

Address correspondence to Dr Brian G. Weinshenker, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, weinb@mayo.edu.

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Acute Disseminated Encephalomyelitis, Transverse Myelitis, and Neuromyelitis Optica

Dean M. Wingerchuk, MD, MSc, FRCP(C), FAAN;
Brian G. Weinshenker, MD, FRCP(C), FAAN

ABSTRACT

Purpose of Review: This review defines current clinical criteria for diagnosis, differential diagnosis, and clinical evaluation of acute disseminated encephalomyelitis, transverse myelitis, and neuromyelitis optica, and summarizes principles of treatment.

Recent Findings: Consensus criteria for transverse myelitis and acute disseminated encephalomyelitis have been proposed. A specific biomarker, aquaporin-4 autoantibody, has been discovered for neuromyelitis optica that allows for early and accurate diagnosis even in the absence of cardinal findings of optic neuritis and myelitis. The antibody is pathogenic and is facilitating an understanding of the pathophysiology of neuromyelitis optica and development of antigen-specific treatments.

Summary: Clinical and radiologic findings combined with serologic findings may permit classification of syndromes of transverse myelitis and acute disseminated encephalomyelitis in ways that may predict risk of relapse, type of relapse, and prognosis. Treatment, especially to prevent relapse, is dependent on the specific disease context in which syndromes such as transverse myelitis occur.

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INTRODUCTION: SYNDROME VERSUS DISEASE

The nosology of demyelinating diseases of the CNS is complex. Multiple sclerosis (MS) has been an umbrella term for recurrent inflammatory disease of the CNS after definable nondemyelinating mimics are excluded. Acute disseminated encephalomyelitis (ADEM), transverse myelitis, and neuromyelitis optica (NMO) are inflammatory conditions that have not been well distinguished from MS or its presenting syndromes (termed “clinically isolated [demyelinating] syndromes”) but are linked by their tendency to relapse and remit and by

their inflammatory characteristics and overlapping pathology.

Distinction between syndromes that reflect localization (eg, optic neuritis and transverse myelitis) and disease entities (eg, ADEM, MS, and NMO) is now feasible. Distinction is important because of the prognostic and treatment implications of different disease entities. For example, transverse myelitis refers to a syndrome of acute or subacute myelopathy accompanied by indicators of inflammation, either radiologically or based on spinal fluid. It may occur as a stand-alone syndrome, a component of ADEM, a relapse of MS or NMO, or a nondemyelinating syndrome

such as an infectious myelitis or a granulomatous myelitis. If due to herpes virus infection, it is best treated with antiviral treatment; if indicative of a relapse or harbinger of MS, an MS immunomodulatory treatment may be appropriate; if a relapse of NMO, an immunosuppressive drug, such as azathioprine, would be appropriate, whereas interferon- β or natalizumab may actually be deleterious. Noninfectious and noninflammatory disorders, such as arteriovenous fistula, may produce syndromes suggestive of transverse myelitis but would require entirely different treatment.

ADEM, as currently defined, is characterized by acute encephalopathy but frequently accompanied by optic neuritis or transverse myelitis. NMO is the first inflammatory demyelinating condition to be defined, in part, by a biomarker that is molding our evolving concept of this condition (an autoimmune aquaporinopathy) and expanding the spectrum of the disease to include non-optic nerve and spinal cord syndromes and MRI-detected brain lesions that, in the past, would have excluded a diagnosis of NMO.

Understanding of the distinction and interrelationships of these syndromes has been facilitated by insights into the pathophysiology, informed by the neuropathology, and illustrated by advances in NMO over the past decade as outlined below.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Although a number of definitions have been proposed for ADEM, it remains a poorly defined syndrome of symptomatic diffuse or multifocal CNS inflammation that is typically, if not always, a monophasic illness. ADEM has been historically regarded as the clinical counterpart of the experimental disease experimental autoimmune en-

cephalomyelitis. ADEM is also known as postvaccinal encephalomyelitis when it follows vaccination. Accordingly, it is believed to be induced by an immune reaction directed at a cross-reacting myelin antigen. Its somewhat unique pathology of perivenous “sleeves” of inflammation and demyelination has been recognized for decades but has been recently rediscovered and expanded.¹ Pathologically, ADEM can be distinguished from fulminant acute MS, which is a major consideration in the differential diagnosis. Acute MS is associated with confluent demyelination and prominent macrophages admixed with reactive astrocytes. When cases are identified based on pathologic features, these features seem to be associated with some of the key clinical characteristics that have been identified in consensus clinical diagnostic criteria (Table 3-1²) to distinguish ADEM from MS—in particular, encephalopathy.¹ Pathology has recently been proposed as the “reference standard” to distinguish ADEM from fulminant MS, although this has not been widely debated and cannot be considered as generally accepted at the present time. Consensus criteria² remain imperfect in distinguishing patients who, in the course of follow-up, will remain free of future relapses. Furthermore, consensus criteria allow for recurrent and even multiphasic ADEM episodes with criteria that might distinguish it from MS (ie, a new episode must also meet the criteria for ADEM and not be those of an attack of MS—see Table 3-1). Controversy persists about whether relapses may occur in ADEM and remain consistent with the diagnosis of ADEM, especially in adult patients.

The key clinical features required for a diagnosis of ADEM include diffuse encephalopathy but may also

KEY POINTS

- Distinguishing between syndromes (eg, optic neuritis and transverse myelitis) and disease entities (multiple sclerosis, neuromyelitis optica, and acute disseminated encephalomyelitis) is vital. Demyelinating syndromes may be a component of different diseases and may have vastly different prognoses depending on the disease context (and may therefore require different treatment).
- Although the proposed consensus criteria for acute disseminated encephalomyelitis allows for recurrent or multiphasic forms of the disease, the existence of relapsing forms remains controversial. A criterion standard for distinguishing acute disseminated encephalomyelitis from multiple sclerosis has not been widely accepted, although pathology has been proposed.

TABLE 3-1 International Pediatric Multiple Sclerosis Study Group Consensus Definitions^a**► Monophasic Acute Disseminated Encephalomyelitis (ADEM)**

A first clinical event with a presumed inflammatory or demyelinating cause

Acute or subacute onset that affects multifocal areas of the CNS

Polysymptomatic and must include encephalopathy, including one or more of the following:

Behavioral change (confusion, irritability)

Alteration in consciousness (lethargy, coma)

Postevent improvement clinically, on MRI, or both; residual deficits permitted

No prior clinical episode consistent with demyelinating event

No other etiologies apparent

New or fluctuating symptoms, signs, or MRI findings occurring within 3 months of the inciting ADEM event permissible

Brain MRI (T2-weighted) with focal or multifocal supratentorial or infratentorial lesions, often large (1 to 2 cm), predominantly involving white matter, but frequently present in gray matter (especially basal ganglia or thalamus), without evidence of previous destructive white matter changes; brain MRI showing a single large lesion (1 to 2 cm), predominantly affecting white matter also possible, although rare

Spinal cord MRI may have confluent intramedullary lesion(s) with variable enhancement, in addition to abnormal brain MRI findings specified previously

► Recurrent ADEM

Recurrence of the initial symptoms and signs of ADEM 3 or more months after the first event

No new lesions based on history, examination, or neuroimaging

Event does not occur while on corticosteroids and occurs at least 1 month after completing therapy

MRI shows no new lesions; original lesions may have enlarged

No better explanation exists

► Multiphasic ADEM

New clinical event also meeting criteria for ADEM but involving new anatomic areas of the CNS as confirmed by history, neurologic examination, and neuroimaging

Subsequent event must occur:

At least 3 months after the onset of the initial ADEM event

At least 1 month after completing steroid therapy

Subsequent event must be a polysymptomatic presentation, including encephalopathy, with neurologic symptoms or signs that differ from the initial event (mental status changes may not differ from the initial event)

Brain MRI shows new areas of involvement and complete or partial resolution of prior ADEM-associated lesion

^a Modified with permission from Krupp LB, et al; International Pediatric MS Study Group, *Neurology*.² © 2007, American Academy of Neurology. www.neurology.org/content/68/16_suppl_2/57.short?sid=d000124e-c5a6-4744-a896-c2c5fcc4545.

include other symptoms characteristic of an inflammatory demyelinating disease, such as optic neuritis or transverse myelitis, including transverse myelitis associated with longitudinally extensive lesions. Clinical features may include seizures or coma; coma is highly suggestive of ADEM in the

appropriate setting of extensive white matter disease (**Case 3-1**). MRI usually shows multiple lesions, although a single large lesion is still felt to be compatible in the consensus criteria. Usually, cerebral lesions occur in both cerebral hemispheres in ADEM.³ Involvement of the deep gray matter is

Case 3-1

A 30-year-old woman with no antecedent illness or vaccination presented with headaches and migratory numbness. Four days later she reported nausea and was confused, asking the same question repetitively. She developed gait unsteadiness, followed within a week by paraplegia and later by paresis of her arms. Examination revealed that she was somnolent but opened her eyes after vigorous stimulation. She had bilateral papilledema, moderate upper extremity paresis, and plegia of the lower extremities. Bilateral Babinski signs and spasticity were present. MRI scan of the brain showed extensive white matter lesions (**Figure 3-1**). CSF analysis revealed 30 white blood cells (WBC)/ μL , primarily mononuclear; elevated protein level of 200 mg/dL, and negative/normal results for IgG index and oligoclonal bands. In spite of high-dose corticosteroids, she continued to deteriorate and developed multiple new lesions of the cerebral hemispheres and brainstem, as well as a herniation syndrome. Pathologic analysis revealed evidence of perivenous demyelination consistent with acute disseminated encephalomyelitis (ADEM).

