

Neuromyelitis optica in western countries: Establishing diagnostic criteria and characterization of the spectrum

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Abstract

Neuromyelitis optica (NMO) can be distinguished from MS by clinical, radiological and serological findings, especially the tendency for spinal cord lesions to be longer than 3 vertebral segments during acute attacks and the presence of aquaporin-4 autoantibodies in NMO. The spectrum of NMO is broader than previously realized and includes recurrent myelitis, recurrent optic neuritis, certain cerebral presentations, including intractable vomiting and posterior reversible encephalopathy. It may coexist with other systemic autoimmune diseases, including systemic lupus erythematosus and Sjogren's syndrome. Whether NMO has a predilection for individuals of Asian ancestry or whether there are differences between NMO and Asian optic-spinal MS other than arbitrary definitions remains to be clarified. Further epidemiological studies using comparable diagnostic criteria, radiological studies and serological tests are required.

Just a decade ago, there was controversy about the distinctness of neuromyelitis optica (NMO) from multiple sclerosis (MS). Over the past three years, investigators worldwide have accepted that these diseases are distinct clinically, radiologically, pathologically, prognostically and in their responsiveness to MS disease-modifying therapies. Questionably, the major factor responsible for this acceptance was the discovery of an IgG biomarker with moderate, but variable among different investigative teams, sensitivity for NMO.^{1,2} However, the uniformly high specificity of this IgG biomarker², that has been termed NMO-IgG, has reassured most about its significance. Virtually every relevant control group that has been studied, including other fulminant demyelinating diseases, systemic autoimmune disease and other neurological diseases, has shown that only in those with typical symptoms of NMO is the test positive. Initial efforts to characterize the specificity of this marker required independent clinical and serological characterization of suspected cases to avoid the pitfall of "circular argument" wherein the biomarker being evaluated influenced the clinical diagnosis with which an association was being explored.¹ However, having established the specificity of the marker beyond doubt², it seemed reasonable to use this marker as a probe to explore disorders with credible clinical relatedness (limited syndromes, such as isolated or recurrent transverse myelitis or optic neuritis; optic-myelitic

syndromes associated with other comorbidities such as systemic autoimmune disorders that raised question about the relationship to NMO; atypical manifestations such as brain syndromes, that occur with unusually high frequency in patients with NMO). While the potential pitfalls of circular reasoning might still raise concerns among some, the alternative of failing to utilize this marker to probe the spectrum of NMO was to ignore the existence of definable syndromes that might be related to NMO and benefit from similar therapeutic strategies as were being developed for clinically definite NMO.

A point of continuing controversy is the relationship of NMO to optic-spinal MS in Asian countries and elsewhere. Final consensus on this issue has yet to be reached, but an analysis of the issues in this debate is now possible that can frame the necessary studies to resolve persisting controversies.

In this review, I will outline the nature of NMO spectrum disorders that are now being recognized and diagnosed in individuals in western countries, and address the issue of similarity and differences between Asian optic-spinal forms of MS and NMO. I will also compare and contrast the recently proposed consensus criteria of the National Multiple Sclerosis Society task force on the diagnosis of MS with the Wingerchuk *et al* (2006) Mayo Clinic criteria for NMO and their implications.

NEW MANIFESTATIONS OF NEUROMYELITIS OPTICA SPECTRUM DISORDERS

Limited manifestations

Several investigators have reported patients with isolated myelitis (i.e. without optic neuritis) who are NMO-IgG positive and who are now considered to have NMO spectrum disorders. The most comprehensive prospective study found that 11/29 (38%) individuals with a first longitudinally extensive transverse myelitis were NMO-IgG positive and seropositivity was strongly predictive of relapse of myelitis or development of optic neuritis.³ However, in a series of unselected demyelinating disease in children the frequency of NMO-IgG seropositivity in this situation was much lower than in adults⁴, suggesting that the etiology of transverse myelitis may differ in children compare to adults. However, a single patient in that series with recurrent transverse myelitis who was seropositive proves that NMO may be the cause of some cases of transverse myelitis in children. That patient presented with a first episode of transverse myelitis at one time, and presumably would have been seropositive at that time. Increasing evidence points to a high frequency of NMO-IgG seropositivity at an early point of the illness, generally at the first attack, and to the pathogenic role of aquaporin-4 antibodies. Further studies are necessary to define the frequency and significance of NMO-IgG in patients with recurrent myelitis.

