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
  o F-Actin (Smooth Muscle) Antibody, IgG
  o Liver-Kidney Microsome – 1 Antibody, IgG
  o Mitochondrial M2 Antibody, IgG (ELISA)
  o 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
  o Negative results do not rule out disease
ANCA-Associated Vasculitis Profile (ANCA/MPO/PR-3) 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)
  o 15-25/100,000 inhabitants in Europe (EASL, 2015)
• Primary biliary cholangitis (PBC)
  o 1.9-40.2/100,000 in European populations (EASL, 2017; Bowlus, 2014)

Incidence
• AIH
  o 0.85-1.9/100,000 per year for adults of white northern European ancestry (Czaja, 2015)
• Primary sclerosing cholangitis (PSC)
  o 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 (eg, alcoholic cirrhosis, chronic viral hepatitis)
• Laboratory findings may include
  o Hypogammaglobulinemia (elevated total protein, decreased albumin, and decreased anion gap)
  o 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
    o 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)
    oTiters may be lower early in disease
    oLow titers in children likely reflect disease
  • Liver biopsy may be appropriate in certain patients
    oShould be performed when diagnosis is still unclear
    oConsidered “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

  • Bowlus CL, Gershwin E. The diagnosis of primary biliary cirrhosis. Autoimmun Rev. 2014; 13(4-5): 441-4

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<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>
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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.