Comment. This case illustrates how fulminant a course ADEM may take in certain individuals and how it may cause cerebral herniation.

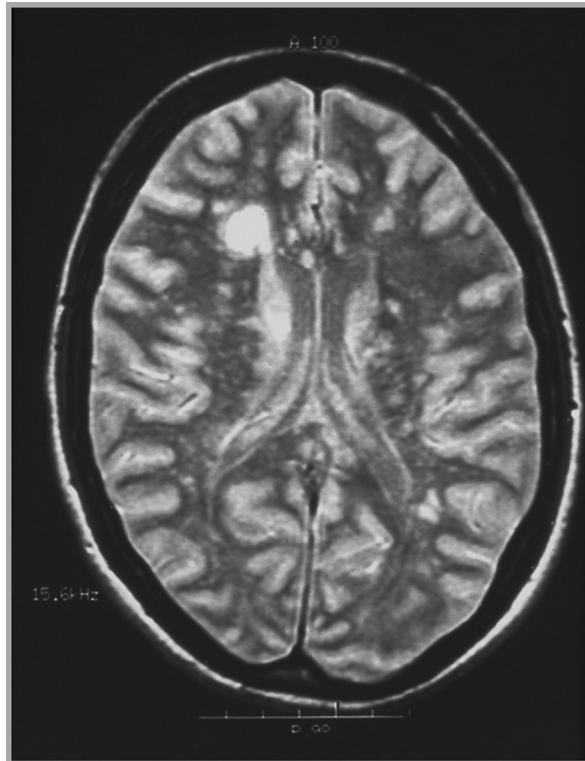


FIGURE 3-1 T2-weighted axial brain image shows multiple lesions of varying size scattered throughout the subcortical and deep cerebral white matter.

not uncommon and is more commonly observed in ADEM than in MS (**Figure 3-2**).⁴ Lesions may also be present in the optic nerves and spinal cord. A key exclusionary criterion is lack of clinical or radiologic evidence of prior CNS pathology that would indicate previous inflammatory demyelination. Typically, CSF pleocytosis is present.

ADEM is more common in children than adults, and diagnosis can be made with greater confidence when it follows an acute infectious illness or vaccination in a child or an adult. A broad differential diagnosis of acute

leukoencephalopathies exists that may produce similar features (**Table 3-2**).⁵ Clinical and radiologic clues are important in distinguishing ADEM from other mimics. Investigations should be targeted to specific suspected competing diagnoses based on demographic, neurologic, and non-neurologic symptomatology and radiologic clues.

The diagnosis of ADEM remains one of exclusion of other competing diagnoses and monitoring of treatment response and clinical course—in particular, whether remission occurs spontaneously or after corticosteroid treatment and whether relapse occurs.

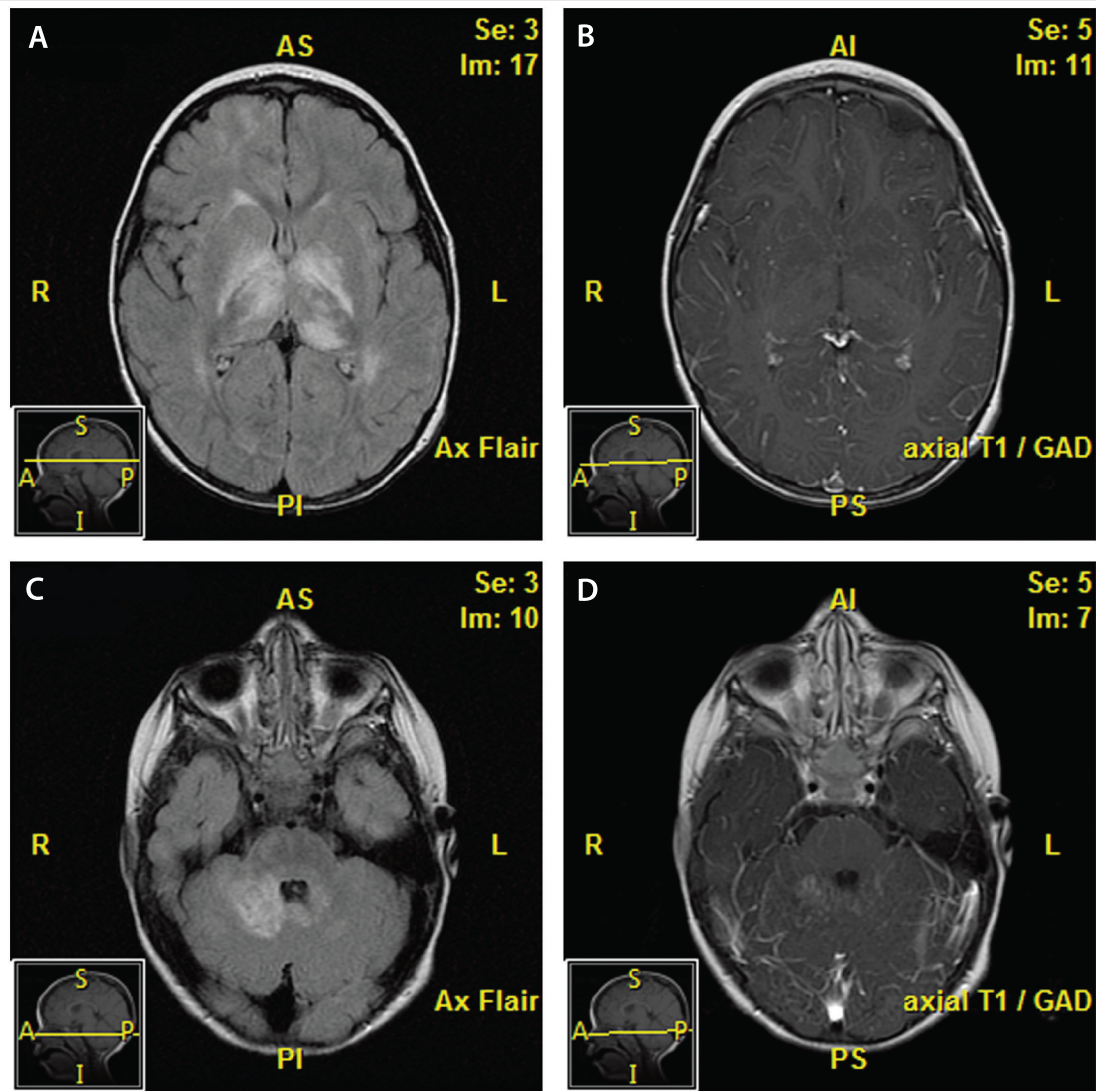


FIGURE 3-2 Acute disseminated encephalomyelitis in a child. Fluid-attenuated inversion recovery (FLAIR) axial images at the level of basal ganglia and pons (A, C) and T1-gadolinium axial images at the same levels (B, D). Note the mostly symmetrical, thalamic gray matter T2 hyperintensity with minimal gadolinium enhancement as well as the bilateral, though asymmetrical, middle cerebellar peduncle T2 hyperintensity with prominent gadolinium enhancement.

Relapse is a strong indicator that a diagnosis of ADEM was incorrect, although, as noted above, pediatric consensus criteria do not consider a relapse as a strict exclusionary characteristic. The radiologic characteristics of ADEM are nonspecific. In the majority of patients, they are difficult to distinguish from those seen in MS, although extensive and symmetric ce-

rebral, cerebellar, and basal ganglia abnormalities have been reported. Serial follow-up in ADEM does not reveal new MRI findings, but this observation can only be made retrospectively. CSF findings are similarly nonspecific. Elevations of IgG index or the presence of oligoclonal bands are usually absent, or when present, are transient. When ADEM is strongly suspected and no

TABLE 3-2 Selected Acute Leukoencephalopathies That Mimic Acute Disseminated Encephalomyelitis and Investigations

Condition	Index of Suspicion	Initial Tests	Confirmatory Tests
Neurosarcoidosis	Extra-CNS disease Persisting enhancement on brain MRI	Serum and CSF angiotensin-converting enzyme level Brain and spinal cord MRIs with and without contrast Imaging for pulmonary disease	CNS or non-CNS biopsy
Vasculitis	Extra-CNS disease Residual infarcts	Sedimentation rate Vasculitis panel (myeloperoxidase, proteinase 3) Angiography	CNS or non-CNS biopsy
Progressive multifocal leukoencephalopathy	Immunosuppressed individual Natalizumab treatment HIV infection	CSF PCR for JC virus MRI sometimes sequential	CNS biopsy
Gliomatosis cerebri	History of brain tumor	Brain MRI with and without gadolinium	CNS biopsy
CNS lymphoma	Prior immunosuppression Homogeneous, nodular enhancement Multifocal tumor	CSF cytology	CNS biopsy
Posterior reversible encephalopathy syndrome	Risk factor (eg, hypertension, cyclosporine) No gadolinium enhancement Indistinct boundaries	Brain MRI with and without gadolinium Imaging may change rapidly	Follow-up MRI
Paraneoplastic disorder	History of cancer	Paraneoplastic antibody	CNS biopsy
Erdheim-Chester disease	Bone pain Exophthalmos Diabetes insipidus	X-ray of long bones	CNS or non-CNS biopsy

other competing diagnosis seems likely or is detected after a comprehensive evaluation, a therapeutic trial of corticosteroids should be administered. Generally, the course of corticosteroids should be initiated within a short time, typically within a few days, because patients with ADEM are often very ill. In patients with clinical deterioration in spite of treatment with high-dose corticosteroids, a brain biopsy should be considered, which can evaluate for both ADEM and other diagnoses.

