NEUROMYELITIS OPTICA SPECTRUM DISORDERS: DIAGNOSIS AND TREATMENT

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LEARNING OBJECTIVES

1. The attendee will be able to recognize the clinical, laboratory, and neuroimaging characteristics of neuromyelitis optica (NMO) and contrast them from characteristics of multiple sclerosis (MS).

2. The attendee will be able to describe the association of the autoantibody NMO-IgG (anti-aquaporin-4) with NMO.

3. The attendee will be able to describe the treatment options for acute relapses and relapse prevention in NMO.

CME QUESTIONS

1. Brain MRI lesions in neuromyelitis optica:
   a. Usually mimic those of typical multiple sclerosis.
   b. Often occur in regions of known high aquaporin-4 density.
   c. Decrease in number during the disease course.
   d. Do not enhance after gadolinium administration.

2. Pathological assessment of neuromyelitis optica lesions reveals:
   a. Deposition of immunoglobulin and complement around blood vessels.
   b. Thinning of penetrating spinal blood vessels.
   c. Predominant T-cell infiltrates.
   d. Multifocal infarctions and vasculitis.

3. Which of the following therapies is not recommended for neuromyelitis optica:
   a. Azathioprine
   b. Mycophenolate mofetil
   c. Rituximab
   d. Interferon beta

KEYWORDS

1. Neuromyelitis Optica
2. Optic Neuritis
3. Transverse Myelitis
4. Aquaporin-4

NEUROMYELITIS OPTICA: BACKGROUND

The last decade has witnessed rapid developments in the clinical understanding and scientific foundation of neuromyelitis optica (NMO). The landmark events were the late 19th century report by Devic and Gault describing the association of severe acute transverse myelitis and optic neuritis and the late 20th century discovery that the syndrome was associated with a specific autoantibody, NMO-IgG, that targets the water channel aquaporin-4 (AQP4). Between these events, there were numerous case series suggesting that the disorder usually followed a relapsing course (rather than being monophasic) and pathological studies, which were limited to technology of the time, revealed inflammatory demyelinating lesions of the optic nerve and spinal cord with sparing of the brain. There was ongoing debate about the relationship between NMO and multiple sclerosis (MS), the prototypic and relatively common (one per thousand population) but whether NMO was distinct or simply a subset of MS was not resolvable with the available science.

Within the last twenty years, new case series emerged and incorporated modern neuroimaging and laboratory studies, especially cerebrospinal fluid analysis, to demonstrate that NMO was associated with certain diagnostic test results that were atypical for MS. These included findings such as a normal brain magnetic resonance imaging (MRI) scan, unusually long spinal cord lesions associated with acute myelitis attacks ("longitudinally extensive transverse myelitis [LETM]), and an unusual cerebrospinal fluid pleocytosis, often with a differential containing neutrophils rather than the lymphocytes more typical for MS. These reports began to consolidate the concept that NMO was a clinical entity distinguishable from MS on objective grounds, something that was affirmed, and subsequently validated by numerous groups worldwide, by the discovery of the specific autoantibody NMO-IgG. Revised NMO...
diagnostic criteria (Table 1) using a combination of clinical, neuroimaging, and NMO-IgG criteria have also been validated.\(^1\) The next step has been to utilize the strong specificity of NMO-IgG to demonstrate that the clinical and neuroimaging features of NMO are actually much broader than just optic neuritis and myelitis; these are collectively referred to as “NMO spectrum disorders” (Table 2).\(^1\)

**Table 1. Diagnostic Criteria for Neuromyelitis Optica\(^1\)**

**Required criteria:**
- Transverse myelitis
- Optic neuritis

**Supportive criteria (at least two of the following three elements):**
1. MRI brain nondiagnostic for MS
2. MRI spinal cord lesion extending over ≥3 vertebral segments
3. NMO-IgG seropositivity

**Table 2. NMO Spectrum Disorders\(^1\)**

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

NMO-IgG testing has allowed early diagnosis of these disorders even after a single event of optic neuritis or LETM.

