Other Liver Diseases

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Abnormal Liver Tests

• Laboratory determinations that reflect liver disease are commonly termed liver function tests.

• Liver function tests is a misnomer, because elevated serum aminotransferase levels and alkaline phosphatase levels are markers of liver injury, not indices of degree of liver function.

• Measures of specific hepatic functions (albumin, bilirubin, prothrombin time) can be affected by extrahepatic factors such as nutrition, hemolysis, antibiotic use, etc.

• Therefore, liver function tests are best referred to as liver tests or liver chemistries.
Clinical Assessment of the Patient

• Clinical symptoms
  • Anorexia, nausea, vomiting, low-grade fever suggest hepatocellular necrosis such as viral hepatitis or autoimmune hepatitis
  • Symptoms of jaundice, pruritus, clay-colored stools and dark urine suggest cholestasis or inadequate bile flow.
  • Fatigue may be the only symptom of chronic liver disease.
  • Family history is also important. In a patient with indirect hyperbilirubinemia, family history suggests hemolysis or Gilbert’s syndrome. Direct hyperbilirubinemia suggests Dubin-Johnson syndrome.
  • Family history of severe liver disease may suggest Wilson’s disease, hemochromatosis or alpha-1 antitrypsin deficiency.
  • Other important factors include sexual history, travel, volume and duration of alcohol use, drug use, history of blood transfusion or needle-stick injury.
Physical Findings

• Jaundice, palmar erythema, spider nevi, parotid enlargement, ascites and encephalopathy are indices of chronic liver disease.

• More important in confirming the presence of liver disease than in determining a specific diagnosis.
Aminotransferases

• ALT and AST are the most widely ordered liver chemistries that reflect injury to the liver.

• ALT is mainly localized in the liver.

• AST is more widely distributed in the liver as well as cardiac, skeletal, kidney and brain tissue

• ALT predominantly localizes to the cytosol; whereas, the AST localizes to the mitochondria.

• These levels increase in the serum with the death of hepatocytes, either by necrosis or apoptosis.
Abnormal Liver Tests- The Approach

• Categorize liver disease
  • Hepatocellular
  • Intrahepatic or extrahepatic cholestasis.

• Transaminase increase is most commonly related to drugs, non-alcoholic steatohepatitis (NASH)/fatty liver, hepatitis C or alcohol use.

• Alkaline phosphatase increase of hepatic origin related to drugs or non-hepatic cause (bone, placenta).

• Many chronic liver diseases may have a completely NL liver panel (fatty liver/NASH, prior alcohol, hemochromatosis, HBV, HCV)
Make A Specific Diagnosis-Hepatocellular

• Viral hepatitis diagnosed on the basis of viral serology
  • Acute hepatitis A: Anti-HAV IgM; Acute hepatitis B: HBsAg, anti-HBc IgM; chronic hepatitis B: HBsAg; Acute hepatitis C: anti-HCV, HCV RNA; chronic hepatitis C: anti-HCV

• Alpha-1 antitrypsin deficiency diagnosed with phenotype (ZZ is responsible for liver disease, heterozygotes may have abnormal liver chemistries)

• Autoimmune hepatitis is diagnosed on the basis of chronic liver disease, chronic (less commonly acute) with positive antinuclear antibody and anti-smooth muscle antibody with elevated globulin level (SPEP), typically in females.

• Wilson’s disease ceruloplasmin is low and urinary copper is high.

• Hemochromatosis: transferrin saturation and ferritin are increased.
HAV - Epidemiology

Prevalence of Hepatitis A in the US

CDC
Typical Serologic Course of Acute Hepatitis A Virus Infection

Months After Exposure

Symptoms

Fecal HAV

ALT

Total anti-HAV

IgM anti-HAV

0 1 2 3 4 5 6 12 24
Hepatitis A Vaccination: Epidemiological Considerations

Many cases occur in community-wide outbreaks
  – No risk factor identified for most cases
  – Highest attack rates in 5-14 year olds
  – Children serve as reservoir of infection

