

Complexity and wide range of neuromyelitis optica spectrum disorders: more than typical manifestations

Jinming Han¹
Meng-ge Yang¹
Jie Zhu^{1,2}
Tao Jin¹

¹Department of Neurology and Neuroscience Center, The First Hospital of Jilin University, Changchun, China; ²Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Stockholm, Sweden

Abstract: Neuromyelitis optica (NMO), considered to be mediated by autoantibodies, often cause severely disabling disorders of the central nervous system, and predominantly cause optic nerve damage and longitudinally extensive transverse myelitis. Remarkable progress has been made in deciphering NMO pathogenesis during the past decade. In 2015, the International Panel for NMO Diagnosis proposed the unifying term “NMO spectrum disorders” (NMOSD) and the updated NMOSD criteria reflects a wide range of disease and maintains reasonable specificity. Moreover, cumulative findings have indicated that NMOSD are frequently associated with multiple autoimmune diseases, thereby presenting complex clinical symptoms that make this disease more difficult to recognize. Notably, most neurologists do not heed these symptoms or comorbid conditions in patients with NMOSD. Whereas previous reviews have focused on pathogenesis, treatment, and prognosis in NMOSD, we summarize the present knowledge with particular emphasis on atypical manifestations and autoimmune comorbidities in patients with NMOSD. Furthermore, we emphasized the identification of these atypical characteristics to enable a broader and better understanding of NMOSD, and improve early accurate diagnosis and therapeutic decision making.

Keywords: neuromyelitis optica spectrum disorders, anti-aquaporin-4 antibody, comorbid conditions, atypical manifestations

Introduction

Neuromyelitis optica (NMO) is an inflammatory disorder of the central nervous system (CNS), which typically presents with clinical signs of optic nerve damage and longitudinally extensive transverse myelitis.¹⁻³ The discovery of aquaporin-4 immunoglobulin G antibody (AQP4-IgG) as a highly specific biomarker for NMO has substantially changed our understanding of NMO immunopathogenesis and revolutionized its diagnostic criteria.⁴⁻¹⁰ In 2015, the International Panel for NMO Diagnosis discarded the term “NMO” for a unifying term “NMO spectrum disorders” (NMOSD).⁵ Serum, and not cerebrospinal fluid AQP4 antibody, plays a central role in the diagnosis of NMOSD in clinical practice at present.¹¹⁻¹³ The revised criteria encompass the core clinical characteristics, namely optic neuritis, acute myelitis, area postrema syndrome (episodes of otherwise unexplained hiccups, nausea, and vomiting), acute brainstem syndrome, symptomatic narcolepsy, or acute diencephalic clinical syndrome with NMOSD-typical diencephalic magnetic resonance imaging (MRI) lesions and a symptomatic cerebral syndrome with NMOSD-typical brain lesions.^{1,5} Moreover, the revised criteria enable the diagnosis of seronegative NMOSD when other supportive clinical and imaging features are present.^{5,14} More importantly, the updated NMOSD

Correspondence: Tao Jin
Department of Neurology and Neuroscience Center, The First Hospital of Jilin University, 71 Xinmin Street, Changchun 130021, China
Tel +86 8878 2378
Email drtao.jin@hotmail.com

criteria reflects a wide range of disease and maintains reasonable specificity. Whereas unexplained hiccups, nausea, vomiting, and symptomatic narcolepsy were earlier considered atypical presentations of NMOSD,^{15,16} these constitute the core clinical characteristics in the present diagnostic criteria.⁵ There is widespread consensus that NMOSD are frequently associated with multiple autoimmune diseases, thereby presenting complex clinical symptoms. In this vein, we have begun to recognize several rare but possible manifestations and overlapping autoimmune diseases in patients with NMOSD.¹⁷ However, these symptoms and comorbid conditions in patients with NMOSD have not aroused much concern among clinical neurologists. This review attempts to present a new message and summarize the present state of knowledge on these significant atypical presentations and comorbid conditions in patients with NMOSD.

What are the typical manifestations of NMOSD?

