

Metabolic, Cholestatic and Alcoholic Liver Diseases

Steven Herrine, MD

Educational Goals

By the completion of this lecture you should be familiar with the:

1. Clinical presentation, diagnostic evaluation and therapeutic options for patients with hemochromatosis.
2. Typical phenotype, frequency of liver disease and clinical course in patients with α_1 -antitrypsin deficiency.
3. Clinical presentation, diagnostic evaluation and therapeutic options for patients with Wilson's disease.
4. Similarities and differences between two important cholestatic liver diseases, primary biliary cirrhosis and primary sclerosing cholangitis.
5. The demographics, spectrum and prognosis of alcoholic liver disease.

Key Words

- α_1 -antitrypsin deficiency
- α_1 -antitrypsin phenotypes
- alcoholic hepatitis
- alkaline phosphatase
- anti-mitochondrial antibody
- ascending cholangitis
- AST/ALT ratio
- C282Y, H63D
- ceruloplasmin
- cholangiocarcinoma
- cholestatic liver disease
- cholestyramine
- chronic non-suppurative cholangitis
- D-penicillamine
- endoscopic retrograde cholangiopancreatography (ERCP)
- fatty liver (steatosis)
- ferritin
- hemochromatosis
- hepatic iron index
- hepatocellular carcinoma
- hepcidin
- inflammatory bowel disease
- Kayser-Fleischer rings
- Mallory bodies
- PAS-positive, diastase-negative globules
- phlebotomy
- primary biliary cirrhosis
- Prussian blue stain
- quantitative hepatic iron
- total iron binding capacity (TIBC)
- transferrin saturation
- trientine
- urinary copper excretion
- ursodeoxycholic acid
- Wilson's disease

I. Hemochromatosis

- A. Normal iron metabolism
 1. In humans, 10 to 20 mg/d of elemental iron is ingested of which 1-2 mg/d is absorbed in the duodenum and upper jejunum
 2. 1-2 mg/d of iron is excreted in bile, skin and GI sloughing. Females lose approximately 30 mg per menstrual cycle
 3. Absorbed iron is transported to liver by transferrin
 4. Transferrin-bound iron is taken up in liver by ferritin. Total body iron stores: approximately 4 g
- B. Hemochromatosis is an autosomal recessive trait, the result of a defective gene on short arm of chromosome 6
 1. This gene abnormality is common: 1 in 400 individuals are homozygotes, 1 in 10-20 are heterozygotes. The distribution of this trait is worldwide
 2. The resulting defect affects iron absorption
 3. Clinical manifestations of the disorder typically are seen in males in their 40's-50's and females in 60's
- C. Pathophysiology
 1. Hepcidin inhibits iron export from enterocytes and macrophages via ferroportin

2. Hpcidin expression is regulated by total body iron stores, inflammatory state, erythroid iron demand, hypoxia by genetic expression of several genes including HFE, TJR1, TJR2, and HJV
- D. Clinical Manifestations - result of tissue iron deposition
 1. Skin bronzing
 2. Decreased gonadotropins - impotence
 3. Heart deposition - cardiomyopathy, arrhythmias
 4. Diabetes Mellitus
 5. Arthropathy - especially metacarpophalangeal and proximal phalangeal joints
 6. Liver: insidious onset with progression to cirrhosis and hepatocellular carcinoma
- E. Diagnosis
 1. Serum tests: high serum iron, low total iron binding capacity (TIBC), high transferrin saturation, high ferritin (Table 1)
 2. Radiologic tests
 - a) Standard radiographs might show arthropathy of the hands and hips
 - b) CT scans will show high attenuation liver, normal spleen. This is not a sensitive technique
 - c) MRI will show a dramatic reduction in liver signal intensity on T2-weighted images. The liver will appear black on this MRI sequence

Table 1. Laboratory tests in hemochromatosis.