Persons at increased risk of infection
  – Travelers to endemic areas
  – Men having sex with men
  – Injecting drug users
  – No consensus for vaccination recommendation with the exception of patients with chronic liver disease
Alpha\textsubscript{1} - Antitrypsin Deficiency

![Genetic diagram showing different phenotypes and inheritance pattern for Alpha\textsubscript{1} - Antitrypsin deficiency.](image)

Pi phenotypes:
- $M_1$ $M_2$
- $M_2Z$
- $M_1M_1$

Inherited as co-dominant
Alpha₁ - Antitrypsin Deficiency

Frequency:
- Common in whites
- 1/30 heterozygote
- 1/2000 homozygote

Genetics:
- Gene on chromosome 14
- Alpha₁-antitrypsin
- Alpha₁-antichymotrypsin

Defect:
- Gene expression defect
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<th>Risk</th>
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<tr>
<td>ZZ</td>
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<td>MS</td>
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Autoimmune hepatitis

• Typically seen in young females (F:M 7-8:1)

Onset between third and fifth decade

Most patients present insidiously, 30 - 40 % may have abrupt onset

Associated autoimmune disorders present in up to 40%
Autoimmune hepatitis: Auto-antibodies

• Type 1 (80% in US): anti-nuclear (ANA), anti-smooth muscle (SMA)

Type 2 (adolescents, rare in US): anti-liver/kidney microsomal (LKM)

Type 3: anti-soluble liver antigen (SLA) titer greater than 1:80
Autoimmune Hepatitis
Hereditary Hemochromatosis (HHC)

• Most common autosomal recessive disorder affecting Caucasians

• Inappropriate increase in intestinal iron absorption

• Autosomal recessive disorder with male/female ratio 2-3:1

• Gene has been identified as the HFE locus, related to the MHC class 1 family on short arm of chromosome 6
HHC: Diagnosis

• Increased serum iron (180-300pg/dl)
• Transferrin saturation (80-100%)
• Ferritin (500-6000 ng/ml)
• Frequently NL liver enzymes
• Hepatic iron index >1.9 (moles/pg dry weight/age in years), requires liver biopsy
• HFE locus testing
  • 1 mutations accounts for 85% of cases
  • C282Y is the most important mutation
  • H63D and S65C are minor mutations
Genetic Hemochromatosis
Genetic Counseling for HHC

WT=(Wild type)
DIAGNOSTIC TESTING

- Ceruloplasmin
- Slit lamp exam
- Urine copper

Ceruloplasmin < 20 mg/dL
K-F rings
Urine copper > 100 μg/24 hr

Liver biopsy with quantitative copper confirms diagnosis
Hepatic Cholestasis

- Defined as an impairment in bile flow.

- Cholestatic liver profile is characterized by an elevation in alkaline phosphatase with or without an elevation in bilirubin.

- Alkaline phosphatase elevation can be normal in those who are less than 18 years old, or in women who are pregnant.
  - In children, the alkaline phosphatase level is increased up to three times the upper limit of normal, and in pregnant patients it can be increased up to two times that of normal.

- A variety of hepatobiliary disorders at the microscopic level (eg primary biliary cirrhosis) or macroscopic (retained common bile duct stone) level can also lead to an elevation in alkaline phosphatase.
Hepatic Cholestasis

- Metabolic bone disease, hyperthyroidism may also lead to an elevated alkaline phosphatase.

- To confirm that elevated alkaline phosphatase is from the liver fractionate alkaline phosphatase (bone fraction is heat labile and liver fraction is heat stable).

- Two enzymes, GGT (least expensive) and 5’nucleotidase may be ordered to confirm an elevated alkaline phosphatase.

