Neuromyelitis optica: current concepts and prospects for future management

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Purpose of review

To present an overview on the clinical manifestations and an update on the current management of neuromyelitis optica (NMO).

Recent findings

NMO is associated with a significant risk of neurological, ocular and systemic morbidity. Many cases of NMO assume a relapsing course, which can lead clinicians to mistake the disease for multiple sclerosis. Distinguishing between the two diseases can be accomplished by recognizing the differences in clinical manifestations, observing the clinical course, obtaining serological testing and appreciating the MRI features. It is also important to maintain a high index of suspicion for NMO in the appropriate clinical setting.

Summary

Clinical features of NMO include visual loss, decreased coordination, widespread asthenia, paraplegia, quadriplegia, and sensory impairment. Severe cases can result in bladder and bowel impairment or fatal respiratory failure. Symptomatic treatment and the currently available therapeutic agents can control the disease in many patients. However, given the lack of a curative treatment, the prognosis of NMO remains poor in some patients underscoring the need for drug development and controlled clinical trials focused on improved treatment strategies.

Keywords

Devic's disease, multiple sclerosis, neuromyelitis optica, optic neuritis, transverse myelitis

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Introduction

Neuromyelitis optica (NMO) or Devic's disease is a rare, idiopathic, autoimmune, inflammatory, demyelinating condition. Presumably, autoantibodies target previously normal tissues, resulting in a clinical picture that is typically characterized by unilateral or bilateral optic neuritis, transverse myelitis or both [1,2]. A significant advancement in our understanding of the pathophysiology of NMO has come from the identification of a specific autoantibody directed against an aquaporin water channel within the central nervous system (CNS). Although the exact series of pathological events is not known, the autoantibody undermines the integrity of the myelin surrounding the optic nerves and the spinal cord leading in most cases to significant visual impairment and neurological compromise in the form of paralysis, paresthesias and varying degrees of autonomic dysfunction [3,4]. For unknown reasons, involvement of the spinal cord and optic nerve is common in NMO, but clinically, the brain and brainstem are generally spared [4].

Clinical course

The clinical course of NMO is variable and may manifest as either a monophasic or polyphasic disease process. In the monophasic variety, episodes typically present within days of one another with little recurrence after the initial onset of symptoms [1]. In the polyphasic form, multiple, repeated episodes of optic neuritis and/or myelitis are separated by months or years [1]. The relapsing course of NMO, particularly in patients within the polyphasic subset, can often be confused with multiple sclerosis (MS) [5]. We agree with those experts who feel that NMO is a distinct disease [6], in contrast to other experts who argue that NMO is a subtype or variant of MS [7]. Despite a clinical picture that resembles MS, the cycle of remission and relapse in NMO tends generally to be more frequent and severe [1,5,8]. Furthermore, visual impairment from optic neuritis in NMO is more often bilateral on presentation, recurrent and more severe than observed in MS and the prognosis for visual improvement worse [2]. Given the intimate relationship with MS and the

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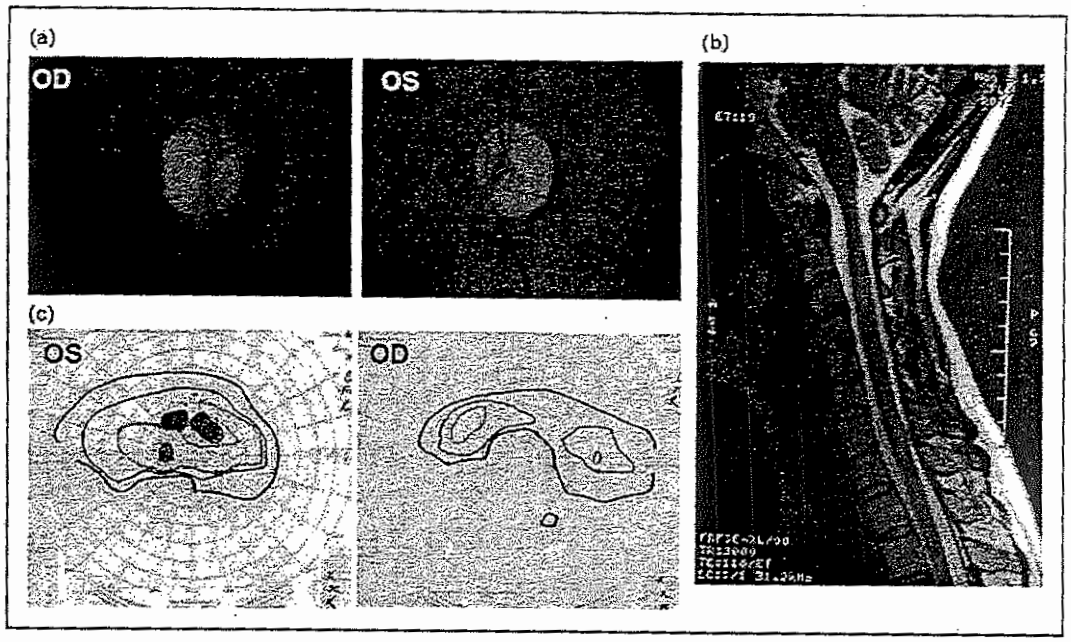
Figure 1 A 21-year-old white woman with multiple recurrent bouts of optic neuritis in each eye resulting in counting fingers vision



