Neuro-Ophthalmology

Global Trends in Diagnosis, Treatment and Management

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Preface

Neuro-ophthalmology is a dynamic and evolving field. Regional, national, and international similarities and differences in clinical approach and philosophy provide an insight into the global nature of the field. This book intends to summarize the key clinical evaluation and management issues for selected neuro-ophthalmic conditions. It is not our intention to comprehensively cover the entire spectrum of neuro-ophthalmology, but instead we propose to highlight a few relevant and timely topics of interest to a general audience interested in neuro-ophthalmic disease. We hope that the reader enjoys this brief entry into global neuro-ophthalmic care.

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Chapter 1
Optic Neuritis

Neil R. Miller

Optic neuritis is the term used for an infection, demyelination, or inflammation of the optic nerve. Although optic neuritis may occur insidiously with and without progression (i.e., chronic optic neuritis), most cases are of sudden onset. Depending on the cause, acute optic neuritis may be unilateral or bilateral, anterior (i.e., papillitis) or retrobulbar, and painful or painless. The treatment of acute optic neuritis depends on the known or presumed etiology [1].

Infectious Optic Neuritis

Acute optic neuritis can be caused by a variety of organisms, including bacteria, viruses, and spirochetes. In most cases, there is sudden loss of vision associated with retro-ocular pain and optic disc swelling. Vitreous cells are commonly present. In some but not all cases, there is extensive macular edema with eventual formation of a macular star or hemi-star pattern (Fig. 1.1) in which case the condition is referred to as "neuroretinitis" [1]. Neuroretinitis is never caused by multiple sclerosis (see below) [2]. The evaluation of presumed infectious optic neuritis depends on the setting. For example, syphilis is the most common cause of optic neuritis in South Africa, whereas tuberculosis is the most common cause in India. Lyme disease should be suspected in areas in which the disease is endemic, whereas infection by *Borrelia* species should be considered in patients with exposure to cats. The treatment of infectious optic neuritis is aimed at the causative organism and may include systemic antibiotics, corticosteroids, or both.

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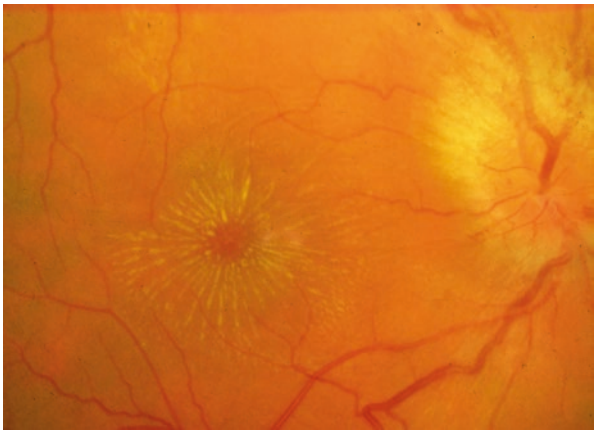

Fig. 1.1 Neuroretinitis in a patient with infection by Bartonella henselae. The optic disc is swollen and there is a macular star consisting of hard exudate

Sarcoid Optic Neuritis

Granulomatous inflammation of the optic nerve may occur in sarcoidosis, producing a typical anterior or retrobulbar optic neuritis [3–7]. In some cases, the optic neuritis occurs during the disease; in others, it is the presenting manifestation. Clinical findings may be indistinguishable from those of demyelinating optic neuritis (see below); however, the optic disc sometimes has a characteristic lumpy, white appearance, suggesting a granulomatous etiology, and there may be an inflammatory reaction in the vitreous. Pain, common in a demyelinating optic neuritis, is often absent in the optic neuropathy of sarcoidosis.

Unlike primary demyelinating optic neuritis, which does not respond dramatically to systemic corticosteroids, the optic neuritis associated with sarcoidosis usually is extremely sensitive to steroids. In most cases, recovery of vision is rapid after treatment is instituted, although vision may decline again once steroids are tapered or stopped. Indeed, it must be emphasized that rapid recovery of vision with corticosteroid treatment and subsequent worsening when the steroids are tapered is atypical for demyelinating optic neuritis and suggests an infiltrative or non-demyelinating inflammatory process, such as sarcoidosis.