The hallmark pathologic characteristic for ADEM is perivenous demyelination, typically distributed in sleeves surrounding areas of perivascular inflammation (Figure 3-3). This pathologic picture is distinct from MS, which features confluent demyelination, prominent and confluent macrophage infiltration, and reactive astrocytes.¹ Recently, a distinctive microglial activation and aggregation without cortical demyelination similar to that seen in MS has been observed in patients

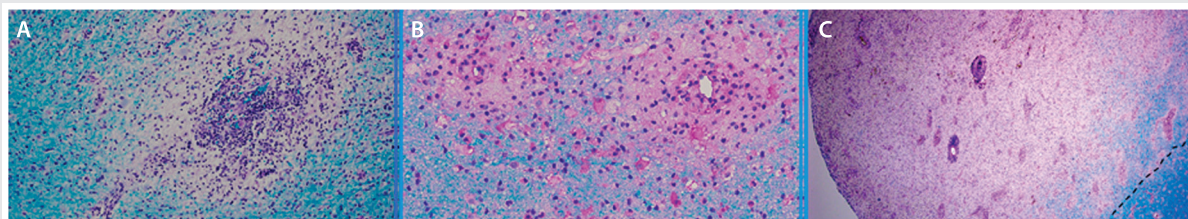


FIGURE 3-3 Representative brain biopsies illustrating the observed patterns of demyelination that may be found in patients with clinically defined acute disseminated encephalomyelitis. *A*, Perivenous sleeve of inflammation and demyelination (20×); *B*, Three coalescing perivenous lesions (60×); *C*, Extensive region of confluent demyelination with areas of perivenous demyelination in the periplaque white matter (4×). Luxol fast blue myelin stain and periodic acid-Schiff counterstain was used for all three images.

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KEY POINT

■ Acute disseminated encephalomyelitis is associated with perivenous sleeves of demyelination and perivascular inflammation, rather than confluent demyelination and macrophages and reactive astrocytes, as in acute multiple sclerosis.

with ADEM, which was highly associated with coma.¹

The prognosis of ADEM is highly variable and depends in large part on the accuracy of the diagnosis, which has been poor in the existing literature because of the lack of a specific diagnostic test and the rarity with which biopsy is obtained to differentiate from fulminant MS or other acute leukoencephalopathies. Therefore, firm guidance for patients and their families regarding prognosis is difficult. In general, the outcome in definite ADEM is favorable if the course is not complicated by supervening complications (eg, sequelae of status epilepticus), because demyelination and acute axonal pathology is usually less severe than other fulminant inflammatory disorders such as Marburg variant MS (an acute, monophasic form of MS that typically leads to death from a herniation syndrome or brainstem dysfunction within days or weeks from onset).

No randomized clinical trials of ADEM have been conducted. The standard of treatment based on empirical studies is high-dose IV corticosteroids, typically administered at 1 g/d (in children 10–30 mg/kg/d) for 5 days followed by a taper of oral prednisone over 3 to 6 weeks. Plasma exchange is effective in acute, severe demyelinating

diseases of a variety of types, although very limited experience is available for ADEM. IV immunoglobulin and other immunosuppressive agents similarly have been supported in case reports and small series.^{6,7}

TRANSVERSE MYELITIS

The term “transverse myelitis” describes a heterogeneous collection of acute and subacute infectious and noninfectious inflammatory spinal cord syndromes. Cases of myelitis were first described in the 19th century. Inflammatory demyelination was recognized as the underlying pathology in fatal postvaccinal encephalomyelitis (smallpox and rabies vaccines) in the 1920s. The annual incidence of postinfectious or idiopathic forms of transverse myelitis is estimated to be 1.3 to 8 cases per million population.⁸ When MS myelitis is included, the annual incidence approaches 25 per million. Modern diagnostic neuroimaging, CSF analysis, and laboratory techniques enable a specific diagnosis and prognosis in most cases of transverse myelitis.

The consensus inclusion criteria for diagnosis of idiopathic transverse myelitis is outlined in **Table 3-3** and includes the clinical features common to all potential etiologies of myelitis.⁹

TABLE 3-3 Diagnostic Criteria for Transverse Myelitis^a

- ▶ Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord.
- ▶ Bilateral signs and/or symptoms (although not necessarily symmetric).
- ▶ Clearly defined sensory level.
- ▶ Exclusion of extra-axial compressive etiology by MRI.
- ▶ Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 days later.
- ▶ Progression to nadir between 4 hours and 21 days following the onset of symptoms.

^a Modified with permission from Transverse Myelitis Consortium Working Group, Neurology.⁹ © 2002, American Academy of Neurology. www.neurology.org/content/59/4/499.short?sid=68d5cae0-275d-41e5-9a2b-9834280d8f5d.

Most patients present with a combination of sensory, motor, and bladder- or bowel-related symptoms suggestive of myelopathy. Lhermitte sign (an electrical or dysesthetic sensation in the spine or limbs, elicited by neck flexion) and paroxysmal tonic spasms (repeated, brief [30- to 90-second], stereotypic attacks of painful limb or truncal muscle spasms, with or without sensory symptoms, often triggered by limb movement) are hallmarks of demyelinating disease and suggest that the myelitis syndrome may be caused by MS or NMO.

Transverse myelitis is classified clinically based on whether it is complete or incomplete, which may assist with differential diagnosis.¹⁰ A “complete” cord lesion, which manifests as a relatively symmetric moderate or severe loss of motor and sensory modalities caudal to the level of the lesion, suggests a monophasic disorder (infectious, parainfectious, or idiopathic transverse myelitis) or relapsing NMO. In contrast, a “partial” myelitis syndrome (ie, incomplete or patchy involvement of at least one spinal segment with mild to moderate weak-

ness and asymmetric or dissociated sensory symptoms) is more likely to herald MS with high risk for future relapses.¹¹ Nonetheless, the clinical presentation may not be concordant with neuroimaging findings, which are likely more reliable than clinical manifestations in determining the underlying etiology. MS-related myelitis is usually characterized by short-segment, peripheral cord lesions, whereas NMO is strongly associated with a longitudinally extensive transverse myelitis (LETM) lesion that extends contiguously over three or more vertebral segments (seen best on sagittal T2-weighted MRI) and usually affects the central cord (Figure 3-4).¹² However, other diseases (including infarction, viral and other infections, syringomyelia, and sarcoidosis) can cause a long cord lesion in the central cord that mimics LETM.¹³

The differential diagnosis of transverse myelitis is extensive and summarized in Table 3-4. Figure 3-5 outlines a systematic diagnostic approach, which focuses on establishing that the myelopathy is inflammatory and then identifying a causative agent or underlying disease (Case 3-2).

KEY POINTS

- Transverse myelitis is classified clinically based on whether it is complete or incomplete, which may assist with differential diagnosis.
- Neuromyelitis optica is strongly associated with a longitudinally extensive transverse myelitis lesion.

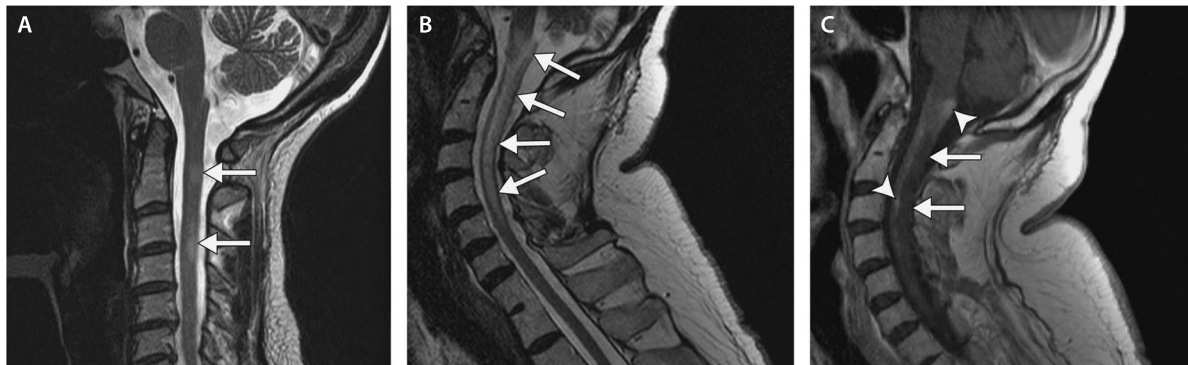


FIGURE 3-4 Spinal cord MRI in multiple sclerosis (MS) and neuromyelitis optica. *A*, Sagittal T2-weighted MRI of the cervical spinal cord demonstrates typical dorsal, short-segment signal abnormalities (*arrows*) characteristic of MS. *B*, In contrast, patients with acute myelitis in the setting of neuromyelitis optica typically have longitudinally extensive, expansile, centrally located cord lesions that may extend into the brainstem (*arrows*) (sagittal T2-weighted cervical spinal cord MRI). *C*, On T1-weighted sagittal MRI sequences, such acute lesions may be hypointense (*arrows*), suggesting necrosis and cavitation, while exhibiting enhancement with IV gadolinium administration (*arrowheads*), indicative of active inflammation.