The patient also complained of parethesias and L'Hermitte phenomenon. (a) Digital fundus photograph showing bilateral optic nerve pallor. (b) Manual perimetry (Goldmann) showing significant bilateral visual field defects. (c) Saggital, T2-weighted, MRI of the cervical spine demonstrating multiple, large segment hyperintense signal abnormalities consistent with demyelinating disease. Cranial MRI was normal.

characteristic involvement of the optic nerve(s) and spinal cord, NMO has often been referred to as an optic–spinal MS [9]. An awareness of the terminology may be relevant, as NMO is primarily referred to as an optic–spinal MS in various international venues, particularly throughout Japan [10].

Clinical manifestations

The clinical presentation of NMO is exceedingly variable. As the disease progresses and inflammation to the optic nerve(s) and spinal cord evolves, a commensurate progression in both visual and spinal cord symptoms arises. The disease can begin with severe unilateral or bilateral visual loss. Frequently, the optic neuritis in patients with NMO is characterized by painful loss of central vision, profound visual field defects and dyschromatopsia (Fig. 1). A recent study [11••] demonstrated a significant correlation between optical coherence tomography (OCT) findings in NMO with visual acuity and visual field measures. Specifically, an analysis of OCT results revealed that the visual acuity and the mean retinal fiber layers were both significantly reduced in patients with NMO compared with controls.

As described above, NMO follows a relapsing–remitting course that can result in severe neurological disability (Table 1) [1,5,12]. Depending on the area of spinal cord involvement, symptoms can range from decreased coordination, widespread asthenia, paraplegia, quadriplegia, and sensory impairment [9,12,13]. Other potentially fatal manifestations of spinal cord dysfunction include respiratory failure secondary to involvement of the upper spinal cord [1,14]. Patients typically develop sudden, multiple episodes of repetitive systemic muscle spasms characterized by intense, sometimes painful, tightening of the limbs lasting for several minutes (Table 2) [1,9]. Despite the presence of similar spasms in some patients with MS, they are far more common and more severe in patients with NMO. Although many of these symptoms wane during periods of stable disease (remission), permanent neurological sequelae often occurs [11••]. Irreversible loss of strength and sensation in the limbs or permanent loss of bowel and bladder control may also occur [9,12]. A recent retrospective study that analyzed 60 patients with NMO between 1985 and 2004 found the mortality rate to be approximately 23.3%, with the highest rate of

Table 1 Characteristics of monophasic and relapsing neuromyelitis optica

	Monophasic	Relapsing
Frequency	Uncommon	More common
Age of onset (median), years	29	39
Sex ratio (female)	≈50%	≈85–90%
History of autoimmune diseases	Rare	≈50%

Data from [1,12].

