

Neuromyelitis Optica (Devic's Syndrome)

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Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the central nervous system that causes severe optic neuritis and myelitis attacks. It tends to spare the brain early in the disease course.

The traditional concept of NMO was that of a monophasic disorder consisting of bilateral optic neuritis and severe 'transverse' myelitis occurring simultaneously or in rapid succession (within two weeks). Late 20th century definitions were more inclusive and allowed for unilateral optic neuritis, a longer inter-attack interval (months or years), and a relapsing course.¹⁻³ Diagnostic criteria have recently been revised.⁴

Characteristics of NMO that help to distinguish it from classical MS include:

- More severe optic neuritis and myelitis attacks
- Prominent CSF pleocytosis (more than 50 WBC) that can be dominated by polymorphonuclear cells¹⁻³
- Lower frequency of CSF oligoclonal banding (15-30% compared with 85% in MS)¹⁻³
- At disease onset, the brain MRI scan is normal or reveals nonspecific white matter lesions that do not meet MS MRI diagnostic criteria.
- During acute myelitis attacks, spinal cord MRI scans disclose a contiguous, longitudinally extensive lesion, centrally based in the cord and extending over three or more vertebral segments. MS lesions are more peripherally located in the cord and are less than one to two segments in length.

Clinical Features of NMO

Optic neuritis

Optic neuritis attacks in NMO are typically more severe than those in MS. Complete visual loss, pain with eye movement, and incomplete recovery are typical. Bilateral simultaneous optic neuritis is a hallmark of NMO but rare in MS.

Myelitis

Spinal cord attacks cause rapidly progressive paraparesis or quadriparesis, loss of sensation below the site of inflammation, and bladder and bowel retention or incontinence. Neck or back pain at or just below the lesion and L'hermitte's symptom (spinal or limb paresthesias elicited by neck flexion) are common. Nearly half of patients also experience repetitive painful spasms of one or more limbs. These 'paroxysmal tonic spasms' last 30-45 seconds and recur dozens of times per day.³

Spinal cord lesions that ascend into the brain stem may cause neurogenic respiratory failure.

Other symptoms

It is now recognized that neurological symptoms in NMO may occur due to involvement of brain structures outside of the optic nerve or spinal cord.⁵ Extension of a cervical spinal cord lesion may cause, in addition to respiratory failure, hiccups, vomiting, vertigo, diplopia, and ataxia.^{3,6,7} Cerebral lesions are rarely symptomatic but when present do not exclude the diagnosis of NMO.

Discovery of NMO-IgG

The association of NMO with the serum autoantibody marker NMO-IgG was reported in 2004.⁸ NMO-IgG is 73% sensitive and 91% specific for distinguishing NMO from optic-spinal presentations of classical MS. In 2006, NMO-IgG was integrated into new NMO diagnostic criteria (Table 1).⁴ The newly-proposed criteria are 99% sensitive and 90% specific for NMO in patients presenting with optic-spinal disease presentations of CNS demyelinating disease. Although the NMO-IgG blood test is a very useful diagnostic tool, a diagnosis of NMO may be achieved using new criteria without the NMO-IgG test and in patients whose NMO-IgG test is negative.

The target antigen of NMO-IgG is aquaporin-4 (AQP4).⁹ AQP4 is the most abundant CNS water channel. It facilitates water transport, especially in “stress situations” such as brain injury. It is not known whether NMO-IgG causes NMO or is simply a marker of the disease. Further experiments will include attempts to establish an animal model of NMO and determine the pathogenic role of NMO-IgG.

The Clinical Spectrum of NMO

The specificity of NMO-IgG has expanded the clinical spectrum of NMO. It allowed confirmation that brain lesions may occur in NMO, occasionally in a rather specific pattern that includes the hypothalamus and regions adjacent to the third and fourth ventricles.^{5, 10} NMO-IgG seropositivity rates are approximately 50% in patients with recurrent longitudinally extensive transverse myelitis (LETM) and about 25% in patients with simultaneous or recurrent optic neuritis and negative brain MRI.⁸ Patients presenting with a first-ever LETM event and who are found to be NMO-IgG seropositive have a 56% risk of LETM recurrence or optic neuritis (conversion to NMO) during the subsequent 12 months.¹¹ These findings suggest that single or recurrent events of LETM, bilateral simultaneous optic neuritis, and recurrent optic neuritis are, at least in some cases, limited or incompletely developed forms of NMO. Furthermore, NMO-IgG appears to be a highly specific marker for Asian optic-spinal MS. In a Japanese cohort, 58% of patients with optic-spinal MS were NMO-IgG seropositive compared with none of the “conventional” or “Western” MS pattern.⁸

NMO-IgG has informed debate about the relationship of systemic autoimmune disorders (e.g., systemic lupus erythematosus (SLE) or Sjögren’s syndrome (SS)) to transverse myelitis and NMO. Some consider that if clinically evident SLE or SS, or positive autoantibodies associated with those disorders (antinuclear antibody; antibody to extractable nuclear antigen), coexist with NMO symptoms and signs that the neurological process is a vasculitic complication of the systemic disorder. However, recent studies^{12, 13} demonstrated that:

- 1) NMO-IgG does not occur in individuals with clinically-defined SLE or SS who lack symptoms or signs of an NMO spectrum disorder
- 2) NMO-IgG is detected more commonly in patients with NMO symptoms who have clinical or serological evidence for SLE or SS than in those who do not.

