Encephalopathy, Autoimmune Evaluation, Spinal Fluid

Useful For
- Evaluating new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dysomnias, ataxias, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation.
- The following accompaniments should increase of suspicion for autoimmune encephalopathy:
  - Headache
  - Autoimmune stigmata (personal or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus)
  - History of cancer
  - Smoking history (20+ pack years) or other cancer risk factors
  - Inflammatory cerebral spinal fluid (or isolated protein elevation)
  - Neuroimaging signs suggesting inflammation
  - Evaluating limbic encephalitis (noninfectious)
  - Directing a focused search for cancer
  - Investigating encephalopathy appearing in the course or wake of cancer therapy and not explainable by metastasis or drug effect.

Reflex Tests & Testing Algorithm
Go to Mayo Medical Laboratories Test Catalog:
http://www.mayomedicallaboratories.com

Clinical Information
Autoimmune encephalopathies extend beyond the classically recognized clinical and radiological spectrum of "limbic encephalitis." They encompass a diversity of neurological presentations with subacute or insidious onset, including confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dysomnias, ataxias, eye movement problems, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation. A diagnosis of autoimmune encephalopathy should be suspected on the basis of clinical course, coexisting autoimmune disorder (eg, thyroiditis, diabetes), serological evidence of autoimmunity, spinal fluid evidence of intrathecal inflammation, neuroimaging or electroencephalographic abnormalities, and favorable response to trial of immunotherapy.

Detection of 1 or more neural autoantibodies aids the diagnosis of autoimmune encephalopathy and may guide a search for cancer. Pertinent autoantibody specificities include: 1) neurotransmitter receptors and ion channels such as neuronal voltage-gated potassium channels (and interacting synaptic and axonal proteins, LGI1 and CASPR2), ionotropic glutamate receptors (NMDA and AMPA), metabotropic GABA-B receptors; 2) enzymes, signaling molecules and RNA-regulatory proteins in the cytoplasm and nucleus of neurons (GAD65, CRMP-5, ANNA-1, and ANNA-2).

Importantly, autoimmune encephalopathies are reversible. Misdiagnosis as a progressive (currently irreversible) neurodegenerative condition is not uncommon and has devastating consequences for the patient. Clinicians must consider the possibility of an autoimmune etiology in the differential diagnoses of encephalopathy. For example, a potentially reversible disorder justifies a trial of immunotherapy for the detection of neural autoantibodies in patients presenting with symptoms of personality change, executive dysfunction, and psychiatric manifestations.

A triad of clues helps to identify patients with an autoimmune encephalopathy: 1) clinical presentation (subacute symptoms onset rapidly progressive course and fluctuating symptoms) and radiological findings consistent with inflammation, 2) detection of neural autoantibodies in serum or cerebral spinal fluid (CSF), and 3) favorable response to a trial of immunotherapy.

Detection of neural autoantibodies in serum or CSF informs the physician of a likely autoimmune etiology, and may heighten suspicion for a paraneoplastic basis and guide the search for cancer. Neurological accompaniments of neural autoantibodies are generally not syndromic, but diverse and multifocal. For example, neuronal voltage-gated potassium channel (VGKC)-complex antibodies were initially considered specific for autoimmune limbic encephalitis or disorders of peripheral
nerve hyperexcitability. However, more diverse presentations are now recognized, including rapidly progressive cognitive decline mimicking frontotemporal dementia and Creutzfeldt-Jakob disease.

Comprehensive antibody testing is more informative than selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example; small-cell lung carcinoma (antineuronal nuclear antibody-type 1: ANNA-1; collapsin response-mediator protein-5 neuronal: CRMP-5-IgG), ovarian teratoma (N-methyl-D-aspartate receptor: NMDA-R), and thymoma (CRMP-5 IgG).

An individual patient's profile autoantibody may be informative for a specific cancer type. For example, detection of muscle acetylcholine receptor (AChR) binding, alpha 3 ganglionic AChR, and CRMP-5 IgG in a patient presenting with encephalopathy suggests thymoma. When an associated tumor is found, its resection or ablation optimizes the neurological outcome.

Testing of CSF for autoantibodies is particularly helpful when serum testing is negative. Simultaneous testing of serum and CSF is recommended for NMDA-R antibody, because CSF is usually more informative.

Interpretation
Neuronal, glial, and muscle autoantibodies are valuable serological markers of autoimmune encephalopathy and of a patient's immune response to cancer. These autoantibodies are usually accompanied by subacute neurological symptoms and signs are not found in healthy subjects. It is not uncommon for more than 1 of the following autoantibody specificities to be detected in patients with an autoimmune encephalopathy:

1. Plasma membrane autoantibodies: These are all potential effectors of neurological dysfunction: neuronal voltage-gated potassium channel (VGKC)-complex, N-methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-aminobutyric acid (GABA-B) receptor; neuronal ACh receptor.
2. Neuronal nuclear autoantibodies: type 1 (ANNA-1), type 2 (ANNA-2), or type 3 (ANNA-3)
3. Neuronal or muscle cytoplasmic antibodies: amphiphysin, Purkinje cell antibodies (PCA-1 and PCA-2), CRMP-5, GA65, or striational.

Cautions
Negative results do not exclude autoimmune encephalopathy or cancer.

The Encephalopathy Autoimmune Evaluation does not detect Ma1 or Ma2 antibodies (alias: MaTa), which are sometimes associated with brainstem and limbic encephalitis in the context of testicular germ cell neoplasms. Scrotal ultrasound is advised for men who present with unexplained subacute encephalitis.

Reference Values
To review all reference values go to http://www.mayomedicallaboratories.com

Analytic Time
3 days if negative / 5 days if positive

Clinical References

For additional interpretation information and clinical references, please visit the following website:
http://www.mayomedicallaboratories.com/test-catalog/Overview/61508