See below for Additional Technical Information topics

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Antibody, IgG
Idiopathic Inflammatory Myopathies (Myositis)

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Antibody, IgG

Indications for Ordering
- Differential diagnosis of myositis in patients with or without statin exposure
- Monitor response to treatment

Test Description
Semiquantitative enzyme-linked immunosorbent assay

Tests to Consider
Primary test
3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase (HMGCR) Antibody, IgG 2013101
- Detects IgG autoantibodies against HMGCR
- In addition to clinical evaluation for muscle strength and serum creatine kinase, may be useful to monitor response to treatment

Related tests
Creatine Kinase, Total, Serum or Plasma 0020010
- Nonspecific indicator of muscle inflammation or damage
- Monitor therapeutic response

Myositis Extended Panel 2013961
- May be useful for differential evaluation of polymyositis, dermatomyositis, necrotizing autoimmune myopathy, or overlap syndromes associated with connective tissue disease

Polymyositis and Dermatomyositis Panel 2013992
- May be useful for evaluation of patients with progressive proximal muscle weakness and/or with cutaneous manifestations suggestive of dermatomyositis and/or associated connective tissue disease

Antinuclear Antibody (ANA) with HEp-2 Substrate, IgG by IFA with Reflex by Pattern 3000601
- Initial screen for autoimmune connective tissue diseases

Connective Tissue Diseases Profile 0051668
- Confirmatory tests for specific connective tissue disease

Disease Overview

Age of onset – 30-70 years

Most common clinical features
- Persistent and progressive proximal weakness
- Myalgia
- Elevated serum creatine kinase concentration
  - >10,000 IU/L mean concentration prior to treatment
  - Range – 950-45,000 IU/L

Physiology
- Presence of anti-HMGCR antibodies is associated with a rare form of idiopathic inflammatory myopathy referred to as necrotizing autoimmune myopathy
- Anti-HMGCR IgG antibodies are mainly associated with exposure to statins
  - Also occur in statin-naïve patients with myositis
- Muscle biopsy is associated with
  - Abundant necrotic fibers
  - Sparse lymphocytic infiltrate
  - Complement deposits on capillaries
  - Increased expression of major histocompatibility complex class 1 molecules
- In most patients, statin-induced myopathy resolves within months after discontinuation of treatment
  - Minority develop a progressive necrotizing myopathy associated with anti-HMGCR antibodies
  - Requires immunosuppressive therapy
- Response to treatment is associated with
  - Decline in antibody titers and creatine concentration
  - Improvement in muscle strength
Idiopathic Inflammatory Myopathies (Myositis)

Indications for Ordering
Differential diagnosis of inflammatory myopathies in conjunction with muscle biopsy and clinical presentation

Test Description

Polymyositis and Dermatomyositis Panel
Myositis Extended Panel
  • Qualitative immunoprecipitation/semiquantitative multiplex bead assay/qualitative immunoblot

Polymyositis Panel
  • Qualitative immunoprecipitation/semiquantitative multiplex bead assay

Dermatomyositis Panel
  • Qualitative immunoprecipitation/qualitative immunoblot

Interstitial Lung Disease Panel
  • Qualitative immunoprecipitation/semiquantitative multiplex bead assay/qualitative immunoblot/semiquantitative enzyme-linked immunosorbent assay/quantitative immunoturbidimetry

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase (HMGCR) Antibody, IgG
  • Semiquantitative enzyme-linked immunosorbent assay

Tests to Consider

Typical testing strategy
Initial screening tests
  • Creatine kinase
  • Erythrocyte sedimentation rate/C-reactive protein
  • Thyroid-stimulating hormone – rule out thyroid disease as etiology for myopathy
  • Metabolic profile
  • Complete blood count
  • Antinuclear antibodies

Antibody testing (minimum recommended)
  • Antisynthetase antibodies – anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ
  • Nonsynthetase antibodies – anti-Mi2, anti-p155/140, anti-SRP
  • Myositis associated antibodies – anti-PM/Scl-100, anti-SSA(RO), anti-U1 RNP

