Anti-NMDA Receptor (NR1) IgG Antibodies

Indications for Ordering

• Confirm diagnosis of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis
• May be used in monitoring treatment response in individuals who are antibody positive

Test Description

N-methyl-D-Aspartate Receptor Antibody, IgG, Serum with Reflex to Titer
N-methyl-D-Aspartate Receptor Antibody, IgG, CSF with Reflex to Titer
• Semiquantitative indirect fluorescence antibody assay (IFA) using a human cell line (HEK293) transfected with the NR1 receptor subunit

Autoimmune Encephalitis Reflexive Panel
• Semiquantitative IFA/semiquantitative enzyme-linked immunosorbent assay (ELISA)

Autoimmune Neurologic Disease Reflexive Panel
• Semiquantitative IFA/qualitative immunoblot/quantitative radioimmunoassay/ semiquantitative ELISA

Tests to Consider

Typical testing strategy
Initial testing to rule out infectious process may include
• Complete blood count with platelet count and differential
• Electrolyte panel
• Cerebrospinal fluid (CSF) testing
  o Protein, glucose, cell count with differential
  o Viral polymerase chain reaction testing
    ▪ Herpes simplex virus
    ▪ Human herpes virus-6
    ▪ Varicella-zoster virus
    ▪ Enterovirus
  o Oligoclonal band profile
  o Bacterial culture and Gram stain
  o Fungal culture
  o CSF antigen testing
• Computerized tomography/magnetic resonance imaging
• Other testing based on symptoms/history (eg, metabolic disorders, multiple sclerosis)

Consider the following tests based on clinical presentation, age, sex, and/or risk for cancer
• Autoimmune serologies for
  o Antinuclear antibodies (ANA)
  o Antineutrophil cytoplasmic antibodies (ANCA)
  o Antiphospholipid syndrome
  o Thyroiditis
• Autoimmune encephalitis evaluation
• Paraneoplastic antibody evaluation
• N-methyl-D-aspartate receptor antibody, serum and CSF

Primary tests

N-methyl-D-Aspartate Receptor Antibody, IgG, Serum with Reflex to Titer 2004221
• Confirm diagnosis of anti-NMDAR encephalitis
• May be used in monitoring treatment response in individuals who are antibody positive

N-methyl-D-Aspartate Receptor Antibody, IgG, CSF with Reflex to Titer 2005164
• Confirm diagnosis of anti-NMDAR encephalitis
• May be used in monitoring treatment response in individuals who are antibody positive

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
  o Refer to Paraneoplastic Antibodies (PCCA/ANNA) by IFA with Reflex to Titer and Immunoblot 2007961
• Individual tests in panel (may also be ordered separately)
  o N-methyl-D-Aspartate Receptor Antibody, IgG, Serum with Reflex to Titer 2004221
  o Glutamic Acid Decarboxylase Antibody 2001771
  o Voltage-Gated Potassium Channel (VGKC) Antibody 2004890
  o Aquaporin-4 Receptor Antibody 2003036
  o Aquaporin-4 Receptor Antibody, IgG by IFA with Reflex to Titer, Serum 2013320
  o Leucine-Rich, Glioma-Inactivated Protein 1 Antibody, IgG with Reflex to Tier 2009456
  o Contactin-Associated Protein-2 Antibody, IgG with Reflex to Titer 2009452
Autoimmune Neurologic Disease Reflexive Panel 2013944

- Comprehensive panel for evaluation of paraneoplastic and neuromuscular junction disorders, and/or encephalitis, in the presence or absence of malignancy
- Individual tests in panel (may also be ordered separately)
  - Paraneoplastic Antibodies (PCCA/ANNA) by IFA with Reflex to Titer and Immunoblot 2007961
  - Amphiphysin Antibody, IgG 2008893
  - CV2.1 Screen by IFA with Reflex to Titer 2013956
  - 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 to Titer 2009452
  - Voltage-Gated Calcium Channel (VGCC) Antibody 0092628
  - Acetylcholine Receptor Binding Antibody 0080009
  - Acetylcholine Receptor Modulating Antibody 0099521
  - Titin Antibody 2005636
  - Striated Muscle Antibodies, IgG with Reflex to Titer 0050746

Related tests

Paraneoplastic Reflexive Panel 2013955

- Aid in the diagnosis of paraneoplastic neurological syndromes associated with ANNA-1 (Hu), ANNA-2 (Ri), PCCA-1 (Yo), amphiphysin, and CV2.1 antibodies

Paraneoplastic Antibodies (PCCA/ANNA) by IFA with Reflex to Titer and Immunoblot 2007961

- Aid in the diagnosis of paraneoplastic neurological syndromes associated with malignancy
- Order based on clinical presentation

Nuclear Antibody (ANA) by IFA, IgG 0050639

- Preferred ANA screening test for connective tissue disease

ANCA-Associated Vasculitis Profile (ANCA/MPO/PR-3) with Reflex to ANCA Titer 2006480

- Preferred reflex panel for the workup of suspected vasculitis
- Panel detects ANCA, MPO, and PR-3 antibodies
- For patients with a history of vasculitis, refer to Anti-Neutrophil Cytoplasmic Antibody with Reflex to Titer and MPO/PR-3 Antibodies 2002068
- Individual antibody tests are available
  - Serine Protease 3 Antibody 0050527
  - Myeloperoxidase Antibody 0050526

Antiphospholipid Syndrome Reflexive Panel 2003222

- Preferred initial panel for strong suspicion of antiphospholipid syndrome

Disease Overview

Incidence – unknown

Age of onset – affects all age groups, with a low prevalence in individuals >50 years

Symptoms

- Prodromal symptoms similar to a nonspecific viral-like illness
  - Low-grade fever
  - Headache
- Rapid progression to other neurological symptoms (psychotic and catatonic phases)
  - Autonomic dysfunction (hypoventilation, tachycardia, hypertension, hyperthermia)
  - Cardiac dysrhythmias
  - Delusions, psychoses
  - Dyskinesia, movement disorders
  - Hallucinations
  - Memory loss
  - Paranoia
  - Seizures
  - Unresponsiveness

- Significant portion are nonparaneoplastic
  - Most common tumor – ovarian teratoma
  - Men, women, and children without tumors have also been diagnosed with anti-NMDAR encephalitis

Diagnostic issues

- Neurological symptoms of anti-NMDAR encephalitis are clinically indistinguishable from encephalitis associated with etiologies of
  - Infection
  - Toxin/metabolic
  - Autoimmune
- Diagnosis is based on excluding other causes
- Anti-NMDAR IgG antibodies detected in serum confirm the diagnosis of anti-NMDAR encephalitis
  - Abdominal imaging (ultrasound or MRI) should be performed due to strong association with ovarian neoplasms
  - Testicular ultrasound should replace abdominal ultrasound in men

Physiology

- NMDA receptors are ligand-gated cation channels necessary for synaptic transmission
  - Highly expressed in the forebrain, limbic system, and hypothalamus
- NMDA receptors are composed of two subunits – NR1 and NR2
- Anti-NMDA IgG binds to NMDA receptors (usually NR1)
  - Decreases their number on postsynaptic neuronal dendrites, causing synaptic dysfunction
  - Presumed cause of psychotic symptoms characteristic of anti-NMDAR encephalitis
Test Interpretation

Sensitivity/specificity
- Analytical sensitivity – unknown
- Analytical specificity – ~100%

Results
- Positive – NMDAR IgG antibody identified in serum
  - Strongly supportive of a diagnosis of anti-NMDAR encephalitis
- Negative – absence of NMDAR antibodies
  - Does not rule out a diagnosis of other forms of autoimmune encephalitis