Therefore, co-occurrence of NMO with SLE or SS, at least in NMO-IgG seropositive patients, represents the coexistence of two autoimmune diseases rather than an indication that patients have developed a secondary vasculitic complication of the systemic disorder.

In summary, the high specificity of NMO-IgG has provided insight into an expanded clinical spectrum of disorders that comprise the NMO spectrum (Table 2).

Diagnostic Approach

NMO should be considered in any patient presenting with simultaneous bilateral optic neuritis or sequential recurrent optic neuritis with a negative brain MRI scan. It should also be considered with presentation of a single event or recurrence of LETM (“transverse myelitis” with a contiguous ≥ 3 segment spinal cord MRI lesion).

All patients should have a cranial MRI scan with intravenous gadolinium administration. Brain imaging will determine the presence and pattern of lesions that assist in diagnosis. At disease onset (first attack), a normal brain MRI, or one that reveals lesions not meeting MS MRI criteria, fulfills one of the three major supportive diagnostic criteria for NMO. If the diagnosis of NMO is being considered months or years after disease onset, it may be necessary to obtain the first MRI, if it exists, to evaluate this criterion. *The presence of brain MRI lesions does not exclude a diagnosis of NMO.* A pattern of T2-weighted abnormality in AQP4-rich areas, such as the hypothalamus or around the third or fourth ventricle, may be specific for NMO. During optic neuritis attacks, an orbital MRI protocol may identify optic nerve gadolinium-enhancement, providing strong evidence toward an inflammatory etiology.

Patients with myelitis should have a cervical and thoracic spinal cord MRI scan with intravenous gadolinium administration to evaluate for the presence of a longitudinally extensive cord lesion, which is the second major supportive diagnostic criterion. The presence of patchy or noncontiguous, short segment lesions in the setting of acute myelitis suggests MS rather than NMO. A caveat, however, is that a longitudinally extensive lesion may “break up” into noncontiguous segments over months or years. Therefore, as with brain MRI scans, it may be necessary to obtain and evaluate a patient’s older MRI scan performed during an acute myelitis attack.

All patients should have blood testing for the presence of NMO-IgG, the third major diagnostic criterion. A negative test does not exclude NMO (the test is about 70-75% sensitive) but a positive test essentially ‘rules in’ the diagnosis. The test may be obtained through Mayo Medical Laboratories:

(<http://www.mayoreferenceservices.org/mrs/mml/index.asp>)

Although no longer part of the formal diagnostic criteria, lumbar puncture for CSF analysis is useful because the detection of an unusual pleocytosis (>50 WBC) or polymorphonuclear cells suggests a higher likelihood of NMO than of MS. In patients with single or recurrent LETM but without a history of visual loss, visual evoked potentials occasionally detect asymptomatic visual pathway impairment supportive of optic-spinal pattern demyelinating disease. The need for additional diagnostic testing to evaluate for competing disorders in the differential diagnosis of the NMO syndrome (e.g., sarcoidosis, paraneoplastic disease, infections) depends on the individual scenario.

Treatment

Acute optic neuritis or myelitis:

- 1) Corticosteroids: IV methylprednisolone 1000 mg/d (or equivalent) for 5 or more days
- 2) Plasmapheresis for attacks that progress or are refractory to corticosteroid therapy¹⁴⁻¹⁶

Attack prevention:

There are no preventative therapies with efficacy demonstrated by controlled trials in NMO. Most agree that long-term immunosuppression is required for established NMO.¹⁷ It has also been recommended for NMO-IgG seropositive patients with single LETM episodes because of the high risk for relapse.¹¹

Current options include:

- 1) Azathioprine (2.5-3.0 mg/kg/d) plus prednisone (~1mg/kg/d to be tapered after azathioprine is fully effective)¹⁸
- 2) Mycophenolate mofetil 1000 mg BID plus prednisone as above
- 3) Rituximab (chimeric anti-CD20 monoclonal antibody)¹⁹
- 4) Mitoxantrone²⁰
- 5) Intravenous immune globulin (IVIG)²¹
- 6) Cyclophosphamide

The absolute and relative efficacy of these therapies have not been established.

Table 1: Proposed Diagnostic Criteria for Neuromyelitis Optica (2006)⁴

Diagnosis requires absolute criteria PLUS at least two of three supportive criteria:

Absolute Criteria:

1. Optic neuritis
2. Acute myelitis

Supportive Criteria:

1. Negative brain MRI at disease onset
2. Spinal cord MRI with contiguous T2-weighted signal abnormality extending over 3 or more vertebral segments
3. NMO-IgG seropositive status

Table 2: NMO Spectrum Disorders

- Neuromyelitis optica (2006 definition)
- Limited forms of NMO
 - “Idiopathic” single or recurrent events of longitudinally extensive myelitis (≥ 3 vertebral segment spinal cord MRI lesion)
 - Bilateral simultaneous or recurrent optic neuritis
- Asian optic-spinal MS
- Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease
- Optic neuritis or myelitis associated with “specific” NMO brain lesions (hypothalamic, periventricular, brainstem)

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