**EPIDEMIOLOGY**

Neuromyelitis optica is a rare disorder but few studies provide population-based incidence and prevalence estimates. A population-based study in the French West Indies and Martinique found NMO prevalence of 2.5 per 100,000 and annualized incidence of 0.1 per 100,000 individuals in a retrospective cross-sectional record review; all NMO cases were of Afro-Caribbean background.\(^4\) A population-based Cuban study reported a prevalence of 0.52 per 100,000 individuals with an average annual incidence rate of 0.53 per million and the rates were similar in self-reported racial groups defined as white, black, mixed, or non-white.\(^5\) These estimates are similar to non-population-based assessments in Mexico (prevalence 1.3 per 100,000 individuals of Mestizo ancestry), the United Kingdom (prevalence 0.44 per 100,000 and annual incidence 0.05 per 100,000; cases were Caucasian), and south Florida (0.99 per 100,000; cases included Caucasians and Hispanics).\(^6,7\) In Italian tertiary MS clinics, 0.5% of 780 patients had NMO.\(^8\)

There may be an overrepresentation of NMO as a proportion of all CNS demyelinating disease cases in patients of non-Caucasian ancestry, such as African-Americans, Hispanics, and Asians. Moreover, at least some cases of Asian “optic-spinal MS”, which represents a sizeable proportion of CNS demyelinating disease in Japan, are in fact NMO. However, more population-based data are needed to better establish this because of the relatively similar prevalence and incidence rates noted in various populations worldwide. However, there are groups, notably black Africans and North American aboriginal peoples, in who typical MS is extremely rare and most if not all cases of CNS demyelinating disease are consistent with NMO. Genetics of NMO may be complex; familial cases exist but are uncommon.\(^9\)

Virtually all reports of NMO worldwide describe female predominance with female: male ratios ranging from 2:1 to 10:1.\(^10\) Up to 90% of patients with relapsing NMO are female. Its incidence rate peaks at approximately age 40 but it can occur at any age.

**CLINICAL CHARACTERISTICS**

The cornerstone clinical syndromes of NMO are optic neuritis and acute transverse myelitis. Occasionally, these events will occur simultaneously but usually they evolve months to years apart. The concept of “NMO spectrum disorders” recognizes that other syndromes involving the cerebrum and neuroendocrine systems occur in patients who are seropositive for NMO-IgG and who may or may not also have experienced optic neuritis and myelitis (Table 2).\(^1\)

Optic neuritis may occur as a unilateral event or as simultaneous or sequential bilateral events. The optic chiasm may be affected and optic nerve lesions tend to be extensive, as detected by orbital MRI with gadolinium. Although visual loss tends to be more severe in NMO, clinical symptoms cannot otherwise differentiate optic neuritis events in MS from NMO. Retinal vascular abnormalities in NMO have been reported, including attenuation of the peripapillary vasculature and focal arteriolar narrowing.\(^11\) Ocular coherence tomography has also demonstrated a greater reduction in the thickness of the retinal nerve fiber layer in NMO than MS as well as asymptomatic nerve fiber layer thinning in NMO-IgG seropositive patients with recurrent transverse myelitis.

Spinal cord attacks in NMO are usually, but not exclusively, clinically severe and accompanied by a MRI lesion that extends over 3 or more vertebral segments; this pattern is termed “longitudinally extensive transverse myelitis” (LETM). Paraparesis or quadriplegia, spinal cord sensory syndromes, sphincter dysfunction occur with spinal cord events. L’hermite’s symptom (paresthesias along the spine
or limbs precipitated by neck flexion) and paroxysmal tonic spasms (repetitive, stereotypic, painful muscle spasms) occur in about 40% of patients.

