Voltage-Gated Potassium Channel Antibody Disorders

Indications for Ordering

- Evaluation of
  - Limbic encephalitis
  - Faciobrachial dystonic seizures
  - Peripheral nerve hyperexcitability disorders
    - Neuromyotonia (Isaacs syndrome)
    - Variant form – Morvan syndrome
- Management of antibody-positive (voltage-gated potassium channel [VGKC], leucine-rich, glioma-inactivated protein 1 [LG1], or contactin-associated protein 2 [CASPR2]) individual following immunotherapy and/or plasmapheresis

Test Description

Voltage-Gated Potassium Channel (VGKC) Antibody
- Quantitative radioimmunoassay (RIA)

Leucine-rich Glioma Inactivated Protein 1 (LG1) Antibody
- Semiquantitative indirect fluorescent antibody (IFA)

Contactin Associated Protein 2 (CASPR2) Antibody
- Semiquantitative IFA

Autoimmune Encephalitis Reflexive Panel
- Semiquantitative IFA/semiquantitative enzyme-linked immunosorbert assay/quantitative radioimmunoassay

Autoimmune Neuromuscular Junction Reflexive Panel
- Quantitative RIA/qualitative radiobinding assay/semiquantitative flow cytometry/semiquantitative IFA

Tests to Consider

Typical testing strategy

Initial testing to rule out central nervous system (CNS) infection may include
- Complete blood count with platelet count and differential
- Electrolyte panel
- Cerebrospinal fluid (CSF) analysis
  - Protein, glucose, cell count
  - Viral polymerase chain reaction testing
    - Herpes simplex virus
    - Human herpes virus-6
    - Varicella-zoster virus
  - Oligoclonal band profile
  - Bacterial culture and Gram stain
  - Fungal culture

Additional and/or follow-up testing – consider based on clinical presentation, age, and history
- Autoimmune serologies for
  - Antinuclear antibodies (ANA)
  - Antineutrophil cytoplasmic antibodies (ANCA)
  - Antiphospholipid syndrome (APS)
- Autoimmune encephalitis evaluation
- Autoimmune neuromuscular junction disorder evaluation
- Paraneoplastic antibody evaluation
- N-methyl-D-aspartate receptor antibody, serum and CSF
- Autoimmune channelopathies evaluation
  - Anti-VGKC antibodies
  - Anti-LG1 antibodies
  - Anti-CASPR2 antibodies

Primary tests

Voltage-Gated Potassium Channel (VGKC) Antibody with Reflex to LG1 and CASPR2 Screen and Titer 2009463
- Screening test for VGKC antibody receptor complex-associated autoantibodies
- Reflexes to CASPR2 and LG1 antibodies
- Antibodies are associated with
  - Acquired neuromyotonia
  - Limbic encephalitis
  - Painful neuropathy
  - Morvan syndrome
  - Rare tumors
    - Thymoma
    - Small-cell lung cancer

Voltage-Gated Potassium Channel (VGKC) Antibody 2004890
- Screening test for VGKC antibody receptor complex-associated autoantibodies
- Does not identify CASPR2 or LG1 antibodies
- Use to manage antibody-positive (VGKC, LG1, or CASPR2) individual following immunotherapy and/or plasmapheresis

Leucine-Rich, Glioma Inactivated Protein 1 Antibody, IgG with Reflex to Titer 2009456
- Aid in diagnosis of LG1 disorders
- Associated with LG1
  - Limbic encephalitis
  - Hyponatremia
  - Myoclonic movements
- Disorders are rarely associated with tumors
- Use to manage antibody-positive (LG1) individual following immunotherapy and/or plasmapheresis
Contactin-Associated Protein-2 Antibody, IgG with Reflex to Titer 2009452
- Aid in diagnosis of CASPR2 disorders associated with
  - Acquired neuromyotonia
  - Limbic encephalitis
  - Painful neuropathy
  - Morvan syndrome
- Use to manage antibody-positive (CASPR2) individual following immunotherapy and/or plasmapheresis

Leucine-Rich, Glioma-Inactivated Protein 1 Antibody, IgG and Contactin-Associated Protein-2 Antibody, IgG with Reflex to Titer 2009460
- Aid in diagnosis of LGI1 and CASPR2 disorders
- See LGI1 test 2009456 and CASPR2 test 2009452 for indications
- Use to manage antibody-positive (LGI1 or CASPR2) individual following immunotherapy and/or plasmapheresis

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 Titer 2009456
  - Contactin-Associated Protein-2 Antibody, IgG with Reflex to Titer 2009452

