Neuromyelitis Optica

Chapter 456 | Part 13: Neurologic Disorders

KEY CLINICAL POINTS

1. NMO is an aggressive, antibody-mediated inflammatory disorder characterized by recurrent attacks of optic neuritis (ON) and myelitis.
2. NMOSD (Neuromyelitis Optica Spectrum Disorder) incorporates partial forms and additional CNS involvement.
3. Anti-AQP4 antibodies are present in ~90% of patients; AQP4 is localized to astrocyte foot processes.
4. Hallmark MRI finding: Longitudinally extensive transverse myelitis (LETM) extending over ≥3 contiguous vertebral segments.
5. Area postrema syndrome (hiccups/vomiting) is a specific clinical feature of NMO.
6. MS therapies (interferon beta, glatiramer acetate) are ineffective or harmful in NMO.
7. MOGAD presents with papillitis and 'fluffy' brain lesions, distinct from NMO.
8. GFAP autoimmunity presents as a paraneoplastic syndrome with meningismus, encephalitis, and optic neuritis.
9. 5-year survival increased from 68–75% (1999) to 91–98% (2017) due to improved immune-suppressing therapies.
10. AQP4-seronegative patients have lower relapse risk (~50% have single attack) but still require monitoring.

1. DEFINITION & OVERVIEW

- **Definition (Harrison's 22e):**
  - NMO is an autoimmune disease associated with a highly specific autoantibody directed against the water channel protein AQP4 that is present in the sera of ~90% of affected patients.
- **NMOSD Classification:**
  - Neuromyelitis Optica Spectrum Disorder (NMOSD) incorporates individuals with partial forms and those with involvement of additional structures in the central nervous system.
- **AQP4 Localization & Pathophysiology:**
  - AQP4 is located in astrocyte foot processes near endothelial surfaces and at paranodal regions near nodes of Ranvier.
  - Pathology involves loss of AQP4, antibody/complement deposition, and cytolysis of astrocytes.
  - Mechanisms: Complement fixation and antibody-dependent cell-mediated cytotoxicity (ADCC) contribute to injury; T17 lymphocytes recognize an immunodominant epitope of AQP4.
- **Clinical Significance:**
  - High specificity of the antibody makes it diagnostic when paired with typical clinical presentation.
  - Seropositive patients have high risk for future attacks; >50% will relapse within 1 year if untreated.

2. EPIDEMIOLOGY

- **Demographics:**
  - Female predominance (9:1).
  - Mean age of onset: 40 years.
- **Prevalence & Geography:**
  - Varies by region; ~4 per 100,000.
  - Disproportionately affects individuals of Asian and African origin.
  - Highest reported prevalence is in Martinique.
- **Comparison to MS:**
  - In white populations, MS is far more common than NMO.
- **Associated Factors:**
  - May follow acute infections (VZV, EBV, HIV, or tuberculosis).
  - Rare cases are paraneoplastic (associated with breast, lung, or other cancers).

3. ETIOLOGY & PATHOPHYSIOLOGY

- **Immune Mechanisms:**
  - Proinflammatory T lymphocytes of the T17 type recognize immunodominant AQP4 epitopes.
  - Potential impairment of B lymphocyte-mediated tolerance in the thymus may contribute to pathogenesis.
- **Biomarkers during Acute Myelitis:**
  - CSF levels of interleukin-6 (IL-6) and glial fibrillary acidic protein (GFAP) are markedly elevated, indicating active inflammation and astrocyte injury.
- **Systemic Associations:**
  - Up to 40% of NMO patients have systemic autoimmune disorders (SLE, Sjögren's, p-ANCA-associated vasculitis, myasthenia gravis, Hashimoto's thyroiditis, or mixed connective tissue disease).
  - Distinct from MS: MS patients rarely have comorbid autoimmune diseases other than hypothyroidism.

MOG Antibody-Associated Disease (MOGAD):

- **Pathology:**
  - Associated with anti-myelin oligodendrocyte glycoprotein (MOG) antibodies.
  - Risk for bilateral, synchronous optic neuritis and myelitis.
- **Distinguishing Features:**
  - Presence of papillitis (common in MOGAD, rare in NMO).
  - Brain MRI: 'fluffy' areas of signal change; lacks MS-typical features (e.g., Dawson fingers).
  - CSF: Pleocytosis with occasional neutrophils; OCBs present in only ~6–13%.
- **Treatment Response:**
  - Often responds rapidly to glucocorticoids; some may become glucocorticoid dependent.
- **Clinical Trials:**
  - Satralizumab and rozanolixizumab (Rystiggo) are under investigation for MOGAD.
- **Off-label Management:**

– Daily prednisone, IVIG, rituximab, and mycophenolate mofetil.