Extension of a myelitis attack into the brain stem, or individual brain stem lesions, can cause nausea, vomiting, and hiccoughs, probably due to involvement of the area postrema and medial and lateral portions of the nucleus tractus solitarius. These symptoms affect up to 40% of patients in some series and in pediatric patients seropositive for NMO-IgG, up to 45% have vomiting and encephalopathy. Brain stem lesions may also cause neurogenic respiratory failure. Other unusual clinical syndromes now linked to NMO or NMO-IgG seropositivity include endocrinopathies (which may be either autoimmune or owing to hypothalamic dysfunction), encephalopathy, and the posterior reversible encephalopathy syndrome (PRES).

**NATURAL HISTORY**

More than 90% of cases follow a relapsing course. After initial presentation, about 60% of patients relapse within one year and 90% within 3 years. Relapsing NMO patients appear to have similar clinical features and course regardless of NMO-IgG autoantibody status. Patients with monophasic disease are more likely to be seronegative and the frequency and severity of relapses appears lower in seronegative patients.

Neuromyelitis optica attacks are usually severe and often only partly recover and secondary progressive disease is very uncommon. Therefore, disability in NMO occurs as a result of the cumulative effect of clinical attacks. In contrast, MS attacks are mild to moderate in severity, usually recover well early in the disease, and secondary progressive disease is the phase the causes late-course disability.

**NEUROIMAGING**

Early in the disease, brain imaging is either normal or shows only nonspecific white matter lesions that do not meet MS criteria. Orbital MRI with gadolinium may reveal enhancement of one or both optic nerves or the optic chiasm with acute optic neuritis. Acute transverse myelitis is strongly linked to “longitudinally extensive” spinal cord lesions, which consist of T2 hyperintensity that is central in cord cross-section and extends over ≥3 vertebral segments. In contrast, MS lesions are usually peripherally-based and about one vertebral segment long. Detection of a LETM lesion on MRI is the most specific indicator of NMO. Acute LETM lesions often evolve over weeks to years such that the longitudinally extensive pattern is no longer evident, therefore, valid assessment of LETM must include MRI studies done during an acute myelitis attack.

The profile of brain MRI abnormalities in NMO has been expanded by studying NMO-IgG seropositive patients who have definite NMO but additional neuroimaging characteristics. Most commonly, at least 60% of NMO patients accrue nonspecific white matter lesions over time and up to 10% have lesions that meet radiological criteria for MS; therefore brain MRI lesions do not exclude diagnosis of NMO. Less common MRI abnormalities are highly variable in appearance. Large, irregular subcortical white matter lesions that are very atypical for MS can occur and in the acute phase may demonstrate “cloud-like” enhancement with gadolinium. Whereas corpus callosum lesions in typical MS are oriented perpendicular to the ventricular surface, in NMO such lesions are often linear and follow the axis of the corpus callosum itself, sometimes with edema in the acute phase. About 10% of patients have T2 signal abnormalities involving the hypothalamic or thalamic regions, the brain stem adjacent to the fourth ventricle or aqueduct; this pattern seems specific for NMO.

**LABORATORY STUDIES**

Cerebrospinal fluid cell counts during active NMO relapses vary but can be very high (50 to 1000 x 10⁶ WBC/L) and sometimes reveal a neutrophil-predominant differential) and high protein level (100 to 500 mg/dL). In typical MS, the CSF may show a mild lymphocytic pleocytosis (fewer than 25 x 10⁶ WBC/L). Unique CSF oligoclonal bands, which are detected in ~85% of MS cases, are found in only 20-30% of NMO cases.

About half of NMO patients harbor one or more serum autoantibodies, such as antinuclear antibody and extractable nuclear antigen and about one-third have one or more systemic autoimmune diseases, typically thyroid disease. Coexisting myasthenia gravis also occurs more often than expected. Patients who meet formal diagnostic criteria for connective tissue diseases such as systemic lupus erythematosus or Sjögren syndrome and also have the clinical NMO syndrome should be tested for NMO-IgG. Those who are seropositive for NMO-IgG most likely have coexisting autoimmune diseases rather than “lupus myelitis” or a Sjögren’s-related myelopathy/myelitis.

