The expanded spectrum of neuromyelitis optica – evidences for a new definition

O espectro expandido da neuromielite óptica – as evidências para nova definição

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ABSTRACT

Neuromyelitis optica (NMO) has been traditionally described as the association of recurrent or bilateral optic neuritis and longitudinally extensive transverse myelitis (LETM). Identification of aquaporin-4 antibody (AQP4-IgG) has deeply changed the concept of NMO. A spectrum of NMO disorders (NMOSD) has been formulated comprising conditions which include both AQP4-IgG seropositivity and one of the index events of the disease (recurrent or bilateral optic neuritis and LETM). Most NMO patients harbor asymptomatic brain MRI lesions, some of them considered as typical of NMO. Some patients with aquaporin-4 autoimmunity present brainstem, hypothalamic or encephalopathy symptoms either preceding an index event or occurring isolatedly with no evidence of optic nerve or spinal involvement. On the opposite way, other patients have optic neuritis or LETM in association with typical lesions of NMO on brain MRI and yet are AQP4-IgG seronegative. An expanded spectrum of NMO disorders is proposed to include these cases.

Key words: neuromyelitis optica spectrum disorders, optic neuritis, longitudinally extensive tranverse myelitis, brainstem, hypothalamus, encephalopathy, MRI, antiaquaporin-4 antibody.

RESUMO

Neuromielite óptica (NMO) tem sido tradicionalmente caracterizada como associação de neurite óptica recorrente ou bilateral e mielite tranversa longitudinalmente extensa (MTLE). O conceito de NMO tem mudado desde a identificação do anticorpo antiaquaporina-4. A NMO é atualmente considerada como um espectro de condições contendo pelo menos um dos eventos índices da doença (neurite óptica recorrente ou bilateral e MTLE) e soropositividade para AQP4-IgG. A maioria dos pacientes apresenta lesões cerebrais à imagem por ressonância magnética (IRM), algumas delas típicas de NMO. Pacientes soropositivos podem desenvolver sintomas de tronco encefálico, hipotálamo e de encefalopatia precedendo os eventos índices, ou isoladamente, na ausência de qualquer evidência de alteração visual ou espinal. Por outro lado, há pacientes soronegativos que apresentam ou neurite óptica ou MTLE associada a lesões cerebrais típicas de NMO à IRM. Todas essas situações estão incluídas no espectro expandido de NMO aqui proposto.

Palavras-Chave: espectro de neuromielite óptica, neurite óptica, mielite transversa longitudinalmente extensa, tronco encefálico, hipotálamo, encefalopatia, IRM, anticorpo antiaquaporina-4.

Association of optic neuritis and myelitis was first described by Giovanni Battista Pescetto in Italy, in 1844[1]. Few other cases were reported until 1894 when Eugène Devic published his own case[2], and along with his student, Fernand Gault, reviewed 16 others they found in the literature, providing a systematic description of the disease[3]. For over 100 years, the terms neuromyelitis optica (NMO) and Devic's disease were employed to identify patients with a condition considered as a variant of multiple sclerosis (MS), in which symptoms were confined to the optic nerves and spinal cord, occurred either simultaneously or within an interval of few weeks, and most frequently had a poor outcome[4].

In the last few years, however, the traditional concept of NMO has dramatically changed as a result of clinical analysis of larger cohorts, magnetic resonance imaging (MRI) studies that characterized acute transverse myelitis as longitudinally extensive spinal cord lesions (LESCL) and disclosed asymptomatic brain lesions in most patients, pathological and immunopathological evidences that suggested predominant humoral autoimmune response, and finally discovery of NMO-IgG and aquaporin-4 (AQP4) as a specific biomarker of the disease and its targeted antigen.

Currently, NMO is considered as a central nervous system (CNS) AQP4 channelopathy which causes variable damage predominantly to the optic nerves and spinal cord, although other CNS structures that highly express AQP4 may be also affected. Identification of the specific antibody in limited phenotypic presentation of the disease and the frequent association of optic neuritis and myelitis with other systemic autoimmune

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diseases have led to the view of NMO as a spectrum of CNS disorders. As further experience, making use of more refined AQP4-IgG assays and testing serum from patients with atypical clinical features continuously increases the observed variability of clinical manifestations at disease onset and during its course broadens. This suggests that periodical revisions of established concepts and diagnostic criteria are necessary.

This paper aimed to analyze the current concept of the spectrum of NMO and to show evidences that support its revision. It also proposed an expanded definition of the spectrum of NMO as a framework for building new diagnostic criteria for the condition.

