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 2003036

Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay

Useful for initial evaluation of NMOSD

Aquaporin-4 Receptor Antibody by ELISA with Reflex to Aquaporin-4 Receptor Antibody, IgG by IFA 2013327

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
- 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 2011699

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 3001277

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[1]

- 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

1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177-189. PubMed

Additional Resources

Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J Neuroinflammation. 2016;13(1):279. PubMed

Related Information

Neuromyelitis Optica Spectrum Disorders

Related Tests

Autoimmune Encephalitis Extended Panel, Serum 3001431

Method: Semi-Quantitative Indirect Fluorescent Antibody/Quantitative Radioimmunoassay/Semi-Quantitative Enzyme-Linked Immunosorbent Assay

Gamma Aminobutyric Acid Receptor, Type B (GABA-BR) Antibody, IgG by IFA with Reflex to Titer, Serum 3001270

Method: Semi-Quantitative Indirect Fluorescent Antibody

Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) Receptor Antibody, IgG by IFA with Reflex to Titer, Serum 3001260

Method: Semi-Quantitative Indirect Fluorescent Antibody

Autoimmune Encephalitis Reflexive Panel, Serum 2013601

Method: Semi-Quantitative Indirect Fluorescent Antibody/Semi-Quantitative Enzyme-Linked Immunosorbent Assay/Quantitative Radioimmunoassay

Leucine-Rich, Glioma-Inactivated Protein 1 Antibody, IgG with Reflex to Titer, Serum 2009456

Method: Semi-Quantitative Indirect Fluorescent Antibody

Contactin-Associated Protein-2 Antibody, IgG with Reflex to Titer, Serum 2009452

Contactin Associated Protein 2 Antibody, IgG with Reflex to Titer, Serum 2004432

Method: Semi-Quantitative Indirect Fluorescent Antibody

Voltage-Gated Potassium Channel (VGKC) Antibody, Serum 2004890

Method: Quantitative Radioimmunoassay

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

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