Autoimmune Neuromuscular Junction Reflexive Panel 2005640
- Acceptable reflexive panel for the differential diagnosis of acquired neuromuscular junction disorders
- Individual tests in panel (may also be ordered separately)
  - Acetylcholine Receptor Binding Antibody 0080009
  - Acetylcholine Receptor Blocking Antibody 0099580
  - Acetylcholine Receptor Modulating Antibody 0099521
  - Voltage-Gated Calcium Channel (VGCC) Antibody 0092628
  - Voltage-Gated Potassium Channel (VGKC) Antibody 2004890
  - Titin Antibody 2005636
  - Striated Muscle Antibodies, IgG with Reflex to Titer 0050746
  - Leucine-Rich, Glioma-Inactivated Protein 1 Antibody, IgG and Contactin-Associated Protein-2 Antibody, IgG with Reflex to Titer 2009460

Related tests
N-methyl-D-Aspartate Receptor Antibody, IgG, Serum with Reflex to Titer 2004221
- Confirm diagnosis of NMDAR antibody 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

Paraneoplastic Antibodies (PCCA/ANNA) by IFA with Reflex to Titer and Immunoblot 2007961
- Aid in the diagnosis of paraneoplastic neurologic 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 the ANCA reflex panel (2002068) that includes a titer, and MPO and PR-3 antibodies
- Individual antibody tests are available
  - Serine Protease 3 Antibody 0050527
  - Myeloperoxidase Antibody 0050526
- Initial test in conjunction with autoimmune liver disease panel for evaluation of autoimmune liver disease

Antiphospholipid Syndrome Reflexive Panel 2003222
- Preferred initial panel for strong suspicion of antiphospholipid syndrome (APS)

Disease Overview

Incidence – unknown

Symptoms
- Limbic encephalitis (mainly LGI1 antibodies)
  - Amnesia
  - Seizures
  - Disorientation
  - Psychiatric disturbance
  - Peripheral nerve hyperexcitability
  - Neuromyotonia
  - CSF usually normal
- Morvan syndrome (mainly CASPR2 antibodies)
  - Limbic encephalitis
  - Neuromyotonia
  - Confusion
  - Amnesia
  - Insomnia
  - Pain
  - Autonomic dysfunction – hyperhidrosis, constipation, urinary incontinence
Diagnostic issues

Antibody testing may aid in diagnosis

- Should be performed only when neuromuscular and/or neurological symptoms are present
- Anti-VGKC disorders are rare and present with symptoms similar to those of other encephalitic disorders
- Antibody testing should not be used for screening
- Antibodies may be associated with paraneoplastic (autoimmune) or nonparaneoplastic neurological disorders
- Not all neurological disorders or antibodies are associated with tumors
  - In most antibody-mediated, non-neoplastic-associated diseases, individuals improve substantially with immunotherapy
  - Important to diagnose these illnesses due to therapeutic responsiveness

Physiology

- VGKC autoantibodies
  - Directed against a protein that is complexed with potassium channels in both peripheral nervous system and CNS
    - CASPR2
      - Present in ~50% of individuals with neuromyotonia
      - CASPR2 antibodies are common in individuals with thymic malignancies
    - LGI1
      - Not directed against the potassium channels
      - Different antibodies from those found in typical paraneoplastic neurological diseases
- VGKC RIA test can be used as a general screen for VGKC-complex antibodies directed against
  - LGI1
  - CASPR2
  - Other unidentified targets

Test Interpretation

Results

VGKC antibody

- Positive – >88 pmol/L
  - Suggests VGKC antibody-related disease
- Indeterminant – 32-87 pmol/L
  - Retest in 2-4 weeks
- Negative – 0-31 pmol/L
  - Likelihood of VGKC antibody-related disease is reduced but not necessarily eliminated

LGI1 antibody

- Positive – ≥1:10
  - Suggests LGI1 antibody-related disease
- Negative – <1:10
  - Does not rule out disorders associated with VGKC complex antibodies

CASPR2 antibody titer, IgG

- Positive – ≥1:10
  - Suggests CASPR2 antibody-related disease
- Negative – <1:10
  - Does not rule out disorders associated with VGKC complex antibodies

Limitations

VGKC antibody

- Presence of VGKC antibodies should be used in conjunction with clinical manifestations for
  - Neuromyotonia spectrum of disorders
  - VGKC antibody-associated limbic encephalitis
- Should not be used as the sole criterion for diagnosis
- VGKC receptor-complex proteins may be co-precipitated by anti-VGKC antibodies, including
  - LGI1
  - CASPR2
  - Other unidentified targets