Rationally, an understanding of the typical clinical features of NMOSD should precede a discussion of atypical presentations. NMOSD preferentially affect the optic nerve and spinal cord. Thus, acute myelitis and optic neuritis are the typical manifestations throughout the duration of the disease. It is highly possible that severe residual visual loss is particularly suggestive of NMOSD. Based on present diagnostic criteria, NMOSD could be further classified into NMOSD with or without AQP4 antibody.⁵ The updated and expanded criteria markedly improve the diagnostic yield by well reflecting a broader clinical spectrum of NMOSD, when compared with the previous criteria.^{12,18} Under the revised criteria, certain clinical manifestations are particularly suggestive of NMOSD, including area postrema clinical syndrome, simultaneous bilateral optic neuritis, optic neuritis that involves the chiasm, and complete transverse myelitis.¹⁹ In addition, clinical and laboratory “red flags” have been well-established to describe several features that signal the possibility of alternative diagnoses.^{5,20–23}

The complexity and wide range of NMOSD

Increasing incidences of uncommon manifestations and signs in patients with NMOSD have been recently reported (Table 1).^{24–36} Although these are not considered to typify NMOSD in the present diagnostic criteria, these manifestations and signs may potentially promote a better understanding of this complex disease. A high frequency of brainstem symptoms could be observed in patients with NMOSD,

Table 1 Rare manifestations in patients with NMOSD

Rare manifestations	References
Brain cortical lesions	Tahara et al, ⁴⁵ Kim et al, ⁴⁶ Han et al ⁴⁸
Epileptic seizures	Cheng et al, ⁵⁹ Nakano et al ⁶⁰
Intractable pruritus	El Otmani et al, ⁷⁵ Xiao et al, ⁷⁶ He et al, ⁷⁷ Netravathi et al, ⁷⁸ Ramasamy et al ⁷⁹
Raynaud's phenomenon	Sergio et al, ⁸² Martin et al, ⁸³ Franciotta et al, ⁸⁴ Jacobi et al ⁸⁵
Cervicogenic headache	Masters-Israilov and Robbins ²⁷
Bilateral hand edema	Sergio et al ⁸²
Erythematous rash	Cooper et al ⁸¹
Pathologic laughing	Ahn et al ²⁵
Hemiageusia	Wang et al ²⁶
Trigeminal autonomic cephalgia	Mathew et al ⁷¹
Hydrocephalus	Clardy et al ²⁴
Sclerodactyly	Parperis ⁸⁰
Horner syndrome	Uludag et al ²⁸
Wernicke commissure syndrome	Zou and Chen ²⁹
Wall-eyed bilateral internuclear ophthalmoplegia	Zou and Chen ²⁹
Hearing loss	Tanaka and Tanaka ³⁰
HyperCKemia	He et al, ³¹ Iyer et al, ³⁶ Guo et al, ³⁵ Abkur et al ³⁴
Paroxysmal sneezing	Lopez-Chiriboga et al ³²

Abbreviation: NMOSD, neuromyelitis optica spectrum disorders.

particularly vomiting, hiccups, oculomotor dysfunction, and pruritus, followed by hearing loss, facial palsy, vertigo, and vestibular and trigeminal neuralgia.³⁷ Some atypical manifestations and comorbid conditions in patients with NMOSD will be discussed below, aiming to update the knowledge of clinical neurologists.

Brain cortical lesions in NMOSD

The pattern of brain lesions observed in NMOSD differs from that in multiple sclerosis (MS), and its appearance in characteristic locations facilitates the diagnosis of NMOSD.^{38,39} Pathologic and imaging studies sensitive to brain cortical lesions have revealed that these lesions are absent in Western patients with NMOSD.^{40–43} Previous studies have also reported that cognitive and cortical neuroimaging abnormalities in NMOSD are not attributable to cortical demyelination.⁴⁴ To date, the absence of cortical lesions has been considered a “red flag” in the diagnosis of NMOSD. However, brain lesions that involve the cerebral cortex in NMOSD have been found in clinical practice among Asians, albeit very rarely. Tahara et al reported that three Japanese patients with anti-AQP4 antibody-positive NMOSD and encephalopathy-like symptoms exhibited brain cortical abnormalities on MRI, which were potentially attributable to the functional involvement of the cerebral cortex.⁴⁵ Furthermore,

Kim et al retrospectively analyzed 215 Korean NMOSD patients with AQP4 antibody. The infiltration of inflammatory cells across the damaged blood–brain barrier and leptomeningeal blood barrier into the adjacent cortex could be the possible explanation of brain cortical lesions in NMOSD.^{46,47} More recently, we noted identical findings and cortical demyelinating lesions could also be seen in a Chinese patient of NMOSD without AQP4 antibody.⁴⁸ It was hypothesized that cortical demyelinating lesions in patients with NMOSD may be more commonly observed in East Asian populations than in Western populations, because the prevalence of NMOSD is considerably lower in regions that comprise mainly of Caucasians. Another possible explanation could be that differences exist with regard to the pathogenesis of NMOSD between patients of Eastern and Western origins.