Recurrent optic neuritis is associated with clinical conversion to NMO and/or NMO-IgG positivity in approximately 20% of cases in both a French⁵ and a US series.⁶ NMO-IgG seropositivity predicts poor visual outcome⁵⁻⁷ and development of severe transverse myelitis.⁶ We have detected several patients who are found to be NMO-IgG seropositive after a first episode of optic neuritis. The frequency of seropositivity in this clinical situation is unknown, but is presumably quite low, although it is possible that for certain high risk presentations (e.g. severe optic neuritis with poor recovery; non-Caucasians; lesions extending over long segments of the optic nerve/chiasm; patients with normal MRI scan), it may be cost effective to test for NMO-IgG given the treatment implications.

Given the high predictive potential of NMO-IgG seropositivity in these clinical contexts, effective preventive therapy for NMO in patients with symptoms that are reasonably considered to have inaugural or limited forms of NMO

“spectrum disorders” is justified.

Association with comorbid “confounding” inflammatory disorders

Systemic autoimmune diseases occur commonly in patients with NMO.^{8,9} These systemic autoimmune diseases are diverse and include systemic lupus erythematosus and Sjogren’s syndrome, but also include myasthenia gravis¹⁰, and many other relatively uncommon autoimmune disorders. Whether or not a diagnosis of NMO can be made in patients who have such a comorbid disorder was unclear. It had been generally accepted that myasthenia gravis, which is not typically associated with optic neuritis, myelitis or other CNS inflammatory lesions, would not preclude a diagnosis of NMO. However, in the cases of systemic lupus erythematosus (SLE) and Sjogren’s syndrome, a variety of central and peripheral nerve symptoms have been attributed to these conditions, often with imperfect evidence that these conditions are directly causal. An even higher proportion of patients with NMO have serological evidence of coexisting autoimmunity. A US and French collaborative study has significantly clarified the relationship between these disorders.¹¹ This study found that a high proportion of patients with NMO are seropositive for antinuclear antibodies (approximately 40%) and Sjogren’s syndrome A and B autoantibodies (approximately 15%), even though only a small proportion (3%) have clinical evidence for these disorders. However, those patients with optic neuritis and/or myelitis with systemic lupus or Sjogren’s were commonly seropositive for NMO-IgG antibodies. Furthermore, this did not represent false positivity in patients with these autoimmune disorders, as patients with SLE or Sjogren’s syndrome were uniformly seronegative for NMO-IgG when neurological symptoms were absent or when they had neurological symptoms other than optic neuritis or myelitis. Thus, patients with lupus or Sjogren’s who have the syndrome NMO (regardless of the sequence in which these syndromes develop) are likely to have coexisting autoimmune conditions rather than a neurological complications of NMO/Sjogren’s.¹¹

Brain Lesions in NMO

While in the past considered an exclusionary characteristic for NMO in both Asian countries¹² and in western countries when symptomatic⁹, brain lesions are now recognized as being common in patients with NMO.¹³ The heterogeneity of

clinical presentations and of the appearance of MRI lesions had been confusing in the past and seemed to defy a rational basis for classification; however, insights into pathogenesis, facilitated in part by enhanced understanding of the nature of the target autoantigen and of its functional properties, as well as documentation, biopsy examination and observation of the course of various brain syndromes that occur in NMO has made a tentative classification scheme possible.

In some instances, brain lesions are necrotizing and on biopsy seem extraordinarily similar to that detected in spinal cord lesions. The distribution of lesions in the brainstem and corpus callosum mirrors the distribution of aquaporin-4 immunoreactivity, and presumably results from the antigenic nature of aquaporin-4 that is targeted by pathogenic immunoglobulin.¹⁴ Syndromes that result include intractable nausea/hiccoughs (area postrema), as recognized initially in Japan¹⁵, but subsequently seen commonly in Western countries¹⁶, endocrinopathies (hypothalamus)¹⁷ and encephalopathies (corpus callosum, hypothalamus and other midline brainstem structures).¹⁸

In some patients, an acute encephalopathic syndrome associated with transient T2 hyperintensities and symmetrical, abnormal signal on diffusion weighted images without restriction of apparent diffusion coefficient have been observed. These imaging findings are consistent with transient vasogenic edema, and the syndrome mimics posterior reversible encephalopathy syndrome (PRES).¹⁹ The MRI characteristics and distribution of these lesions presumably results from effects of NMO-IgG on the function of aquaporin-4. Similarly, large asymmetrical lesions with considerable surrounding vasogenic edema have been reported^{19,20}, which have been suggested by some to show an overlap between NMO and acute disseminated encephalomyelitis.²⁰ Similar to the situation in rodents, where deficiency of aquaporin-4 limits resorption of fluid infused into the brain²¹, blockade of aquaporin-4 in patients with NMO seems to predispose to this syndrome of vasogenic edema.