Patients with possible sarcoid optic neuritis should undergo an evaluation that includes a careful history and physical examination, a chest radiograph or computed tomographic (CT) scan, serum chemistries, an assay for angiotensin converting enzyme (ACE) in the serum and cerebrospinal fluid (CSF), a gallium scan, and in some cases bronchoscopic lavage or biopsy of skin, conjunctiva, lung, liver, or other organs looking for noncaseating granulomas.

Demyelinating Optic Neuritis

Acute demyelinating optic neuritis may be the presenting sign of, or occur in the setting of multiple sclerosis (MS) or neuromyelitis optica spectrum disease (NMOSD) with serum antibodies to aquaporin-4 (AQP4), or it may be associated

with antibodies directed against myelin oligodendrocyte glycoprotein (MOG). In some cases, it occurs in isolation, and affected, otherwise healthy patients never develop any subsequent neurological or systemic deficits. The optic neuritis thus is considered "idiopathic" and it is assumed that the pathogenesis is demyelination.

Typical optic neuritis that is unassociated with anti-AQP4 or anti-MOG antibodies usually occurs in one eye only but occasionally in both eyes simultaneously, and is associated with retro-ocular pain that usually increases with movement of the eyes [1]. It occurs most often in women between 15 and 45 years of age. The degree of visual loss varies considerably [8]. Some patients are aware of minimal loss of central vision and actually retain visual acuity of 20/20 or better, whereas others lose all or almost all perception of light. In some patients, visual loss from optic neuritis is associated with flashes of light called **phosphenes** that may be precipitated by eye movement [9] or certain sounds [10]. Patients with optic neuritis not only have loss of visual acuity but also have decreased color vision that is often more severe than the level of visual acuity would predict [11]. A central visual field defect is common in patients with optic neuritis, but a typical central scotoma occurs in a minority of patients. Instead, a variety of patterns of visual field loss may occur in patients with acute optic neuritis, including altitudinal, arcuate, cecocentral, diffuse, and even unilateral hemianopic visual field defects [12]. Patients with unilateral acute optic neuritis invariably have a relative afferent pupillary defect (RAPD) in the affected eye unless they have some type of related or unrelated organic visual disturbance in the contralateral eye, and such patients also have a reduced sensation of brightness in the affected eye that can be demonstrated by simply asking them to compare the brightness of a light shined in one eye and then another. Slit lamp biomicroscopy in patients with demyelinating optic neuritis is almost always normal. There may be a few cells in the vitreous overlying the optic disc, but there is rarely if ever any significant cellular reaction. In the Western hemisphere, the optic disc is normal in about two-thirds of patients [8]. The condition is then called "retrobulbar optic neuritis" or, simply, "retrobulbar neuritis."

The natural history of acute demyelinating optic neuritis that is unassociated with anti-AQP4 or anti-MOG antibodies is to worsen over several days to 2 weeks, and then to improve. The improvement is initially fairly rapid with nearly all patients beginning to improve within the first month [13]. It then levels off, but further improvement can continue to occur up to 1 year after the onset of visual symptoms [14]. The mean visual acuity 12 months after an attack of otherwise uncomplicated optic neuritis is 20/15, and fewer than 10% of patients have permanent visual acuity less than 20/40 [14, 15]. Even patients who lose all perception of light may regain 20/20 or better vision. The only factor of value in predicting visual outcome is initial severity of visual loss [13]. Other parameters of visual function, including contrast sensitivity, color perception, and visual field, improve in conjunction with improvement in visual acuity [16]. Nevertheless, there remain some patients who have persistent severe visual loss after a single episode of optic neuritis [14], and even patients with improvement in visual function to "normal" may complain of movement phosphenes and may have persistent visual deficits when tested using more sensitive clinical, electrophysiologic, or psychophysical tests. Such patients may be

found to have thinning of the retinal nerve fiber layer when optical coherence tomography (OCT) is performed, indicating permanent loss of axons rather than simple demyelination.

