MAYO CLINIC LABORATORIES

Test Definition: NMS1

Necrotizing Myopathy Evaluation, Serum

Overview

Useful For

Evaluating patients with suspected necrotizing autoimmune myopathy

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
NSI1	Necrotizing Myopathy Interp, S	No	Yes
HMGCR	HMG-CoA Reductase Ab, S	Yes	Yes
SRPIS	SRP IFA Screen, S	No	Yes

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
SRPBS	SRP Immunoblot, S	No	No
SRPTS	SRP IFA Titer, S	No	No

Testing Algorithm

A thorough understanding of a patient's history, along with clinical examination and laboratory testing, are needed for a clinico-sero-pathological diagnosis of immune-mediated necrotizing myopathy (IMNM). To assess the probability of your patient having IMNM, see the Immune-mediated necrotizing myopathy calculator.

This focused algorithmic test is designed to achieve high sensitivity for identification of antibodies specific for necrotizing autoimmune myopathy (HMGCOA-IgG and SRP-IgG). This test is unique in the market by having an initial screen for signal recognition particle (SRP) antibodies performed using tissue indirect immunofluorescence, which increases clinical sensitivity as compared to SRP immunoblot methodologies.

If the indirect immunofluorescence assay (IFA) pattern suggests signal recognition particle (SRP) antibody, then the SRP IFA titer and SRP54 immunoblot will be performed at an additional charge.

Highlights

The utilization of this combinatorial immunoassay provides accuracy and speed in diagnosis of necrotizing autoimmune myopathy (NAM). Early diagnosis facilitates better prognosis through initiation of aggressive immune treatments, typically requiring more than 1 agent, and discontinuation of statin medications. Persons without access to specialty muscle biopsy testing services may be afforded an early diagnosis through application of this testing.

Identification of NAM may indicate the presence of a paraneoplastic disorder.

Method Name

SRPIS, SRPTS: Indirect Immunofluorescence Assay (IFA)
SRPBS: Immunoblot

HMGCR: Chemiluminescent Assay (CIA)
NSI1: Medical Interpretation

NY State Available
Yes

Specimen

Specimen Type
Serum

Ordering Guidance
Before ordering this test, assess the probability of the patient having immune-mediated necrotizing myopathy by using the Immune-mediated necrotizing myopathy calculator.

Necessary Information
Provide the following information:
-Relevant clinical information
-Ordering provider name, phone number, mailing address, and e-mail address

Specimen Required
Collection Container/Tube:
Preferred: Red top
Acceptable: Serum gel
Submission Container/Tube: Plastic vial
Specimen Volume: 3 mL
Collection Instructions: Centrifuge within 2 hours of collection and aliquot serum into a plastic vial.

Forms
If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Specimen Minimum Volume
2 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	28 days	
	Ambient	72 hours	
	Frozen	28 days	

Clinical & Interpretive

Clinical Information

Necrotizing autoimmune myopathy (NAM) is a serious, but rare muscle disease strongly associated with autoantibodies to either signal recognition protein (SRP) or 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR).(1) NAM typically manifests with subacute proximal limb muscle weakness and persistently elevated serum creatine kinase (CK) concentrations, but slower onsets can occur and complicate diagnosis. Muscle biopsies in affected patients can demonstrate necrotic and regenerating myofibers without inflammatory infiltrates, suggesting the diagnosis.(2) However, sampling issues and lack of access to persons having expertise in obtaining, preparing, and interpreting muscle biopsy specimens may delay a diagnosis.(3)

Early identification of NAM and subsequent aggressive immune-modulating therapy is critical.(1,3) Discovery of SRP- or HMGCR–IgG autoantibodies can aid in establishing an earlier diagnosis and treatment initiation. In addition, the discovery of SRP or HMGCR autoantibodies should prompt a search for an underlying malignancy.(4) Serial testing for these autoantibodies can delay diagnosis with the discovery of either antibody aiding in establishing an earlier diagnosis and treatment initiation.(1,3)

The clinical onsets are not specific to NAM consisting of proximal limb weakness in associations with an elevated serum creatinine kinase, with or without exposure to lipid lowering statin medications.(1,3-9) The clinical presentation can be confused with forms of inflammatory (dermatomyositis, polymyositis), toxic, metabolic or even neurodegeneration (ie, muscular dystrophy) and the diagnosis delayed without serological testing by SRP- or HMGCR-autoantibody testing. Panel testing of both HMGCR and SRP autoantibodies is the preferred strategy for the best patient care.

Reference Values

3-Hydroxy-3-Methylglutaryl Coenzyme-A (HMG-CoA) Reductase:
<20.0 CU

Signal Recognition Particle Antibody Screen:
Negative

Signal Recognition Particle Antibody:
Negative

Signal Recognition Particle Antibody, Titer:
<1:240

Interpretation

Seropositivity for 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) or signal recognition protein (SRP) autoantibodies supports the clinical diagnosis of necrotizing autoimmune myopathy (NAM). A paraneoplastic basis should be

considered, according to age, sex, and other risk factors. In cases of NAM, immune therapy is required and often multiple simultaneously utilized immunotherapies are needed to successfully treat patients.

Cautions

Antibodies against 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) or signal recognition protein (SRP) may be detected in cases of polymyositis, dermatomyositis, or other autoimmune disorders. It is recommended that serology results be interpreted along with muscle biopsy findings and in the appropriate clinical context.