DIAGNOSTIC CRITERIA FOR NEUROMYELITIS OPTICA

Throughout the last century, as the number of reports on patients with the association of optic neuritis and myelitis increased, authors in both Western and Eastern countries were concerned with formulation of diagnostic criteria for NMO in order to guiding practitioners and providing researchers with a common ground for communicating their observations[3,5-7]. Although some of the proposed diagnostic criteria accepted attack recurrences[7], all of them required absence of signs of brain involvement, except for "minor brainstem symptoms". Following incorporation of MRI into clinical practice, some authors included negative brain MRI as a requirement for diagnosis[6] whereas others[7] contemplated the diagnosis of NMO even in patients with brain lesions "which would be unexpected in multiple sclerosis" (Table 1).

By the end of the twentieth century, a review of a large cohort at Mayo Clinic[8] showed that (1) optic neuritis in NMO patients might be unilateral or bilateral; (2) the interval over which patients developed the disease index events (optic neuritis and myelitis) had no diagnostic significance; (3) the majority of patients had a relapsing course; (4) the clinical manifestations were frequently severe; (5) cerebrospinal fluid (CSF) abnormalities were characterized by neutrophilic pleocytosis or a greater number of nucleated cells usually associated with negative oligoclonal bands; (6) abnormal signal on spinal cord MRI extended over ≥3 vertebral segments; and (7) brain MRI was either normal or showed unspecific lesions. These features could promptly help to distinguish NMO from MS and were used, therefore, for formulation of the 1999 diagnostic criteria for NMO[8] (Table 2).

The discovery of the NMO-specific antibody in 2004[9] and of AQP4, as its targeted antigen in the following year[10], is recognized as a turning point in the concept and understanding of the disease. Aquaporin-4 is the most abundant water channel in the central nervous system, expressed in the foot processes of astrocytes in contact with blood vessels throughout the brain, spinal cord and optic nerves. The periventricular area, the hypothalamus and the brainstem are also considered sites of high expression of AQP-4. It is particularly concentrated underlying the pia mater and the ependymal cells in contact with the CSF, and its expression is critical for normal regulation of water flux at the blood-brain barrier and CSF-brain interfaces[11]. Although AQP-4 predominates in the CNS, it is also found in other organs such as the kidneys, stomach, airways, glands and skeletal muscle[12]. However, the paucity of clinical abnormalities outside the CNS remains to be explained.

Discovery of AQP4-IgG as a sensitive and highly specific serum biomarker for NMO provided a sound basis to incorporate its serum detection in the 2006 revised diagnostic criteria (Table 3)[13].

Table 1. Diagnostic criteria for neuromyelitis optica prior to 1999.

Author (y)	Optic neuritis	Myelitis	Interval	Monophasic/Relapsing	Brain symptoms	CSF	MRI
Devic/Gault (1894)[3]	B	Acute	S	M	Rare		
Shibasaki et al. (1981)[5]	B	Acute	S	M	No		
Mandler et al. (1993)[6]	U/B	Acute	S/Mos–Yrs	NI	No	No OB	Br: normal SC: cavitation
O'Riordan et al. (1996)[7]	U/B	Severe transverse	Mos-Yrs	M/R	No	Rare OB	Br: N/Abn SC: usually LSCL

B: bilateral; U: unilateral; S: simultaneous; Mos: months; Yrs: years; M: monophasic; R: relapsing; NI: not informed; OB: oligoclonal bands; Br: brain; SC: spinal cord; N: normal; Abn: abnormal; LSCL: long spinal cord lesion; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.

Table 2. Wingerchuk's 1999 diagnostic criteria for neuromyelitis optica[8].

Absolute criteria (all required)	Supportive criteria (either 1 major criterion or 2 minor criteria)	
	Major supportive criteria	Minor supportive criteria
Optic neuritis Acute myelitis No evidence of clinical disease outside of the optic nerve and spinal cord	Negative brain MRI at onset (does not meet Paty radiological criteria for MS) Spinal cord MRI with signal abnormality extending over >3 vertebral segments CSF pleocytosis of >50 WBC/mm^3 OR >5 neutrophils/mm^3	Bilateral optic neuritis Severe optic neuritis with fixed VA worse than 20/200 in at least one eye Severe, fixed, attack-related weakness (MRC grade <2) in one or more limbs

CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; WBC: white blood cells; VA: visual activity; MRC: Medical Research Council scale.

