOG, sarcoid, SLE, Behcet's, GPA)
Relapse on steroid withdrawal		CRION, atypical inflammatory

A-ON- atypical optic neuritis; AQ4- aquaporin-4 antibody related optic neuritis; CRION- chronic relapsing inflammatory optic neuritis; GPA- Granulomatosis with polyangiitis; HIV- human immunodeficiency virus; LHON- Leber's hereditary optic neuropathy, MOG- myelin oligodendrocyte glycoprotein antibody-related optic neuritis; SLE- systemic lupus erythematosis; T-ON- typical optic neuritis

Table 2 Investigations to consider in cases of A-ON

Investigation	Looking for…	Comments

Cranial MRI	Intracranial inflammation in sarcoid, SLE, AQ4, MOG, etc	Also useful in T-ON to diagnose or stratify risk of MS
Orbital MRI	Optic nerve compression- mostly painless (except aneurysm and mucocoele)	Optic nerve sheath meningioma, optic nerve glioma, metastases, lymphoma, mucocoele, aneurysms
Cerebrospinal fluid	Elevated cell count and protein in AQ4, sarcoidosis, SLE, MOG, Behcet's, GPA, infections	A low grade inflammatory response (CSF WCC<50 may be seen in MS)
AQ4 antibodies	NMO spectrum disorder	Guarded visual prognosis
Anti-MOG antibodies	NMO spectrum disorder	Perform if AQ-4 negative; may be milder phenotype than AQ4
Other blood tests: serum ACE, ANA, ANCA	Sarcoid, SLE, GPA	Especially severe visual loss in non-Caucasian patients
Chest radiograph	Sarcoid, TB	
Infectious serology: HIV, VDRL, Lyme, Bartonella, TB	Bilateral disease, other neurological signs, neuroretinitis	

Genetics	LHON, autosomal dominant optic atrophy mutations	

ACE- angiotensin converting enzyme; A-ON- atypical optic neuritis; ANCA- anti-neutrophil cytoplasmic antibody; AQ4- aquaporin-4 antibody related optic neuritis; CSF- cerebrospinal fluid; GPA- Granulomatosis with polyangiitis; LHON- Leber's hereditary optic neuropathy; MOG- myelin oligodendrocyte glycoprotein antibody-related optic neuritis; MRI- magnetic resonance imaging; MS- multiple sclerosis; NMO- neuromyelitis optica; OPA- opSLE- systemic lupus erythematosis; T-ON- typical optic neuritis; VDRL- venereal disease research laboratory test for syphilis; WCC- white cell count

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