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Finding NMO: The Evolving Diagnostic Criteria of Neuromyelitis Optica

Jeffrey L. Bennett, MD, PhD

Departments of Neurology, Ophthalmology, and Program in Neuroscience, University of Colorado Denver, Aurora, Colorado

Abstract

Neuromyelitis optica (NMO) is an autoimmune demyelinating disorder of the central nervous system (CNS) with predilection for the optic nerves and spinal cord. Since its emergence in the medical literature in the late 1800's, the diagnostic criteria for NMO has slowly evolved from the simultaneous presentation of neurologic and ophthalmic signs to a relapsing or monophasic CNS disorder defined by clinical, neuroimaging, and laboratory criteria. Due to the identification of a specific autoantibody response against the astrocyte water channel aquaporin-4 (AQP4) in the vast majority of affected individuals, the clinical spectrum of NMO has greatly expanded necessitating the development of new international criteria for the diagnosis of NMO spectrum disorder (NMOSD). The routine application of new diagnostic criteria for NMOSD in clinical practice will be critical for future refinement and correlation with therapeutic outcomes.

NEUROMYELITIS OPTICA: A CLINICAL DIAGNOSIS

Neuromyelitis optica (NMO) is a rare inflammatory disorder of the central nervous system (CNS) that commonly presents with either monophasic or recurrent attacks of optic neuritis (ON) and transverse myelitis (TM) (1,2). The first clinical account of presumed NMO is often attributed to Sir Clifford Allbutt, a pioneering physician who promoted the adoption of the direct ophthalmoscope in clinical practice (3). However, even before Albutt's seminal publication, "On the Ophthalmoscopic Signs of Spinal Disease," clinicopathologic reports of individuals with concurrent vision loss and myelitis by Antoine Portal in 1804, Giovanni Pescetto in 1844, and Jacob Clarke in 1865 likely represent the earliest accounts of NMO in the literature (4). The term "neuro-myélite optique aiguë" was originally coined in 1894 by Eugene Devic and Fernand Gault when they presented a case of concurrent ON and TM and reviewed 16 additional cases from the literature (5). Although their initial article included patients with simultaneous and relapsing episodes of ON and TM, NMO was initially defined as a monophasic disorder. Interestingly, in the early 1900s, more than 100 cases had been reviewed in the literature, and an increasing number of relapsing cases were reported (6).

Address correspondence to Jeffrey L. Bennett, MD, PhD, Department of Neurology, University of Colorado Denver, 12700 E. 19th Avenue, Box B-182, Aurora, CO 80045; jeffrey.bennett@ucdenver.edu.

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Wingerchuk et al (2) performed the first systematic evaluation of the demographics, clinical presentation, neuroimaging, and cerebrospinal fluid (CSF) in cases of monophasic and relapsing NMO. “Strict” NMO was defined as bilateral ON and TM occurring within a 2-year interval, whereas NMO “not meeting strict criteria” included cases of unilateral ON or recurrent demyelinating events occurring over greater than a 2-year period. Relapsing cases of NMO, which outnumbered monophasic cases by two-fold, were defined by the occurrence of additional clinical attacks outside the incident event. Although demographics distinguished monophasic and relapsing patients with NMO, common clinical, imaging, and CSF findings allowed the first modern diagnostic criteria to be proposed (Table 1). Several tenets of the 1999 NMO criteria persist in subsequent criteria including the clinical hallmarks of ON and TM, and also spinal cord magnetic resonance imaging (MRI) demonstrating a signal abnormality extending over 3 vertebral segments (longitudinally extensive TM, LETM). Other criteria such as a neutrophilic CSF pleocytosis have been moved to the realm of supportive paraclinical evidence. Minor criteria, such as bilateral ON, severe vision loss, or severe weakness, are no longer considered to have sufficient diagnostic sensitivity.

CHANGING FACE OF NEUROMYELITIS OPTICA: AQUAPORIN-4 AUTOANTIBODIES

In 2004, Lennon et al made the groundbreaking observation that most patients with NMO express serum autoantibodies (aquaporin-4 immunoglobulin G [AQP4-IgG]) against the aquaporin-4 (AQP4) water channel (9,10). Subsequently, multiple investigators devised a variety of assays to detect AQP4-IgG in serum and CSF. Although the sensitivity and specificity of individual assays vary, AQP4-IgG seropositivity is generally considered to have 75% sensitivity and 99% specificity for disease (9,11–15). Importantly, AQP4 autoantibodies are typically undetected in clinically definite multiple sclerosis (MS) (9,12,16).