Table 2 Common clinical manifestations of monophasic and relapsing neuromyelitis optica

	Monophasic	Relapsing
Optic neuritis or myelitis only	48%	90%
Bilateral optic neuritis only	17%	8%
Simultaneous optic neuritis and myelitis	31%	0%
Severity	More severe	Less severe
Respiratory failure	Rare	≈33%
Mortality rate (5 years)	10%	32%

Data from [1,12].

mortality exhibited in individuals who developed respiratory failure secondary to cervical myelitis [13,15]. The median survival was found to be 8 years from the time of diagnosis, with mortality rates highest in individuals of African descent [15]. MS also has been shown to have an increased mortality rate compared with the general population but not to the same magnitude as seen in NMO. A population-based survey performed in the UK (South Wales) found that MS patients had a three times higher rate of dying prematurely when compared with the general population [16].

Epidemiology

NMO is a rare condition that can be overlooked and confused with MS especially if the clinical entity is not considered in the differential diagnosis [5]. Documenred cases have noted a predilection in young women, comprising greater than 65% of all cases and over 80% of the polyphasic subset [5,13]. A recent population-based study [17] found the mean age of onset of NMO to be 31.2 years (±11 years). Asian individuals are more likely to develop NMO in comparison to their white and African–American counterparts [3]. Incidentally, NMO is believed to be linked in up to 30–40% of MS cases in Japan, underscoring the increased prevalence of NMO amongst the Asian population [3,18]. Similar findings were noted amongst individuals of African ancestry with 27% of MS cases linked to NMO [17].

Despite the perceived sex and racial predilection, there does not appear to be a major genetic component in NMO. In fact, the preponderance of patients with NMO does not have affected relatives with the vast majority of cases being sporadic in nature [5,19].

Etiopathophysiology

Histopathologic analyses of NMO lesions have offered valuable insight into the pathogenesis of the disorder. Lesions in NMO are typically characterized by widespread deposition of immunoglobulins in association with various products of the complement activation cascade [20,21]. These substances often exist in a vasculocentric pattern in blood vessels, suggesting a pathogenetic role for humoral immunity, which targets antigens in the perivascular space [21,22]. Recent studies [23,24] have found that autoantibodies derived from peripheral B-cells cause a cascade of events initiated by the targeting of water channel proteins in the CNS resulting in activation of complement, inflammatory demyelination and widespread necrosis. Specifically, the autoantibodies in NMO target aquaporin-4 (AQP4), a water channel protein in the CNS, are expressed mainly in astroglial foot processes [21,23]. Thus, immunohistochemical analysis of spinal cord lesions in NMO patients will reveal a lack of AQP4. In contrast, the demyelinating spinal cord lesions of patients with MS express AQP4 [22].

Although most cases of NMO are idiopathic in nature, cases of postinfectious NMO have been reported [25–27]. Syphilis and HIV are the most common infectious triggers; however, other bacterial and viral agents such as chlamydia, varicella, cytomegalovirus and the Epstein–Barr virus have been described as possible precursors for the development of NMO [7,12,26,27]. Humoral immunity plays a central role in NMO with B-cell activation resulting in the formation of NMO autoantibodies as well as activation of eosinophils and T-helper cells [3,5]. Although the exact mechanism remains unclear, the postinfectious forms of NMO may arise as a result of humoral activation in those patients predisposed to the condition [27,28]. The activation of B-cells in NMO offers insight into the successful therapeutic response that many NMO patients exhibit when treated with agents that cause B-cell depletion, such as rituximab (see below) [29].

Diagnosis

NMO can pose a diagnostic challenge to clinicians. Given the myriad of disorders that mimic NMO, it behooves the clinician to be familiar with the recently proposed diagnostic criteria [3,8,9]. In addition, establishing a comprehensive and reflective differential diagnosis may also help minimize the likelihood of misdiagnosis (Table 3) [3,9,20]. Table 4 provides an overview of the current concepts in the diagnosis of NMO with a particular focus on distinguishing NMO from MS [3,20].

