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 3002479

- 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 (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 (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
  - Associated autoimmune diseases
    - Thyroiditis
    - Rheumatoid arthritis

- AIH type 2: usually presents in childhood; rare in adults
  - 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
    - Same presentation and histology as antibody-positive AIH
    - 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
    - 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
- Clinical features
  - Most patients are asymptomatic or only mildly fatigued at time of diagnosis
  - Chronic pruritus, hyperpigmentation
  - Jaundice, hepatomegaly, splenomegaly, upper abdominal pain
    - Progression to cirrhosis and liver failure possible
  - Many overlapping features with AIH
  - Associated with other autoimmune disorders (eg, CREST syndrome, rheumatoid arthritis)
- Laboratory tests
  - AMA: specific for PBC
  - 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
  - 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
  - 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)
  - Titers may be lower early in disease
  - Low titers in children likely reflect disease
- Liver biopsy may be appropriate in certain patients
  - Should be performed when diagnosis is still unclear
  - 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
  - There may be overlap between diseases and antibodies detected
  - No single test shows absolute specificity

References

- Bowlus CL, Gershwin ME. The diagnosis of primary biliary cirrhosis. Autoimmun Rev. 2014;13(4-5):441–444. PubMed
- Czaja AJ. Diagnosis and management of autoimmune hepatitis. Clin Liver Dis. 2015;19(1):57–79.PubMed
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67(1):145–172. PubMed

Associated Autoantibody Profile										
Disease	**ANA Pattern**	**ANCA Pattern**	**SMA**	**F-actin**	**AMA (M2)**	**GP210**	**SP-100**	**LKM-1**	**LC-1**	**SLA**
AIH-1	Homogenous pattern most common		+	+	-	-	-	-	-	+/-
AIH-2	-	Rare	-	-	-	-		+	+	-
PSC	+	Atypical p-ANCA	+/-	-	-	-	-	-	-	+/-
PBC	Nuclear dot or nuclear envelope pattern on HEp-2 cell substrate	-	-	-	+	+	+	-	-	-

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