The high specificity of AQP4-IgG for NMO prompted a revision in the diagnostic criteria in 2006 (Table 1). In the revised criteria, NMO was defined by the absolute requirement of simultaneous or sequential attacks of ON and TM, and the presence of 2 of 3 minor criteria: brain MRI inconsistent with MS, LETM, or positive serum AQP4-IgG (7). Using a cohort of 129 patients with NMO and MS, the revised 2006 criteria were found to be 94% sensitive and 96% specific for NMO; in comparison, the original 1999 criteria were only 85% sensitive and 48% specific for disease as assessed on 96 patients with NMO (7).

One of the immediate results of the adoption of AQP4-IgG serology in the revised 2006 criteria was the identification of seropositive patients with spatially limited or atypical clinical presentations. AQP4-IgG–seropositive patients with monophasic or recurrent events of ON or TM were termed NMO spectrum disorders (NMOSDs) (1), and affected individuals often demonstrated additional signs or symptoms of systemic autoimmunity or NMO-specific brain MRI abnormalities (Fig. 1; Table 2) (18). Atypical clinical presentations included protracted nausea and vomiting, narcolepsy, encephalopathy, and brainstem syndromes reflective of lesions in the dorsal medulla (area postrema), hypothalamus, limbic

regions, brainstem, and cerebral white matter (1,19). Although not meeting the revised 2006 diagnostic criteria, these clinical presentations were considered *formes frustes* of disease as they occurred in definite patients with NMO, and affected individuals typically developed future attacks of TM or ON.

NEUROMYELITIS OPTICA SPECTRUM DISORDERS: NEW INTERNATIONAL CONSENSUS CRITERIA

The rapidly expanding clinical spectrum of patients with seropositive AQP4-IgG required the development of new diagnostic criteria that would capture the clinical experience of physicians and provide a codification for future translational and clinical research. The International Panel for NMO Diagnosis (IPND) was convened in 2011 and tasked with developing new diagnostic criteria based on clinical, laboratory, and neuroimaging data (8). In recognition of accumulating data that the clinical behavior, treatment, and pathology of AQP4-IgG–seropositive patients with incomplete or atypical presentations of NMO are not different from patients fulfilling previous diagnostic criteria (20), the term NMOSD was chosen as a new diagnostic moniker. Because approximately 25% of patients meeting previous NMO criteria were seronegative for AQP4-IgG, separate diagnostic criteria for seronegative NMOSD were formulated using a mixture of clinical and radiologic criteria. The result was the generation of 2 new diagnoses: NMOSD with AQP4-IgG and NMOSD with negative or unknown AQP4-IgG.

The diagnosis of NMOSD with AQP4-IgG requires one of 6 core clinical characteristics and a positive test for AQP4-IgG. The core clinical presentations are distinguished by their neuro-anatomic locations: optic nerve, spinal cord, area postrema (dorsal medulla), diencephalon, brainstem, and cerebrum. Involvement of the optic nerves and spinal cord manifests as ON or TM. ON typically presents as acute vision or visual field loss in one or both eyes, whereas TM may present with a variety of motor, sensory, or sphincter problems. TM is commonly longitudinally extensive (3 or more vertebral segments) (Fig. 1A), involving the central cord (Fig. 1B) with contrast enhancement (Fig. 1B’). Optic nerve lesions are typically gadolinium enhancing and extensive (Fig. 1C) and often involve the prechiasmatic optic nerve and optic chiasm (Fig. 1D). An area postrema syndrome (incidence: 16%–43%) (19,21,22) is characterized by intractable hiccups or nausea/vomiting occurring for 7 consecutive days without, or 2 days with, an accompanying MRI lesion in the dorsal medulla (Fig. 1E). Acute brainstem symptoms include ocular motor, motor, sensory, or cerebellar dysfunction associated with parenchymal (Fig. 1F) or ependymal lesions (Fig. 1G) that may or may not be contiguous with spinal cord injury (Fig. 1A). Diencephalic syndromes include hypersomnolence, narcolepsy, anorexia, hypothermia, hypo-natremia, and behavioral changes associated with a MRI lesion in the thalamus, hypothalamus, or third ventricular region (Fig. 1H, J). Cerebral syndromes include hemiparesis, hemi-sensory loss, encephalopathy, postchiasmal visual field loss, and cortical vision loss that are often associated with large, confluent subcortical or deep white matter lesions (Fig. 1I, J).

