Test Definition: MGMR

Myasthenia Gravis Evaluation with
Muscle-Specific Kinase (MuSK) Reflex, Serum

Overview

Useful For

Diagnosing autoimmune myasthenia gravis (MG) in adults and children

Distinguishing autoimmune from congenital MG in adults and children or other acquired forms of neuromuscular junction transmission disorders

Establishing a quantitative baseline value that allows comparison with future levels if weakness is worsening

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
MGMRI	MG with MuSK Interpretation, S	No	Yes
ARBI	ACh Receptor (Muscle) Binding Ab	Yes	Yes

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
ACMFS	AChR Modulating Flow Cytometry, S	No	No
MUSK	MuSK Autoantibody, S	Yes	No

Testing Algorithm

If acetylcholine receptor (AChR)-binding antibodies are greater than 0.02 nmol/L, then AChR muscle modulating antibody will be performed at an additional charge.

If AChR-binding antibodies are 0.02 nmol/L or less, then muscle-specific kinase (MuSK) autoantibody will be performed at an additional charge.

If unable to report AChR binding antibody due to interfering substances, then AChR muscle modulating antibody will be performed at an additional charge.

If unable to report AChR binding antibody due to interfering substances and AChR muscle modulating antibody is negative, then MuSK autoantibody will be performed at an additional charge.

Method Name

ARBI, MUSK: Radioimmunoassay (RIA)
ACMFS: Flow Cytometry

MGMRI: Medical Interpretation

NY State Available

Yes

Specimen

Specimen Type

Serum

Ordering Guidance

This test **should not be requested** for patients who have recently received radioisotopes, therapeutically or diagnostically, because of potential assay 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 screened for radioactivity prior to analysis. Radioactive specimens received in the laboratory will be held 1 week and assayed if sufficiently decayed or canceled if radioactivity remains.

Specimen Required

Patient Preparation: For optimal antibody detection, specimen collection is recommended prior to initiation of immunosuppressant medication or intravenous immunoglobulin treatment.
Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Red top
Acceptable: Serum gel
Submission Container/Tube: Plastic vial
Specimen Volume: 3 mL
Collection Instructions: Centrifuge 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

Fatigable weakness due to impaired postsynaptic transmission at the neuromuscular junction is characteristic of myasthenia gravis (MG). A clinical diagnosis should be supported by electrodiagnostic testing, ie, clinical-electrodiagnosis (EDX). Positive autoimmune serology increases certainty of MG diagnosis but needs to be interpreted in the proper clinical-EDX context with response to anticholinesterase medications supporting the diagnosis. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules (nicotinic muscle acetylcholine receptor [AChR] or its interacting proteins, such as muscle-specific kinase [MuSK]). Serologically, the detection of AChR binding antibody provides the best diagnostic sensitivity. However, the presence of both AChR binding and modulating activity improves diagnostic accuracy. Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (72% are positive for AChR binding antibodies) and highest in patients with generalized weakness due to MG (92% are positive for AChR binding antibodies). In adults with MG and AChR antibodies, approximately 20% will have thymoma and, very rarely (<1%), extrathymic cancers. Computerized tomography imaging of the chest is considered the standard of care to evaluate for thymoma.

MuSK antibody is detectable in more than one-third of patients with MG who are seronegative for muscle AChR antibodies. MuSK is involved in integrating and stabilizing AChR clusters at the motor endplate. MuSK is activated when the nerve-derived proteoglycan agrin binds to its receptor, lipoprotein-related protein 4 (LRP4). Patients with MuSK MG are more commonly female. Onset can occur at any age (pediatric to older adult). Patients derive less benefit from anticholinesterase medications, and no neoplasm has been associated with MuSK MG. Although beneficial, thymectomy has not been demonstrated to be helpful in MuSK MG. Patients with both AChR and MuSK autoantibodies benefit from immunotherapy, however, patients with MuSK autoantibodies tend to have more steroid dependence.

In patients with seronegative MG, reconsideration of the diagnosis is important. If clinical-EDX criteria are still met, repeating serological testing within one year can increase serological positivity for AChR antibodies by 15%. The diagnostic sensitivity of these tests depends on the disease severity and duration of symptoms. AChR binding antibodies may be undetectable for 6 to 12 months after MG symptom onset. Only about 5% of adult patients with generalized MG who are not immunosuppressed remain seronegative for muscle AChR beyond 12 months. Objective improvement by electrodiagnostic and strength testing following a therapeutic trial of plasmapheresis or intravenous immune globulin can justify consideration of long-term immunosuppression in patients who are seronegative meeting clinical-EDX criteria.

Note: Single antibody tests may be requested in the follow-up of patients with positive results previously documented in this laboratory.

Reference Values

Test ID	Reporting Name	Methodology	Reference Value
MGMRI	MG with MuSK Interpretation, S	Interpretation	NA
ARBI	ACh Receptor (Muscle) Binding Ab	Radioimmunoassay (RIA)	< or =0.02 nmol/L

Reflex Information:

Test ID	Reporting Name	Methodology	Reference Value
ACMFS	AChR Modulating Flow Cytometry, S	Flow Cytometry	Negative
MUSK	MuSK Autoantibody, S	RIA	< or =0.02 nmol/L

Interpretation

Positive results in this antibody evaluation are indicative of autoimmune myasthenia gravis (MG). These results should be interpreted in the appropriate clinical and electrophysiological context.

