

Commentary

Neuromyelitis optica (NMO) was originally recognized as a clinical syndrome characterized by bilateral optic neuritis and severe myelitis that occur simultaneously or in quick succession. Although recognized by several authors in the late 19th century, Devic's description of a single case with neuropathological analysis led to name this disease after him. The similarities and potential differences between multiple sclerosis (MS) and NMO were a matter of debate until recently. In general, most pre-1990 reports emphasized the nonrelapsing nature of NMO and its tendency to spare the brain as the key features differentiating it from MS. In the 1990s, reports from Japan described a condition called opticospinal MS, which was described as a relapsing disorder, but was differentiated from MS by its frequent and severe attacks specifically targeting the optic nerve and spinal cord and by infrequent detection of oligoclonal bands in the cerebrospinal fluid (CSF). The key differentiating feature between opticospinal MS and NMO was the temporal course: Monophasic for NMO and relapsing for opticospinal MS.

An important observation in 2004 reported a high frequency of a specific autoantibody in both Western NMO and typical Japanese opticospinal MS.^[1] One year later, the NMO autoantibody was found to be specific for Aquaporin-4 (AQP4).^[2] Subsequent clinical experience with AQP4-seropositive patients revealed that while NMO has a predilection for the optic nerves and spinal cord, 40–60% of the patients develop brain abnormalities that can be seen on magnetic resonance imaging (MRI), especially in the AQP4-rich periventricular regions.^[3]

This led, in 2006, to revised diagnostic criteria for NMO that no longer excluded patients with brain involvement and that also incorporated AQP4 seropositivity as a supporting criterion. In 2007, NMO spectrum disorders (NMOSD) were introduced and included the following entities:^[4]

- Standard Devic's disease (classical NMO)
- Limited forms of Devic's disease such as single or recurrent events of longitudinally extensive myelitis and bilateral simultaneous or recurrent optic neuritis
- Asian opticospinal MS
- Longitudinally extensive myelitis or optic neuritis associated with systemic autoimmune disease
- Optic neuritis or myelitis associated with lesions in specific brain areas such as the hypothalamus, periventricular nuclei, and brainstem
- AQP4 antibody-seronegative NMO.

The limited forms affecting the brainstem can present with intractable hiccuping and nausea or vomiting, as in the case reported in this issue,^[5] and the hypothalamic disorders can present with the syndrome of inappropriate antidiuretic hormone secretion and may herald the onset of a more typical NMO.

Imaging in NMOSD usually reveals a lack of brain MRI lesions resembling MS, but instead, shows longitudinally extensive transverse myelitis of more than three vertebral segments. Optic neuropathy episodes are also frequently seen on MRI, and sometimes bilateral, with large T2-weighted hypersignals on the optic chiasma or optic

nerve. Brain MRI abnormalities are uncommon, although the location of lesions is clearly different compared with MS.^[3] Oligoclonal bands are observed in CSF in only about 30% of the cases against 90% in MS.^[6] AQP4 is found to be 70–80% of the NMOSD cases and its specificity is around 99%. Myelin oligodendrocytic glycoprotein is found in around 20% of the AQP4-seronegative patients and seems to be associated with a less severe course of the disease.^[7]

NMO is commonly associated with other autoimmune diseases, especially systemic lupus erythematosus and Sjögren syndrome. The association with systemic autoimmunity has led to confusion in the past. Patients who have NMO with concomitant systemic lupus erythematosus or high-titer anti-nuclear autoantibodies have been commonly labeled as having lupus myelitis in the past and are now increasingly accepted as having concomitant NMO and systemic autoimmune disease.^[6]

Considering the antibody-mediated mechanisms, treating NMO with immunosuppressant medications seems logical. However, little high-quality evidence exists for the role of the various immunosuppressant therapies. Acute attacks are typically treated with intravenous (IV) corticosteroids and if necessary, rescue plasma exchange. Relapse prevention strategies are meant to reduce or eliminate the effects of pathogenic AQP4 antibodies, either directly or indirectly. Azathioprine and mycophenolate have delayed the onset of action and typically require bridge therapy for 4–6 months, usually with oral prednisone (40–60 mg/d). Rituximab (1 g/d twice, 2 weeks apart, with retreatment every 6 months) is fully active within about 2 weeks. Mitoxantrone, methotrexate, IV cyclophosphamide, and the new anti-CD20 such as ocrelizumab have been tried with some success.^[6]

Untreated or inadequately treated typical NMO has a poor prognosis. More than half of the patients develop severe visual loss in at least one eye, or have the inability to ambulate without assistance within 5 years of disease and another 30% are dead. However, more recent data, including that in the new era of NMO IgG testing and early treatment, have been encouraging. In a recent British–Japanese study, only 10/106 (9%) had died at the last follow-up, and the median time to death was 8 years.^[8]

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