GFAP Autoimmunity:

- **Clinical Presentation:**
  – Symptoms include meningismus, encephalitis, myelitis, and optic neuritis; often follows a viral prodrome.
- **Imaging:**
  – Serpiginous pattern in brain parenchyma; periependymal spinal cord involvement. Similar to neurosarcoidosis.
- **Paraneoplastic Link:**
  – ~25% are paraneoplastic (e.g., ovarian teratoma); can coexist with NMDAR encephalitis or AQP4 NMO.
- **Treatment:**
  – Generally glucocorticoid responsive; early intervention improves outcomes.

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4. CLINICAL FEATURES

- **Course of Disease:**
  – Typically recurrent; monophasic in <10%.
  – AQP4-negative patients are more likely to have a monophasic course.
  – Significant disability: 1/3 with respiratory failure from cervical myelitis; high rates of blindness and paralysis after 8 years.
- **Optic Neuritis (ON):**
  – Often bilateral and severe (uncommon in MS).
- **Myelitis:**
  – Causes accumulation of disability via attack-related injury.
- **Brain MRI Findings:**
  – Non-specific signal changes; specific syndromes: area postrema (hiccups/vomiting), hypothalamus (sleep disorder/endocrinopathy), and cerebral hemispheres (focal symptoms, encephalopathy, or seizures).
  – Cerebral lesions are often 'cloud-like' and may resolve completely.
- **Spinal Cord MRI:**
  – Focal enhancing areas of swelling/destruction; ≥3 segments; centered on gray matter.
- **CSF Findings:**
  – Pleocytosis > MS; neutrophils and eosinophils common in acute cases.
  – Oligoclonal bands (OCBs): uncommon (<20%).

Core Clinical Characteristics:

1. Optic neuritis.
2. Acute myelitis.
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea or vomiting.
4. Acute brainstem syndrome.
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome (hypothalamic dysfunction) with NMOSD-typical diencephalic MRI lesions.
6. Symptomatic cerebral syndrome with NM10-typical brain lesions.

Associated Conditions:

- Up to 40% have systemic autoimmune disorders (SLE, Sjögren's, p-ANCA-associated vasculitis, myasthenia gravis, Hashimoto's, or MCTD)."

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5. DIFFERENTIAL DIAGNOSIS

- **NMO vs. MS:**
  - Opt1ic Neuritis: NMO is often bilateral/severe; MS is usually unilateral.
  - Myelitis: NMO is longitudinally extensive (≥3 segments); MS is typically short.
  - Progression: NMO rarely has progressive symptoms; MS does.
  - MRI: MS shows Dawson fingers and T1 hypointense lesions (rare in NMO).
- **MOGAD vs. NMO/MS:**
  - MOGAD features papillitis; differentiation from NMO is key.
  - MOGAD may be monophasic (like ADEM) but can be recurrent.
- **GFAP Autoimmunity:**
  - Presents with meningismus and encephalitis; often paraneoplastic."

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6. INVESTIGATIONS & DIAGNOSIS

- **Diagnostic Criteria (Table 456-1):**
- **With AQP4-IgG:**
  - At least one core clinical characteristic.
  - Positive test for AQP4-IgG (cell-based assay).
  - Exclusion of alternative diagnoses.
- **Without/Unknown AQP4-IgG:**
  - At least two core clinical characteristics from one or more attacks.
  - Must meet:

a. At least one must be optic neuritis, acute myelitis with LETM, or area postrema syndrome.

b. Dissemination in space (two or more different clinical characteristics).

c. Fulfillment of specific MRI requirements (see below).

  - Negative test for AQP4-IgG or testing unavailable.
  - Exclusion of alternative diagnoses.

- **Additional MRI Requirements (for AQP4-negative/unknown):**

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

- **MOGAD Criteria (Table 456-3):**

1. At least one core clinical event (Optic neuritis, Myelitis, ADEM, Cerebral/Brainstem/Cerebellar deficits, or Encephalitis).
2. Positive MOG IgG test (cell-based assay).
   - – Clear positive: No additional requirements.
   - – Low/No titer or CSF only: Must be AQP4-seronegative and have supporting features:
   - • Optic neuritis: bilateral synchronous, >50% of length of optic nerve involvement, perineural optic nerve sheath enhancement, disc edema.
   - • Myelitis: longitudinally extensive, central cord involvement or "H sign," conus involvement.
   - • Brain/brainstem/cerebellar: ill-defined lesions, deep gray matter involvement, cortical lesions with or without overlying meningeal enhancement.
3. Exclusion of better diagnoses including MS.

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7. MANAGEMENT & TREATMENT

1. **Acute Attack Management:**

→ High-dose glucocorticoids (e.g., methylprednisolone 1 g/d for 5–10 days) followed by a prednisone taper.