Because of increased sensitivity (14,15,23), cell-based serum assays using microscopy-based or flow cytometry–based detection are recommended for AQP4-IgG serologic testing. Enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence (IIF) of tissue sections are typically less sensitive and often yield lower-titer and false-positive tests (24,25). Therefore, caution is recommended in making a diagnosis of NMOSD with AQP4-IgG in cases where low-titer AQP4-IgG is detected by ELISA or IIF, and symptoms are outside the 3 most common core clinical presentations: ON, TM, or area postrema syndrome. Confirmatory testing using more than one assay is generally recommended.

A diagnosis of NMOSD without AQP4-IgG requires additional clinical and radiologic criteria that are not mandated for seropositive patients. Patients with NMOSD who do not have detectable AQP4-IgG must have a minimum of 2 core clinical presentations, and 1 presentation must be ON, TM, or an area postrema syndrome. The clinical presentation may be simultaneous or sequential. Additional radiologic criteria are required based on the type of core presentation. For ON, the brain MRI should be normal if the optic nerve lesion is not extensive (half the length of the optic nerve) or involving the optic chiasm. For TM, spinal cord MRI should demonstrate a central medullary lesion or focal atrophy involving 3 contiguous segments. Area postrema syndromes require a dorsal medulla lesion, and acute brainstem syndromes should demonstrate periependymal lesions. These additional radiologic criteria were deemed necessary to provide additional specificity for NMOSD in the absence of AQP4-IgG. Because patients may convert to a positive AQP4-IgG serostatus over time, repeat serologic testing is recommended in relapsing seronegative patients before immunosuppressive or B-cell ablative therapies are initiated. Rarely, AQP4-IgG has been detected only in CSF (26,27). Therefore, routine CSF testing of AQP4-IgG–seronegative patients is generally not recommended. Additional CSF features such as extensive pleocytosis (>50 leukocytes/ μL), presence of neutrophils or eosinophils (>5/μL), absence of oligoclonal bands, or elevation of glial fibrillary acidic protein are considered supportive but not confirmatory evidence of NMOSD (2,28,29).

Because the diagnosis of NMOSD without AQP4-IgG may be difficult, the 2015 IPND criteria highlight multiple “red flags” that should caution clinicians against a NMOSD diagnosis. Clinical red flags include progressive disease course, hyperacute onset (<4 hours to symptom nadir), presence of CSF oligoclonal bands, partial TM, chronic infection, or clinical features suggestive of cancer or sarcoidosis (8). Radiologic red flags include brain MRI findings suggestive of MS, persistent contrast enhancement, (>3 months) short and predominantly peripheral spinal cord lesions, and diffuse, indistinct T2-weighted lesions (8).

NEUROMYELITIS SPECTRUM DISORDERS: MOVING FORWARD IN CLINICAL PRACTICE

The 2015 IPND criteria represent a substantial departure from previous diagnostic measures. In the near term, the institution of the new NMOSD criteria in clinical practice will facilitate the early identification of AQP4-IgG–seropositive patients. Previous diagnostic criteria had required the simultaneous or sequential presentation of ON and TM. In clinical practice, however, patients with atypical presentations related to cerebral, diencephalic, and brainstem

pathology had been reported in association with AQP4-IgG, and their subsequent clinical course often included ON and LETM. The inclusion of these individuals, along with AQP4-IgG–seropositive patients with isolated or recurrent events of ON and TM, under the umbrella of NMOSD will allow rapid adoption of prophylactic therapy and aggressive treatment of acute attacks. As neurologists and ophthalmologists recognize the core clinical symptoms of NMOSD, by presentation or history, serologic testing for AQP4-IgG will expand leading to earlier diagnosis. In addition, the recognition of clinical presentations and neuroimaging typical of NMOSD will foster testing of AQP4-IgG in high-risk monosymptomatic cases of ON or TM. For instance, in monosymptomatic ON, bilateral ON, poor visual recovery (<20/200), severe visual field depression, altitudinal visual field loss, posterior nerve or optic chiasm involvement, extensive visual pathway lesions, or severe and diffuse peripapillary retinal nerve fiber layer loss should prompt AQP4-IgG testing (30–36).

In the long term, the 2015 IPND criteria also will be a guide for evaluating the natural history and treatment response of AQP4-IgG–seronegative patients. Patients with NMO diagnosed by the 2006 Wingerchuk criteria may transition between AQP4-IgG seropositive and seronegative states, indicating that all AQP4-IgG–seronegative cases are not merely phenotypic mimics. Therefore, monitoring the progress of patients meeting criteria for NMOSD without AQP4-IgG will be critical for developing future diagnostic criteria that delineate those patients with seronegative NMOSD at high risk for relapse and those that are responsive to therapy.

