Lab Dept: Serology

Test Name: ENCEPHALOPATHY AUTOIMMUNE EVALUATION

General Information

Lab Order Codes: ENS1

Synonyms: Autoimmune Encephalopathy Evaluation

CPT Codes: 83519 x3 – Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, quantitative by radioimmunassay
86255 x19 – Fluorescent noninfectious agent, antibody screen, each antibody
86341 – Islet cell antibody

Possible reflex testing (at an additional charge):

84182 x7 – Western blot, with interpretation and report, each
86255 x7 – Fluorescent noninfectious agent, antibody screen, each antibody
86256 x8 – Fluorescent noninfectious agent, titer, each antibody
83519 x2 – Immunoassay for analyte, other than infectious agent antibody or infectious agent antigen, quantitative by radioimmunoassay

Test Includes: If IFA patterns suggests CRMP-5-IgG then CRMP-5 IgG Western blot, ACh receptor (muscle) binding antibody, and ACh receptor (muscle) modulating antibody are performed at an additional charge.

If IFA pattern suggests AMPA-receptor antibody and AMPA-receptor antibody cell-binding assay (CBA) is positive, then AMPA-receptor antibody IFA titer assay is performed at an additional charge.

If IFA pattern suggest GABA-B-receptor antibody, and GABA-B-R receptor antibody is positive, then GABA-B-R receptor antibody IFA titer assay is performed at an additional charge.

If IFA pattern suggests GFAP antibody, then GFAP IFA titer and GFAP CBA are performed at an additional charge.

If IFA pattern suggests NMDA-receptor antibody, and NMDA-receptor antibody CBA is positive, then NMDA-receptor antibody IFA titer assay is performed at an additional charge.

If IFA pattern suggest DPPX antibody, then DPPX antibody CBA and DPPX titer are performed at an additional charge.

If IFA pattern suggests mGluR1 antibody, then mGluR1 antibody CGA and mGluR1 titer are performed at an additional charge.

If IFA patterns suggest AGNA-1 antibody, then AGNA-1 immunoblot is performed at an additional charge.

If IFA patters suggest amphiphysin antibody, then amphiphysin immunoblot is performed at an additional charge.

If IFA patterns suggest ANNA-1 antibody, then ANNA-1 immunoblot is performed at an additional charge.

If IFA patterns suggest ANNA-2 antibody, then ANNA-2 immunoblot is performed at an additional charge.

If IFA patterns suggest PCA-1 antibody, then PCA-1 immunoblot is performed at an additional charge.

If IFA patterns suggest PCA-Tr antibody, then PCA-Tr immunoblot is performed at an additional charge.

If IFA patterns suggest IgLON5 antibody, the IgLON5 IFA titer and IgLON5 cell binding assay (CBA) is performed at an additional charge.

If IFA pattern suggests NIF antibody, then alpha internexin CBA, NIF heavy chain CBA, NIF light chain CBA, and NIF titer are performed at an additional charge.

Logistics

Test Indications:

Evaluating new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorder, sensory or motor complaints, seizures, dyssonmnias, ataxias, nausea, vomiting, inappropriate antiduresis, coma, dysautonomias, or hypventialation in serum specimens.

The following accompaniments should increase 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 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

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, psychoses, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures,

dyssomnias, ataxias, eye movement problems, nausea, vomiting, inappropriate antiduresis, 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 one 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), metabotrophic GAGA-B recptors; 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 conditions 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 identifying patients with an autoimmune encephalopathy: 1) clinical presentation (subacute symptoms onset rapidlay progressive course and fluctuating symptoms) and radiological findings consistent with inflammation, 2) detection of neural autoantibodies in serum or cerebrospinal fluid (CSF), and 3) favorable respone 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 gude the search for cancer. Neurolgoical accompaniments of neural autoantibodies are generally not syndromic, but divers 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 hyperexcitablilty. However, more diverse presentations are now recognized, including rapidly progressive cognitive decline mimicking frontotemporal dementia and Creutzfeldt-Jakob diseae.

Comprehensive antibody testing is more informative then selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example, small-cell lung carcinoma (ANN-1, CRMP-5-IgG, ovarian teratoma (NMDA-R) and thymoma (CRMP-5-IgG).

An individual patient’s profile autoantibody may be informative for a specific cancer type. For example, in a patient presenting with encephalitis who has CRMP 5 IgG, and subsequent reflex reveals muscle actylcholine receptor (AChR) binding antibody, the findings should raise a high suspicion from thymoma. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative, though in some circumstances testing both serum

	and CSF simultaneously is pertinent. Testing of CSF is recommended for some antibodies in particular (such as NMDA-R-antibody and GFAP-IgG) because CSF testing is both more sensitive and specific. In contrast, serum testing for LGi1 antibody is more sensitive than CSF testing.
Lab Testing Sections:	Serology - Sendouts
Referred to:	Mayo Clinic Laboratories (Mayo Test: ENS2)
Phone Numbers:	MIN Lab: 612-813-6280 STP Lab: 651-220-6550
Test Availability:	Daily, 24 hours
Turnaround Time:	Results in 4-10 days
Special Instructions:	See Patient Preparation