- Distinguish between intrahepatic and extrahepatic causes
  - structural study to look for evidence of biliary dilatation with either an ultrasound (the best test, least expensive, but operator dependent) or CT scan (less operator dependent, but more expensive).
Hepatic Cholestasis

• If the ultrasound/CT is normal, blood tests for intrahepatic cholestatic liver disorders should be considered
  – Anti-mitochondrial Ab, anti-nuclear Ab, anti-smooth muscle Ab, p-ANCA, ACE levels

• If autoimmune markers are unremarkable, a cholangiogram should be done, either MRCP, endoscopic retrograde cholangiopancreatography (ERCP) or by a percutaneous route (percutaneous transhepatic cholangiogram or PTC).
Make A Specific Diagnosis - Cholestatic

• Common intrahepatic cholestatic conditions include primary biliary cirrhosis (PBC), sarcoidosis, drug induced cholestasis and primary sclerosing cholangitis (PSC). Common extrahepatic conditions include PSC, choledocholithiasis (gallstones) or tumors obstructing the common bile duct (pancreatic adenoca, cholangioca or ampullary ca).

• To diagnose PBC, antimitochondrial antibody (AMA)

• To diagnose PSC, MRCP/ERCP is abnormal
  
  • Liver biopsy is essential to stage both PSC and PBC

• Extrahepatic cholestasis is diagnosed by ultrasound or computed tomography and confirmed by ERCP.

• For infiltrative diseases (such as amyloidosis), liver biopsy is essential.
PBC: Diagnosis

• Middle-aged women with chronic cholestasis
• Alkaline phosphatase is usually 3 – 4 times normal,
• AMA present in titer > 1:40
• Most common symptom is fatigue; pruritus is the most specific symptom
• Liver biopsy shows portal tract granulomas, bile duct destruction
PRIMARY BILIARY CIRRHOSIS

ASSOCIATED DISORDERS
Thyroiditis
Sicca
CRST
Raynaud’s

Abnl
NI
Onset
TIME
Death

Bili
Alk Phos
AMA

NI
Primary Sclerosing Cholangitis (PSC)

• Chronic cholestatis liver disease that progresses to cirrhosis

• Characterized by obliteratorative fibrosis of intra- and extra-hepatic bile ducts

• Frequently found in association with IBD (most commonly with ulcerative colitis, less commonly Crohn’s colitis)

• Pathogenesis is unknown though likely autoimmune; should be considered in patients with chronic cholestasis in the setting of inflammatory bowel disease
SCLEROSING CHOLANGITIS

IMAGING TECHNIQUES

Direct Cholangiography
- PTC
- ERCP
DRUG INDUCED CHOLESTASIS

LABS
- Cholestasis/hepatitis

IMAGING
- Normal

EXAMPLES
- Phenothiazines
- Oral contraceptives
- Erythromycin
ALCOHOLIC LIVER DISEASE

Fatty Liver
Alcoholic Hepatitis
Cirrhosis

[Graph showing AST and ALT levels]

[Image of a man and woman at a table]
Clinical outcome with excess alcohol consumption

Diagram:
- Normal liver
- Fatty liver
- Alcoholic hepatitis
- Cirrhosis
- Fibrosis

The diagram shows the progression of liver damage with excess alcohol consumption, starting from normal liver to fatty liver, then to alcoholic hepatitis, cirrhosis, and finally fibrosis.
Approach to patient with elevated aminotransferase level

AST elevated
  ↓
ALT elevation
  ↓
  Yes
  ↓
ALT > 3-5 ×
  ↓
  No
  ↓
  Other causes of AST elevation
  No
  ↓
  Patient symptomatic or
      • Bilirubin/alkaline phosphatase elevated or
      • ALT elevation > 6 months
  No
  ↓
  Recheck 3-6 months

Yes
  ↓
Investigate for liver disease
  Yes
  ↓
Viral serology
  ANA
  AMA
  Copper
  Ceruloplasmin
  Ferritin
  Alpha-1-antitrypsin
  Liver ultrasound
  ↓
Consider liver biopsy
Approach to patient with elevated alkaline phosphatase level

Alkaline phosphatase elevated

Liver fraction or GGT elevated

Yes

Alk phos > 2 x

No

Non-hepatic causes

Yes

Biliary dilatation on liver ultrasound

Yes

Consider ERCP

No

AMA

Consider liver biopsy

Recheck 3-6 months

Alk phos ↑ > 6 months

Patient symptomatic

No