Some patients have combinations of inflammatory lesions and prominent surrounding vasogenic edema, presumably reflecting the duality of the pathogenesis of brain lesions in NMO: aquaporin-4 as an antigenic target, and aquaporin-4 as a functional water channel. Such patients have focal neurological findings and may develop significant encephalomalacia, consistent with sequelae of inflammation and axonal destruction; acutely, however, these lesions

may be associated with florid vasogenic edema associated with coma that may rapidly improve, consistent with dysfunction of resorptive capacity of aquaporin-4 at the blood brain barrier.

NMO in WESTERN COUNTRIES: DOES IT DIFFER FROM NMO IN ASIAN COUNTRIES?

The arguments that have been mounted supporting a difference between NMO in Asian and Western countries are:

1. The clinical and radiological manifestations of NMO that are considered highly specific for NMO in Western countries are less specific in Asian countries; in particular, the longitudinally extensive intraparenchymal spinal cord lesion that extend over three or more segments that is highly specific for NMO and discriminates NMO from MS, is seen at a clinically important rate in classical MS in Japan.¹² In other words, there are “transitional” cases between NMO and MS in Asians, suggesting that the differences between NMO and MS represent a continuum rather than a dichotomy.
2. NMO is commoner in individuals of Asian ancestry than of Caucasian or other ancestry.
3. Aquaporin-4 autoantibodies, which are highly specific for NMO, are either less specific and or less sensitive in Asians.¹²

Each of these points is subject of debate and they are discussed individually below.

Clinical differences between NMO and Optic-spinal MS

The clinical criteria that are applied presently in both Asian and western countries require specificity criteria in addition to the presence of optic neuritis and myelitis to adequately distinguish NMO from MS. However, the application of these specificity criteria differs in Japanese and western series^{12,22}, and as a result, a number of patients may be classified differently in Asian and western countries as having NMO versus MS. In western countries, investigators have recently espoused a long spinal cord lesion as a specificity criterion. However, it is important to recognize that long spinal cord lesions are only reliably detected in the acute phase of a myelitis attack, and may or may not leave long residual T2 lesions or longitudinally extensive atrophy in their wake. Another difference that confounds a comparison of NMO in western and

Asian countries is controversy about the treatment of brain lesions. Criteria proposed for NMO no longer require that brain MRI be normal. Although a normal scan was never a requirement of the 1999 Wingerchuk *et al* criteria⁹, current criteria (2006 Wingerchuk *et al* criteria²²) permit symptomatic brain lesions whereas in Japan and other Asian countries, such lesions exclude a diagnosis of NMO in patients with clinical and/or radiological findings suggestive of MS.¹² This modification to the recently proposed diagnostic criteria from Mayo Clinic reflects recent recognition of a broad spectrum of brain involvement in patients with NMO as is later discussed. Asian countries, while increasingly recognizing that brain lesions in patients with NMO albeit with some distinctive characteristics compared to MS brain lesions²³, have traditionally used brain lesions as an exclusionary criterion. Hence, it is difficult to comment on claims that long spinal cord lesions occur in some patients with classical MS, as it remains uncertain whether or not such patients would have been classified as NMO rather than classical MS in western countries.

A set of broadly agreed-upon criteria for NMO that may be applied in western and Asian countries would help resolve this issue. A task force of the National Multiple Sclerosis Society (NMSS) that involved western and Asian investigators attempted to create such criteria.²⁴ The task force's recommendations represent a useful compromise, but are likely not the final word on the disorder. These new NMSS criteria recognize that some of the now well-accepted brain lesions that occur in the context of NMO do not exclude the diagnosis, but do not accept that all brain lesions, for example the transient vasogenic edema lesions recently described, may be consistent with NMO. The new criteria require the presence of longitudinally extensive spinal cord lesions, which can be problematic in situations where a residual lesion that would have met this criterion has resolved by the time of neuroimaging, which is a particular problem in countries where rapidly accessible, high quality neuroimaging of the cord is not available. The new criteria reject a diagnosis of NMO in the context of clinically manifest systemic autoimmune diseases such as lupus erythematosus (although not in the situation where serological evidence for systemic autoimmunity is present without clinical manifestations). Evidence outlined above shows that NMO and systemic autoimmune disease, including SLE and Sjogren's syndrome, even clinically manifest, may coexist, and this represents a coincidence between these

disorders, not a neurological manifestations of the systemic autoimmune disease (i.e. so-called "lupus myelitis"). The task force criteria reject the concept of a broader spectrum of "NMO spectrum disorders", including those with limited manifestations in association with NMO-IgG seropositivity as described above, but recognized that further studies of that issue are necessary.

Relatively uncommon and recently recognized clinical-radiological phenomena of NMO, such as the presence of hypothalamic lesions and lesions of the dorsal medulla that lead to intractable nausea and hiccoughs have been recognized in Asian and western countries, arguing to the similarity of these conditions on both sides of the Pacific Ocean.