**NMO-IgG AND AQUAPORIN-4**

The original serological test, NMO-IgG, was based on an indirect immunofluorescence technique using mouse cerebellum tissue. It was found to be 73% sensitive and 91% specific for distinguishing NMO from optic-spinal presentations of MS. Soon after, the antibody target was discovered to be the water channel aquaporin-4. This and other assay techniques, including detection of aquaporin-4 antibodies using cell based assays, radioimmunoprecipitation assays (RIPA), fluororimmunoprecipitation assays (FIPA), and enzyme-linked immunosorbent assays (ELISA) have since consistently replicated the original results with reported specificities between 85-100%. Sensitivity rates are somewhat lower and less consistent, ranging from 47-91%, which may reflect actual assay differences, variability in the clinical gold standard definition, control group characteristics, treatment status and other factors. Cell-based assays may
have the best diagnostic accuracy but studies are ongoing to optimize assay technique. Occasionally, retesting initially seronegative NMO-IgG patients will yield a positive result and rare cases in which NMO-IgG was detected in CSF but not serum have been reported. Therefore, when diagnostic suspicion is high but there remains uncertainty, retesting serum or testing CSF is reasonable.

Some evidence suggests that antibody levels rise prior to clinical relapses, are reduced with immunosuppressive therapy, and that attack severity may be related to the degree of complement activation initiated by antibody. However, it remains to be determined if antibody titers or other similar data can be used to inform therapeutic decisions.

Aquaporin-4 is the most common of the aquaporin family of water transport proteins in the CNS. It regulates bidirectional water flux between blood and brain or CSF. It is expressed on astrocyte foot processes and the abluminal surface of blood vessels and is not found on neurons, oligodendroglia, or choroid epithelium cells. Normally, aquaporin-4 is expressed at high levels in the spinal cord (relatively more in gray matter), optic nerve, brain stem, hypothalamus, and periventricular regions. It is also expressed highly in perivascular, periependymal, and subpial regions as well as areas such as the area postrema (likely accounting for episodic nausea/vomiting events), and the supraoptic nucleus. There is an association between these high-density regions and patterns of MRI lesions in some NMO patients.

There are numerous ongoing efforts to establish an animal model of NMO. Three of these have exposed Lewis rats to aquaporin-4 antibodies after induction with experimental allergic encephalomyelitis (EAE), a T-cell mediated CNS inflammatory disease, and each model resulted in NMO-like pathology. Fourth model, which did not utilize EAE induction, showed that intracerebral injection of NMO-IgG and human complement produces pathological lesions in mice very much like that seen in human NMO. These exciting advances promise to further elucidate the pathogenic mechanisms underlying the disease though passive transfer models and models of relapsing disease have not yet been reported.

**PATHOLOGY AND PATHOGENESIS OF NMO**

Focal NMO lesions in the optic nerve and spinal cord reveal inflammation and demyelination. In the cord, both gray and white matter is typically involved, sometimes with necrosis and cavitiation. Unlike MS lesions, eosinophils and neutrophils are common in the inflammatory infiltrates of active NMO lesions and penetrating spinal vessels may be thickened and hyalinized.

Immunoglobulin and complement are deposited in a vasculocentric “rim” and “rosette” pattern in active NMO lesions. Postmortem studies confirm that brain lesions visualized on MRI in NMO patients have the same immunohistochemical characteristics as spinal cord lesions and that these are distinct from both MS and acute disseminated encephalomyelitis.

Aquaporin-4 immunoreactivity is strikingly depleted in NMO lesions regardless of the stage of demyelinating activity or extent of tissue necrosis. This contrasts from active demyelinating MS lesions, in which aquaporin-4 expression is increased. Furthermore, a novel NMO lesion type, encountered in the spinal cord and medullary tegmentum and extending into the area postrema, shows loss of aquaporin-4 with inflammation and edema, but neither demyelination nor necrosis.