More importantly, the possibility of alternative diagnoses must be considered by clinical neurologists. For example, NMOSD overlapping autoimmune encephalitis has been increasingly recognized and reported.^{49–51} Autoimmune encephalitis is also a severe inflammatory disorder mediated by antibodies against neuronal cell surface or synaptic proteins. Memory deficits, psychiatric symptoms, brain cortical lesions, behavioral disturbances, and decreased level of consciousness are typical of autoimmune encephalitis.⁵² In addition, alternative diagnoses such as Susac syndrome should also be ruled out during follow-up.⁵³ Furthermore, Luo et al reported on a patient with anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis that occurred sequentially with NMOSD. The patient initially presented with cortical lesions in the brain MRI that bilaterally involved the medial temporal lobes.⁴⁹ For this reason, the clinical diagnosis of NMOSD with brain cortical lesions should be considered with caution without excluding resembling diseases. Recognizing and accurately diagnosing autoimmune encephalitis coexisting with NMOSD, particularly patients who mainly present with brain cortical involvement, remain challenging for clinical neurologists.⁵⁴ Further evaluations are needed to push the boundaries of NMOSD diagnosis through advanced MRI techniques or pathological investigations that reveal the characteristics of cortex involving lesions in NMOSD.⁵⁵

Epileptic seizures

Epileptic seizures are not rare and have a greater incidence in patients with MS than in the general population.^{56–58} However, epileptic seizures as early symptoms are rarely presented in patients with NMOSD. For example, none of the patients developed any seizures in a study of 69 Chinese patients with

NMOSD, giving rise to speculations that seizures may be an atypical presentation in NMOSD.⁵⁹ However, a contradictory finding has been reported that patients with NMOSD may possibly have a higher risk of developing epileptic seizures compared to the general population.⁶⁰ Furthermore, Nakano et al reported higher expanded disability status scale scores for NMOSD patients with seizures, suggesting a poorer prognosis compared with patients without seizures.⁶⁰ A possible explanation for the association between epileptic seizures and NMOSD is that severe prominent inflammation and axonal damage in NMOSD may cause epileptic seizures.

Furthermore, a subset of patients with NMOSD and positive for myelin oligodendrocyte glycoprotein (MOG) may further extend the spectrum of clinical phenotypes than we had previously thought.^{61–65} More recently, researchers have reported that MOG-IgG is closely correlated to generalized epileptic seizure and unilateral cerebral cortical encephalitis.⁶⁶ Further studies are warranted to characterize the clinical features of epileptic seizures in patients with NMOSD, in order to reveal the mechanism underlying the development of epileptic seizures.

Intractable pruritus

Pruritus can be viewed as an unpleasant sensation which provokes a desire to scratch and relieve the symptom.⁶⁷ Pruritus and pain have been known to closely interact.⁶⁸ We are beginning to reach the realization that sensory symptoms including neuropathic pain, painful tonic spasms, and trigeminal autonomic cephalalgia constitute presenting features in patients with NMOSD.^{69–74} However, the symptom of intractable pruritus in patients with NMOSD does not cause much concern among clinical neurologists. In fact, 12 patients reported pruritus during their illness in a well-defined cohort of 45 British patients with NMOSD.⁷⁵ In this regard, Xiao et al retrospectively analyzed 64 Chinese NMOSD patients who were AQP4-IgG positive, and found that 28% (18/64) of these patients had the symptom of pruritus.⁷⁶ Furthermore, recent studies have reported identical findings and further revealed that pruritus can be detected as an initial symptom before the attack. Hence, this may indicate a new episode of myelitis in patients with NMOSD.^{77,78} Although it has only been supported by case reports so far, intractable pruritus could be an underestimated characteristic feature of NMOSD. Several possible mechanisms could explain intractable pruritus as a symptom in patients with NMOSD. First, the inflammatory involvement of dorsal horn neurons in the spinal cord, spinal nucleus of the trigeminal nerve, or periaqueductal pathways may subsequently induce

an itching sensation.^{77,79} Second, a partial demyelinating lesion insufficient to produce a permanent neurological deficit might cause minor irritation of the surrounding axons, leading to paroxysmal pruritus. This reflects the typical centralized location of lesions in the spinal cord that affects dorsal horn neurons and gray matter in patients with NMOSD.⁷⁶ A third possible mechanism may be that neurons involved in the regulation of neuropathic pruritus may highly express AQP4, and thereby be preferentially involved in NMOSD.⁷⁵

