Anti-NMDA Receptor (NR1) IgG Antibodies

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disease caused by antibodies against the brain protein, NMDA. Affected individuals display distinctive symptoms, including significant psychiatric disturbances, seizures, confusion, memory loss, and agitation. Women are affected more often than men. Testing is used to confirm a diagnosis of NMDAR encephalitis and to monitor disease progression and treatment response.

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 of patients are nonparaneoplastic
  - Ovarian teratoma is the most common tumor-related cause
  - Men, women, and children without tumors have also been diagnosed with anti-NMDAR encephalitis

Tests to Consider

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

Autoimmune Encephalitis Reflexive Panel, Serum 2013601
Method: Semi-Quantitative Indirect Fluorescent Antibody/Semi-Quantitative Enzyme-Linked Immunosorbent Assay/Quantitative Radioimmunoassay
- Differential evaluation of encephalitis of unknown origin with subacute onset of seizures, confusion, memory loss, and/or behavioral change
- Testing for LGI1 and CASPR2 antibodies always performed
- Panel includes NMDA receptor antibody, VGKC antibody, GAD65 antibody, AQP4 antibody.
- For adults and patients with suspicion of cancer, additional evaluation of paraneoplastic autoantibodies is recommended
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 the exclusion of other causes
- Anti-NMDAR IgG antibody detected in serum confirms the diagnosis of anti-NMDAR encephalitis
  - Abdominal imaging (ultrasound or MRI) should also 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 the number of receptors on postsynaptic neuronal dendrites, causing synaptic dysfunction
  - Presumed cause of psychotic symptoms characteristic of anti-NMDAR encephalitis

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
  - Protein, glucose, cell count with differential
  - Viral polymerase chain reaction testing
    - Herpes simplex virus
    - Human herpes virus-6
    - Varicella-zoster virus
    - Enterovirus
  - Oligoclonal band profile
  - Bacterial culture and Gram stain
  - Fungal culture
  - 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
- Antinuclear antibodies (ANA)
- Antineutrophil cytoplasmic antibodies (ANCA)
- Antiphospholipid syndrome (APS)
- Thyroiditis
- Autoimmune encephalitis evaluation
- Paraneoplastic antibody evaluation
- N-methyl-D-aspartate receptor antibody, serum or CSF

Test Interpretation

Sensitivity/Specificity
- Analytical sensitivity: unknown
- Analytical specificity: ~100%

Results
- Positive: NMDAR IgG antibody identified in serum strongly supports a diagnosis of anti-NMDAR encephalitis
- Negative: absence of NMDAR IgG antibody does not rule out a diagnosis of other forms of autoimmune encephalitis

Related Information

N-methyl-D-Aspartate (NMDA)-Type Glutamate Receptor Autoantibody Disorders - Anti-NMDA-Receptor Encephalitis

Related Tests

Antinuclear Antibody (ANA) with HEp-2 Substrate, IgG by IFA 3000082
Method: Semi-Quantitative Indirect Fluorescent Antibody

Paraneoplastic Reflexive Panel (Temporary Referral as of 01/30/20) 2013955
Method: Semi-Quantitative Indirect Fluorescent Antibody/Qualitative Immunoblot

Paraneoplastic Antibodies (PCCA/ANNA) by IFA with Reflex to Titer and Immunoblot 2007961
Method: Semi-Quantitative Indirect Fluorescent Antibody/Qualitative Immunoblot

ANCA-Associated Vasculitis Profile (ANCA/MPO/PR3) with Reflex to ANCA Titer 2006480
Method: Semi-Quantitative Indirect Fluorescent Antibody/Semi-Quantitative Multiplex Bead Assay

Antiphospholipid Syndrome Reflexive Panel 2003222
Method: Electromagnetic Mechanical Clot Detection/Semi-Quantitative Enzyme-Linked Immunosorbent Assay

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