The treatment for acute demyelinating optic neuritis that is not associated with anti-AQP4 or anti-MOG antibodies is somewhat controversial. The use of a short course of intravenous methylprednisolone (250 mg every 6 h for 72 h) followed by a 2-week course of oral prednisone given orally (11 days of 1 mg/kg/day followed by a 3-day taper) is associated with an increase in the speed of recovery of vision by 2–3 weeks compared with no treatment [14, 15], but the ultimate visual function at 5, 10, and 15 years is the same as it would be if no treatment were given [17, 18]. The use of oral corticosteroids alone when given to patients with acute optic neuritis at a dose of 1 mg/kg/day not only does not improve visual outcome or speed recovery but is associated with a significantly higher incidence of recurrent attacks of optic neuritis in the same eye and new attacks in the contralateral eye than in patients who either are not treated or receive intravenous corticosteroids before a short oral course of steroids [14, 17, 18]. In view of these findings, we and others believe it is **inappropriate** to treat any patient with acute demyelinating optic neuritis with oral corticosteroids alone at this dosage [14, 15, 19]. However, it is now clear that a much higher dose of prednisone, given orally, has the same effect on vision as intravenously administered methylprednisolone [20].

The combination of acute optic neuritis with at least one high-signal abnormality in the white matter on brain magnetic resonance imaging (MRI) define a patient who is monosymptomatic but at high risk for the development of MS. There are several class I studies, including the Optic Neuritis Treatment Trial (ONTT), the Controlled High-Risk AVONEX Multiple Sclerosis (CHAMPS) Trial, and the Early Treatment of Multiple Sclerosis (ETOMS) that help guide the management of such a patient [14, 21, 22]. The findings of these studies strongly suggest that such a patient not only should be treated with a course of high-dose followed by low-dose systemic corticosteroids as described above but also should be considered for treatment with interferon beta-1a therapy. The use of corticosteroids is supported by the findings of the ONTT, that showed that the risk of MS could be delayed over a 2-year period time frame by the regimen described above [14]. The 2-year risk of developing MS was 8% for patients in this trial who received the IV/oral regimen compared with 17% for patients who were treated either with low-dose prednisone alone or placebo. The ONTT also determined that the most important predictor of the development of MS in a patient with isolated acute optic neuritis was an abnormal MRI [23]. The initial findings suggested that the risk of MS increased with the number of white-matter lesions; however, the most recent data indicate that it is the presence or absence of any lesions that conveys the increased risk [24].

The CHAMPS Trial was designed to determine if the administration of interferon beta-1a could further delay the onset of MS in patients with a clinically isolated demyelinating syndrome (about 50% of whom had optic neuritis) and two or more high-signal abnormalities on brain MRI [21]. In this trial, all patients received IV and oral corticosteroids as per the ONTT protocol; patients then received either

interferon beta-1a in the form of AVONEX or placebo. Patients receiving AVONEX had a 44% reduction in the cumulative probability of developing clinically definite MS (CDMS) over a 3-year time period. Brain MRI findings also confirm the strong effect of AVONEX, with treated patients showing a reduction in both the volume of white-matter lesions and the number of active white-matter lesions compared with patients receiving placebo.

Patients in the ETOMS who were treated with recombinant interferon beta-1a (Rebif) demonstrated a 24% reduction in CDMS over a 2-year time frame compared with patients who received placebo [22]. Treated patients showed changes in their MRI similar to those seen in the CHAMPS Trial.

Finally, it should be noted that the α4 integrin antagonist, natalizumab (Tysabri®), has shown great promise in the treatment of relaping MS despite it's potential to cause progressive multifocal leukoencephalopathy [25]. Although Class I studies are lacking with respect to the potential of this drug to prevent the development of MS in high-risk patients with isolated optic neuritis, it, or a drug similar to it, may become the treatment of choice in such patients in the future.

Acute Optic Neuritis Associated with Anti-Aquaporin-4 Antibodies

Only about 5% of cases of unilateral optic neuritis are associated with AQP4 antibodies in the serum [26–31]. Indeed, an analysis of the serum of 177 participants in the ONTT revealed no evidence of AQP4 antibodies [29]. This is not surprising, as although the initial presentation of AQP4-antibody-positive optic neuritis may be similar to that of the retrobulbar optic neuritis that occurs in isolation or that is related to MS, many cases are bilateral, anterior, painless, and associated with severe and permanent visual loss. In addition, whereas recurrent AQP4-antibody-negative optic neuritis recurs in about 20–25% of cases, AQP4-antibody-positive optic neuritis is frequently recurrent, thus leading to even worse visual function. As if this were not enough, patients with AQP4-antibody-positive optic neuritis have a significant risk of other neurological deficits, including transverse myelitis that may leave the patient paraplegic or cause death.