Definitive diagnosis
  • Muscle biopsy (which can be guided by MRI) is gold standard

References

Primary tests

**Polymyositis and Dermatomyositis Panel 2013992**

- May be useful for evaluation of patients with progressive proximal muscle weakness and/or with cutaneous manifestations suggestive of dermatomyositis and/or associated connective tissue disease

- Components
  - Jo-1 antibody, IgG
  - PL-7 (threonyl-tRNA synthetase) antibody
  - PL-12 (alanyl-tRNA synthetase) antibody
  - EJ (glycyl-tRNA synthetase) antibody
  - SRP (signal recognition particle) antibody
  - OJ (isoleucyl-tRNA synthetase) antibody
  - Mi-2 (nuclear helicase protein) antibody
  - P155/140 antibody
  - SAE1 (SUMO activating enzyme) antibody
  - MDA5 (CADM-140) antibody
  - NXP-2 (nuclear matrix protein-2) antibody
  - TIF1-gamma (TIF1-y) antibody

**Myositis Extended Panel 2013961**

- May be useful for differential evaluation of polymyositis, dermatomyositis, necrotizing autoimmune myopathy, or overlap syndromes associated with connective tissue disease

- Components
  - SSA 52 and 60 (Ro) (ENA) antibodies, IgG
  - RNP (U1) (ribonucleic protein) (ENA) antibody, IgG
  - Jo-1 antibody, IgG
  - Mi-2 (nuclear helicase protein) antibody
  - PL-7 (threonyl-tRNA synthetase) antibody
  - PL-12 (alanyl-tRNA synthetase) antibody
  - P155/140 (TIF1-gamma) antibody
  - EJ (glycyl-tRNA synthetase) antibody
  - Ku antibody
  - U2 sn (small nuclear) RNP antibody
  - SRP (signal recognition particle) antibody
  - OJ (isoleucyl-tRNA synthetase) antibody
  - SAE1 (SUMO activating enzyme) antibody
  - MDA5 (CADM-140) antibody
  - NXP-2 (nuclear matrix protein-2) antibody
  - TIF1-gamma (TIF1-y) antibody

**Polymyositis Panel 20139390**

- May be useful for evaluation of patients with proximal muscle weakness and antisynthetase syndrome

- Components
  - Jo-1 antibody, IgG
  - PL-7 (threonyl-tRNA synthetase) antibody
  - PL-12 (alanyl-tRNA synthetase) antibody
  - EJ (glycyl-tRNA synthetase) antibody
  - SRP (signal recognition particle) antibody
  - OJ (isoleucyl-tRNA synthetase) antibody

**Dermatomyositis Panel 2013991**

- May be useful for evaluation of patients with characteristic cutaneous manifestations of dermatomyositis with or without muscle weakness

- Components
  - Mi-2 (nuclear helicase protein) antibody
  - P155/140 (TIF1-gamma) antibody
  - SAE1 (SUMO activating enzyme) antibody
  - MDA5 (CADM-140) antibody
  - NXP-2 (nuclear matrix protein-2) antibody
  - TIF1-gamma antibody

**Interstitial Lung Disease Panel 2013993**

- May be useful for evaluation of interstitial lung disease in the context of connective tissue disease

- Components
  - SSA 52 and 60 (Ro) (ENA) antibodies, IgG
  - Scleroderma (Scl-70) (ENA) antibody
  - Jo-1 antibody, IgG
  - PL-7 (threonyl-tRNA synthetase) antibody
  - PL-12 (alanyl-tRNA synthetase) antibody
  - EJ (glycyl-tRNA synthetase) antibody
  - Ku antibody
  - SRP (signal recognition particle) antibody
  - OJ (isoleucyl-tRNA synthetase) antibody
  - PM/Scl-100 antibody, IgG by immunoblot
  - MDA5 (CADM-140) antibody
  - NXP-2 (nuclear matrix protein-2 Ab)
  - Rheumatoid factor
  - Cyclic citrullinated peptide (CCP) antibody, IgG
  - Nuclear antibody (ANA) by IFA, IgG

