DISCUSSION

A highly specific autoantibody directed against aquaporin-4 is present in the sera of approximately two-thirds of patients with a clinical diagnosis of NMO. Seropositive patients have a very high risk for future relapses; more than half will relapse within 1 year if untreated. Aquaporin-4 is localized to the foot processes of astrocytes in close apposition to endothelial surfaces, as well as at paranodal regions near nodes of Ranvier. It is likely that aquaporin-4 antibodies are patho-

Diagnostic criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses[a]

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status

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. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses[a]

Core clinical characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis lesions; NMOSD = neuromyelitis optica spectrum disorders.

Table 2 Red flags: Findings atypical for NMOSD

Red flags (clinical/laboratory)
1. Clinical features and laboratory findings
Progressive overall clinical course (neurologic deterioration unrelated to attacks; consider MS)
Atypical time to attack nadir: less than 4 hours (consider cord ischemia/infarction); continual worsening for more than 4 weeks from attack onset (consider sarcoidosis or neoplasm)
Partial transverse myelitis, especially when not associated with LETM MRI lesion (consider MS)
Presence of CSF oligoclonal bands (oligoclonal bands occur in <20% of cases of NMO vs >80% of MS)
2. Comorbidities associated with neurologic syndromes that mimic NMOSD
Sarcoidosis, established or suggestive clinical, radiologic, or laboratory findings thereof (e.g., mediastinal adenopathy, fever and night sweats, elevated serum angiotensin converting enzyme or interleukin-2 receptor levels)
Cancer, established or with suggestive clinical, radiologic, or laboratory findings thereof; consider lymphoma or paraneoplastic disease (e.g., collapsin response mediator protein-5 associated optic neuropathy and myelopathy or anti-Ma-associated diencephalic syndrome)
Chronic infection, established or with suggestive clinical, radiologic, or laboratory findings thereof (e.g., HIV, syphilis)

Red flags (conventional neuroimaging)
1. Brain
a. Imaging features (T2-weighted MRI) suggestive of MS (MS-typical)
Lesions with orientation perpendicular to a lateral ventricular surface (Dawson fingers)
Lesions adjacent to lateral ventricle in the inferior temporal lobe
Juxtacortical lesions involving subcortical U-fibers
Cortical lesions
b. Imaging characteristics suggestive of diseases other than MS and NMOSD
Lesions with persistent (>3 mo) gadolinium enhancement
2. Spinal cord
Characteristics more suggestive of MS than NMOSD
Lesions <3 complete vertebral segments on sagittal T2-weighted sequences
Lesions located predominantly (>70%) in the peripheral cord on axial T2-weighted sequences
Diffuse, indistinct signal change on T2-weighted sequences (as sometimes seen with longstanding or progressive MS)

Abbreviations: LETM = longitudinally extensive transverse myelitis lesions; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders. These are some common or key findings that should prompt thorough investigation for competing differential diagnoses before making a diagnosis of NMOSD.