CURRENT DEFINITION OF SPECTRUM OF NEUROMYELITIS OPTICA

Aquaporin-4 IgG seropositivity status in patients whose clinical features do not meet current diagnostic criteria for definite NMO has led to the recognition of the disease as a spectrum of CNS AQP4 autoimmune disorders rather than a well-defined restrictive condition in which occurrence of both optic neuritis and acute transverse myelitis is an absolute requisite for NMO diagnosis[13]. As a matter of fact, 19–31% of seropositive patients had the limited form of NMO[14-16], and in one study 20% of the seropositive patients did not fulfill the 2006 diagnostic criteria even over ten years following disease presentation[17].

Current definition of spectrum of NMO disorders encompasses conditions in patients who have in addition to serum anti-AQP4 antibodies at least one of the key clinical elements for diagnosis of NMO (idiopathic myelitis extending over ≥3 vertebral segments, or bilateral simultaneous or recurrent optic neuritis)[18]. It also recognizes the association of optic neuritis or longitudinally extensive transverse myelitis (LETM) with systemic autoimmune disorders, as well as with brain MRI lesions that are now considered as typical of neuromyelitis optica (Table 4)[18].

Requirement of AQP4 seropositivity status as a pitfall for the definition of neuromyelitis spectrum disorders (NMOSD)

As the current concept of NMOSD is based on the concomitance of AQP4-IgG seropositive status and one of the index events lacks of, any of these requisites rules out the diagnosis. On the other hand, it has been observed that even the most refined AQP4-IgG assays fail to detect serum antibodies in a proportion of patients who fulfill the revised diagnostic criteria for NMO. Although the underlying mechanisms of AQP4-IgG seronegative status in these patients remain to be clarified, presumed reasons include suboptimal sensitivity of the currently available assays, very low serum concentration of the antibodies or their absence at some periods in the disease course, and the inhibitory effect of previous treatment with corticosteroids or immunosuppressive agents[19]. It is also possible that in some NMO patients other antigens may play a role in the pathogenesis of the disease[18,20]. Therefore, notwithstanding a positive serum AQP4-IgG test is of utmost importance for the diagnosis of NMOSD, a negative result alone cannot rule out the diagnosis.

Table 3. Revised diagnostic criteria for neuromyelitis optica, 2006[13].

Definite NMO
Optic neuritis
Acute myelitis
At least two of three supportive criteria
1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status

NMO: neuromyelitis optica; MRI: magnetic resonance imaging.

Table 4. Neuromyelitis optica spectrum[18].

Neuromyelitis optica
Limited forms of neuromyelitis optica
• Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord lesion seen on MRI)
• Optic neuritis: recurrent or simultaneous bilateral
Asian optic-spinal multiple sclerosis
Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease
Optic neuritis or myelitis associated with brain lesions typical of neuromyelitis optica (hypothalamic, corpus callosal, periventricular, or brainstem)

MRI: magnetic resonance imaging.

Aquaporin 4-IgG assays

Serum AQP4-IgG can be detected in the sera of NMO patients by a variety of techniques[21]. The antibody was first identified among 102 North American patients with NMO or syndromes that suggest high risk of NMO and 12 Japanese patients with optic-spinal multiple sclerosis (OSMS) by indirect immunofluorescence with a composite substrate of mouse tissues[9]. Sensitivity and specificity were 73 and 91% for NMO and 58 and 100% for OSMS, whereas the antibody was found in 50% of patients with high-risk syndromes[9]. The serum antibody has been variably detected in different populations[22]. Currently available assays include a tissue-based indirect immunofluorescence (IIF) assay; ELISA; fluorescence immunoprecipitation assay (FIPA)[23,24]; fluorescence-activated cell sorting (FACS) assay; and visual fluorescence-observation cell-based assay (CBA)[24-26]. A recent international comparative study of the different techniques to detect AQP4-IgG in sera of patients with NMO and NMOSD showed that, although their specificities were excellent, their sensitivities were variable[27]. Whereas the most sensitive techniques were human AQP4-transfected cell-based assays (73–77%), fluorescence immunoprecipitation assay (FIPA) and the mouse tissue-based indirect immunofluorescence assay were the least sensitive (around 50%)[27]. The commercially introduced ELISA which is a simple and relatively sensitive technique may make AQP4-IgG serum assessment more widely available[28].