Cutaneous manifestations

Nonspecific cutaneous manifestations such as erythematous rash, sclerodactyly, and bilateral edema of the hands have been noted in the setting of NMOSD, although these have been limited to isolated case reports.^{80–82} Among these, Raynaud's phenomenon was the most common cutaneous presentation in patients with NMOSD.^{82–85} These case studies highlight the importance of the early recognition of cutaneous signs, which may help optimize clinical neurologists' decision making. Martin et al reported the case of a 60-year-old Chinese patient who initially presented with nonspecific cutaneous findings such as Gottron's papules and bilateral hand edema. However, it was finally found that the patient had features of overlapping autoimmune diseases, including rheumatoid arthritis and amyopathic dermatomyositis in the setting of NMOSD with AQP4-IgG.⁸³ Furthermore, Delman et al recently reported dermatomyositis as a clinical presentation in a 40-year-old Caucasian NMOSD patient with AQP4-IgG. The patient also tested positive for anti-melanoma differentiation-associated gene 5 antibody, which is one of the most common dermatomyositis-specific antibodies.⁸⁶ Therefore, clinical neurologists must focus more attention on these clinical features and antibody testing for additional overlapping autoimmune diseases.

NMOSD coexisting with subacute combined degeneration

NMOSD is often idiopathic, although it has been strongly associated with other autoimmune diseases and non-organ-specific autoantibodies (Table 2).^{34–36,87–101} Apparently, NMOSD is not related to subacute combined degeneration to some extent. Interestingly, Ishii et al reported the case of a 36-year-old Japanese woman who simultaneously had NMOSD with AQP4-IgG and subacute combined degeneration.¹⁰² Cervical MRI revealed that long cord lesions around the central spinal canal were typical for NMOSD. MRI scans also revealed bilateral symmetric hyperintense signals in posterior columns, which are the so-called "inverted V" sign in patients

Table 2 Coexisting conditions associated with NMOSD

Comorbid conditions	References
Subacute combined degeneration	Ishii et al ¹⁰²
Autoimmune encephalitis	Luo et al, ⁴⁹ Qin et al, ⁵⁰ Ran et al ⁵¹
Idiopathic intracranial hypertension	Viswanathan and Wong ⁸⁷
Hematological immune disease	Patejdl et al ⁸⁸
Thrombopenic purpura	Wang et al ⁸⁹
Hypertrophic pachymeningitis	Kon et al ⁹⁰
Postural orthostatic tachycardia syndrome	Barun et al ⁹¹
Osmotic demyelination syndrome	Adamec et al ⁹²
Posterior reversible encephalopathy syndrome	Magana et al ⁹³
Autoimmune lymphoproliferative syndrome	Cooper et al ⁸¹
Systemic sclerosis	Pereira et al ⁹⁴
Systemic lupus erythematosus	Pereira et al, ⁹⁴ Asgari et al ⁹⁵
Sjögren's syndrome	Zhong et al, ⁹⁶ Kahlenberg, ¹⁰⁸ Jayarangaiah et al, ¹⁰⁹ Qiao et al, ¹¹¹ Birnbaum et al ¹¹²
Mixed connective tissue	Parperis ⁸⁰
Hashimoto thyroiditis	Pereira et al ⁹⁴
Myasthenia gravis	Ikeguchi et al, ⁹⁷ Jarius et al ¹⁰¹
Dermatomyositis	Martin et al ⁸³
Bacterial meningomyelitis	Li et al ⁹⁸
Celiac disease	Matijaca et al ⁹⁹
Spinocerebellar ataxia type 31	Takahashi et al ¹⁰⁰

Abbreviation: NMOSD, neuromyelitis optica spectrum disorders.

with subacute combined degeneration.¹⁰² Furthermore, vitamin B12 deficiency may be associated with AQP4-IgG in this patient, in view of no prior history of gastrointestinal disorders. Recent studies have highlighted that low levels of vitamin B12 were found in NMOSD patients with AQP4-IgG.¹⁰³ It is a well-established fact that AQP4 is not only mainly expressed in astrocytes within the CNS, but also in diverse organs such as the stomach, skeletal muscle, inner ear, and kidneys.^{17,104} Thus, AQP4-IgG may inhibit the production of intrinsic factor and gastric acid secretion by parietal cells with resultant vitamin B12 malabsorption. In summary, the presence of AQP4 receptors outside the CNS may help explain some of the unusual features of NMOSD. It is highly desirable that physicians note this atypical phenomenon in clinical practice.