Brain MRI is frequently normal in patients with AQP4-antibody-positive optic neuritis but can show brainstem or periventricular (particularly periependymal) lesions, especially in young patients, and MRI of the spinal cord may show extended T2 hyperintensity, encompassing three vertebral segments or more (Fig. 1.2) [32, 33]. The differentiation between AQP4 antibody-positive and AQP4 antibody-negative optic neuritis is essential because the natural histories are so different. Patients with AQP4-antibody-positive optic neuritis often need both acute and long-term immunosuppression, particularly if the risk of relapse is high or if relapses have occurred.

Several drugs to treat NMO-related optic neuritis have been proposed, most based on retrospective studies. These include azathioprine with and without predni-

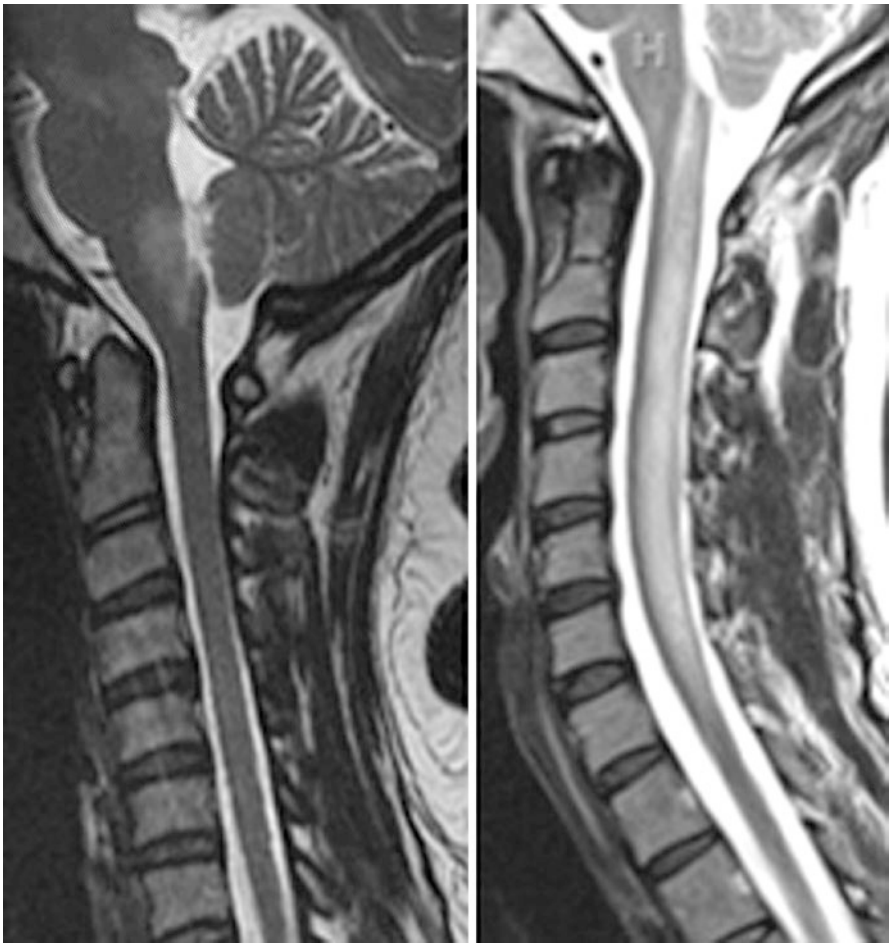

Fig. 1.2 Sagittal section through the spinal cord showing an extensive lesion in a patient with neuromyelitis optica

sone [34–37], methotrexate [38], rituximab [37, 39–41], mycophenolate mofetil [39, 41], and eculizumab [42]. Evidence is scarce or mixed for other treatments, including mitoxantrone [43], cyclophosphamide [44], plasma exchange [45–47], cyclosporin A [48], tacrolimus [41], intravenous immunoglobulins [49], and tocilizumab [50]. The most successful results appear to be obtained with initial steroid treatment followed by either rituximab or plasma exchange [37, 46, 47]. In the meantime, it is important that the use of MS-targeted drugs such as interferon-beta, fingolimod, and natalizumab be avoided in patients with AQP4-antibody-positive optic neuritis as there is strong evidence that these drugs do not result in clinical improvement and, in fact, can worsen the prognosis [51–55].