Clinical

In most cases, an accurate diagnosis of NMO can be made based on a thorough medical history followed by a comprehensive neuro-ophthalmologic examination, targeted neuroimaging, cerebrospinal fluid (CSF) analysis and serological testing [1,20]. As no single test can definitively identify NMO, and because many other conditions can mimic the disorder, accurately diagnosing NMO necessitates appropriate interpretation of clinical features supplemented by results of paraclinical studies (Table 1) [1,5]. Furthermore, many patients with

Table 3 Diagnostic criteria for neuromyelitis optica

Imaging criteria	MRI: normal-appearing brain
	MRI: spinal cord enlargement and cavitation involving at least three vertebral segments
CSF criteria	Decreased serum/CSF albumin ratio with normal IgG synthesis rate and general absence of oligoclonal bands
Clinical criteria	Acute involvement of spinal cord and optic nerve separated by months or years, independent of subsequent progression, but without other clinical features at any time during disease course

At least two criteria required. CSF, cerebrospinal fluid; IgG, immunoglobulin G. Data from [3,9,20].

otherwise typical NMO present with clinical features, including fever, appetite changes, muscle spasms, and headaches, which are not due to direct inflammation of the optic nerve(s) or spinal cord [3,9,12].

Given the widespread involvement of the spinal cord associated with NMO (typically greater than three vertebral segments long), a comprehensive neurological evaluation is warranted to rule out asthenias, coordination or balance difficulties, bladder or bowel dysfunction, limb weakness or any impairment in visual, cognitive or speech function.

Neuroimaging

Neuroimaging, particularly MRI, is very helpful in recognizing cases with diffuse spinal cord demyelination [30]. Unlike the cranial MRI findings in MS, which typically reveal widespread areas of inflammation or 'plaques' involving the white matter, in NMO, up to 60% of cases can demonstrate cerebral white matter lesions but most are asymptomatic or considered 'atypical' as defined by lesion size, location, configuration, enhancement status and mass effect [30,31]. Typical MRI features of MS include multiple, ovoid-shaped lesions, located in the cerebellar, infratentorial and periventricular regions [6,32]. Any of the aforementioned lesions that are greater than 3 mm on MRI that occur in the brainstem or cortical gray matter may aid in the diagnosis of MS [32]. Lesions in NMO can be seen in the diencephalon and brainstem [31]. It should be kept in mind, however, that the presence of symptomatic and 'typical MS-like' brain lesions does not exclude the possibility of NMO [31]. The seemingly contradictory nature of these MRI findings underscores the importance of revising current diagnostic criteria for NMO as it relates to involvement of the CNS in the disease process.

Cerebrospinal fluid

Lumbar puncture can be very helpful in securing the diagnosis, particularly as the CSF of patients with NMO often demonstrates white blood cell (WBC) counts that exceed 50 cells/μl. This increased CSF WBC count tends to be especially pronounced during acute attacks [33]. Pleocytosis in the setting of clinical and MRI diagnostic criteria is very suggestive of NMO [33]. In addition, unlike in MS, the CSF in NMO is often free of oligoclonal bands, and there is no increased immunoglobulin synthesis [30,33,34].

Serology

Laboratory confirmation with serologic testing represents another critical element of arriving at an accurate diagnosis of NMO [20]. Seropositivity for NMO–immunoglobulin G (IgG) autoantibodies is useful in establishing the diagnosis of NMO [1,35]. On the basis of the original study, the diagnostic test used to identify NMO–IgG was reported to have a sensitivity of 73% [95% confidence interval (CI) 60–86%] and a specificity of 91% (95% CI 79–100%) [36]. Testing for this serum autoantibody should improve recognition of subclinical or early cases of NMO [3,37]. Furthermore, a recent study [38] demonstrated that NMO–IgG seropositivity has a prognostic value in predicting a poor visual outcome and the development of NMO in patients with recurrent optic neuritis.

Neurophysiology

Evoked potentials, which utilize electrodes to measure the CNS sensitivity to various stimuli such as sound, light and touch may be helpful in the evaluation of a patient suspected of having NMO. Evoked potentials are sensitive in detecting lesions in the brain and brainstem and

Table 4 Differential diagnosis of neuromyelitis optica

Disseminated demyelinating disorders	Systemic diseases	Transverse myelitis spectrum	Optic nerve spectrum
Multiple sclerosis	Neurosarcoidosis,	Acute transverse myelitis	Recurrent optic neuritis,
Acute disseminated encephalitis	Systemic lupus erythematosus,	Progressive necrotic myelopathy	CRION
Myelinoclastic diffuse sclerosis (Schilder's disease)	Progressive necrotic myelopathy	Relapsing myelitis	LEON
Disseminated encephalitis	Neuro-Behçet's disease	Longitudinally extensive transverse myelitis	Retinal ischemia
	Connective tissue disorders	Idiopathic transverse myelitis	Relapsing optic neuritis
	Neurosyphilis	Tropical spastic paraparesis	
	Illicit drug use	Viral encephalomyelitis	
	Vascular occlusive disease		
	HIV-related vacuolar myelopathy		

