Neuromyelitis Optica

Neuromyelitis optica spectrum disorders (NMOSD) are rare relapsing autoimmune disorders that cause inflammation specifically in the optic nerve and spinal cord. Aquaporin-4 receptor (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibody testing is used for diagnosis and evaluation of neuromyelitis optica (NMO), acute myelitis, spinal cord lesions, autoimmune encephalitis, or NMOSD.

**DISEASE OVERVIEW**

**Incidence**

Acute transverse myelitis (TM) – 1-4/100,000
- <1% is NMOSD
  - Female: male, 5:1 for relapsing NMOSD associated with AQP4 antibodies
  - Gender ratio closer to 1:1 for MOG antibodies

**Symptoms**

- Ophthalmic – ocular pain, visual disturbances, optic neuritis
- Neurological – symmetrical para- or quadriparesis, bowel and bladder dysfunction

**Diagnostic Issues**

- NMOSD is often mistaken for multiple sclerosis (MS)
- Individuals with NMOSD have a worse prognosis
- Treatment differs between NMOSD and MS
  - NMOSD – immunosuppressive therapy or plasmapheresis
  - MS – immune-modulation therapy
    - Corticosteroids administered only during periods of worsening inflammation

**Physiology**

- Neuromyelitis optica-specific immunoglobulin (NMO-IgG) recognizes the water-channel protein AQP4
- Presence of AQP4 antibody is important in the differential diagnosis of NMOSD from other TM diseases
  - ~75% of patients with NMO express antibodies to the AQP4 receptor
  - A subset of patients with NMOSD who are seronegative for AQP4 antibodies express antibodies to MOG
- MOG antibody is found in a subset of patients with NMOSD, including optic neuritis and TM, brainstem encephalitis, and acute disseminated encephalomyelitis (ADEM)
  - Persistence of antibody positivity may be associated with a relapsing course
- TM disorders
  - MS
  - NMO
  - ADEM
  - Optic spinal MS (OSMS)
  - Longitudinally extensive spinal cord lesions/TM (LESCL/LETM)
  - Acute complete TM (ACTM)
  - Acute partial TM (APTM)

**TESTS TO CONSIDER**

**Aquaporin-4 Receptor Antibody**
- **Method:** Semi-Quantitative Enzyme-Linked Immunosorbent Assay
  - Aid in evaluation of NMO and NMOSD
- **Aquaporin-4 Receptor Antibody, IgG by IFA with Reflex to Titer, Serum**
  - **Method:** Semi-Quantitative Indirect Fluorescent Antibody
    - Useful for initial evaluation of NMOSD
- **Aquaporin-4 Receptor Antibody by ELISA with Reflex to Aquaporin-4 Receptor Antibody, IgG by IFA**
  - **Method:** Semi-Quantitative Enzyme-Linked Immunosorbent Assay/ Semi-Quantitative Indirect Fluorescent Antibody
    - For evaluation of optic neuritis, acute myelitis, spinal cord lesions, or autoimmune encephalitis
    - Useful in the interpretation of low-positive ELISA results when suspicion for disease is low or questionable
    - ELISA is less subjective than CBA by IFA and has comparable diagnostic performance, with a slight increase in sensitivity
    - CBA by IFA may provide additional support of a positive ELISA result
    - If CBA by IFA and ELISA are both positive, ELISA is preferred method for monitoring patients over time, as it is less subjective
- **Aquaporin-4 Receptor Antibody, IgG by IFA, CSF with Reflex to Titer**
  - **Method:** Semi-Quantitative Indirect Fluorescent Antibody
    - Use in conjunction with serum autoantibody tests to diagnose NMO
- **Myelin Oligodendrocyte Glycoprotein (MOG) Antibody, IgG by IFA with Reflex to Titer, Serum**
  - **Method:** Semi-Quantitative Indirect Fluorescent Antibody
    - Useful for initial evaluation of central nervous system (CNS) demyelinating disease or autoimmune encephalitis
Autoimmune CNS Demyelinating Disease Reflexive Panel 3001283
Method: Semi-Quantitative Indirect Fluorescent Antibody
Useful for initial evaluation of inflammatory CNS demyelinating disease, including NMOSD and NMOSD-like disorders, or autoimmune encephalitis

See Related Tests

Differentiated from other TM disorders
- Clinical course (monophasic or relapsing)
- The presence and extent of lesions evident with magnetic resonance imaging (MRI)
  - Spinal cord
  - Brain
- Accompanying presence of optic nerve inflammation (optic neuritis)
- Presence of AQP4 or MOG autoantibodies