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TABLE 3-4 Concise Differential Diagnosis and Evaluation for Transverse Myelitis^a

Etiology	Diagnostic Tests
Infection	Blood serology CSF culture, serologies, PCR Chest radiograph; other imaging as indicated
Systemic autoimmune/inflammatory disease	Clinical examination findings Serologic studies Chest and joint radiographs Other tests and/or imaging directed by history and examination
Paraneoplastic	Chest radiography, CT, and/or body imaging Comprehensive serum and CSF paraneoplastic antibody panel
Acquired CNS demyelinating disease (multiple sclerosis/neuromyelitis optica)	Brain MRI with gadolinium CSF examination for cell count/differential, oligoclonal bands, and IgG index Visual evoked potentials
Postinfectious or postvaccinal	Clear, recent history of infection or vaccination Serologic confirmation of recent infection Exclusion of other causes

^a Data from Frohman EM, Wingerchuk DM, *N Engl J Med*.¹⁰ www.nejm.org/doi/full/10.1056/NEJMcp1001112.

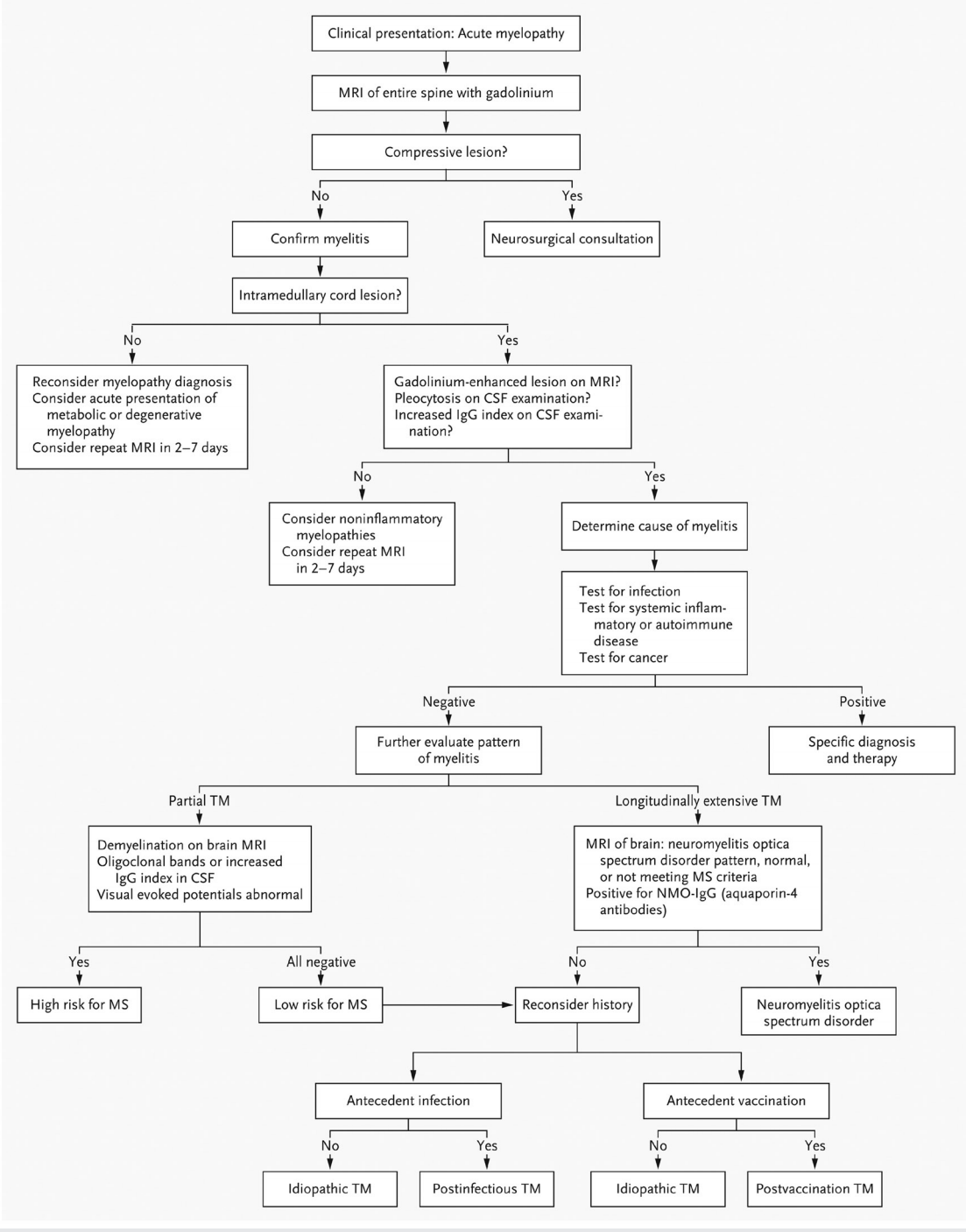


FIGURE 3-5

Diagnostic algorithm for acute myelopathies and myelitis. A systematic approach to the evaluation of acute myelopathy syndromes allows for diagnosis of transverse myelitis and its etiology.

MS = multiple sclerosis; NMO-IgG = neuromyelitis optica-immunoglobulin G; TM = transverse myelitis.

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Case 3-2

A 52-year-old woman with a history of vitiligo and hypothyroidism experienced progressive truncal and bilateral lower extremity numbness over 9 days. She lost the ability to walk and developed urinary retention at day 14. Examination revealed moderately severe paraparesis, a T8 sensory level, and repetitive, involuntary, painful right lower extremity spasms each lasting 30 to 40 seconds. MRI (**Figure 3-6**) revealed an active longitudinally extensive transverse myelitis (LETM) lesion. Brain MRI was normal, CSF showed a lymphocytic pleocytosis (44 white blood cells/ μ L) but normal IgG index and no oligoclonal bands. Laboratory testing revealed vitamin B₁₂ deficiency (level 169 ng/L) with positive parietal cell antibodies, positive antinuclear antibody (1:160), and positive neuromyelitis optica (NMO)-IgG (aquaporin-4 antibody). Her spasms resolved within 6 hours of receiving 200 mg oral carbamazepine. She made a complete neurologic recovery after corticosteroid infusions and vitamin B₁₂ replacement. She was also treated with mycophenolate mofetil with no evidence of recurrent CNS disease 3 years later.

Comment. This case illustrates a first-ever attack of LETM; aquaporin-4 seropositivity denotes an NMO spectrum disorder with high risk for relapse and need for immunosuppression. The paroxysmal tonic spasms are common in LETM and usually respond well to carbamazepine therapy. The vitamin B₁₂ deficiency and positive antinuclear antibody reflect coexisting systemic autoimmunity in the context of NMO.

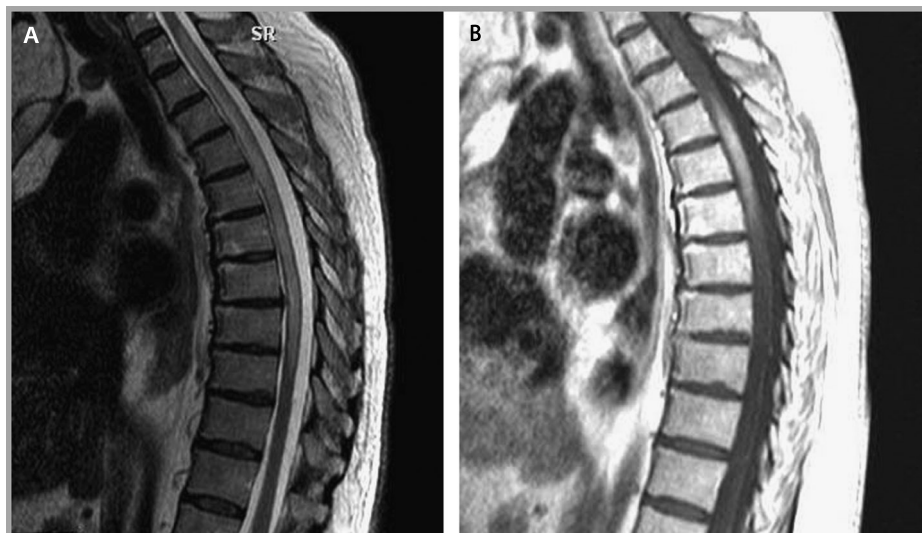


FIGURE 3-6 Sagittal thoracic spine MRI shows a longitudinally extensive transverse myelitis lesion (A, T2-weighted sequence) and gadolinium enhancement (B, T1-weighted sequence).

