Neuromyelitis Optica

Indications for Ordering

For evaluation of optic neuritis, acute myelitis, spinal cord lesions, or autoimmune encephalitis

Test Description

Aquaporin-4 Receptor Antibody
- Semiquantitative enzyme-linked immunosorbent assay (ELISA)

Aquaporin-4 Receptor Antibody, IgG by IFA, CSF with Reflex to Titer
- Semiquantitative cell-based assay (CBA) detected using indirect fluorescent antibody (IFA)

Aquaporin-4 Receptor Antibody, IgG by IFA with Reflex to Titer, Serum
- Semiquantitative IFA

Aquaporin-4 Receptor Antibody by ELISA with Reflex to Aquaporin-4 Receptor Antibody, IgG by IFA
- Semiquantitative ELISA/semiquantitative IFA

Autoimmune Encephalitis Reflexive Panel
- Semiquantitative indirect fluorescent antibody/semiquantitative enzyme-linked immunosorbent assay/quantitative radioimmunoassay

Tests to Consider

Primary tests

Aquaporin-4 Receptor Antibody 2003036
- Aid in evaluation of neuromyelitis optica (NMO) and NMO spectrum disorders

Aquaporin-4 Receptor Antibody, IgG by IFA, CSF with Reflex to Titer 2011699
- Use in conjunction with serum autoantibody tests to diagnose NMO

Aquaporin-4 Receptor Antibody, IgG by IFA with Reflex to Titer, Serum 2013320
- Useful for initial evaluation of NMO spectrum disorders

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

Autoimmune Encephalitis Reflexive Panel 2013601
- Differential evaluation of encephalitis of unknown origin with subacute onset of seizures, confusion, memory loss, and/or behavioral change
- For adults and patients with suspicion of cancer, additional evaluation of paraneoplastic autoantibodies is recommended
  - Refer to paraneoplastic antibodies (PCCA/ANNA) reflex test (2007961)
- Individual tests in panel (may also be ordered separately)
  - N-methyl-D-Aspartate Receptor Antibody, IgG, Serum with Reflex to Titer 2004221
  - Glutamic Acid Decarboxylase Antibody 2001771
  - Voltage-Gated Potassium Channel (VGKC) Antibody 2004890
  - Aquaporin-4 Receptor Antibody 2003036
  - Aquaporin-4 Receptor Antibody, IgG by IFA with Reflex to Titer, Serum 2013320
  - Leucine-Rich, Glioma-Inactivated Protein 1 Antibody, IgG with Reflex to Tier 2009456
  - Contactin-Associated Protein-2 Antibody, IgG with Reflex tot Titer 2009452

Disease Overview

Incidence

Acute transverse myelitis (TM) – 1-4/100,000
- <1% is NMO
  - Female:male=5:1 for relapsing NMO

Symptoms

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

Diagnostic issues

- NMO is often mistaken for multiple sclerosis (MS)
- Individuals with NMO have a worse prognosis
- Treatment differs between NMO and MS
  - NMO – 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 aquaporin-4 (AQP4)
- Presence of antibody is important in the differential diagnosis of NMO from other TM diseases
  - ~75% of patients with NMO express antibodies to the AQP4 receptor
- TM disorders
  - MS
  - NMO
  - Optic spinal MS (OSMS)
  - Longitudinally extensive spinal cord lesions/TM (LESCL/LETM)
  - Acute disseminated encephalomyelitis (ADEM)
  - Acute complete TM (ACTM)
  - Acute partial TM (APTM)
- 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 autoantibodies

Diagnostic criteria

Required for diagnosis of NMO (Wingerchuk, 2006)

- Major criteria
  - Presence of optic neuritis, acute myelitis, and at least two of the following minor criteria
- Minor criteria
  - Contiguous spinal cord lesions on MRI extending ≥3 vertebral segments
  - Brain MRI findings not consistent with MS
  - NMO-IgG seropositive status (anti-AQP4-positive)
    - ~75% sensitivity in individuals with NMO

Test Interpretation

Sensitivity/specificity

- 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%

Results

- Positive
  - AQP4 receptor antibody – ≥3 U/mL
  - AQP4 receptor antibody with reflex – antibody detected and titered
  - AQP4 receptor antibody, CSF, with reflex – antibody detected and titered
- Negative
  - AQP4 receptor antibody – ≤3 U/mL
  - AQP4 receptor antibody, with reflex – <1:10
  - AQP4 receptor antibody, CSF, with reflex – <1:1

Limitations

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

Reference

Wingerchuk DM, Lennon VA, et al. Revised diagnostic criteria for neuromyelitis optica. Neurology. 2006; 66(10):1485-1489