Requirement of optic neuritis or myelitis presence as a pitfall for the definition of neuromyelitis spectrum disorders

Requirement of presence of either optic neuritis or LETM is a second pitfall in the current definition of NMOSD. It has been now well established that brain symptoms are not only frequent during disease course (Table 5), but may antedate optic neuritis or acute transverse myelitis for months or years[17,29]. Incoercible vomiting and hiccups result from involvement of the area postrema at the floor of the fourth ventricle. In addition to being the

vomiting reflex center[27], area postrema also plays an important role in the regulation of blood pressure, cerebral blood flow and osmolarity[30,31]. This region highly expresses AQP4[32-35] and is more susceptible to frequent attacks by anti-AQP4 antibodies as it lacks blood-brain barrier. Intractable hiccups, nausea and vomiting are the most frequent brain symptoms in NMO, preceding and accompanying optic neuritis or acute myelitis[36].

A number of hypothalamic symptoms, such as narcolepsy with decreased hypocretin-1 CSF level, anorexia and weight loss, hyperphagia and obesity, hypothermia or fever of unknown etiology, syndrome of inappropriate secretion of antidiuretic hormone, diffuse anhydrosis, bradycardia and hypotension, as well as recurring episodes of coma, have all been described in association with NMOSD[32,37-41]. Interestingly, enough in some patients, these symptoms have been observed preceding optic neuritis or myelitis, whereas in others they occurred in association with both AQP4-IgG seropositivity and hypothalamic abnormalities on brain MRI, but with no subsequent development of optic neuritis or myelitis[40-43].

Symptoms of encephalopathy may also occur in patients with established diagnosis of NMO or may in some patients precede the onset of optic neuritis or myelitis. Development of posterior reversible encephalopathy syndrome (PRES) in NMO patients has been ascribed to occurrence of transient vasogenic edema in areas with increased blood-brain permeability as a result of disruption of the normal water flux due AQP4 autoimmunity. Symptoms of PRES include confusion, decreased consciousness and coma, ocular movement disturbances, retrochiasmal visual field defects and cortical blindness, seizures and aphasia[44,45].

Decreased mental status, impairment of consciousness, confusion and seizures have been reported as presenting symptoms of AQP4 autoimmunity. Optic neuritis or myelitis followed the cerebral symptoms at a variable time interval ranging from 3 to 110 months[41,46,47].

Table 5. Brain symptoms in neuromyelitis optica

Brainstem symptoms	• Hiccups • Nausea, vomiting • Vertigo • Dysarthria, dysphagia • Ataxia • Ocular movement disorders • Facial paralysis • Facial pain or dysesthesia • Hearing loss, tinnitus
Hypothalamic symptoms	• Narcolepsy and other sleep disorders • Anorexia and weight loss • Hyperphagia and obesity • Disturbances of body temperature • Anhydrosis • Inappropriate secretion of antidiuretic hormone syndrome • Hypotension • Bradycardia • Excessive sweating • Symptoms of hypopituitarism • Presyncopal symptoms • Recurrent coma
Cortical/subcortical symptoms	• Posterior reversible encephalopathy syndrome • Aphasia • Seizures • Disturbances of consciousness • Psychiatric symptoms • Cognitive symptoms

Typical brain MRI lesions in neuromyelitis optica

Following identification of AQP4-IgG, it was observed that 60% of the NMO patients presented signal abnormalities on brain MRI. Most of these abnormalities were non-specific lesions, 10% were multiple sclerosis-like lesions and 8% were lesions atypical of MS[32]. Although NMO MRI lesions may fulfill the current MS spatial dissemination criteria[48], subsequent studies have further characterized the MRI findings in NMO patients, showing distinctive features which help to differentiate NMOSD brain lesions from those characteristically found in MS patients[49-55].

The most distinctive brain lesions found on MRI of patients with NMOSD are listed below and illustrated by examples in Figure:

1. Extensive and confluent hemispheric white matter lesions which may be edematous, tumefactive and have a radial-shaped or spindle-like form. These lesions may shrink or disappear in subsequent studies.
2. Corticospinal tract lesions, frequently bilateral, involving the posterior limb of the internal capsule and the cerebral peduncle, which are usually longitudinally extensive following the pyramidal tract from subcortical area to the mesencephalon or pons.
3. Gadolinium-enhanced lesions with heterogeneous intensity and poor-defined borders (cloud-like lesions).
4. Lesions localized at sites of high AQP4 expression, such as the hypothalamus, and the ependymal surface around the third ventricle, aqueduct and fourth ventricle.
5. Lesions lining the ependymal surface of the lateral ventricles, sometimes involving the corpus callosum or the cerebrum.
6. Large edematous and heterogenous lesions in the corpus callosum, with higher intensity in the rim and lower in the core (marble-like lesions) in the acute phase, and reduction in their size and intensity, or its disappearance in the chronic phase.
7. Brainstem lesions that most frequently involve its central and dorsal aspects, including area postrema and nucleus tractus solitarius. These lesions may be associated with intractable vomiting and hiccups and may extend caudally to the upper cervical spinal cord.