Diagnostic Criteria
Required for diagnosis of NMOSD
- NMOSD with AQP4-IgG
  - At least one core clinical characteristic
  - Positive for AQP4-IgG (cell-based assay by IFA or FACS preferred)
  - Exclusion of alternative diagnoses
- NMOSD without AQP4-IgG (negative or unknown)
  - At least two core clinical characteristics associated with one or more clinical attacks meeting the following criteria:
    - Presence of at least one of the first three core clinical characteristics (if myelitis, one characteristic should be LETM)
    - Dissemination in location (at least two different core clinical characteristics)
    - MRI findings consistent with respective core clinical characteristics
  - Negative for AQP4-IgG (or testing unavailable)
  - Exclusion of alternative diagnoses
- Core clinical characteristics
  - Optic neuritis
  - Acute myelitis
  - Area postrema syndrome (episode of otherwise unexplained intractable nausea and vomiting or hiccups)
  - Acute brainstem syndrome
  - Symptomatic diencephalic clinical syndrome with NMOSD-typical MRI lesions or narcolepsy
  - Symptomatic cerebral syndrome with NMOSD-typical brain lesions

TEST INTERPRETATION

Sensitivity/Specificity

AQP4 Antibody
- When criteria are met
  - Clinical sensitivity – 76% for NMO
  - Clinical specificity – 94% for NMO
- AQP4 antibody detection by ELISA compared to IFA
  - Analytical sensitivity – 97%
  - Analytical specificity – 96.3%
- Detection of AQP4-IgG by IFA compared to ELISA
  - Analytical sensitivity – 91%
  - Analytical specificity – 99%
- Overall agreement between ELISA and IFA detection methods – 96%

MOG Antibody
- Detection of MOG-IgG by IFA compared to FACS
  - Analytical sensitivity – 90.9% (10/11; one low-positive FACS specimen was negative by IFA)
  - Analytical specificity – 100%
  - Overall agreement between IFA and FACS detection methods – 98.8%

Results

Positive

AQP4 Antibody
- AQP4 receptor antibody – ≥3 U/mL
- AQP4 receptor antibody with reflex – antibody detected and titered
- AQP4 receptor antibody, cerebrospinal fluid (CSF), with reflex – antibody detected and titered
MOG Antibody

- MOG antibody with reflex – antibody detected and titered

Negative

AQP4 Antibody

- AQP4 receptor antibody – ≤3 U/mL
- AQP4 receptor antibody, serum, with reflex – <1:10
- AQP4 receptor antibody, CSF, with reflex – <1:1

MOG Antibody

- MOG antibody, with reflex – <1:10

Limitations

- Absence of antibodies to the AQP4 receptor or MOG does not rule out a diagnosis of NMOSD
- A negative result can occur in the setting of immunosuppression therapy
- Testing by ELISA is not a suitable method for detecting AQP4 antibodies in CSF
- Test performance may vary due to differences in methods and/or new versus established disease states

REFERENCES


RELATED INFORMATION

Multiple Sclerosis
Neuromyelitis Optica Spectrum Disorders

RELATED TESTS

Autoimmune Encephalitis Reflexive Panel 2013601
Method: Semi-Quantitative Indirect Fluorescent Antibody/Semi-Quantitative Enzyme-Linked Immunosorbent Assay/Quantitative Radioimmunoassay

Autoimmune Encephalitis Extended Panel 3001431
Method: Semi-Quantitative Indirect Fluorescent Antibody/Quantitative Radioimmunoassay/Semi-Quantitative Enzyme-Linked Immunosorbent Assay

N-methyl-D-Aspartate Receptor Antibody, IgG, Serum with Reflex to Titer 2004221
Method: Semi-Quantitative Indirect Fluorescent Antibody

Glutamic Acid Decarboxylase Antibody 2001771
Method: Semi-quantitative Enzyme-Linked Immunosorbent Assay

Voltage-Gated Potassium Channel (VGKC) Antibody, Serum 2004890
Method: Quantitative Radioimmunoassay

Leucine-Rich, Glioma-Inactivated Protein 1 Antibody, IgG with Reflex to Titer 2009456
Method: Semi-Quantitative Indirect Fluorescent Antibody

Contactin-Associated Protein-2 Antibody, IgG with Reflex to Titer 2009452
Method: Semi-Quantitative Indirect Fluorescent Antibody

Alpha- amino-3-hydroxy-5-methyl-4-isoxazolopropionic Acid (AMPA) Receptor Antibody, IgG by IFA with Reflex to Titer, Serum 3001260
Method: Semi-Quantitative Indirect Fluorescent Antibody

Gamma Aminobutyric Acid Receptor, Type B (GABA-BR) Antibody, IgG by IFA with Reflex to Titer, Serum 3001270
Method: Semi-Quantitative Indirect Fluorescent Antibody