MAYO CLINIC LABORATORIES

Test Definition: CDS1

CNS Demyelinating Disease Evaluation, Serum

Overview

Useful For

Diagnosis of inflammatory demyelinating diseases (IDDs) with similar phenotype to neuromyelitis optica spectrum disorder (NMOSD), including optic neuritis (single or bilateral) and transverse myelitis

Diagnosis of autoimmune myelin oligodendrocyte glycoprotein-opathy

Diagnosis of neuromyelitis optica

Distinguishing NMOSD, acute disseminated encephalomyelitis (ADEM), optic neuritis, and transverse myelitis from multiple sclerosis early in the course of disease

Diagnosis of ADEM

Prediction of a relapsing disease course

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
CSI1	CNS Demyelinating Disease Interp, S	No	Yes
NMOFS	NMO/AQP4 FACS, S	Yes	Yes
MOGFS	MOG FACS, S	Yes	Yes

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
NMOTS	NMO/AQP4 FACS Titer, S	No	No
MOGTS	MOG FACS Titer, S	No	No

Testing Algorithm

When the results of this assay require further evaluation of myelin oligodendrocyte glycoprotein (MOG-IgG1), the MOG-IgG1 titer will be performed at an additional charge.

When the results of this assay require further evaluation of neuromyelitis optica (NMO)/Aquaporin-4-IgG, the neuromyelitis optica (NMO)/aquaporin-4-IgG titer will be performed at an additional charge.

For more information, see the following algorithms:
-Pediatric Autoimmune Central Nervous System Demyelinating Disease Diagnostic Algorithm
-Central Nervous System Demyelinating Disease Diagnostic Algorithm

Special Instructions

- Pediatric Autoimmune Central Nervous System Demyelinating Disease Diagnostic Algorithm
- Central Nervous System Demyelinating Disease Diagnostic Algorithm

Highlights

Myelin oligodendrocyte glycoprotein (MOG)-IgG with a neuromyelitis optica spectrum disorder like phenotype is now recognized as a sensitive and specific diagnostic antibody biomarker of inflammatory demyelinating disorders (IDDs).

Approximately 80% of patients fulfilling 2006 Wingerchuk criteria for neuromyelitis optica are seropositive for aquaporin-4-IgG. Of the remaining 20%, one-third harbor MOG-IgG. Seropositivity predicts a relapsing phenotype and warrants immunosuppressive therapy. Patients only rarely harbor both antibodies.

There is currently no biomarker specific for MS (multiple sclerosis). Patients seropositive for MOG-IgG are commonly misdiagnosed as MS. Detection of MOG-IgG implies an inflammatory demyelinating disorder distinct from MS. MS therapies may worsen MOG-IgG associated IDDs, so correct diagnosis is important.

Seropositivity for MOG-IgG, in NMOSD like disorders, including optic neuritis, transverse myelitis, and acute disseminated encephalomyelitis, predicts relapse and warrants consideration for maintenance immunosuppression.

Seropositivity for MOG-IgG in the setting of a severe relapse of central nervous system demyelination warrants aggressive therapy with intravenous methylprednisolone or plasmapheresis.

Method Name

Flow Cytometry

NY State Available

Yes

Specimen

Specimen Type

Serum

Ordering Guidance

Multiple neurological phenotype-specific autoimmune/paraneoplastic evaluations are available. For more information as well as phenotype-specific testing options, refer to Autoimmune Neurology Test Ordering Guide.

For a list of antibodies performed with each evaluation, see Autoimmune Neurology Antibody Matrix.

Specimen Required

Patient Preparation: For optimal antibody detection, specimen collection is recommended before initiation of immunosuppressant medication.
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

Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis (MS) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease (IDD) that predominantly affects optic nerves and spinal cord.(1) The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders: NMOSD).(1-3) Brain lesions are observed in more than 60% of patients with NMOSD and approximately 10% will be MS-like.(4) Children tend to have greater brain involvement than adults, and brain lesions are more symptomatic than is typical for adult patients.(3) The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Some patients may present with acute disseminated encephalomyelitis (ADEM). Many patients with NMOSD are misdiagnosed as having MS. More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes.