Unspecific white matter lesions have been described on brain MRI in 68% of NMO patients and on conventional

MRI they do not differ from those found in MS patients[32]. However, a recent study showed that, by making use of 7-T MRI scans, these unspecific lesions as seen on conventional MRI are quite distinct in NMOSD and MS[56]. They differ with regard to their location and expression of a hypointense rim. Whereas 92% of the MS plaques are centered by a small vein and express a hypointense rim, only one third of the white matter lesions in NMOSD have perivascular localization. Additionally, they rarely show the characteristic hypointense rim. A further differential feature between NMOSD and MS was the failure to find cortical lesions in NMOSD, as opposed to identification of lesions at this location in over one-half of the MS patients[56].

The strict and the expanded concept of the spectrum of neuromyelitis optica

The continued advances in the understanding of the NMO pathophysiology, the use of more refined MRI techniques and the development of more sensitive anti-AQP4 antibody assays associated and their broader availability to investigators around the world have all led to a rapid and deep change in the concept of the spectrum of NMO. The identification of a large number of patients with AQP4-IgG seropositive status who do not meet the 2007 definition of NMOSD suggests that a wider range of clinical phenotypic presentations have to be included in an expanded spectrum of NMO. The increasing number of reported "atypical NMO cases" or of patients with "cerebral aquaporin