Nevertheless, multiple investigations on independent cohorts of patients with AQP4-IgG–seronegative NMO have demonstrated distinct demographics and clinical characteristics (37). AQP4-IgG–seronegative patients are more often Caucasian (38,39); show a lower female/male ratio (38–41); have a shorter disease duration (38); are more frequently monophasic (40,42); exhibit fewer features of concurrent autoimmunity (40,42); and more often present with simultaneous ON and TM (38–40). These distinctions suggest that a significant portion of seronegative patients represent disorders with overlapping phenotypic presentations of ON and TM. Similar demographic and clinical distinctions have been observed among a small fraction of AQP4-IgG–seronegative patients who are sero-positive for antibodies against myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) (43,44). The 2015 IPND NMOSD criteria may differentiate some cohorts of patients previously labeled as seronegative NMO and may identify alternative cohorts at higher risk for relapse. Indeed, 2 studies with longer follow-up have revealed that a significant fraction of NMO-seronegative patients have disease recurrence (38,39).

Interestingly, the initial application of the new 2015 IPND NMOSD criteria in clinical practice has demonstrated enhanced diagnostic sensitivity. In adult cohorts, the 2015 IPND NMOSD criteria identified novel AQP4-IgG–seronegative patients (45,46), and, because of the need for only a single core presentation (8), detected AQP4-IgG–seropositive patients significantly faster following symptom onset (45). As a result, patients with NMOSD at risk for future relapse and disability progression are likely to be rapidly identified and treated. Similarly, in a study of pediatric patients with demyelinating disease, 97% of the panel-defined patients with NMOSD were correctly identified by the IPND 2015 NMOSD criteria;

however, only 49% were diagnosed by 2006 Wingerchuk NMO criteria. This may be due in part to the distinct presentations of pediatric and adult NMO cases (47) and the new diagnostic criteria for monophasic AQP4-IgG–seropositive patients (8).

FUTURE CLASSIFICATION OF NEUROMYELITIS SPECTRUM DISORDERS

Each iteration of diagnostic criteria for NMO has attempted to aid clinicians in the recognition of this relatively rare but devastating CNS inflammatory disorder. Although the gold standard of diagnostic accuracy, lesion histopathology (48,49), remains unobtainable in most cases, the progressive incorporation of new clinical, radiologic, and serologic criteria seems to be improving both diagnostic sensitivity and specificity. Nonetheless, because of the limited sensitivity of the AQP4-IgG serologic assay and the limited specificity of clinical and radiologic presentations, a clear categorization of NMOSD among other demyelinating disorders remains murky.

The ultimate classification of NMOSD may be molecular (50), using multiple discrete biomarkers to combine seemingly diverse demyelinating disorders into a common nosologic category based on shared immunopathology and histopathology. For NMOSD, progress has been made in the identification of potential cellular, serum, and CSF bio-markers (51). The most notable has been AQP4-IgG, a serum biomarker of humoral immunopathology that is highly specific for NMOSD and has important prognostic and therapeutic implications. Unfortunately, additional bi-omarkers of NMOSD immunopathology and CNS injury (51) lack the sensitivity and specificity to provide successful categorization of all cases of seronegative NMOSD (46). In addition, it remains unclear which cases of clinically defined AQP4-IgG–seronegative NMOSD show NMO-specific lesional histopathology.

As noted previously, approximately 20% of AQP4-IgG–seronegative patients are seropositive for MOG-IgG. Multiple immunologic and histopathologic features of MOG-IgG–seropositive NMOSD indicate that this condition is nosologically distinct from AQP4-IgG–seropositive NMOSD despite its overlapping clinical presentation. Patients with MOG-IgG–seropositive NMOSD are typically male and more often have simultaneous ON and TM, monophasic disease, inflammation of the conus, cauda equina, and deep brain nuclei, and improved functional recovery (43,44). The intracerebral microinjection of MOG-IgG–seropositive patient serum into murine brain produces no inflammation or significant CNS injury (52), and brain lesions from a patient with MOG-IgG–seropositive NMOSD revealed MS-type II pathology (53). The combined clinical and experimental data indicate that MOG-IgG–seropositive patients with TM and ON should be classified outside NMOSD and may represent a subgroup of patients with MS or acute disseminated encephalomyelitis.

