Autoimmune Liver Disease

Indications for Ordering

Differential evaluation of autoimmune liver disease (ALD) after exclusion of viral and drug-induced hepatitis, alcoholism, and specific hereditary risk factors

Test Description

Autoimmune Liver Disease Evaluation with Reflex to Smooth Muscle Antibody (SMA), IgG by IFA
- Semiquantitative enzyme-linked immunosorbent assay/semiquantitative indirect fluorescent antibody
- Components
  - F-Actin (Smooth Muscle) Antibody, IgG
  - Liver-Kidney Microsome – 1 Antibody, IgG
  - Mitochondrial M2 Antibody, IgG (ELISA)
  - Smooth Muscle Antibody, IgG Titer

ANCA-Associated Vasculitis Profile (ANCA/MPO/PR-3) with Reflex to ANCA Titer
- Semiquantitative indirect fluorescent antibody/semiquantitative multiplex bead assay

Tests to Consider

Primary Tests
Autoimmune Liver Disease Evaluation with Reflex to Smooth Muscle Antibody (SMA), IgG by IFA 2007210
- Recommended first-line panel for evaluation of ALD
  - Negative results do not rule out disease

ANCA-Associated Vasculitis Profile (ANCA/MPO/PR3) with Reflex to ANCA Titer 2006480
- Initial test for evaluation of ALD in conjunction with autoimmune liver disease evaluation with reflex to SMA

Related tests
- Antinuclear Antibody (ANA) with HEP-2 Substrate, IgG by IFA 3000082
- F-Actin and Mitochondrial M2 Antibodies, IgG by ELISA with Reflex to Smooth Muscle Antibody (SMA), IgG by IFA 2007209
- F-Actin (Smooth Muscle) Antibody, IgG by ELISA with Reflex to Smooth Muscle Antibody, IgG Titer 0051174
- Liver Cytosolic Antigen Type 1 (LC-1) Antibody, IgG 2010711
- Liver-Kidney Microsome Antibody, IgG 0099270
- Liver-Kidney Microsome – 1 Antibody, IgG 0055241
- Mitochondrial M2 Antibody, IgG (ELISA) 0050065
- Smooth Muscle Antibody, IgG Titer 0051244
- Soluble Liver Antigen Antibody, IgG 0055235

Disease Overview

Prevalence
ALD: ~5% of all liver diseases
- Autoimmune hepatitis (AIH)
  - 15-25/100,000 inhabitants in Europe (EASL, 2015)
- Primary biliary cholangitis (PBC)
  - 1.9-40.2/100,000 in European populations (EASL, 2017; Bowlus, 2014)

Incidence
- AIH
  - 0.85-1.9/100,000 per year for adults of white northern European ancestry (Czaja, 2015)
- Primary sclerosing cholangitis (PSC)
  - 0.3-5.8/100,000 per year in European populations (EASL, 2017)

Physiology
ALD
- Etiology: antibodies directed against the liver
- Chronic course with slow progression: may resemble other chronic liver diseases (e.g., alcoholic cirrhosis, chronic viral hepatitis)
- Laboratory findings may include
  - Hypergammaglobulinemia (elevated total protein, decreased albumin, and decreased anion gap)
  - Elevated liver enzymes in the absence of chronic or drug-induced hepatitis
AIH: two main types, AIH types 1 and 2
• A variant of type 1, referred to as type 3, has been described
• AIH type 1: most common
  o Female preponderance (70-80% of cases)
  o Seen in all ethnic groups, with a predominance in Caucasians
  o Affects individuals of all ages, but less common in children
  o Associated autoimmune diseases
    ▪ Thyroiditis
    ▪ Rheumatoid arthritis
• AIH type 2: usually presents in childhood; rare in adults
  o Clinical features vary widely
    ▪ Arthralgias
    ▪ Anorexia, fatigue, jaundice, lethargy, malaise
    ▪ Hepatomegaly, nausea, upper abdominal pain
    ▪ Progression to cirrhosis and liver failure possible
  o Antibody-negative disease
    ▪ Same presentation and histology as antibody-positive AIH
    ▪ Diagnosis of exclusion
    ▪ No other etiology found for liver disease/cirrhosis – key to this diagnosis
  o Overlap syndrome (AIH present with one of the following)
    ▪ Autoimmune cholangitis
    ▪ Antimitochondrial antibodies (AMA)-negative PSC
    ▪ Autoimmune sclerosing cholangitis
    ▪ IgG4 cholangitis
    ▪ PBC
    ▪ PSC
  o Laboratory tests: several antibodies may be present, depending on AIH type (see table)

PBC
• Female preponderance (~90% of cases)
• Age: primarily >40 years
• Clinical features
  o Most patients are asymptomatic or only mildly fatigued at time of diagnosis
  o Chronic pruritus, hyperpigmentation
  o Jaundice, hepatomegaly, splenomegaly, upper abdominal pain
    ▪ Progression to cirrhosis and liver failure possible
  o Many overlapping features with AIH
  o Associated with other autoimmune disorders (eg, CREST syndrome, rheumatoid arthritis)
• Laboratory tests
  o AMA: specific for PBC
  o Some patients with PBC may be negative for AMA but positive for GP210 or SP100 antibodies

PSC
• Male preponderance
• Age: ~40 years at time of diagnosis
• Strongly associated with inflammatory bowel disease (IBD): 75-90%

• Clinical features mimic those of PBC
  o Clinical course varies widely
  o Asymptomatic patients: 20-40%
  o Fatigue, jaundice, pruritus, upper abdominal pain
    ▪ Progression to cirrhosis and liver failure possible
  o Increased risk for
    ▪ Cholangiocarcinoma
    ▪ Colorectal cancer if PSC is concurrent with ulcerative colitis (compared to patients with only ulcerative colitis)
• Laboratory tests
  o Predominant: Atypical p-ANCA, ANA, +/- SLA

Diagnostic/Prognostic Issues
• May be difficult to diagnose AIH initially as symptoms may mimic those of chronic hepatitis
• No single diagnostic test for AIH
• Antibody testing may be helpful in diagnosing/distinguishing ALD subtype after more common etiologies of hepatitis have been ruled out (see table)
  o Titors may be lower early in disease
  o Low titors in children likely reflect disease
• Liver biopsy may be appropriate in certain patients
  o Should be performed when diagnosis is still unclear
  o Considered “gold standard”

Test Interpretation

Clinical Sensitivity
~85-90% for AMA

Results
See table

Limitations
• Negative antibody testing does not rule out ALD
• All interpretation of antibody patterns must be done in conjunction with clinical presentation
  o There may be overlap between diseases and antibodies detected
  o No single test shows absolute specificity

References
<table>
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<tr>
<th>Disease</th>
<th>ANA Pattern</th>
<th>ANCA Pattern</th>
<th>SMA</th>
<th>F-actin</th>
<th>AMA (M2)</th>
<th>GP210</th>
<th>SP-100</th>
<th>LKM-1</th>
<th>LC-1</th>
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<tr>
<td>PSC</td>
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<td>Atypical p-ANCA</td>
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<td>Nuclear dot or nuclear envelope pattern on HEP-2 cell substrate</td>
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AIH, autoimmune hepatitis type 1 or 2; AMA, antimitochondrial antibody; ANA, antinuclear antibody; GP210, glycoprotein-210; LC-1, liver cytosolic antigen type 1; LKM-1, liver-kidney microsome-1 (cytochrome P450 2D6); M2, mitochondrial antigen 2 (PDH-E2); p-ANCA, perinuclear antineutrophil cytoplasmic antibody; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLA, soluble liver antigen; SMA, smooth muscle antibody