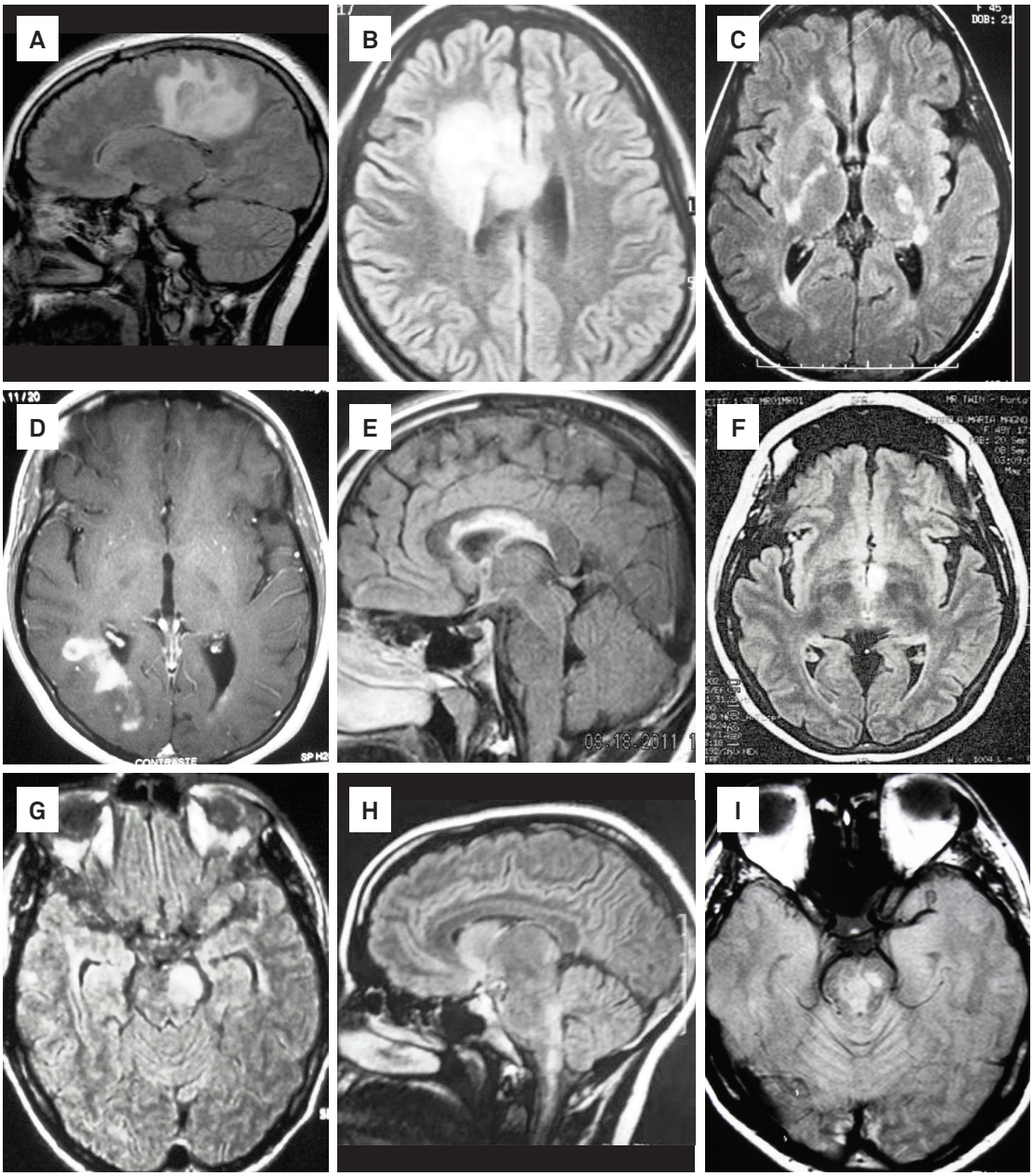

Figure. Typical brain magnetic resonance imaging in neuromyelitis optica. (A) Extensive edematous white matter lesion. (B) Tumefactive frontal lobe lesion. (C) Bilateral lesions in the posterior limb of the internal capsule. (D) Cloud-like gadolinium-enhanced lesion. (E) Heterogeneous extensive callosal lesion. (F) Bilateral lesions in the hypothalamus. (G) Large mesencephalic lesion. (H) Lesion involving area postrema. (I) Central brainstem lesion.

autoimmunity" in whom AQP4-IgG seropositive status is associated with symptoms of encephalopathy, hypothalamic or brainstem involvement, either preceding for months or years the development of myelitis or optic neuritis, or occurring as an isolated clinical phenomenon — i.e., with no past or present evidences of optic neuritis or myelitis — suggests that the 2007 definition of the spectrum of NMO is in need of expansion.

Optic neuritis and acute transverse myelitis usually have well-defined characteristics in patients with definite NMO. Most frequently, optic neuritis is recurrent or simultaneously occurs on both sides, severely affects the visual functions and may respond poorly to corticosteroid treatment. On its turn, acute transverse myelitis in NMO is typically longitudinally extensive and preferentially affects the central part of the cord or its entire diameter, showing an edematous tumefactive aspect in the acute phase. Only in few cases these features cannot distinguish optic neuritis and acute transverse myelitis found in NMOSD from those occurring in MS or other conditions[55-57]. In these instances, appropriate workup including brain MRI, CSF analysis, as well as specific tests for other conditions, help to define the diagnosis.

The finding of AQP4-IgG seropositive status in patients with recurrent or simultaneous bilateral optic neuritis or with LETM would make them meet present definition of NMOSD. However, the majority of patients who develop these symptoms are AQP4-IgG seronegative by currently available assays and, therefore, do not fulfill the accepted definition of spectrum of NMO. Some of them will present a second index event of the disease later on and may even convert to seropositive status during the course of their disease. Likewise, patients with cerebral symptoms not associated with recurrent optic neuritis or LETM will not be included in the current spectrum of NMO notwithstanding the possibility of their being AQP4-IgG seropositive or having brain MRI lesions typical of NMO.

Table 6. Expanded spectrum of neuromyelitis optica

Conditions with at least 1 of the following:
• Single, recurrent or simultaneous bilateral optic neuritis
• Longitudinally extensive myelitis (≥3 vertebral segments)
• Recurrent brainstem symptoms
• Recurrent hypothalamic symptoms
• Recurrent cerebral symptoms
Plus at least 1 of the following:
• Positive AQP4-IgG serum status
• Brain MRI lesions typical of neuromyelitis optica

MRI: magnetic resonance imaging; AQP4: aquaporin-4.

It would be highly desirable if all these patients could be recognized as part of an expanded spectrum of NMO as prophylactic treatment may preserve them from a subsequent and potentially disabling attack of the disease. Brain MRI lesions typical of NMO may be considered as an alternate supportive evidence for the diagnosis of NMOSD in patients with recurrent optic neuritis, LETM, recurrent brainstem, hypothalamic or encephalopathy symptoms, and AQP4-IgG seronegative status (Table 6).

Although this proposed expanded spectrum of NMO incorporates some non-conventional presentations of the disease, the full phenotypic components of the disease spectrum remain to be identified through better understanding of its immunopathogenetic mechanisms and development of more sensitive biomarkers.

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