Neuroimaging characteristics are critical for diagnosis. Identification of an intramedullary cord lesion, especially if it exhibits postgadolinium enhancement, is very helpful in sup-

porting a diagnosis of myelitis. As discussed above, the lesion pattern (short peripheral lesions versus longitudinally extensive central lesions) offers substantial diagnostic guidance. In

the setting of partial myelitis, detection of brain MRI lesions characteristic for MS (eg, periventricular, juxtacortical, or posterior fossa lesions) strongly predicts future conversion to MS. Revised MS diagnostic criteria permit a diagnosis of MS in the presence of a combination of gadolinium-enhancing and nonenhancing white matter lesions.¹⁴ Detection of CSF pleocytosis supports an inflammatory etiology, and other tests on CSF, including serology and PCR, may establish a specific inflammatory or infectious cause. CSF oligoclonal bands are an independent predictive factor for later conversion to MS.¹⁵ No clinical, biological, or MRI factor at onset is predictive of long-term disability. Laboratory studies for viral, rickettsial, and other infectious diseases; serologic testing; and selected cultures obtained at presentation may be informative under specific circumstances. Autoimmune serology should be obtained, especially to detect aquaporin-4 (AQP4) antibodies (also known as NMO-IgG) associated with NMO.¹¹ Some non-infectious inflammatory disorders require systemic evaluation, such as body imaging (eg, for sarcoidosis) or paraneoplastic antibody panel for myelitis related to occult malignancy. Spinal cord biopsy should be reserved for situations in which there is concern for a neoplastic, vasculitic, or other disorder that has evaded diagnosis and in which no other site presents a likely informative biopsy target. Attention has recently been drawn to the substantial risk of further neurologic deficit complicating spinal cord biopsy that can be eliminated by a positive test for AQP4 antibodies in many patients with NMO.¹⁶

Up to half of myelitis events are preceded or accompanied by an identifiable viral illness, a clinical prodrome suggestive of infection (eg, upper re-

spiratory tract syndrome or fever), or a vaccination. Because a systemic infection or vaccination may trigger inflammatory neurologic events in patients with underlying diseases such as MS or NMO, comprehensive diagnostic evaluation is still indicated before concluding that the infection or vaccination is the primary cause of the myelitis. A presumed diagnosis of monophasic parainfectious, postinfectious, or postvaccinal transverse myelitis may be appropriate when the workup is negative, recognizing its inherent limitations. In one-third to one-half of transverse myelitis cases, an extensive neurologic and medical investigation reveals no underlying cause or disease, and the term “idiopathic transverse myelitis” is applied. Patients in this category generally have a low risk of either recurrent myelitis or other disorders such as MS or NMO.

Treatment of transverse myelitis depends on its etiology.^{10,11} Acute treatment of noninfectious myelitis includes a trial of IV methylprednisolone (ie, 1 g/d for 3 to 5 days), with an optional oral prednisone taper afterwards. Severe attacks that do not respond well to corticosteroids may improve with a course of plasma exchange (five to seven exchanges over 10 to 14 days).¹¹ The need for plasma exchange would be more common with NMO, postinfectious, or idiopathic myelitis than with MS. Immunomodulatory or immunosuppressive therapy is only indicated if the cause of myelitis poses significant risk of relapse. MS disease-modifying therapy is indicated after a single episode of myelitis in which MS is the likely cause. AQP4 antibody-positive LETM is highly likely to relapse early (approximate 60% risk at 1 year), and immunosuppressive therapy is recommended (see section on NMO treatment). Diagnosis of specific infections, connective tissue diseases, vascular

KEY POINTS

- Spinal cord biopsy should be reserved for situations in which there is concern for a disorder requiring pathologic diagnosis, especially if progressive neurologic dysfunction continues despite therapy and no other site presents a likely informative biopsy target.
- Because a systemic infection or vaccination may trigger inflammatory neurologic events in patients with underlying diseases such as multiple sclerosis or neuromyelitis optica, comprehensive diagnostic evaluation is still indicated before concluding that the infection or vaccination is the primary cause of the myelitis.
- Severe myelitis attacks that do not respond well to corticosteroids may improve with a course of plasma exchange.
- Aquaporin-antibody-positive longitudinally extensive transverse myelitis is highly likely to relapse early (approximately 60% risk at 1 year), and immunosuppressive therapy is recommended.

causes, or paraneoplastic disease may require interventions such as antiviral or other antimicrobial therapies, immunosuppression, or detection and removal of the underlying malignancy, as appropriate.

The prognosis for a patient to regain function after transverse myelitis is highly dependent on its etiology. Partial cord syndromes seen in MS are typically mild to moderate in severity and plateau after days to 2 to 4 weeks, and patients typically recover well, although achievement of final recovery may take several months. Patients with complete cord syndromes may also recover, but these syndromes are more likely to result in substantial residual neurologic deficits. Overall, 50% to 70% of patients achieve at least partial recovery and ability to walk with or without assistance. Neurologic follow-up is required, particularly for those patients judged to be at high risk for recurrent CNS disease.

NEUROMYELITIS OPTICA Historical Perspective

NMO was originally recognized as a clinical syndrome characterized by bilateral optic neuritis and severe myelitis that occurred in quick succession. Although recognized by several authors in the late 19th century, Devic's description of a single case with neuropathologic analysis and a thesis by his student, Gault, captured the most attention and led Acchiotte to propose the eponym "Devic disease."^{17,18} The similarities between MS and NMO have been recognized, and the potential differences were a matter of debate until the 21st century. In general, most pre-1990 reports emphasized the nonrelapsing nature of NMO and its tendency to spare the brain as key features differentiating it from MS. Around the same time, reports from Asia, especially Japan, described a condition called optico-spinal MS, which had a higher frequency compared to classic MS. Opticospinal MS, like its "conventional" MS counterpart, was described as a relapsing disorder, but was differentiated from MS by virtue of its frequent and severe attacks specifically targeting the optic nerve and spinal cord and by infrequent detection of CSF oligoclonal bands. At that time, the key differentiating feature between opticospinal MS and NMO was the temporal course: monophasic for NMO and relapsing for opticospinal MS. In the late 20th century, several groups recognized that the majority of patients with severe optic nerve and spinal cord selective demyelinating disease in western countries typically had a relapsing course, blurring the distinction between NMO and opticospinal MS. Diagnostic criteria for NMO were proposed, emphasizing specific clinical, MRI, and CSF features that appeared to distinguish NMO

TABLE 3-5 Diagnostic Criteria for Neuromyelitis Optica^a

- ▶ **Optic Neuritis**
- ▶ **Acute Myelitis**
- ▶ **At Least Two of the Three Supportive Criteria Below:**
 - Contiguous spinal cord MRI lesion extending over three or more vertebral segments (reliably assessed in the context of an acute myelitis)
 - Brain MRI not meeting diagnostic criteria for multiple sclerosis
 - Neuromyelitis optica-IgG seropositive status

^a Adapted from Wingerchuk DM, et al, *Neurology*.²² © 2006, American Academy of Neurology. www.neurology.org/content/66/10/1485.short?sid=c5435b8d-ac14-439a-9754-e244754ec58f.

from MS. A landmark observation in 2004 reported a high frequency of a specific autoantibody in both western NMO and typical Japanese opticospinal MS. One year later, the NMO autoantibody was found to be specific for AQP4.¹⁹ Later immunopathologic studies and passive transfer experiments provided strong evidence for the pathogenic nature of this autoantibody.²⁰ At the present time, no clear distinguishing characteristics between Asian opticospinal MS and relapsing NMO have been documented.

Definitions and Classification

The most widely accepted diagnostic criteria were those proposed by investigators at Mayo Clinic originally in 1999²¹ and then revised in 2006 (Table 3-5).²² The 1999 criteria predated the novel biomarker. Furthermore, the 1999 criteria proved insufficiently rigorous to distinguish NMO from some cases of MS with normal brain MRI scan at presentation. The revised criteria in 2006 were simplified and modified to include an independent criterion of AQP4 autoantibody seropositivity, although its detection was not required because of its imperfect sensitivity. Respecting historical tradition and clinical observations at that time, those criteria require both optic neuritis and transverse myelitis for diagnosis. At approximately the same time, a variety of clinical observations emerged in patients with otherwise definite NMO and in some patients who had limited symptoms of NMO. These observations suggested that an even broader spectrum of syndromes existed under the NMO designation, such as intractable vomiting and lesions (both symptomatic and asymptomatic) of the circumventricular organs. These syndromes sometimes preceded other,

more typical symptoms of NMO and were associated with AQP4-specific autoantibodies. Patients with NMO typically present with isolated transverse myelitis or unilateral optic neuritis. They are frequently, if not usually, seropositive at initial presentation. To embrace these patients under a more general rubric, the term “neuromyelitis optica spectrum disorders” was proposed to comprise a group of patients who probably had the same biological disorder even though they did not satisfy the strict 2006 criteria.¹² An international panel is currently determining the syndromes that warrant inclusion under this rubric. Several of the brain syndromes seem to be united by their tendency to target AQP4, which is identified either by MRI lesions in AQP4-rich areas or selective loss of AQP4 demonstrated on brain biopsy tissue.