CRION, chronic relapsing inflammatory optic neuropathy; LEON, longitudinally extensive optic neuritis. Data from [3,20].

are particularly suited for detecting subclinical bilateral optic nerve dysfunction when clinical history and physical examination confirm only unilateral deficits [1,39]. Evoked potential studies [5,40] most commonly detect silent lesions in MS, but given the relative paucity of such lesions in NMO, the utility of these studies lies in their ability to distinguish NMO from MS.

Pathology

A detailed discussion of the pathologic features of NMO is beyond the scope of this review article. Suffice it to say that in the early stages of NMO, perivascular deposition of an immunoglobulin such as IgM is common in association with local activation of the complement system and significant eosinophilic infiltration [3,11••,13]. The histopathological changes in the early stages are often accompanied by widespread activation of macrophages and microglial cells resulting in axonal damage [1,3,13]. Only in unique circumstances is the diagnosis of NMO established by tissue sampling of effected areas in the CNS.

Treatment

Although there is no known curative treatment for NMO, disease modification can be established in many patients with the currently available therapies. However, the treatment effect is unpredictable and, on occasions, ineffective in certain individuals.

Acute treatment

Visual or neurological complications from an acute attack are often treated with high-dose intravenous corticosteroids such as methylprednisolone (i.e.,1 g/day for 3–5 days) [1,41,42]. In patients with aggressive or refractory disease unresponsive to corticosteroid therapy, plasmapheresis has been used in the acute setting with some success [25,28].

Relapse prevention

Long-term complications from relapses often can be controlled prophylactically with azathioprine or long-term prednisone therapy [41–43]. Rituximab, a B-cell-specific humanized mAb, has also shown promise in patients whose symptoms fail to respond to more traditionally used immunosuppressant medications such as azathioprine or prednisone [12,43,44••]. Its efficacy is thought to derive from the B-cell origin of the autoantibodies targeting AQP4 [43]. Interferon-beta (IFNβ) therapy has demonstrated clinically significant improvements in patients with chronic forms of NMO; however, its use is also associated with increased risk of irreversible brain lesions [28,45]. Mycophenolate mofetil, mitoxantrone, intravenous immunoglobulin and cyclophosphamide have also been used effectively in reducing relapses in some patients with NMO [12,40,46,47].

Symptomatic treatment

Anticonvulsant medications have been successful in treating the painful muscle spasms that plague patients throughout the course of the disease [25,43,48,49]. Inpatient clinical rehabilitation programs have revealed comprehensive functional gains in the form of improved function and recovery of function [14,50].

Future directions

With further insight into the clinical, neuroimaging, pathological and laboratory features of NMO, clinicians will be able to establish the diagnosis earlier than ever before, thereby reducing the debilitating complications associated with the disease. There has been a remarkable increase in our knowledge of NMO due to the identification of an autoantibody and its targeted CNS antigen. In the absence of randomized trials to validate their future use, it remains uncertain whether IFNβ or glatiramer acetate, both of which have been effectively used in preventing attacks in MS patients, can be equally effective in the treatment of NMO. In a recent multicenter case series of 25 patients, rituximab showed promise as an agent capable of reducing the frequency of attacks, with subsequent stabilization or improvement in the disabilities associated with NMO [44••]. Agents with novel mechanisms of action and improved efficacy need to be developed and tested in clinical trials to improve the current status of the therapeutic options available to patients with NMO.

Conclusion

Although the clinical features of NMO are variable, the constellation of clinical manifestations, disease course, CSF analysis, radiologic findings and serological testing can assist the clinician in arriving at an accurate diagnosis.

Early diagnosis is critical in order to institute prompt immunosuppressive therapy, such as prednisone, azathioprine or rituximab rather than IFNβ, which may be potentially detrimental by altering the delicate T-helper cell balance of the immune system.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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