NMOSD coexisting with anti-NMDAR encephalitis

Anti-NMDAR encephalitis is also a severe autoimmune disease that has been commonly associated with the production of antibodies against NMDAR.^{52,105} NMOSD in coexistence with anti-NMDAR encephalitis is relatively rare, but cannot be ignored as a possibility.¹⁰⁶ A previous study revealed that NMDAR autoimmunity is in fact not involved in NMOSD

because a total of 98 NMOSD patients with AQP4-IgG showed negative results for NMDAR antibodies.¹⁰⁷ However, recent studies have inferred the opposite conclusion that NMOSD overlapping anti-NMDAR encephalitis is increasingly noted, as evidenced by the simultaneous detection of both NMDAR antibodies and AQP4-IgG in serum samples.^{49–51} In 2017, Ran et al succinctly summarized the clinical characteristics of 34 patients who presented with both NMOSD and anti-NMDAR encephalitis.⁵¹ Among these patients, some who presented with obvious symptoms of anti-NMDAR encephalitis at onset subsequently manifested concurrent or separate episodes of NMOSD during the following time. Conversely, some patients with NMOSD in the early stages subsequently presented with anti-NMDAR encephalitis, while others simultaneously suffered from NMOSD and anti-NMDAR encephalitis during the disease period. The possibility of a direct or indirect connection between these two immune-mediated disorders was also proposed, which predisposes its susceptibility to other autoimmune-associated disorders.⁵¹ Further studies are still needed to thoroughly investigate the association between NMOSD and anti-NMDAR encephalitis.

NMOSD coexisting with Sjögren's syndrome (SS)

SS is a chronic systemic illness typically characterized by the dysfunction and inflammatory infiltration of the exocrine glands. Although it has been increasingly recognized that SS mimics and coexists with NMOSD, distinguishing between these two disorders has been proven to be difficult for neurologists and rheumatologists.^{108,109} Specifically, patients with SS can commonly experience extraglandular manifestations such as CNS involvement, and appear as transverse myelitis, optic neuritis, and brain abnormalities, which complicate the diagnosis.¹¹⁰ Qiao et al retrospectively analyzed 616 patients with SS in a Chinese single center study and found that 7% (43/616) of these patients had coexisting NMOSD. Based on this finding, they hypothesized that NMOSD and SS in fact share common pathophysiological features and that NMOSD is a neurological complication of SS.¹¹¹ However, contradictory findings have been reported that the complex relationship between NMOSD and SS can be attributed to co-occurring autoimmunity, instead of directly implicating CNS involvement in patients with SS. Researchers revealed that AQP4 antibodies were only detected in SS with NMOSD versus non-NMOSD patients with SS.¹¹² In addition, AQP5 rather than AQP4 contributes to salivary secretion in SS patients with NMOSD.¹¹³

Moreover, another recent study found that patients with NMOSD and SS have higher non-organ-specific antibodies and enhanced autoimmune responses compared to non-SS patients with NMOSD.⁹⁶ Hence, only sufficient knowledge of NMOSD patients with and without SS could facilitate prompt recognition and decision making for this condition.

Conclusion

Some atypical manifestations and comorbid conditions in NMOSD have been reported as rare events, but may represent a broader spectrum of symptoms, compared to those previously described in conventional descriptions. The awareness that NMOSD is frequently associated with other autoimmune diseases is important to facilitate specific antibody testing when diagnosing cases with an associated autoimmune disease. Ruling out other entities during follow-up is of importance for clinical neurologists. Future studies with larger NMOSD cohorts may confirm the accumulated knowledge base from these case series, and identify additional clues with regard to the heterogeneous features of NMOSD. This calls for greater efforts in identifying its etiopathogenic mechanisms in NMOSD patients with atypical manifestations and comorbidities, in order to broaden our knowledge of this complex disease spectrum. We believe that research on NMOSD in the next decade will promise to be as exciting as that in the past decade.

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Disclosure

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