NMO is currently classified as being either monophasic (nearly simultaneous bilateral optic neuritis and myelitis with no subsequent relapses) or relapsing (usually, but not always, presenting with unilateral optic neuritis or myelitis, followed by relapses that can include either optic neuritis or myelitis, or less frequently cerebral involvement). These subtypes seem to differ in important ways; the relapsing form is more commonly associated with AQP4 autoantibodies and also affects women and older individuals more commonly than the monophasic form.²³ Some have suggested that the much less common monophasic form may be a limited form of ADEM. Familial cases have been reported but constitute fewer than 5% of cases.²⁴

Pathophysiology

NMO has been suspected to have unique pathogenesis and to be a vasculocentric disease based on immunopathologic studies reported in

KEY POINTS

- The term “neuromyelitis optica spectrum disorders” includes a series of well-described clinical and radiologic syndromes associated with aquaporin-4 seropositivity.
- After an initial clinical presentation of a neuromyelitis optica-typical clinical syndrome such as intractable vomiting and hiccup, isolated longitudinally extensive transverse myelitis, or optic neuritis, detection of aquaporin-4 autoantibodies predicts a high risk of subsequent attacks.

KEY POINT

■ Patients with neuromyelitis optica with concomitant systemic lupus erythematosus or high-titer antinuclear autoantibodies have been commonly labeled as having lupus myelitis in the past and are now increasingly accepted as having concomitant neuromyelitis optica and systemic autoimmune disease.

the early 2000s.²⁵ The presence of perivascular immunoglobulin and activated complement suggested a humoral-mediated injury to an antigen expressed on or near microvessels. With the discovery of a specific autoantibody, advances rapidly led to the identification of AQP4-specific antibodies that target extracellular domains of this protein. This targeting is particularly avid when the protein forms large aggregates, as occurs when a certain long AQP4 isoform called M23 is expressed. Although no active immunization model has yet been reported, numerous investigators have been able to use different passive transfer strategies when the blood-brain barrier is directly bypassed (ie, by intracerebral injection) or opened either by concomitant induction of T-cell-mediated experimental allergic encephalomyelitis²⁶ or by injection of complete Freund adjuvant.²⁷ Lesions produced by passive transfer have many of the characteristic immunopathologic findings of NMO. AQP4-specific autoantibodies are of IgG1 isotype and are therefore believed to be dependent on T-cell help. A variety of studies support the importance of T-helper 17 (Th17) cells in this condition, including similar pathology (frequent neutrophilic infiltration) to Th17-polarized experimental allergic encephalomyelitis,²⁸ elevated serum and CSF levels of interleukin 6 (IL-6)²⁹ (which is a potent inducer of Th17 differentiation), elevated levels of IL-17 in CSF of NMO patients, and the predilection of an immunodominant residue of AQP4 to induce a Th17-polarized response.³⁰

Clinical Features

The dominant manifestations in most patients are optic neuritis and myelitis. In a recent series of seropositive patients, the frequencies of specific presentations were as follows: 41% optic

neuritis, 43% myelitis, 5% brain or brainstem presentations in isolation, 4% optic neuritis and simultaneous myelitis, and 7% mixed presentations (eg, optic neuritis and brain).³¹ Optic neuritis and myelitis may be difficult to distinguish from those that occur in MS, and are variable in severity. Typically, the clinical manifestations are more severe than those in MS. Transverse myelitis in NMO may be partial (ie, unilateral, motor, or sensory) or complete (ie, bilateral, motor, and sensory); by contrast, transverse myelitis due to MS is rarely complete. Radiologically, the manifestations overlap, although lesions tend to be considerably longer, especially in the spinal cord. A lesion length of three or more spinal segments is widely accepted to effectively distinguish NMO from MS. Some NMO exacerbations may not be associated with long spinal cord lesions, particularly in patients receiving immunosuppressive treatment.

Non-optic nerve and spinal cord symptoms include the following, in general order of frequency:

1. Intractable vomiting and/or hiccup typically associated with lesions in the area postrema, either in contiguity with a myelitis lesion or as an isolated lesion (**Case 3-3**)—this occurs in approximately 20% to 30% of cases and can be the first manifestation of the disease³²
2. Symptomatic forms of narcolepsy or states of altered consciousness associated with hypothalamic lesions and reduced CSF hypocretin levels³³
3. Encephalopathy associated with diffuse white matter CNS lesions that may appear similar to ADEM

Other uncommon presentations or complications include posterior reversible encephalopathy syndrome (PRES) and hyponatremia during attacks of NMO.

Case 3-3

A 34-year-old man presented with recurrent vomiting that remained unexplained after thorough gastroenterologic evaluation. The vomiting subsided but was shortly followed by imbalance and leg weakness. A lesion was detected in his cervical spinal cord extending from the medulla through C6 on T2-weighted sequences, and focal gadolinium enhancement was evident in the medulla, as well as some subpial/leptomeningeal enhancement (**Figure 3-7**). He improved after corticosteroid treatment. CSF revealed 12 white blood cells/ μL , absent oligoclonal bands, and a total protein level of 80 mg/dL. He had multiple recurrent events of myelitis over the ensuing months, all associated with longitudinally extensive spinal cord lesions. Episodes of myelitis were prevented by azathioprine treatment, but stopping azathioprine was followed by recurrent episodes of myelitis. He responded satisfactorily to treatment with corticosteroids after each attack. Repeated tests for aquaporin-4 autoantibodies in serum and testing of CSF on one occasion yielded negative results. Chest x-ray and serum angiotensin-converting enzyme were normal.

Comment. This case illustrates that recurrent attacks of longitudinally extensive myelitis, especially when preceded by intractable vomiting (a signature syndrome of neuromyelitis optica [NMO]), may lead to a working diagnosis of NMO spectrum disorder; this is true even when there has been no history of optic neuritis. Similarly, recurrent optic neuritis alone may be an indicator of NMO syndrome when NMO-IgG is detected; the proportion of cases with recurrent optic neuritis that are seropositive for NMO-IgG is lower than cases of recurrent myelitis. Often NMO-IgG may be negative in cases of clinically definite NMO; depending on the specific assay used, the seronegative rate in highly suspect cases is between 30% and 50%.

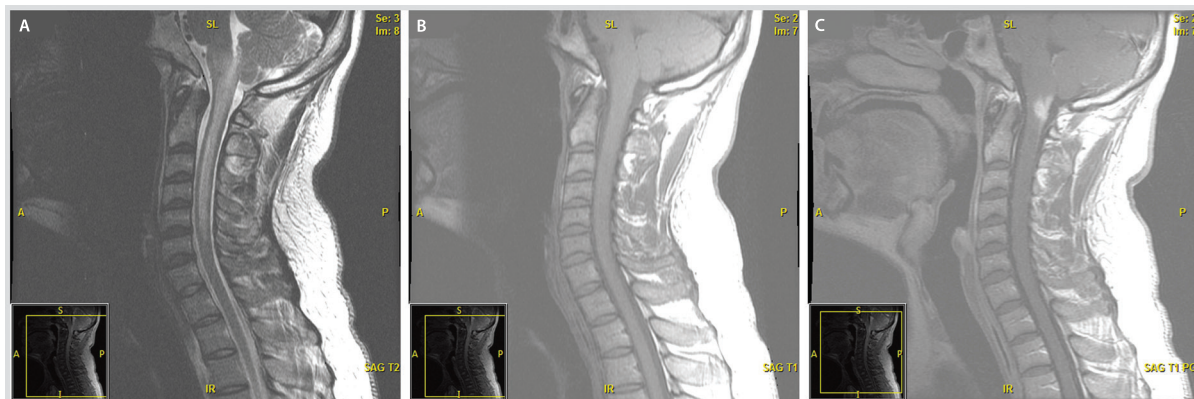


FIGURE 3-7 Cervical spinal cord MRI. Sagittal imaging reveals a longitudinally extensive transverse myelitis lesion (A, T2-weighted sequence) associated with cord swelling (B, T1-weighted sequence) and focal gadolinium enhancement (C, T1-weighted sequence).

NMO is commonly associated with other autoimmune diseases, especially systemic lupus erythematosus and Sjögren syndrome.³⁴ Myasthenia gravis occurs more commonly than expected in NMO.³⁵ The association with systemic autoimmunity has led to confusion in the past. Patients who have NMO with concomitant systemic lupus erythematosus or high-titer anti-

nuclear autoantibodies have been commonly labeled as having lupus myelitis in the past and are now increasingly accepted as having concomitant NMO and systemic autoimmune disease.

Differential Diagnosis

The differential diagnosis is largely that of optic neuritis and of myelitis as most patients present with one of

KEY POINTS

- A broad range of brain lesions have been described in association with neuromyelitis optica and aquaporin-4 antibodies.
- Aquaporin-4 antibody testing is approximately 70% sensitive and more than 90% specific for neuromyelitis optica.

these syndromes. Once other ophthalmic disorders such as acute glaucoma or retinal venous occlusion have been excluded, the major entities to be considered in the differential diagnosis of optic neuritis are ischemic optic neuropathy (sometimes associated with giant cell arteritis), toxic and metabolic amblyopia, compressive lesions of the optic nerve, sarcoidosis, and other infiltrative disorders of the optic nerve. The entities to be considered in the differential diagnosis of acute longitudinally extensive myelitis are spinal cord infarction, viral myelopathies, postinfectious inflammatory transverse myelitis (which is clinically and radiologically indistinguishable from trans-

verse myelitis in NMO), intrinsic tumors of the spinal cord (which rarely present acutely), and other inflammatory and paraneoplastic disorders.

