

## Mellen Center Approaches: Neuromyelitis Optica

### What is Neuromyelitis Optica?

Neuromyelitis optica (NMO) is an idiopathic, inflammatory disease of the central nervous system with classically severe attacks affecting the optic nerves and spinal cord. It causes destructive lesions in eloquent areas of the central nervous system. In most patients the brain is initially relatively spared. A series of patients with this pattern of CNS involvement was described by Devic and Gault in 1894 giving NMO the eponym, Devic's disease. In the past NMO was lumped with MS but recent research has emphasized that it is different from MS pathophysiologically. It appears to be an antibody mediated disease directed against astrocytes and not a primarily demyelinating syndrome. It appears more like myasthenia gravis or paraneoplastic antibody diseases than like MS in this regard.

### How do patients with NMO present?

Consecutive or less commonly, simultaneous, occurrence of optic neuritis and transverse myelitis is the hallmark of NMO. Optic neuritis (often with ocular pain) may be bilateral or unilateral and is often associated with severe vision loss and incomplete recovery. Attacks of transverse myelitis are typically complete with profound bilateral motor weakness, prominent dysesthesias, a sensory level and sphincter dysfunction. Ocular coherence tomography shows more retinal nerve fiber dropout in NMO patients than with optic neuritis associated with MS.

Patients with symptomatic brainstem disease (medulla near 4th ventricle) may have intractable emesis or hiccups.

Approximately 80-90% of patients with NMO experience a relapsing course. More than half of patients will have a relapse in the first year. Relapse occurs in 90% by 3 years. While progression in NMO is primarily related to relapses, at the Mellen Center we have also seen gradual progression in some patients with long standing NMO, possibly due to secondary axonal degeneration.

### Is NMO the same as multiple sclerosis (MS)?

A: No. Devic's disease is clinically and neuropathologically distinct from multiple sclerosis. In general, patients with Devic's disease have a more rapid progression to disability than most patients with MS. Attacks are severe with incomplete recovery. MRI of the brain is usually normal or shows changes that differ from MS (See below). The longitudinally extensive cord lesions (typically 3 vertebral segments long) characteristic of NMO are rarely seen in MS (MS lesions are usually one vertebral segment long). CSF may show a striking pleocytosis or a neutrophilic predominance which would be unusual for multiple sclerosis. Oligoclonal bands are found in only 15-30% with NMO versus 90% with MS. Worsening in Devic's disease is related to attacks, and does not usually show a secondary progressive course. Necrotic, cavitory lesions involving grey and white matter in the spinal cord and optic nerves are characteristic of NMO. Eosinophils and neurophils are commonly found in these lesions. Active NMO lesions involve a vasocentric deposition of immunoglobulins and complement.

### What are the criteria for the diagnosis of Devic's disease?

The proposed diagnostic criteria include:

1. Optic neuritis and
2. Acute myelitis
3. And at least two of three supportive criteria
  - a. Contiguous spinal cord MRI lesion extending over 3 vertebral segments
  - b. Brain MRI not meeting diagnostic criteria for multiple sclerosis
  - c. NMO-IgG seropositive status

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### How common is NMO? Who gets it?

Devic's disease is more common than previously thought, but the specific incidence and prevalence are unknown. The median age of onset is 39 years, older than that in MS. It is five to nine times more prevalent in females than males. In North America most patients with Devic's are Caucasian. However worldwide NMO is frequent in Asian populations. It is generally regarded as a non-familial disease.

### Is there a test for NMO?

A recently developed antibody, the neuromyelitis optica-IgG antibody (NMO-IgG), recognizes aquaporin 4, a protein expressed on renal tubules, cerebellum, and the end feet of astrocytes. Serum NMO-IgG testing is positive in 70% of clinically diagnosed NMO. The test is more than 90% specific for NMO. Some case of seronegative NMO will have positive CSF NMO-IgG, but this test is not widely available. At the Mellen Center we have not been routinely testing for NMO-IgG in the CSF. The correlation of NMO-IgG titer with severity or stage of the disease and response to therapy is not clear at this time.