Acute Optic Neuritis Associated with Anti-MOG Antibodies

Since the introduction of live transfected cell-based assays, MOG-IgG has emerged as a reproducible marker for a subset of patients with optic neuritis [56, 57]. Recent studies have suggested an association of MOG-IgG seropositivity with recurrent attacks of optic neuritis attacks that can lead to significant visual morbidity in both adults and children [56]. In adults, MOG antibodies are most often found in cases of isolated optic neuritis, whereas in children, they are more often found in association with acute disseminated encephalomyelitis (ADEM). Matsuda et al. reported the clinical profile in 18 patients with MOG-antibody-positive optic neuritis [57]. Eight (44%) presented with bilateral involvement and five (28%) had associated ocular pain. A study by Chen et al. [58] identified anti-MOG antibodies in 87 patients with optic neuritis. Over a 3-year period, 10% had a unilateral, single event, whereas 31% experienced recurrent optic neuritis, and 16% had a chronic relapsing steroid-responsive condition. In these individuals, 86% of episodes were characterized by ocular pain and optic disc swelling, sometimes associated with peripapillary retinal hemorrhages. MRI showed perineural enhancement in about 50% of cases, and the CSF showed a lymphocytic pleocytosis and elevated protein but no oligoclonal bands. Unlike AQP4-antibody-positive optic neuritis, the outcome was good, with 6% of patients having final acuity less than 20/200. As is the case in patients with AQP4-antibody-positive optic neuritis, some treatments for idiopathic or MS-related optic neuritis are not only ineffective but may be associated with a worse prognosis. Thus, most patients are treated with systemic steroids alone, with plasmapheresis reserved for those who do not show evidence of recovery within a few weeks.

Summary

In summary, acute optic neuritis may be caused by a variety of infectious, demyelinating, and inflammatory disorders. In particular, patients who experience an attack of acute optic neuritis have a definite risk of developing MS, particularly when they are found to have at least one white-matter lesion on brain MRI. There is increasing evidence that early treatment of such patients with immunomodulatory drugs may prevent them from developing MS. In addition, however, the recognition of acute (usually anterior) optic neuritis as the presenting sign of either NMOSD or an anti-MOG syndrome requires that a cell-based assay for both be performed in both adults and children who present with acute optic neuritis, particularly but not exclusively that which is bilateral, anterior, and/or recurrent, as these patients may require a very different treatment than patients who have no antibodies to either AQP4 or MOG.

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Chapter 2
Optic Neuritis as the Presenting Feature of Neuromyelitis Optica (NMO): Diagnosis and Management

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Case

A 45 year old Afro-Caribbean female presents with acute bilateral simultaneous loss of vision to 20/200 in both eyes (OU). Both optic discs are edematous. Three weeks prior to presentation, the patient reported a bout of unexplained nausea and vomiting as well as hiccups. Cranial magnetic resonance imaging (MRI) shows chiasmal and optic nerve enhancement OU but no demyelinating periventricular white matter lesions.

Introduction

Since its description in 1894 by Eugene Devic, many had considered neuromyelitis optica (NMO) to be a "variant" of multiple sclerosis (MS). Clinical and MRI differences between MS and NMO along with the landmark discovery of highly specific anti-aquaporin 4 (AQP4) antibodies in 2004 indicated that NMO is a distinct disease marked by severe demyelination of the central nervous system (CNS) with particular predilection for the optic nerves, spinal cord, and area postrema in the medulla. Over the last 13 years, there has been a plethora of research and clinical interest in NMO facilitating improved awareness among physicians. Despite this, controversies on how to best diagnosis and treat NMO persist. This chapter will

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