Approximately 80% of patients with NMO are seropositive for aquaporin-4 (AQP4)-IgG.(5-7) In the remaining 20% of patients, myelin oligodendrocyte glycoprotein (MOG)-IgG is detected in up to a third.(8) The pathogenic target for the remaining patients remains unknown. Detection of MOG-IgG is diagnostic of central nervous system (CNS) inflammatory demyelination, where the clinical phenotype (NMOSD, optic neuritis, transverse myelitis, ADEM) may be similar, but the

immunopathology (astrocytopathy vs oligodendrogyopathy) and clinical outcome (worse vs better) is different.(9) Detection of MOG-IgG also predicts relapse.(10) More importantly, however, is that MOG-IgG seropositive IDDs are distinct from MS and treated differently.(8,9) Treatments for IDDs seropositive for MOG-IgG include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Disease modifying agents, treatments promoted for MS, have been reported to exacerbate MOG-IgG1 seropositive IDDS. Therefore, early diagnosis and initiation of appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. In 2015, Waters and colleagues (11) from Oxford University established a novel cell based assay for the measurement of IgG1 MOG antibodies based on previous findings that MOG antibodies are almost exclusively of the IgG1 subclass. They showed that their MOG-IgG1 flow cytometry assay eliminated false-positives without losing true-positives with low titers. The detection of MOG-IgG1 allowed non MS demyelinating diseases (ADEM, AQp4-IgG negative neuromyelitis optica spectrum disorder: including ON,TM) to be distinguished from MS.(12)

Using a similar assay to our MOG-IgG1 flow cytometry assay, Wingerchuk et al demonstrated high specificity of their MOG-IgG1 assay in which 49 patients with MS, 13 healthy control sera, and 37 AQP4-seropositive serum samples were all negative at a dilution of 1:20. Of 58 patients fulfilling 2006 Wingerchuk criteria for NMO, 21 (36%) tested negative for AQP4-IgG MOG-IgG1 was detected by cell based assay in 8 (38%) of these cases. (13)

Testing of 1,109 consecutive sera sent for AQP4-IgG testing,(11) revealed 40 AQP4-IgG and 65 MOG-IgG1 positive cases. None were positive for both. The clinical diagnoses obtained in 33 MOG-IgG1 positive patients included 4 NMO, 1 ADEM and 11 optic neuritis (n = 11). All 7 patients with probable MS were MOG-IgG1 negative. This study provides Class II evidence that the presence of serum MOG-IgG1 distinguishes non-MS central nervous system (CNS) demyelinating disorders from MS (sensitivity 24%, 95% confidence interval [CI] 9%-45%; specificity 100%, 95% CI 88%-100%).

The assay validated here, was developed using the MOG construct provided by Dr Waters(11) and the validation was based on a blinded comparison with the Oxford assay. Comparison was also made with the Euroimmun fixed cell-based kit assay.(14)

A recent longitudinal analysis with 2 year follow-up suggested that persistence of MOG-IgG is associated with relapses thus warranting relapse preventing.(10) Detection of MOG-IgG1 allows distinction from MS and is generally indicative of a relapsing disease, mandating initiation of immunosuppression, even after the first attack in some, thereby reducing attack frequency and disability in the future.

Reference Values

MYELIN OLIGODENDROCYTE GLYCOPROTEIN FLORESCENCE-ACTIVATED CELL SORTING(FACS)
Negative
Reference values apply to all ages.

NEUROMYELITIS OPTICA/AQUAPORIN-4-IgG FACS
Negative
Reference values apply to all ages.

Interpretation

A positive value for aquaporin-4 (AQP4)-IgG is consistent with an autoimmune astrocytopathy/neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 3 to 6 months if NMOSD

is suspected.

A positive value for myelin oligodendrocyte glycoprotein (MOG)-IgG is consistent with a neuromyelitis optica-like phenotype and in the setting of acute disseminated encephalomyelitis, optic neuritis and transverse myelitis, indicates an autoimmune oligodendrogliopathy with potential for relapsing course. Identification of MOG-IgG allows distinction from multiple sclerosis (MS) and may justify initiation of appropriate immunosuppressive therapy (not MS disease-modifying agents) at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 6 to 12 months as persistence of MOG-IgG seropositivity predicts a relapsing course.

Detection of both antibodies is rare and unusual.

AQP4-IgG and MOG-IgG are not found in MS or healthy subjects.

Cautions

Aquaporin-4-IgG and myelin oligodendrocyte glycoprotein-IgG antibodies may drop below detectable levels in setting of therapies for acute attack (IV methylprednisolone or plasmapheresis) or attack prevention (immunosuppressants).