2. **Refractory Acute Episodes:**

→ Plasma exchange: typically 5–7 exchanges of 1.5 plasma volumes per exchange.

3. **Prophylaxis (General):**

→ Recommended for nearly all patients due to poor natural history.

4. **Approved Prophylactic Agents (AQP4-positive) & Risk Reductions (Table 456-2):**
   - • Eculizumab: 94% risk reduction in AQP4-seropositive cases.
   - • Inebilizumab: 78% risk reduction.
   - • Satralizumab: 74% risk reduction.
5. **Management of AQP4-negative Patients:**

→ Risk of relapse is lower (half have only one attack).

→ Treatment: Empiric therapies such as rituximab or mycophenolate mofetil.

6. **MOGAD Management:**

→ Standard options include prednisone, IVIG, rituximab, and mycophenolate mofetil."

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8. PROGNOSIS & COMPLICATIONS

- **Survival:**
  - – Improved from 68–75% (1999) to 91–98% (2017) due to improved diagnosis and immune-suppressing therapies.
- **Disability:**
  - – Untreated NMO is severely disabling; high risk of blindness and paralysis.
  - – Progression: Rare in NMO; disability is usually attack-related.
  - – Respiratory failure from cervical myelitis occurs in 1/3 of patients."

9. SPECIAL CONSIDERATIONS

- **Pediatric & Infectious:**
  - MOGAD more common in children; often presents as ADEM.
  - Some cases associated with VZV, EBV, HIV, or TB."

10. KEY PEARLS & CLINICAL TRAPS

- **NMO vs. MS:**

→ NMO: ≥3 segments (LETM), bilateral ON, area postrema syndrome, high IL-6/GFAP.

→ MS: <3 segments, unilateral ON, Dawson fingers, OCBs present.

- **Area Postrema Syndrome:**

→ Hallmark of NMO; presents as intractable hiccups or vomiting.

- **MOGAD Distinction:**

→ Look for papillitis and 'fluffy' lesions to differentiate from NMO/MS.

- **Treatment Choice:**

→ Use Inebilizumab or Satralizumab as first-line for AQP4+; use Rituximab/Mycophenolate for AQP4-."

REFERENCE TABLES

TABLE 456-1

Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder (NMOSD) Diagnostic Criteria for NMOSD with AQP4-IgG 1....

- Diagnostic Criteria for NMOSD with AQP4-IgG
- 1. At least one core clinical characteristic 2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) 3. Exclusion of alternative diagnoses
- Diagnostic Criteria for NMOSD without AQP4-IgG or NMOSD with Unknown AQP4-IgG Status
- 1. At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: a. At least one core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome b. Dissemination in space (two or more different clinical characteristics) c. Fulfillment of additional MRI requirements, as applicable 2. Negative test for AQP4-IgG using best available detection method or testing unavailable 3. Exclusion of alternative diagnoses
- Core Clinical Characteristics
- 1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea or vomiting 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome (hypothalamic dysfunction) with NMOSD-typical diencephalic MRI lesions 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions
- 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 of T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm 2.

Acute myelitis: requires associated intramedullary MRI lesion extending ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis 3. Area postrema syndrome requires associated dorsal medulla/area postrema lesions 4. Acute brainstem syndrome requires periependymal brainstem lesions

TABLE 456-2

Attack Risk Reductions of Approved Neuromyelitis Optica Spectrum Disorder (NMOSD) Treatments

	RISK REDUCTION IN AQUAPORIN-4–SEROPOSITIVE NMOSD
Eculizumab (add-on to immune suppression)	94%, p <.001
Inebilizumab (monotherapy)	78%, p = .01
Satralizumab (add-on to immune suppression)	74%, p = .001

TABLE 456-3

Diagnostic Criteria for Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disease (MOGAD) Diagnostic Criteria for...

- Diagnostic Criteria for MOGAD
- 1. At least one core clinical event: Optic neuritis Myelitis ADEM Cerebral monofocal or polyfocal deficits Brainstem or cerebellar deficits Cerebral or cortical encephalitis often with seizures
- 2. Positive MOG IgG test (cell-based assay) Clear positive – no additional requirements Low positive, or positive without titer or CSF positive only – Must be AQP4 seronegative and have one or more of the following supporting features
- Supporting clinical or radiographic features: Optic neuritis – bilateral synchronous, >50% of length of optic nerve involvement, perineural optic nerve sheath enhancement, disc edema Myelitis – longitudinally extensive, central cord involvement or "H sign," conus involvement Brain/brainstem/cerebellar – ill-defined lesions, deep gray matter involvement, cortical lesions with or without overlying meningeal enhancement
- 3. Exclusion of better diagnoses including MS