**3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase (HMGCR) Antibody, IgG 2013101**

- Differential diagnosis of myositis in patients with or without statin exposure

- In addition to clinical evaluation for muscle strength and serum creatine kinase, may be useful to monitor response to treatment

**Related tests**

- Creatine Kinase, Total, Serum or Plasma 0020010
- Antinuclear Antibodies (ANA), IgG by ELISA with Reflex to ANA, HEP-2 Substrate, IgG by IFA 0050080
- SSA 52 and 60 (Ro) (ENA) Antibodies, IgG 2012173
- Jo-1 Antibody, IgG 0099592
- RNP (U1) (Ribonucleic Protein) (ENA) Antibody, IgG 0050470
- Signal Recognition Particle (SRP) Antibody 2002098
- PM/Scl-100 Antibody, IgG by Immunoblot 2003040
- Fibrillarin (U3 RNP) Antibody, IgG 2012173

**Disease Overview**

**Incidence** – 4-10/million adults; rare in children

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Age of onset – varies by disorder
- Dermatomyositis (DM)
  - Bimodal – childhood and 50-70 years
- Polymyositis (PM) – rare in childhood, typically >20 years
- Inclusion body myositis (IBM) – >50 years
- Necrotizing autoimmune myositis – primarily adults, often older

Syndromes
- DM – associated with cancer
- PM
- IBM
- Necrotizing autoimmune myositis
- Overlap syndrome
- Juvenile DM and PM

Symptoms
General features
- Musculoskeletal – progressive muscle weakness (usually symmetrical and proximal)
  - Pharyngeal and neck flexion muscles frequently involved
- Arthralgias/arthritis – wrists, knees, small joints of hands
- Constitutional – fever, weight loss
- Pulmonary – fibrosing alveolitis, aspiration pneumonia
- Gastrointestinal – esophageal dysfunction, dysphagia
- Cardiovascular – myo-/pericarditis, valvular disease, rhythm disturbances
- Renal – rarely myoglobinuria, glomerulonephritis
- Dermatologic – Raynaud phenomenon, rashes, calcinosis over bony prominences

Antisynthetase syndrome
- Found almost exclusively in middle-aged women with DM or PM
- Characterized by
  - Low-grade fevers
  - Interstitial pneumonitis – major determinant of morbidity and mortality
  - Hyperkeratosis, cracking of lateral and palmar aspects of the fingers (mechanic’s hands)
  - Raynaud phenomenon
  - Inflammatory polyarthritis, myalgias
- Presence of antinuclear antibodies known as antisynthetases

DM
- Characteristic photosensitive rash accompanied by symmetrical, subacute, proximal muscle weakness
  - Rash usually precedes muscle symptoms
  - Blue-purple rash – symmetrical distribution
  - Violaceous discoloration of upper eyelids with periorbital edema (heliotrope rash)
  - Erythema of metacarpophalangeal proximal and distal joints
    - Raised violaceous rash (Gottron sign) or scaly erythematous plaques over dorsal surface of bony prominences (Gottron papules) – considered pathognomonic for DM
  - Macular erythema over the lower neck and upper chest in a V-distribution (V-sign), over upper back (Shawl sign), or over upper thighs (Holster sign)
  - Telangiectasias at base of fingernails, cuticular overgrowth and periungual erythema
  - Vasculitic skin changes
    - Subcutaneous nodules, periungual infarcts, digital ulcerations
- Cancer-associated myositis
  - Most commonly associated with DM, but can be found in PM
  - May be diagnosed prior to, simultaneously with, or after myopathy
  - Increased risk of malignancy (20-25%) of any of the following types (highest risk in first 2-3 years after diagnosis)
    - Ovarian
    - Breast
    - Melanoma
    - Colorectal
    - Non-Hodgkin lymphoma
- Amyopathic DM
  - Characteristic cutaneous findings of DM >6 months without muscle involvement
  - May progress to DM
  - Some risk for lung disease, malignancy
  - Electromyography may demonstrate subtle myopathy