Mounting evidence supports the potential for NMO-IgG as the primary cause of NMO. The association of NMO with other serum autoantibodies and systemic autoimmune diseases, together with the beneficial treatment effects seen with plasma exchange, implicate humoral immune pathways. Lesional immunoglobulin and complement deposition also suggests a primary antibody-mediated or initiated mechanism. Also, areas of aquaporin-4 loss coincide with sites of vasculocentric immune complex deposition, suggesting that a complement-activating, aquaporin-4-specific autoantibody is the primary initiator of the NMO lesion. In vitro experiments support these findings; they have demonstrated that NMO-IgG modulates expression of aquaporin-4 on the astrocyte surface. Moreover, in the presence of complement, NMO-IgG initiates cell membrane injury, cell death, disruption of the blood-brain barrier, and enhances granulocyte recruitment. Paranodal aquaporin-4 disruption may result in demyelination with loss of astrocyte endfoot integrity and failure of osmotic regulation, among other mechanisms. Finally, NMO-IgG modulates the glutamate transporter EAAT2 and reduces glutamate reuptake. Therefore, the cumulative evidence supports the likelihood that NMO-IgG directly causes tissue injury through complement-initiated inflammatory mechanisms and excitotoxic pathways.

TREATMENT

1. **ACUTE ATTACKS**

Acute clinical relapses are treated with intravenous corticosteroids such as methylprednisolone (1000 mg daily for five consecutive days). For severe relapses that worsen or fail to respond promptly despite corticosteroid therapy, evidence from a randomized, controlled trial supports use of rescue plasma exchange. The standard course involves treatment on alternate days for a total of seven exchanges. Subsequent observational experience also supports use of plasma exchange for treatment-refractory myelitis and optic neuritis attacks in NMO.
2. RELAPSE PREVENTION

Prophylactic immunotherapy is indicated for patients who have established relapsing disease or who have experienced a first-ever clinical event (such as LETM) and are seropositive for NMO-IgG. In NMO spectrum disorders, disability is related entirely to the residual effects of attacks because secondary progressive disease is very uncommon. Anecdotal experience and case series indicate that standard MS immunomodulatory therapies (e.g., interferon-beta, glatiramer acetate) are likely ineffective for NMO; in fact, interferons may aggravate the disease. Instead, either general immunosuppression or B cell depletion regimens seem to improve the natural history of the disease by reducing attack frequency. Oral azathioprine (target daily dose 2.5-3 mg/kg) may be employed by starting therapy along with an oral prednisone “bridge” of 0.5-1 mg/kg/d. The goal is to establish azathioprine monotherapy by beginning a gradual prednisone dose reduction when azathioprine exerts its full effect, typically within 4-6 months. Oral mycophenolate mofetil, typically 1000 mg twice daily, is sometimes used in place of azathioprine. The chimeric anti-CD20 monoclonal protein rituximab is now commonly used because it quickly and selectively depletes B cells. Two reports demonstrated favorable post-rituximab clinical courses after rituximab therapy. Repeated infusions are required every 6-12 months to maintain B cell depletion. Other immunosuppressive approaches include cyclophosphamide, mitoxantrone, or intravenous immune globulin.

Patients with established relapsing NMO require long-term immunosuppression. There are no data regarding if and when it is reasonable to discontinue therapy in patients who have been clinically stable for several years. Five years of relapse-free immunosuppression has been recommended for NMO-IgG seropositive patients with a single clinical event such as a LETM attack who are at high risk for relapse, with the rationale that the risk of adverse effects of therapy (e.g. malignancy) begin to emerge beyond that time frame.

Advances in the understanding of the sequential mechanisms that result in NMO lesions are expected to identify many new and specific targets for long-term immunotherapy in NMO.

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CME ANSWERS

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REFERENCES