Occasional patients present with simultaneous optic neuritis and myelitis, in which case the differential diagnosis is more limited. Rare patients have independent causes for optic neuropathy and myelopathy syndromes (eg, ischemic optic neuropathy and a viral myelitis). Conditions other than NMO that result in both inflammatory optic neuropathy and myelopathy include other CNS demyelinating syndromes (MS, ADEM), sarcoidosis, paraneoplastic disorders (ie, syndromes associated with collapsing

TABLE 3-6 Diagnostic Utility of Characteristics of Neuromyelitis Optica

Characteristic	Findings in Neuromyelitis Optica	Relative Diagnostic Utility
Race/ethnicity	NMO affects any race/ethnicity but accounts for a smaller proportion (approximately 1% to 2%) of cases of CNS demyelinating disease in white patients as compared to other groups (eg, 30% or more of African, Asian, and American Indian patients)	++
Gender	Predilection for women (80% in NMO versus 65% in MS)	+
Attack severity	Optic neuritis and transverse myelitis attacks are more severe than in MS	++
Attack characteristics	Paroxysmal tonic spasms	++
	Greater risk for neurogenic respiratory failure from acute, ascending cervical transverse myelitis in NMO compared with MS	++
Attack residual	Greater residual impairment than in MS attacks	++
Brain MRI	Normal or nonspecific findings not meeting MS MRI criteria	+++
	Hypothalamic lesions	++++
Spinal cord MRI	T2-weighted lesion extending contiguously over at least three vertebral segments	++++
CSF cell count and differential	>50 white blood cells/μL; neutrophil predominance	+++
CSF immunoglobulin studies	Negative IgG index and absence of unique oligoclonal bands	+
NMO-IgG	Seropositive	++++

NMO = neuromyelitis optica; MS = multiple sclerosis.

response mediator protein-5 [CRMP-5], which can include optic neuritis and myelitis), and rarely CNS malignancy.

The potential overlap with systemic lupus erythematosus-associated optic neuritis and myelitis was discussed above, and most such cases probably reflect coexistent NMO rather than a causative role of systemic lupus erythematosus.

Clinical, radiologic, and other laboratory characteristics that should be used in differentiating MS from NMO are outlined in **Table 3-6**.

Diagnostic Methods

Beyond recognition of clinical syndromes associated with NMO and exclusion of competing diagnoses, the main contributors to NMO diagnosis are brain and spinal cord MRI and serologic assessment.

Neuroimaging. At or near clinical onset, brain MRI in roughly 90% of patients is either normal or reveals only nonspecific white matter lesions that do not fulfill MS criteria.²¹ Serial imaging reveals new asymptomatic brain lesions in more than 60% of patients, but the pattern usually remains subcortical and nonspecific. In fact, the MRI pattern is typically not distinguishable from those caused by small vessel cerebrovascular disease.³⁶ In the context of acute optic neuritis, increased T2 signal and gadolinium enhancement of the affected optic nerve or chiasm may be seen and sometimes is longitudinally extensive. The discovery of AQP4 antibodies has allowed recognition of a broader spectrum of brain MRI lesions in the disease (**Figure 3-8**). Cerebral white matter lesions include large, confluent subcortical lesions, sometimes with cloudlike gadolinium enhancement or transient lesions reminiscent of PRES.³⁷ Corpus callosum lesions tend to be block-shaped rather than the perpendicular “Dawson fingers”

typical of MS. Diencephalic and periaqueductal lesions are also typical in NMO. Lesions may occur in the area postrema within the dorsal medulla, particularly in patients with bouts of nausea, vomiting, or hiccups.

Detection of a LETM lesion on spinal cord T2-weighted sagittal MRI is a common and very specific neuroimaging finding for NMO. In the acute phase, the lesion usually exhibits gadolinium enhancement, and on pre-gadolinium T1-weighted imaging may appear hypointense. Acute cervical cord lesions sometimes ascend into the brainstem. After several weeks or months, LETM lesions may disappear or resolve into several small, patchy lesions that can be mistaken for smaller MS plaques.

Serology. The detection of serum AQP4 antibodies is approximately 70% sensitive and more than 90% specific for NMO.¹⁹ In the setting of optic neuritis, LETM, or both, the presence of AQP4 antibodies provides strong evidence for the diagnosis of NMO or a NMO spectrum disorder and indicates high risk for recurrent optic neuritis or myelitis. The likelihood of a positive result diminishes if the patient is already receiving immunosuppressive therapy or after plasma exchange. Antibody levels may rise in association with disease activity. Therefore, it is reasonable to retest a previously seronegative patient during a new relapse. Rare patients who have been repeatedly seronegative have had AQP4 antibody detected in CSF.³⁸

Several immunologic assays have been developed for AQP4-antibody detection. The original test was an indirect immunofluorescence assay.¹⁹ At present, the most widely available test is an enzyme-linked immunosorbent assay (ELISA), and laboratories may report either dichotomous results (ie, positive or negative) or a quantitative titer. Other assay methods

KEY POINTS

- Permanent neurologic disability from neuromyelitis optica is almost all attack-related (secondary progressive neuromyelitis optica is rare); therefore, attack-prevention strategies are the key to preservation of function.
- Standard multiple sclerosis therapies such as interferon- β , natalizumab, or fingolimod may worsen neuromyelitis optica. If it is unclear whether a patient has neuromyelitis optica or multiple sclerosis, an immunosuppressive treatment strategy typically used for neuromyelitis optica should be considered to avoid inadvertent disease aggravation.

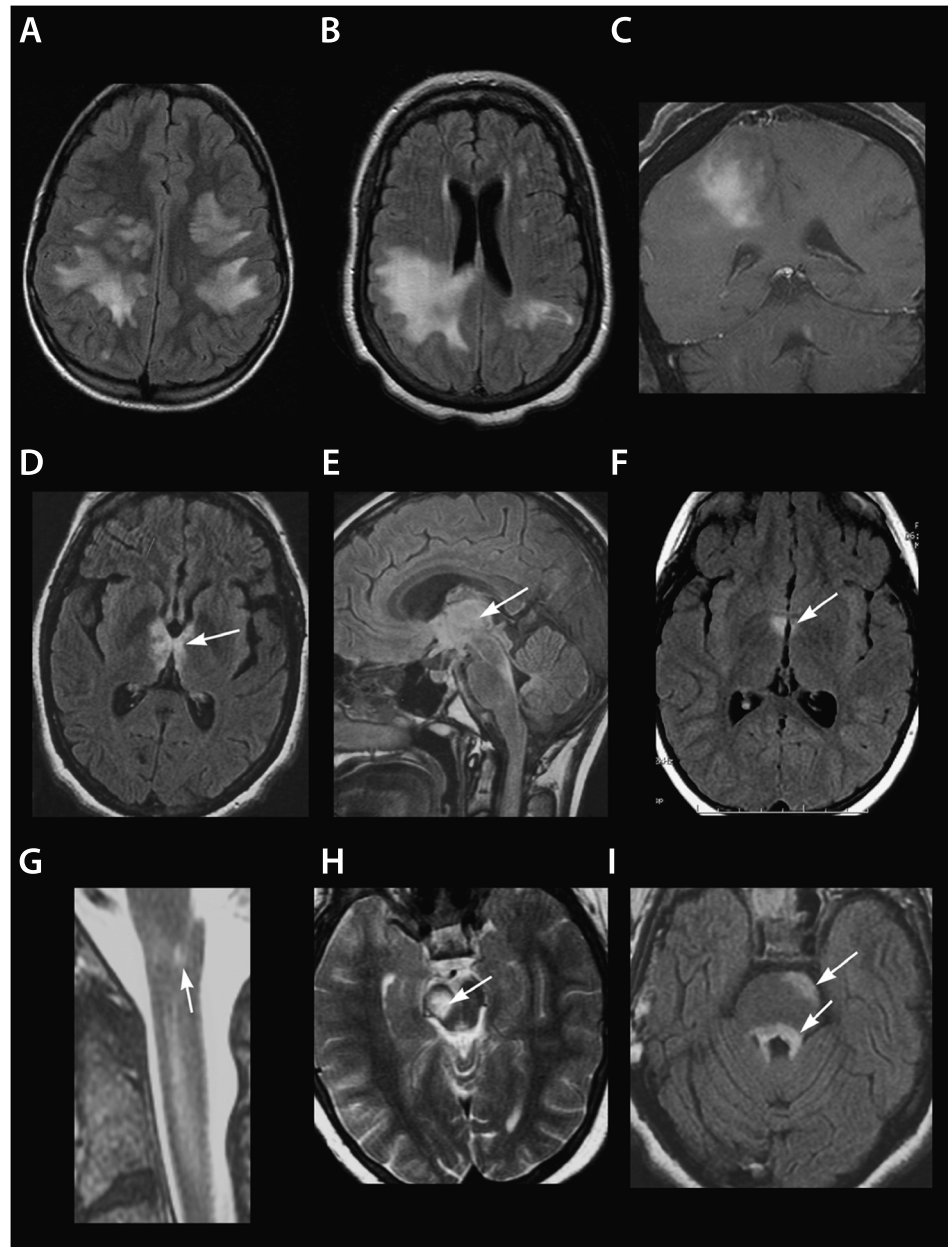


FIGURE 3-8 Brain lesions in patients with neuromyelitis optica (NMO) and NMO spectrum disorders. *Panels A, B, and C* show cerebral hemispheric white matter lesions; *panels D, E, and F* show diencephalic lesions; *panels G, H, and I* show brainstem lesions. Extensive bihemispheric subcortical nonenhancing white matter fluid-attenuated inversion recovery (FLAIR) signal abnormality (A). Large confluent FLAIR signal abnormality in the right parietal area (B) with diffuse gadolinium enhancement (C). Images from one patient show FLAIR abnormality in the hypothalamus (F, arrow) and right cerebral peduncle (H, arrow). FLAIR signal abnormality in the thalamus (E, arrow), hypothalamus, and optic chiasm extending into the superior cerebellar peduncle and the floor of the fourth ventricle. Images from a patient with a confluent nonenhancing signal abnormality from the anterosuperior thalamus-hypothalamus (D, arrow) to the optic tracts behind the chiasm to the superior surface of the mesencephalon extending to the periaqueductal area (right to left) to the superior cerebellar peduncles, and the pontine tegmentum (I, arrows). Extension of T2-weighted MRI signal abnormality into the medulla (G, arrow).