Clinical Reference

1. Kassardjian CD, Lennon VA, Alfugham NB, et al: Clinical Features and Treatment Outcomes of Necrotizing Autoimmune Myopathy. JAMA Neurol 2015 Sep;72(9):996-1003
2. Emslie-Smith A M, Engel A G: Necrotizing myopathy with pipestem capillaries, microvascular deposition of the complement membrane attack complex (MAC), and minimal cellular infiltration. Neurology 1991;41(6):936-939
3. Ramanathan S, Langguth D, Hardy T, et al: Clinical course and treatment of anti-HMGCR antibody-associated necrotizing autoimmune myopathy. Neurol Neuroimmunol Neuroinflamm 2015 June;2(3):e96
4. Allenbach Y, Keraen J, Bouvier AM, et al: High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. Brain 2016 Aug;139(Pt 8):2131-2135
5. Christopher-Stine L, Casciola-Rosen L, Hong G, et al: A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. Arthritis Rheum 2010 May;62(9):2757-2766
6. Mammen AL, Chung T, Christopher-Stine L, et al: Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum 2011 Mar;63(3):713-721
7. Hengstman GJ, ter Laak HJ, Vree Egberts WT, et al: Anti-signal recognition particle autoantibodies: marker of a necrotising myopathy. Ann Rheum Dis 2006;65(12):1635-1638
8. Miller T, Al-Lozi MT, Lopate G, Pestronk A: Myopathy with antibodies to the signal recognition particle: clinical and pathological features. J Neurol Neurosurg Psychiatry 2002 Oct;73(4):420-428
9. Watanabe Y, Uruha A, Suzuki S, et al: Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. J Neurol Neurosurg Psychiatry 2016 Oct;87(10):1038-1044

Performance

Method Description

Signal Recognition Protein Indirect Immunofluorescence Assay:
The patient's sample is tested by a standardized indirect immunofluorescence assay (IFA) that uses composite frozen sections of mouse cerebellum, kidney, and gut tissues. After incubation with patient sample and washing, fluorescein-conjugated goat antihuman IgG is applied. Signal recognition protein (SRP)-specific autoantibodies are identified by their characteristic fluorescence staining patterns. Samples that are scored positive are titrated. Interference by coexisting non-neuron-specific autoantibodies is eliminated or lessened by serologic absorption. This method does not distinguish between antibodies against different SRP proteins.(Package insert: EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (IgG) test instruction. EUROIMMUN Medizinische Labordiagnostika AG; Version: 03/2018)

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase:
IgG antibodies to 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) are detected by a chemiluminescent assay using the Inova BIO-FLASH instrument. HMGCR antigen is coated on to paramagnetic beads, which are stored in

the reagent cartridge lyophilized. When the assay cartridge is ready to be used for the first time, a buffer solution is added to the tube containing the beads, and the beads are resuspended with the buffer. The reagent cartridge is then loaded onto the BIO-FLASH instrument. A patient serum sample is diluted 1:17 by the instrument in a disposable plastic cuvette. An aliquot of the diluted patient serum, HMGCR-coupled beads, and assay buffer are combined into a second cuvette and mixed. This cuvette is incubated at 37 degrees C. The beads are then magnetized and washed several times. Isoluminol conjugated anti-human IgG antibody is then added to the cuvette, and incubated at 37 degrees C. Again, the beads are magnetized and washed repeatedly. The isoluminol conjugate produces a luminescent reaction when "trigger" reagents are added to the cuvette. The light produced from this reaction is measured as relative light units (RLU) by the BIO-FLASH optical system. RLU values are proportional to the amount of bound isoluminol conjugate, which in turn is proportional to the amount of anti-HMGCR antibodies bound to the antigen on the beads. The QUANTA Flash HMGCR assay utilizes a predefined lot specific master curve that is uploaded into the instrument through the reagent cartridge barcode. Based on the results obtained by running two calibrators, an instrument specific working curve is created, which is used by the software to calculate chemiluminescent units from the RLU value obtained for each sample.(Package insert: QUANTA Flash HMGCR 701333. Inova Diagnostics, Inc; v04, 09/2018)

SRP Immunoblot:
The assay is performed using the EUROBlotOne instrument. All reagents required are supplied in the kit. Samples are diluted 1:100 (15 mcL in 1.5 mL sample buffer) and added to the strips placed in incubation trays. The sample and test strips are incubated for 30 minutes at room temperature. Unbound antibodies are removed from trays by washing steps using wash buffer. Bound patient IgG antibodies are detected by adding antihuman-IgG antibodies coupled to horse radish peroxidase followed by incubation at room temperature for 30 minutes. The strips are washed again to remove excess antihuman-IgG antibodies. The substrate is added for 10 minutes (room temperature) and the reaction is subsequently stopped. The strip is scanned, and band intensities are digitized. The digital image is converted to band signal intensities by the EUROLineScan software, which are normalized to an internal standard. Bands corresponding to SRP with signal intensities of 15 U (arbitrary) or greater are reported as positive. The SRP antigen used is recombinant SRP 54. Positive immunoblot results confirm that a patient's serum contains antibodies directed against the SRP 54 subunit. Negative immunoblot results do exclude the presence of SRP antibodies.(Package insert: EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (IgG) test instruction. EUROIMMUN Medizinische Labordiagnostika AG; Version: 03/2018)

PDF Report
No

Day(s) Performed
Tuesday, Thursday

Report Available
10 to 14 days

Specimen Retention Time
28 days

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

86255
82397
86256 (if appropriate)
84182 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
NMS1	Necrotizing Myopathy Evaluation, S	97561-5

Result ID	Test Result Name	Result LOINC® Value
603543	Necrotizing Myopathy Interp, S	69048-7
603540	SRP IFA Screen, S	97562-3
607414	HMG-CoA Reductase Ab, S	93493-5