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
  - Recommended first-line panel for evaluation of ALD
  - Negative results do not rule out disease

ANCA-Associated Vasculitis Profile (ANCA/MPO/PR-3) with Reflex to ANCA Titer 2006480
  - Initial test in conjunction with autoimmune liver disease with reflex to SMA for evaluation of ALD

Related tests

Liver Cytosolic Antigen Type 1 (LC-1) Antibody, IgG 2010711
  - Evaluate for suspected autoimmune hepatitis (AIH) type 2 with childhood onset

Anti-Nuclear Antibodies (ANA), IgG by ELISA with Reflex to ANA, IgG by IFA 0050080

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-Kidney Microsome Antibody, IgG 0099270

Liver-Kidney Microsome – 1 Antibody, IgG 0055241

Mitochondrial M2 Antibody, IgG (ELISA) 0050065

Soluble Liver Antigen Antibody, IgG 0055235

Disease Overview

Prevalence

ALD – 5% of all liver diseases
  - Autoimmune hepatitis (AIH)
    - 16.9/100,000
    - Most common type of ALD
  - Primary biliary cirrhosis (PBC)
    - Females – 65.4/100,000
    - Males – 12.1/100,000
  - Primary sclerosing cholangitis (PSC)
    - ~6.3/100,000 in U.S.

Incidence

AIH – ~1.9/100,000 per year for white adults of northern European ancestry

Physiology

ALD
  - Etiology – antibodies directed against the liver
  - Chronic course with slow progression – may resemble other chronic liver diseases (eg, 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
    - Female preponderance (70-80% of cases)
    - Seen in all ethnic groups, with a predominance in Caucasians
    - Affects individuals of all ages, but less common in children
    - Underlying 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
• Antibody-negative disease
  o Clinical features vary widely
    ▪ Same presentation and histology as antibody-positive AIH
• Progression to cirrhosis and liver failure possible
  o Antibody-negative disease
  ▪ Diagnosis of exclusion
  ▪ No other etiology found for liver disease/cirrhosis – key to this diagnosis
• Overlap syndrome (AIH present with one of the following)
  ▪ Autoimmune cholangitis
  ▪ Autoimmune cholangitis
  ▪ Antimitochondrial antibodies (AMA)-negative PSC
  ▪ Autoimmune sclerosing cholangitis
  ▪ IgG4 cholangitis
  ▪ PBC
  ▪ PSC
  ▪ Laboratory tests – several antibodies may be present, depending on AIH type (see table)

PBC
• Female preponderance (~90% of cases)
• Age – primarily >40 years of age
• 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
• 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

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
    ▪ Asymptomatic patients – 20-40%
    ▪ Fatigue, jaundice, pruritus, upper abdominal pain
  ▪ Progression to cirrhosis and liver failure possible
  ▪ Increased risk for
    ▪ Cholangiocarcinoma
    ▪ Colorectal cancer if PSC is concurrent with ulcerative colitis (compared to patients with only ulcerative colitis)
• Laboratory tests
  o Predominant – pANCA, 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 titers 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

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

<table>
<thead>
<tr>
<th>Antibody Patterns</th>
<th>Disease</th>
<th>ANA</th>
<th>pANCA</th>
<th>SMA</th>
<th>F-actin</th>
<th>AMA M2</th>
<th>LKM-1</th>
<th>LC-1</th>
<th>SLA</th>
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<tbody>
<tr>
<td>AIH-1</td>
<td>Homogenous pattern most common</td>
<td>+</td>
<td>+</td>
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<td>+/-</td>
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<td>AIH-2</td>
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<td>Rare</td>
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<tr>
<td>PSC</td>
<td>+</td>
<td>Atypical staining</td>
<td>+/-</td>
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<td>+/-</td>
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<tr>
<td>PBC</td>
<td>Multiple nuclear dot or rim-like membranous pattern on Hep-2 or HeLa cells</td>
<td>-</td>
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DISEASE KEY
AIH = autoimmune hepatitis type 1 or 2; PSC = primary sclerosing cholangitis; PBC = primary biliary cirrhosis

TEST KEY
AMA = antimitochondrial antibody; ANA = antinuclear antibody; LC-1 = liver cytosolic antigen type 1; LKM-1 = liver-kidney microsome-1 (cytochrome P450 2D6); M2 = mitochondrial antigen 2 (PDH-E2); pANCA = perinuclear antineutrophil cytoplasmic antibody; SLA = soluble liver antigen; SMA = smooth muscle antibody

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