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include immunoprecipitation and cell-based assays, the latter of which involves cells that express human AQP4. In a blinded, direct comparison of these methods, all assays had strong specificity, but the cell-based assays demonstrated the highest sensitivity and may eventually become the reference standard.³⁹

Pathologic examination. The vast majority of NMO cases can be identified using clinical criteria, MRI, and serologic testing. Some perplexing cases have undergone spinal cord or brain biopsy or come to autopsy, revealing immunopathologic differences between NMO and MS. In particular, NMO is associated with vasocentric deposition of immunoglobulin and complement.

Lesions may reveal eosinophils within a vigorous cellular infiltrate. Moreover, in actively demyelinating NMO lesions, AQP4 is depleted, whereas in MS, similarly active plaques reveal AQP4 upregulation (Figure 3-9).^{40,41} The authors do not generally advocate biopsy for NMO diagnosis, but in unusual situations, such as seronegative patients with progressive leukoencephalopathy or extensive, treatment-unresponsive cord lesions, biopsy may be considered.

Prognosis

NMO is generally a more severe disease than MS. Individual attacks are more likely to result in a permanent neurologic deficit. In one study,

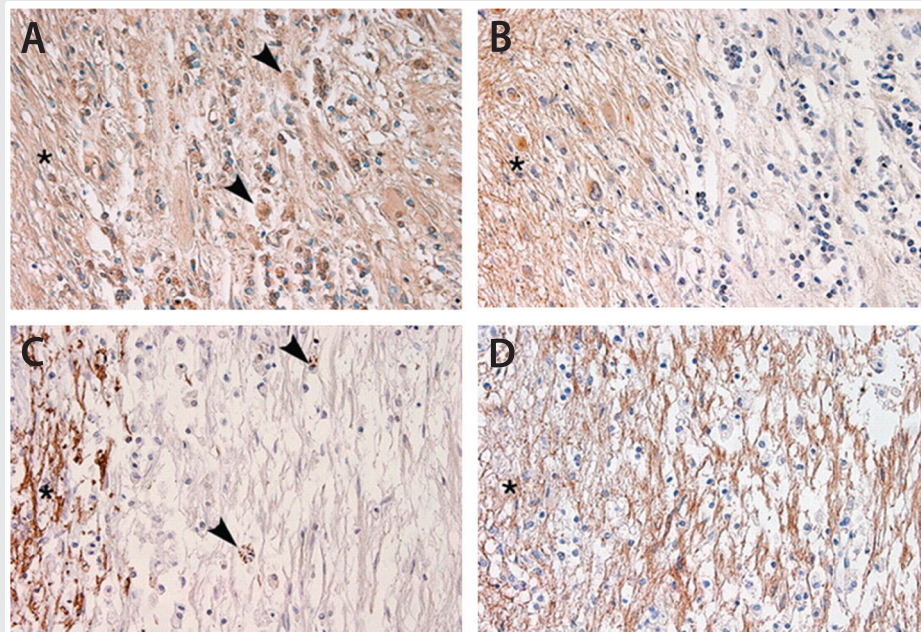


FIGURE 3-9 Comparison of aquaporin-4 (AQP4) immunoreactivity (IR) in active neuromyelitis optica (A, B) and multiple sclerosis (C, D) optic nerve lesions. A, Active demyelination with macrophages containing myelin oligodendrocyte glycoprotein (MOG)-immunoreactive myelin debris (*arrowheads*), adjacent to periplaque white matter (*asterisk*). B, AQP4 is lost in the active lesion but retained in the periplaque white matter (*asterisk*). C, Active demyelination with macrophages containing proteolipid protein-immunoreactive myelin debris (*arrowheads*), adjacent to periplaque white matter (*asterisk*). D, AQP4 IR is increased in both the active lesion and periplaque white matter (*asterisk*). Immunohistochemistry: A, MOG; B, D, AQP4; C, proteolipid protein.

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50% of NMO patients were blind in at least one eye or required ambulatory assistance within 5 years of disease onset.⁴² Unlike typical MS, in which most disability accrues during a secondary progressive disease phase, NMO disability occurs as a result of individual attacks, and gradually progressive disability like that seen in secondary progressive MS is rare.⁴³ The expansion of the NMO spectrum has probably uncovered milder and more heterogeneous cases. Recently, French investigators asked whether “benign” NMO exists by evaluating outcomes of 175 patients with NMO over 10 years.⁴⁴ Although mild disability was noted in about 12% of these patients (compared with 22% of MS patients over that time frame), several of them experienced a disabling attack before year 15. Therefore, all NMO patients should be considered at risk of disabling attacks. Together with the rarity of a secondary progressive NMO course, this attack-related threat emphasizes the importance of attack-prevention strategies to prevent disability.

Treatment

Treatment of NMO is evolving because of collective longitudinal experience in large care centers and advances in understanding disease pathobiology. There are no randomized controlled trials for NMO therapies.

Acute attacks are typically treated with corticosteroids and, if necessary, rescue plasma exchange as outlined in the discussion of transverse myelitis. Relapse prevention strategies are meant to reduce or eliminate the effects of pathogenic AQP4 antibodies, either directly or indirectly. The importance of accurate diagnosis has been heightened recently because of a number of reports indicating that the standard MS therapy interferon- β aggravates NMO.⁴⁵ Furthermore, worsening of NMO has

been reported with other MS therapies such as natalizumab and, less convincingly, fingolimod.^{46,47} Therefore, in situations where the diagnosis remains uncertain between NMO and MS, the authors favor starting with an NMO immunosuppression strategy because it is likely to provide benefit in treating either disease, and the subsequent clinical course will usually reveal the correct diagnosis.

General immunosuppression strategies. Patients with established relapsing NMO and those deemed to be at high risk for relapse (eg, patients with seropositive NMO spectrum disorder such as those with first-ever LETM or optic neuritis) require long-term immunosuppressive therapy.^{12,48} The most common approaches to immunosuppression include oral drugs (eg, azathioprine or mycophenolate mofetil) or parenteral drugs (eg, rituximab). In retrospective series, these agents appear to reduce relapse rates by 30% to 70%, but no controlled or comparative studies have confidently established the magnitude of treatment effect. Azathioprine and mycophenolate have delayed onset of action and typically require bridge therapy for 4 to 6 months, usually with oral prednisone (40 to 60 mg/d). Rituximab (1000 mg/d twice, 2 weeks apart, with retreatment approximately every 6 months) is fully active within about 2 weeks but is substantially more expensive. In some countries, mitoxantrone, methotrexate, or chronic oral prednisone represent the mainstay of preventive therapy; a consensus summary review of the use of these therapies was recently published.⁴⁸

Regardless of which drug is selected, the goal of therapy is elimination of acute relapses by optimizing drug dosage, retreatment frequencies, and compliance. Patient compliance can be monitored unequivocally for rituximab but only indirectly for azathioprine (ie,

elevation in mean corpuscular volume). The key outcome evaluation is the occurrence of breakthrough attacks. Unfortunately, no predictive or therapeutic biomarkers in NMO have been validated. Repeat neuroimaging will usually not yield treatment-changing information. AQP4 antibody titer tends to decrease with immunosuppression, but this is not consistently associated with clinical course.

Rapid advances in our understanding of immunopathogenic mechanisms in NMO are informing therapeutic strategies.⁴⁹ A recent open-label study of eculizumab, a monoclonal antibody that affects cleavage of complement, showed a marked reduction in on-study attack rate and resumption of attacks in some patients after the drug was discontinued.⁵⁰ Inference from human immunopathology and animal-model data suggests potential roles for therapies aimed at interrupting B-cell, T-cell, complement, or cytokine function. Moreover, particularly interesting strategies are now being developed to interfere with AQP4 antibody structure or antigen binding. Aquaporin is a nonpathogenic recombinant antibody that competes with anti-AQP4 for antigen binding.⁵¹ In cell cultures and in a passive-transfer animal model, aquaporin eliminated complement-mediated and cell-mediated cytotoxicity induced by AQP4 antibody. Small-molecule screening has identified a series of compounds that can also interfere with antibody binding. Some of these agents, including antivirals, flavonoids, and berbamine alkaloids, are available for testing.⁵² Selective deglycosylation of the AQP4 antibody heavy chain mitigates its pathogenic effects and may convert it to an aquaporin-like blocking antibody.⁵³ Antigen-specific treatment strategies are some distance from clinical use but illustrate rapid application of

emerging pathophysiologic information toward therapy.

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