In the presence of either acetylcholine receptor antibodies, a paraneoplastic basis should be considered with thymoma being the most frequently associated tumor with myasthenia gravis. Currently, muscle-specific kinase antibody positive MG is not associated with a paraneoplastic etiology.

Negative results do not exclude the diagnosis of an autoimmune neuromuscular junction disorder. If clinical suspicion remains and symptoms persistent or worsen, consider re-testing.

Cautions

These results should only be interpreted in the appropriate clinical and electrophysiological context and are not diagnostic in isolation.

Specimens should be collected prior to administration of immunosuppressant therapy as this may reduce the diagnostic sensitivity of the assay; the neurological diagnosis is further confounded if steroid myopathy develops.

Positive muscle acetylcholine receptor (AChR) may occur in autoimmune liver disorders and in patients with graft-versus-host disease and recipients of D-penicillamine.

Weakly positive results may occur with hypergammaglobulinemia and should be interpreted with caution in the appropriate clinical context.

AChR modulating antibodies will only be performed if AChR binding antibodies are present or if there is an interfering substance present that precludes testing for AChR binding antibodies.

Seropositive rates and quantitative results differ across laboratories and patient results tested at different laboratories should not be treated equivalently.

The presence of alpha-bungarotoxin antibodies may interfere with the AChR muscle binding antibody assay and therefore if detected, AChR binding results will not be reported.

Clinical Reference

1. Li Y, Arora Y, Levin K. Myasthenia gravis: Newer therapies offer sustained improvement. Cleve Clin J Med. 2013;80(11):711-721. doi:10.3949/ccjm.80a.13044
2. Vernino S, Lennon VA. Autoantibody profiles and neurological correlations of thymoma. Clin Cancer Res. 2004;10(21):7270-7275. doi:10.1158/1078-0432.CCR-04-0735
3. Skjei KL, Lennon VA, Kuntz NL. Muscle specific kinase autoimmune myasthenia gravis in children: A case series. Neuromuscul Disord. 2013;23(11):874-882. doi:10.1016/j.nmd.2013.07.010
4. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med. 2001;7(3):365-368. doi:10.1038/85520
5. Chan KH, Lachance DH, Harper CM, Lennon VA. Frequency of seronegativity in adult-acquired generalized myasthenia gravis. Muscle Nerve. 2007;36(5):651-658. doi:10.1002/mus.20854
6. Shelly S, Paul P, Bi H, et al. Improving accuracy of myasthenia gravis autoantibody testing by reflex algorithm. Neurology. 2020 1;95(22):e3002-e3011. doi:10.1212/WNL.0000000000010910

Performance

Method Description

Radioimmunoassay:
(125)I-labeled recombinant human antigens or labeled receptors are incubated with patient sample. After incubation, anti-human IgG is added to form an immunoprecipitate. The amount of (125)I-labeled antigen in the immunoprecipitate is measured using a gamma-counter. The amount of gamma emission in the precipitate is proportional to the amount of antigen-specific IgG in the sample. Results are reported as units of precipitated antigen (nMol) per L of patient sample.(Griesmann GE, Kryzer TJ, Lennon VA: Autoantibody profiles of myasthenia gravis and Lambert-Eaton myasthenic syndrome. In: Rose NR, Hamilton RG, et al. eds. Manual of Clinical and Laboratory Immunology. 6th ed. ASM Press; 2002:1005-1012; Jones AL, Flanagan EP, Pittock SJ, et al: Responses to and outcomes of treatment of autoimmune cerebellar ataxia in adults. JAMA Neurol. 2015;72[11]:1304-1312. doi:10.1001/jamaneurol.2015.2378)M

Flow Cytometry:
This method uses flow cytometry to measure the loss of acetylcholine receptor (AChR) molecules expressed on the surface of live cells expressing AChR on the cell surface. The cell line used is an immortalized human rhabdomyosarcoma cell line that expresses endogenous muscle-type nicotinic AChR on its surface. Cells are plated in a 96-well plate and cultured 72 hours prior to the addition of patient sample for an additional 18 to 22 hours to enable internalization of AChR receptors (modulation). Modulation is then stopped by placing cells on ice. The amount of remaining AChRs on the cell surface is measured by flow cytometry. On ice, cells are incubated with a recombinant rat monoclonal antibody against alpha-subunit of the AChR followed by a secondary goat anti-rat IgG antibody conjugated with allophycocyanin (APC). The amount of AChR on the cell surface is proportional to the median fluorescence intensity (MFI) of APC. To calculate the amount of modulation (ie, % loss of AChR) the APC MFI is compared between cells treated with patient sample and cells treated with serum lacking AChR modulating antibodies. Background signal is established in each experiment utilizing cells stained with secondary antibody alone (no patient sera). The percent loss of AChR is calculated as 1-([Patient MFI-Background MFI])/([Negative calibrator MFI - Background MFI])*100%.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed
Profile tests: Monday through Sunday; Reflex tests: Varies

Report Available
3 to 10 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
86041
86043 (if appropriate)
86366 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
MGMR	MG Evaluation MuSK Reflex, S	53706-8

Result ID	Test Result Name	Result LOINC® Value
8338	ACh Receptor (Muscle) Binding Ab	97558-1
608981	MG with MuSK Interpretation, S	69048-7