A molecular classification of demyelinating disorders may ultimately require substantial advances in technology to reach fruition. Improvement in serologic, radiologic, and immunologic assays is likely to be required to reach levels of sensitivity and specificity necessary to delineate closely aligned demyelinating disorders with overlapping clinical presentations and immunopathologies. High throughput analysis of large biologic data sets from affected individuals may hold the key to discovering groups of biomarkers that can define molecular boundaries between NMOSD and phenotypic mimics. Ultimately, a

molecular nosology of CNS demyelinating disorders will result in targeted immunotherapy and improved clinical outcomes in patients with NMOSD.

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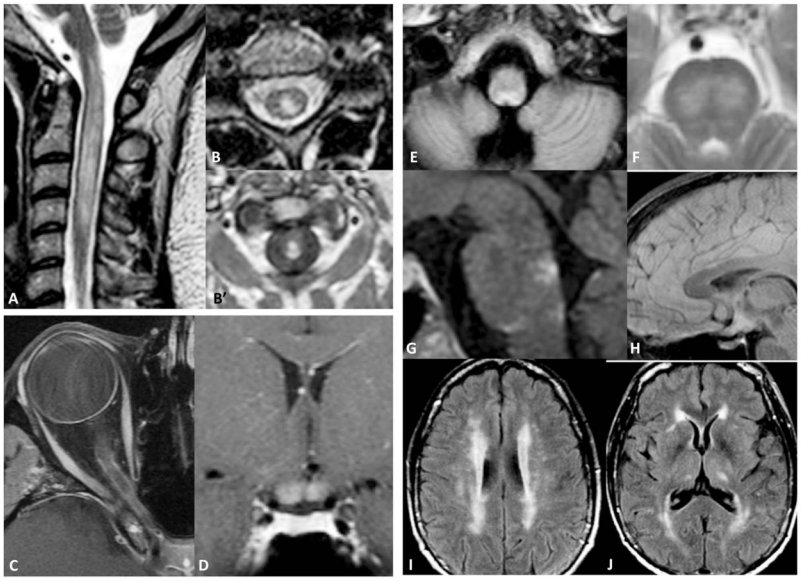

FIG. 1.

Magnetic resonance imaging in neuromyelitis optica spectrum disorders. **A**. Sagittal T2 scan shows longitudinally extensive cervical cord lesion extending into dorsal medulla. T2 (**B**) and postcontrast T1 (**B′**) central spinal cord lesions. **C**. Postcontrast T1 scan reveals extensive enhancing lesion of the optic nerve. **D**. Fluid-attenuated inversion recovery (FLAIR) imaging demonstrates bilateral prechiasmal and chiasmal optic nerve inflammation. **E**. Bilateral FLAIR lesions involve the dorsal medulla (area postrema). **F**. Bilateral confluent T2 lesions in the mid-pons. **G**. Sagittal FLAIR image demonstrates periependymal lesions around the fourth ventricle. **H**. Sagittal FLAIR image reveals diffuse hypothalamic inflammation. Axial FLAIR images show bilateral, confluent deep white matter (**I**, **J**) and thalamic (**J**) lesions.

TABLE 1

Historical classification of Neuromyelitis Optica and Neuromyelitis Optica Spectrum Disorder

Wingerchuk 1999 NMO Criteria (2)	Wingerchuk 2006 NMO Criteria (7)	IPND 2015 NMOSD Criteria (8)
Diagnostic criteria		
All absolute criteria and 1 major or 2 minor supportive criteria Absolute criteria **1** Optic neuritis **2** Acute myelitis **3** No evidence of clinical disease outside optic nerve or spinal cord Supportive criteria Major **1** Negative brain MRI at onset **2** Spinal cord MRI with lesion extension over 3 vertebral segments **3** CSF pleocytosis of 50 WBC/mm^3 or 5 neutrophils/mm^3 Minor **1** Bilateral optic neuritis **2** Severe optic neuritis with fixed visual acuity worse than 20/200 in at least one eye **3** Severe, fixed, attack-related weakness (MRC grade 2) in one or more limbs	All absolute criteria and 2 supportive criteria Absolute criteria **1** Optic neuritis **2** Acute myelitis Supportive criteria **1** Contiguous spinal cord MRI lesion extending over 3 vertebral segments **2** Brain MRI not meeting diagnostic criteria for MS **3** AQP4-IgG–seropositive status	NMOSD with AQP4-IgG **1** At least 1 core clinical characteristic **2** Positive test for AQP4-IgG using best available detection method* **3** Exclusion of alternative diagnoses NMOSD without AQP4-IgG **1** At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements **a.** At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome **b.** Dissemination in space (2 or more different core clinical characteristics) **c.** Additional MRI requirements, as applicable **2** Negative tests for AQP4-IgG using best available detection method* or testing unavailable **3** Exclusion of alternative diagnoses Core clinical characteristics: Optic neuritis; acute myelitis; area postrema syndrome (hiccups; nausea and vomiting); acute brainstem syndrome; symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (Table 2, Fig. 1); symptomatic cerebral syndrome with NMOSD-typical brain lesions (Table 2, Fig. 1) *AQP4-IgG serology: Cell-based assay is strongly recommended
Methodology		
Criteria were defined by chart analysis of the clinical, radiologic, and laboratory data from 71 patients	Criteria were defined by the evaluation of data from 129 patients ascertained through the Mayo Clinic MS Centers in Rochester, MN, and	Criteria were developed by an 18-member panel of NMO physicians from 9 countries; working groups in clinical presentation, neuroimaging, laboratory studies/serology, pediatrics, systemic autoimmunity, and opticospinal MS