Different frequency of optic-spinal MS in Asian vs western countries

Some would argue that NMO is a common disease in Asians and an uncommon disease in Caucasians. Asian investigators were the first to recognize the distinctiveness of optic-spinal forms of MS compared to classical MS as long ago as the 1970's.²⁵ Only in the last decade has this distinction been accepted and patients with relapsing forms of NMO are being diagnosed as having an illness separate from MS in western countries. Accordingly, whereas comprehensive epidemiological studies have been reported from Japan²⁶, incidence and prevalence data for NMO in western countries are scarce. Accepting this limitation, the contention that NMO is commoner in Asian countries is not established. With the current prevalence estimates of MS-like illnesses in Japan (approximately 8/10⁵) and the relative frequency of NMO and MS (NMO constitutes approximately 17% of Japanese MS nationwide) [Kira J, personal communication], the prevalence of NMO in Japan is approximately 1.4/10⁵. A rough estimate based on observed cases in Olmsted County MN would suggest a NMO: MS ratio of 1:100 to 1:200. Given the much higher frequency of MS-like illnesses in Rochester MN (approximately 160/10⁵), the prevalence of NMO is estimated at 1-2/10⁵, which may not differ from that in Japan. Furthermore, the disease occurs in a racial/ethnic distribution that parallels that of the general population. Thus, the vast majority of cases seen at the Mayo Clinic in Rochester MN are Caucasian, although relative to MS, more Asian, African and Hispanic patients are identified. Certain ethnic groups that may have been considered as more susceptible to NMO²⁷ seem to be resistant to classical MS (e.g.

Amerindians). The most credible interpretation of current data is that Asians and Amerindians are **resistant to MS rather than more susceptible to NMO**. Demyelinating disease is much rarer among Amerindians than Caucasians, but when it does occur, it commonly has an NMO phenotype. In both Asian and western countries, women are particularly susceptible to NMO with 80-90% of cases occurring in women.

Specificity of aquaporin-4 autoantibodies in Asians vs western Caucasians

Aquaporin-4 antibodies occur in both Asian and Caucasian patients with NMO.^{1,12,28,29} In fact, there is substantial variation in the frequency of autoantibody among different Japanese series, but in several series, as in Western countries, when patients with long spinal cord lesions are identified, the majority are positive.^{28,29} Asians in North America as well as Asians in Japan and elsewhere have been documented to be seropositive for NMO-IgG. Low rates of seropositivity¹² in some series likely relate to differences in diagnostic criteria and/or their application, and possibly to higher rates of other diseases that mimic NMO in Asian countries,

not because aquaporin-4 autoimmunity does not occur in Asians. In fact, pathological studies in Japan³⁰ have found parallel results to those reported from two western countries (Northern Ireland and USA)^{31,32} with respect to abolition of aquaporin-4 immunoreactivity from lesions of patients with NMO.

CONCLUSION

Although still unconventional and controversial, we believe that the spectrum of NMO is broader than originally conceived and includes limited optico-myelitic syndromes as well as some cerebral syndromes, including isolated medullary or isolated hypothalamic syndromes, such as intractable nausea and vomiting, that may be confidently recognized as NMO spectrum disorders when aquaporin-4 autoantibodies are detected. Systemic autoimmune disease, such as SLE, may coexist with NMO and does not immediately exclude NMO.

The epidemiology of NMO should be carefully studied using rigorous and specific criteria, but criteria that recognize the broader spectrum of this disease. It remains to be determined whether there are important differences between Caucasians

Table 1: Comparison of NMSS (2008) NMO Criteria²⁴ and Wingerchuk (2006) Criteria²²

<i>Category</i>	<i>NMSS Criteria</i>	<i>Wingerchuk 2006 Criteria</i>
<i>Required</i>	Optic neuritis	Optic neuritis
	Myelitis	Myelitis
	MRI T2 hyperintense >3 vertebral segments and T1 hypointense during myelitis	
	Sarcoidosis, vasculitis or lupus erythematosus (clinically manifest) exclude diagnosis of NMO	
<i>Additional specificity criteria</i>	1 of 2	2 of 3
	Initial brain MRI normal (doesn't satisfy McDonald dissemination in space criteria)	Initial brain MRI normal (doesn't satisfy McDonald dissemination in space criteria)*
		MRI T2 lesion >3 vertebral segments during myelitis
	Positive serology for NMO-IgG (aquaporin-4 autoantibodies)	Positive serology for NMO-IgG (aquaporin-4 autoantibodies)

*Exceptions: hypothalamic, brainstem/dorsal medulla, linear corpus callosum lesions

and Asians with NMO/optic-spinal forms of MS in the absolute incidence and prevalence of these disorders as well as the phenotype and seropositivity to aquaporin-4.

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