PM
- Dominated by muscular presentation
  - No rash
- Usually subacute presentation
- May be associated with other autoimmune diseases
- Diagnosis of exclusion – must rule out the following
  - Neuromuscular disease
  - Endocrinopathy
  - Muscular dystrophy
  - Known biochemical muscle disorder or familial biochemical disorder
  - Drug-induced myopathy

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Juvenile polymyositis

- Two types – sporadic, hereditary
- Muscle involvement
  - Muscle atrophy early in disease
  - Distal weakness is most common – deep finger flexors and foot extensors common
  - Asymmetric distribution is common
  - Proximal muscles less frequently involved
- Specific muscles
  - Small muscles in hand frequently involved
  - Quadriceps involvement common – associated with frequent falls
  - Facial muscles frequently involved
- Extramuscular disease rare – dysphagia is the exception (>50% of patients)
- May be misdiagnosed as PM, adult-onset muscular dystrophy, or motor neuron disease
- Associated with other autoimmune diseases

Necrotizing autoimmune myositis

- Acute or subacute presentation
- Severe proximal muscle weakness – clinically indistinguishable from PM
- May occur in association with cancer, other CT diseases, or drug use (eg, statins)
- Diagnosis of exclusion

Overlap syndrome

- Most common in DM but can occur with other inflammatory myopathies
- Myositis in conjunction with connective tissue disease
  - Most common – systemic sclerosis, mixed connective tissue disease, systemic lupus erythematosus
- Rash – faint or transient
- Frequent association with antisynthetase antibodies
- Myopathy varies from mild to dominant presentation

Juvenile polymyositis

- 4-8%
- Proximal and distal muscle weakness
- Frequent falling episodes
- Cardiac damage

Juvenile connective tissue disease myositis

- 6-11% of JIIM
- Occurs in conjunction with another connective tissue disease
- Raynaud phenomenon
- Arthritis
- Malar rash
- Interstitial lung disease

Diagnostic issues

May be difficult to distinguish between myopathies
- Antibody testing in conjunction with clinical presentation and muscle biopsy help to confirm the diagnosis
- Distinction may be important for therapy and prognosis

Antibody testing

- Myositis-specific antibodies
  - Antisynthetase antibodies
    - Anti-PL7 (threonyl-tRNA synthetase)
    - Anti-PL-12 antibodies (anti-alanyl-tRNA synthetase)
    - Anti-EJ (glycy1-ts RNA synthetase)
    - Anti-OJ (anti-isoleucyl-tRNA synthetase)
    - Anti-KS (asparaginyl tRNA synthetase)
    - Anti-Ha (tyrosyl tRNA synthetase)
    - Anti-Zo (phenylalanyl tRNA synthetase)
  - Nonsynthetase antibodies
    - Anti-signal recognition particle (anti-SRP)
    - Necrotizing myopathy
    - Severe cardiac involvement
    - Anti-p155/140
    - JDM, DM, and ulceration
    - Adults – DM, increased malignancy risk
- Anti-Mi-2
  - DM
  - Not associated with increased malignancy risk
  - Steroid responsiveness
- Anti-CADM-140
- CADM
- Rapidly progressive ILD
- Anti-p140
- JDM, DM, and calcinosis
- Adults – DM, increased malignancy risk, ILD
- Anti-SAE
  - DM
  - Anti-HMGCR
  - Necrotizing myopathy
- Response to short-term statin withdrawal
- Myositis-associated antibodies – usually associated with connective tissue disease/overlap syndrome
  - Anti-PM-Scl – polymyositis-scleroderma
  - Anti-U1 RNP
  - Anti-Ku
  - Anti-Ro (SSA)
Test Interpretation

Results

- Positive – as a single test, not diagnostic for inflammatory myopathy
- Negative – does not rule out inflammatory myopathy

Limitations

- Results by themselves are not diagnostic; strong clinical correlation is recommended
- Negative results do not rule out a diagnosis of inflammatory myopathy or overlap syndrome