### Who do we test using NMO-IgG?

The group of patients where NMO-IgG testing is indicated continues to increase. Because of the major difference in therapeutic approach to NMO-IgG positive patients, it is important to identify NMO-IgG positive patients as well as NMO-IgG negative patients meeting Devic's disease criteria. Patient groups to consider testing in:

- Longitudinally extensive or severe transverse myelitis
- Severe unilateral, recurrent, or bilateral optic neuritis
- Some patients with the above features who also have unusual brain or brainstem lesions.

In patients with a single episode of transverse myelitis or severe optic neuritis who have NMO-IGG positive there is an increased risk of future relapses.

### Does the presence of brain lesions on MRI exclude Devic's disease?

No. Early in NMO the brain is typically normal on MRI. However new brain lesions are detected in 60% of patients within 6 years after diagnosis. More recent literature has emphasized a variety of 'atypical' brain lesion occurring in NMO including hemispheric, callosal, brainstem, and hypothalamic lesions, many of which occur at locations high in aquaporin-4 positivity. On occasion lesions ascending from the spinal cord into the brainstem can occur. There are reports of Balo-type concentric sclerosis occurring in NMO positive patients. Cases of PRES (posterior reversible encephalopathy syndrome) have also been reported in association with NMO-IgG positivity.

### Are any other diseases associated with NMO?

Neuromyelitis optica is more strongly associated with other autoimmune diseases than MS. It is unclear at present if there is a higher incidence of malignancy in NMO. It may be worth assessing for other disorders of the immune system (e.g. lupus, Hashimoto's thyroiditis, etc.) in patients with NMO.

### What is the general approach to an NMO relapse? Is it different from an MS relapse?

At the Mellen Center we treat NMO relapses urgently because of the rapidity, severity, as well as potential irreversibility of relapses in this disorder. Brainstem and cervical cord involvement may lead to fulminant neurogenic respiratory failure. We also make sure the patient is started on long term disease therapy as well (*See below*).

Intravenous corticosteroids are our initial treatment for an acute attack. The typical Mellen Center regimen is methylprednisolone 1000mg IV as a single daily dose on 3-5 consecutive days followed by a prolonged steroid taper. We use various tapering regimens but these range from 2-6 months and some of our group switch over to an alternating dose prednisone treatment during this taper. Patients with severe myelitis or brainstem symptoms should be given steroids in an inpatient setting. We consider plasmapheresis as an early second line treatment for patients with an acute attack who do not respond promptly to corticosteroids.

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### Other than medication, what types of support are needed in an NMO relapse?

Other considerations during an NMO relapse with spinal cord involvement include attention to skin hygiene, DVT prophylaxis, symptomatic treatment for painful spasms, and early physical therapy. Patients with cervical cord and/or brainstem involvement may require close monitoring of pulmonary mechanics and cardiac telemetry.

### What therapies are available to prevent attacks?

Treatment differs from standard MS, but there are no randomized trials to guide therapy. Anecdotal reports suggest an increase in disease activity in NMO with interferons, but this has not been substantiated. Neuromyelitis optica does not appear to respond to the usual immunomodulating agents used in R-R MS, but has been traditionally treated with a combination of azathioprine plus corticosteroids. At the Mellen Center we start azathioprine with oral steroids.

We titrate the azathioprine slowly up to 2-3 mg /kg daily. Some clinicians check white cell counts and MCV frequently and titrate to these counts, while others check a TMPT (thiopurine methyltransferase enzyme) level for patients with low metabolism of azathioprine (about 0.3% of the population). If patients are low metabolizers they may require much lower doses of azathioprine to affect white count and MCV. We target a white count of 2,500 and MCV <103 as therapeutic indicators of immune effect. We also monitor clinical tolerance. In general we try to limit azathioprine use to a total dose of 600 grams or 10 years of continuous therapy to reduce the long term risk of malignancy.

We taper off of oral steroids over a few months time, with or without switching to an alternate days schedule. Some patient may require continued low dose steroids with azathioprine but we try to limit this if possible.

If azathioprine is not effective we switch to either rituximab (Rituxan) or mycophenolate mofetil (Cellcept) in a standard dosing (e.g. rituximab 1000 mg IV repeated at 2 weeks then every 6 months depending on response and hematological parameters; Cellcept titration up to 1000 mg bid or tolerance with hematological and liver monitoring).

Other protocols that we consider if needed include continuous low dose prednisone; mitoxantrone; and IVIG.

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