Specimen

Specimen Type:	Blood
Container:	SST (Marble, gold or red)
Draw Volume:	12 mL (Minimum: 6 mL) blood
Processed Volume:	4 mL (Minimum: 2 mL) serum
Collection:	Routine blood collection
Special Processing:	Lab Staff: Centrifuge specimen, remove serum from cells, aliquot into a screw-capped round bottom vial. Store and ship at refrigerated temperatures.
Patient Preparation:	For optimal antibody detection, specimen collection is recommended prior to initiation of immunosuppressant medication. This test should not be requested in patients who have recently received radioisotopes, therapeutically or diagnostically, because of potential interference. The specific waiting period before specimen collection will depend on the isotope administered, the dose given, and the clearance rate in the individual patient. Specimens will be assayed if sufficiently decayed, or canceled if radioactivity remains. Patient should have no general anesthetic or muscle-relaxant drugs in previous 24 hours.
Sample Rejection:	Gross hemolysis; grossly icteric; mislabeled or unlabeled specimens

Interpretive

Reference Range:

Antibody:	Reference Range:
Neuronal Nuclear Antibodies	
ANNA-1	<1:240
ANNA-2	<1:240
ANNA-3	<1:240
AGNA-1	<1:240
Neuronal and Muscle Cytoplamic Antibodies	
PCA-1	<1:240
PCA-2	<1:240
PCA-Tr	<1:240
Amphiphysin Ab	<1:240
CRMP-5-IgG	<1:240
Islet Cell Antibodies	
GAD65 Ab	< or =0.02 nmol/L
Cation Channel Antibodies	
P/Q-Type Calcium Channel Ab	< or =0.02 nmol/L
AChR Ganglionic Neuronal Ab	< or =0.02 nmol/L
N-Type Calcium Channel	< or =0.03 nmol/L
Other Antibodies	
NMDA-R CBA	Negative
AMPA-R CBA	Negative

GABA-B-R CBA	Negative
LGI1-IgG CBA	Negative
CASPR2-IgG CBA	Negative
GAD65 Ab	< or =0.02 nmol/L
GFAP IFA	Negative
IgLON5 IFA	Negative
LGI1-IgG CBA	Negative
mGluR1 Ab IFA	Negative
DPPX Ab IFA	Negative
GABA-B-R Ab CBA	Negative
mGluR1 Ab IFA	Negative
mGluR1 Ab IFA Titer	<1:240
NIF IFA	Negative
NMDA-R Ab IF Titer	<1:120
NMDA-R Ab CBA	Negative

Neuron-restricted patterns of IgG staining that do not fulfill criteria for ANNA-1, ANNA-2, CRMP-5-IgG, PCA-1, PCA-2 or PCA-Tr may be reported as “unclassified anti-neuronal IgG.” Complex patterns that include nonneuronal elements may be reported as “uninterpretable.”

Note: CRMP-5 titers lower than 1:240 are detectable by recombinant CRMP- Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy.

Reflex Information:

Ach Receptor (Muscle) Binding Ab	< or = 0.02 nmol/L

Ach Receptor (Muscle) Modulating Ab	0 – 20%
AGNA-1 Immunoblot	Negative
Alpha Internexin CBA	Negative
AMPA-R Ab IF Titer	<1:120
Amphiphysin Immunoblot	Negative
ANNA-1 Immunoblot	Negative
ANNA-2 Immunoblot	Negative
CRMP-5-IgG Western blot	Negative
DPPX Ab CBA	Negative
DPPX Ab IFA Titer	<1:240
GABA-B-R Ab IFA Titer	<1:240
GFAP CBA	Negative
GFAP IFA Titer	<1:240
IgLON5 CBA	Negative
IgLON5 IFA Titer	<1:240
mGluR1 Ab CBA	Negative
mGluR1 Ab IFA	<1:240
NIF Heavy Chain CBA	Negative
NIF IFA Titer	<1:240
NIF Light Chain CBA	Negative
NMDA-R Ab IF Titer	<1:120

PCA-1 Immunoblot	Negative
PCA-Tr Immunoblot	Negative

Critical Values: N/A

Limitations: Negative results do not exclude autoimmune encephalopathy or cancer.

This test does not detect Ma1 or Ma2 antibodies, 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 encephalitits.

Methodology: ANN1S, ANN2S, ANN3S, AGN1S, PCABP, PCAB2, PCATR, AMPHS, CRMS, DPPIS, DPPTS, GL1IS, GFAIS, GFATS, AMPIS, GABIS, NIFIS, IG5IS, IG5TS, GL1TS, NIFTS, NMDIS: Indirect Immunofluorescence Assay (IFA)

CCN, CCPQ, GANG, GD65S, ARBI: Radioimmunoassay (RIA)

CRMWS: Western Blot

AMPCS, GABCS, NMDCS, LG1CS, CS2CS, DPPCS, GL1CS, GFACS: Cell Binding Assay (CBA)

ARMO: Live Cell Assay (LCA)

CS2CS, GABCS, LG1CS, NMDCS, AINCS, GFACS, IG5CS, GL1CS, NFHCS, NFLCS, DPPCS (CBA)

AGNBS, AMIBS, AN1BS, AN2BS, PC1BS, PCTBS (IB)

References: Mayo Clinic Laboratories May 2020

Updates: 6/11/2019: Updated algorithm to enhance testing panel, new antibodies added.
5/14/2020: Updated algorithm and addition reflex testing per Mayo