Clinical Reference

1. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol. 2007;6(9):805-815. doi:10.1016/S1474-4422(07)70216-8
2. Apiwattanakul M, Popescu BF, Matiello M, et al: Intractable vomiting as the initial presentation of neuromyelitis optica. Ann Neurol. 2010;68(5):757-761
3. McKeon A, Lennon VA, Lotze T, et al. CNS aquaporin-4 autoimmunity in children. Neurology. 2008;71(2):93-100
4. Pittock SJ, Weinshenker BG, Lucchinetti CF, et al. Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol. 2006;63(7):964-968
5. Fryer JP, Lennon VA, Pittock SJ, et al. AQP4 autoantibody assay performance in clinical laboratory service. Neurol Neuroimmunol Neuroinflamm. 2014;1(1):e11. Published 2014 May 22. doi:10.1212/NXI.0000000000000011
6. Waters PJ, McKeon A, Leite MI, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. Neurology. 2012;78(9):665-669. doi:10.1212/WNL.0b013e318248dec1
7. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;364(9451):2106-2112
8. Peschl P, Bradl M, Hoftberger R, et al. Myelin Oligodendrocyte Glycoprotein: Deciphering a target in inflammatory demyelinating diseases. Front Immunol. 2017;8:529
9. Pittock SJ, Lucchinetti CF. Neuromyelitis optica and the evolving spectrum of autoimmune aquaporin-4 channelopathies: a decade later. Ann N Y Acad Sci. 2016;1366(1):20-39. doi:10.1111/nyas.12794
10. Hyun JW, Woodhall MR, Kim SH, et al. Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases. J Neurol Neurosurg Psychiatry. 2017;88(10):811-817
11. Waters P, Woodhall M, O'Connor KC, et al. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. Neurol Neuroimmunol Neuroinflamm. 2015;2(3):e89
12. Reindl M, Jarius S, Rostasy K, Berger T. Myelin oligodendrocyte glycoprotein antibodies: How clinically useful are they? Curr Opin Neurol. 2017;30(3):295-301
13. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85(2):177-189
14. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and

origin. J Neuroinflammation 2016;13(1):279
15. Sechi E, Buciuc M, Pittock SJ, et al. Positive Predictive Value of myelin oligodendrocyte glycoprotein autoantibody testing. JAMA Neurol. 2021;78(6):741-746. doi:10.1001/jamaneurol.2021.0912
16. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. Lancet Neurol. 2023;22(3):268-282. doi:10.1016/S1474-4422(22)00431-8

Performance

Method Description

NMO-IgG Fluorescence-Activated Cell Sorting Assay
Human embryonic kidney cells (HEK 293) are transfected transiently with a plasmid (pIRES2- *Aequorea coerulescens* green fluorescent protein [AcGFP]) encoding both green fluorescent protein (AcGFP) and AQP4-M1. After 36 hours, a mixed population of cells (transfected expressing AQP4 on the surface and AcGFP in the cytoplasm and nontransfected lacking AQP4 and AcGFP) are lifted and resuspended in live cell-binding buffer. Cells are incubated with patient serum and an AlexaFluor 647-labeled secondary antibody is added. Two populations are gated on the basis of AcGFP expression: positive (high AQP4 expression) and negative (low or no AQP4 expression). Positivity is based on the ratio (Positive >2.0) of the average MFI of each cell population (MFI GFP positive:MFI GFP negative).(Unpublished Mayo method)

If AQP4 cell based flow cytometry (FACS) assay is positive at screening dilution, AQP4 FACS Titer Assay is performed at an additional charge.

MOG-IgG1 Fluorescence-Activated Cell Sorting Assay
Human embryonic kidney cells (HEK 293) are transfected transiently with a DNA plasmid that allows coexpression of both a reporter fluorescent protein (green fluorescent protein [AcGFP]) and full-length MOG. After 36 hours, a mixed population of cells (transfected expressing MOG on the surface and AcGFP in the cytoplasm and nontransfected lacking MOG and AcGFP) are lifted and resuspended in live cell-binding buffer. Cells are incubated with patient serum and an AlexaFluor 647 labeled secondary antibody is added. Two populations are gated on the basis of AcGFP expression: positive (high MOG expression) and negative (low or no MOG expression). Positivity is based on the ratio (Positive >2.5) of the average MFI of each cell population (MFI GFP positive:MFI GFP negative).(Unpublished Mayo method)

If MOG-IgG1 cell based flow cytometry (FACS) assay is positive at screening dilution, the MOG-IgG1 flow cytometry titer assay is performed at an additional charge.

PDF Report

No

Day(s) Performed

Monday, Tuesday, Thursday

Report Available

7 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

86053
86363
86053-Titer (if appropriate)
86363-Titer (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CDS1	CNS Demyelinating Disease Eval, S	102085-8

Result ID	Test Result Name	Result LOINC® Value
38324	NMO/AQP4 FACS, S	43638-6
65563	MOG FACS, S	90248-6
113625	CNS Demyelinating Disease Interp, S	69048-7