Wingerchuk 1999 NMO Criteria (2)	Wingerchuk 2006 NMO Criteria (7)	IPND 2015 NMOSD Criteria (8)
Diagnostic criteria		
with NMO at the Mayo clinic; there was no independent validation cohort	Scottsdale, AZ, and tested for NMO-IgG; there was no independent validation cohort	conducted systematic literature reviews, and initial characteristics for NMOSD were rated and further refined by panel members using electronic surveys and clinical vignettes; those characteristics endorsed by a two-thirds majority were used to develop criteria for AQP4-IgG–seropositive and AQP4-IgG–seronegative NMOSD

AQP4-IgG, anti–aquaporin-4 immunoglobulin G; CSF, cerebrospinal fluid; IPND, International Panel for NMO Diagnosis; LETM, longitudinally extensive transverse myelitis; MRC, Medical Research Council; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMO, neuro-myelitis optica; NMOSD, neuromyelitis optica spectrum disorder; WBC, white blood cell.

TABLE 2

Neuromyelitis Optica Spectrum Disorders—Magnetic Resonance Imaging features and systemic autoimmunity

Associated MRI and Autoimmune Features of NMOSD
Optic nerve MRI
Increased T2 signal (standard T2 or STIR sequences) or T1 gadolinium enhancement of one or both optic nerves (Fig. 1C)
Additional characteristic features
Lesions are typically long (encompassing more than half of the optic nerve) or involve multiple regions of the nerve
Lesions typically involve the posterior, intracranial portion of the optic nerve and optic chiasm (Fig. 1D)
Spinal cord MRI
Longitudinally extensive lesion demonstrating increased T2 signal (standard T2, proton density, or STIR sequences) involving 3 or more contiguous vertebral segments (Fig. 1A)
Central cord predominance (>70% of the lesion residing within the central gray matter) (Fig. 1B)
Postcontrast enhancement of the lesion on T1 sequences (Fig. 1B′)
Additional characteristic features
Rostral extension into brainstem (Fig. 1A)
Cord edema
Cord atrophy may be observed in cases with long-standing injury
Cerebral MRI lesions
Large, confluent subcortical or deep white matter lesions (Fig. 1I, J)
Long diffuse or edematous corpus callosum lesions (typically involving half the length of the corpus callosum)
Diencephalic MRI Lesions
Thalamic (Fig. 1J)
Hypothalamic lesions (Fig. 1H)
Periependymal lesions around the third ventricle
Brainstem MRI lesions
Lesions of the dorsal medulla (area postrema) (Fig. 1E)
Additional characteristic features
Unilateral or bilateral lesions (Fig. 1F)
Often contiguous with an upper cervical spinal cord lesion (Fig. 1A)
Periependymal lesions around the fourth ventricle (Fig. 1G)
Extensive postcontrast enhancing periependymal brain lesions
Long corticospinal tract lesions involving internal capsule and cerebral peduncle
Associated systemic autoimmunity (1,17)
Antinuclear autoantibodies
Neural autoantibodies (anti-GAD, anti-CRMP5, anti-Ro, anti-VGC, anti-AchR)
Autoimmune disorders: thyroiditis, Sjogren disease, systemic lupus erythematosus, myasthenia gravis

AchR, acetylcholine receptor; CRMP5, collapsin response-mediator protein 5; GAD, glutamic acid decarboxylase; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; STIR, short tau inversion recovery; VGC, voltage-gated channel.