IS ASIAN OSMS A DISTINCT ENTITY OR PART OF THE NMO SPECTRUM? - PART OF THE SPECTRUM

Brian G. Weinshenker
Mayo Clinic, Rochester MN, USA

The nosology of CNS demyelinating diseases that selectively or relatively selectively target the optic nerves and spinal cord sparing other parts of the brain remains confusing and controversial, and is mired in historical precedent. Furthermore, with evolving knowledge about the pathophysiology of NMO, the nosology that is applied has evolved, adding additional confusion to the issue.

Historically, NMO has been regarded as a monophasic disease targeting the optic nerves and spinal cord, but typically the symptoms do not develop entirely simultaneously, but in quick succession[1]. Devic's case was rapidly fatal[2], so it is impossible to say whether that patient may have had further relapses. However, the older literature clearly documents that some patients had relapses, and also documents the bias against labeling any case with relapses as having NMO, because of the precedent that arose that MS was defined entirely by the presence of "lesions disseminated in time and space". Any relapsing CNS demyelinating disease was, by definition, regarded as MS.

In the 1950's through 1980's, it was recognized that there was a common phenotype of relapsing CNS demyelinating disease with prominent optic nerve and spinal involvement in Asia; it was known as opticospinal or optic-spinal MS, also known as Asian opticospinal MS (OSMS)[3]. Its potential relationship to Devic's neuromyelitis optica was recognized, but it was differentiated from Devic's by the occurrence of relapses[4].

In Western countries, a variety of series explored the clinical characteristics and natural history of individuals with prominent and severe optic neurits and myelitis in the 1990's and early 21st century. It became clear that there was an entity that seemed to be separable from prototypic MS based on definable clinical and radiological criteria; this not uncommon variant was usually relapsing and not monophasic and most cases would not be identified by relying on the definition suggested by historical precedent. It is now most commonly referred to as relapsing neuromyelitis optica and that this disorder is vastly more common than monophasic NMO. The definition of monophasic NMO remains unclear; specifically, it is unclear whether unilateral or bilateral optic neuritis are required; what period of observation should be required before declaring NMO "monophasic and what interval between attacks is allowable even if there are no further relapses beyond the index attacks of optic neuritis and myelitis[5, 6].

The critical issue facing us today is whether relapsing NMO is the same disorder as OSMS and whether either is entirely separable from conventional MS, or whether they represent a continuum? In Asia, more so than in other parts of the world, the relationship of OSMS or relapsing neuromyelitis optica to conventional MS remains uncertain. These issues are not purely semantic. It has been clear that the prognosis and treatment of relapsing neuromyelitis optica and MS are very different. Relapsing neuromyelitis optica tends to have much more severe relapses than conventional MS. Furthermore, one of the most widely applied disease modifying treatments for MS appears to be ineffective or possibly even deleterious to patients with NMO[7, 8].

There are two broad schools of thought:

1. NMO and conventional MS are distinct; the vast majority of relapsing patients may be eventually classified in one or other category based on a combination of clinical, radiological, and serological tests; OSMS is a historical term, of little current value, and as currently used represents an admixture of cases of NMO and conventional MS.
2. OSMS and conventional MS represent two sides of an admixture of patients with inflammatory demyelinating disease in Asia[9]. OSMS has many of the demographic features as does NMO, including greater female predominance, tendency to long spinal cord lesions, more severe optic neuritis, more frequent presence of anti-AQP4 antibodies, but it is impossible to draw any exact boundaries.

I will argue that NMO and conventional MS are entirely distinct, although there are potentials for misclassification, especially for the following reasons:

1. Symptomatic brain lesions may occur in NMO[10] contrary to previous thinking, although the spectrum of these brain lesions and their clinical manifestations differ qualitatively from those seen in conventional MS in most cases (e.g. intractable vomiting or hiccup; symptomatic narcolepsy; PRES encephalopathy)[11]
2. Longitudinally extensive spinal cord lesions extending over 3 or more spinal segments may not be detected with EACH attack of NMO, especially when modified by immunosuppressive therapy
3. It is only possible to detect a longitudinally extensive lesion when an MRI of the spinal cord is done in the context of an acute attack, and not during remission; it may be possible to see a long segment of atrophy, a pseudo syrinx or multiple shorter lesions in the inter-attack interval, but occasionally no residual lesion or a nonspecific small lesion may be all that can be detected[12].

4. current generation testing for AQP4 antibodies is about 60-70% sensitive; it is predicted to improve somewhat with new techniques and substrates for ELISA and immunofluorescence.

OSMS is a phenotypic descriptor for distribution of lesions….not a diagnosis! The diagnosis, as is the case in most of clinical medicine, is dependent on an integration of clinical symptoms and signs, radiological and laboratory findings. There are no pathognomonic signs for NMO, although anti-AQP4 antibodies, when detected, seem to be highly specific. It is probably premature to conclude that anti-AQP4 antibodies are entirely specific, however, and that the diagnosis can be made exclusively based on serology or any other single finding.

Opticospinal MS is a historical term, and should disappear. To provide optimal care of patients, clinicians must endeavor to definitively classify patients as having NMO versus conventional MS or other mimic, of which there are some rare entities (e.g. CRMP-5 associated paraneoplastic myelopathy and optic neuropathy).

1. *Stansbury F. Neuromyelitis optica; presentation of five cases, with pathologic study, and review of literature. Arch Ophthal. . 1949;42:465-501*
2. *Devic C. Myelite subaigue compliquee de nevrite optique. Bull Med. 1894;35:18-30*
3. *Kuroiwa Y, Shibasaki H. Epidemiologic and clinical studies of multiple sclerosis in Japan. Neurology. 1976;26:8-10*
4. *Kuroiwa Y. Neuromyelitis optica (Devic's disease, Devic's syndrome). In: Vinken PJ, Bruyn GW, Klawans HL, eds. Handbook of Clinical Neurology. Vol. 47. Amsterdam: Elsevier Science Publishers, 1985:397-408*
5. *Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology. 1999;53:1107-1114*
6. *O'Riordan JI, Gallagher HL, Thompson AJ et al. Clinical, CSF, and MRI findings in Devic's neuromyelitis optica. J Neurol Neurosurg Psychiatry. 1996;60:382-387*
7. *Papeix C, Vidal JS, de Seze J et al. Immunosuppressive therapy is more effective than interferon in neuromyelitis optica. MS. 2007;13:256-259*
8. *Shimizu Jun, Hatanaka Yuki, Hasegawa Michiko et al. IFN β-1b may severely exacerbate Japanese optico-spinal MS in neuromyelitis optica spectrum. Neurology. 2010;75:1423-1427*
9. *Nakashima I, Fukazawa T, Ota K et al. Two subtypes of optic-spinal form of multiple sclerosis in Japan: clinical and laboratory features. Journal of Neurology. 2007;254:488-492*
10. *Pittock SJ, Lennon VA, Krecke K et al. Brain abnormalities in neuromyelitis optica. Arch Neurol. 2006;63:390-396*
11. *Kim W, Park M-S, Lee S-H et al. Characteristic brain magnetic resonance imaging abnormalities in central nervous system aquaporin-4 autoimmunity. Mult Scler. 2011;16:1229-1236*
12. *Collongues N, Cabre P, Marignier R et al. A benign form of neuromyelitis optica: Does it exist? Arch Neurol. 2011;68:918-924*