	Serum iron ($\mu\text{g/dl}$)	TIBC ($\mu\text{g/dl}$)	Transferrin Saturation (%)	Ferritin ($\mu\text{g/L}$)	Hepatic Iron ($\mu\text{g/g dry weight}$)
Normal	50-150	230-370	20-50	30-270	150-1850
Hemochromatosis	> 175	< 300	> 50	> 300	> 5600

3. Genetic testing
 - a) Two missense mutations (C282Y and H63D) in the HLA-H gene accounts for 90% of hereditary hemochromatosis
 - b) Homozygosity for these alleles implies hemochromatosis with high accuracy
 - c) Genetic testing is the standard of care for hereditary hemochromatosis
4. Liver biopsy
 - a) Standard H&E stain will show increased hepatocellular iron. Qualitative iron staining can be performed using the Prussian Blue stain
 - b) Quantitative hepatic iron can be measured, and will be dramatically increased, in a fresh liver specimen
 - c) Hepatic iron index (quantitative iron/age) remains the most sensitive and specific test for genetic hemochromatosis
5. Response to phlebotomy
 - a) The usual phlebotomy protocol is 250-500 cc of blood removal per week, as tolerated
 - b) It may take 6-20 g of iron removal (24-80 units of blood) to cause anemia in a homozygote. Progress is followed by the hematocrit and the serum ferritin
 - c) Once the initial iron overload is relieved, intermittent phlebotomy is usually needed to keep ferritin < 50 $\mu\text{g/L}$
- E. Prognosis
 1. Liver disease is reversible prior to onset of cirrhosis
 2. Hepatocellular carcinoma (HCC)
 - a) HCC risk in patients with hemochromatosis and cirrhosis is 220 times greater than the general population
 - b) HCC is the leading cause of death in untreated patients with hereditary hemochromatosis
 3. Screening of family

- a) All siblings, parents and children over the age of 10 should be screened
- b) Serum iron, TIBC and ferritin are the usual screening labs
- c) Genetic testing will have an increased role in screening in the future
- d) Suspicion of hereditary hemochromatosis should prompt a liver biopsy

II. α_1 -Antitrypsin Deficiency

A. Genetic basis of disease

1. Individual's phenotype inherited in autosomal codominant fashion
2. One allele (Pi) is inherited from each parent
3. The normal phenotype is PiMM
4. Phenotypes PiMZ and PiZZ are associated with disease

B. α_1 -Antitrypsin

1. This protein, which comprises 90% of the α_1 band on serum protein electrophoresis, is synthesized by the liver
2. α_1 -antitrypsin functions as a protease inhibitor, particularly against elastases
3. Deficiency presents as precocious emphysema, usual in male smokers

C. Liver disease in α_1 -antitrypsin deficiency

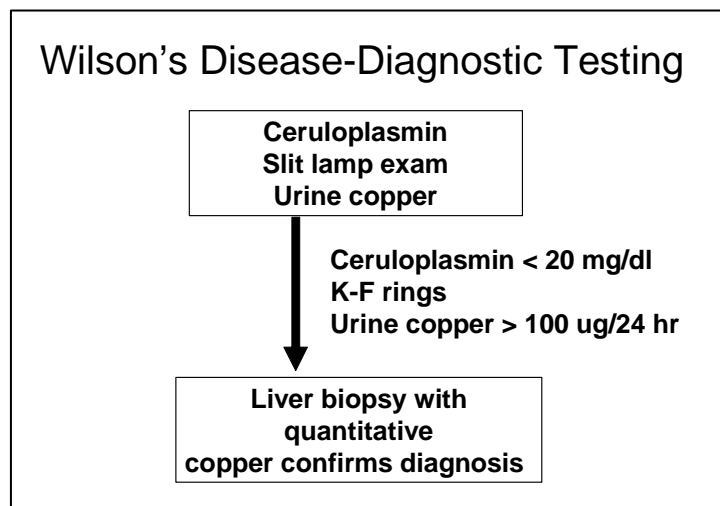
1. Liver disease is seen in 10-15% of individuals with the PiZZ phenotype. Liver disease has been described, but is rare in the PiMZ phenotype
2. Liver disease results from inability of liver to excrete the abnormal protein, not from protein deficiency
3. α_1 -antitrypsin deficiency is most common in Europeans and Scandinavians. In US 1/2,000 are homozygous, while 1/30 are heterozygous
4. Neonatal jaundice is seen in 10% of PiZZ individuals - α_1 -antitrypsin deficiency is the most frequent inherited cause for pediatric liver transplantation
5. In adolescents, liver disease in α_1 -antitrypsin deficiency presents as chronic active hepatitis or cirrhosis
6. In adults, the usual presentation is cryptogenic cirrhosis with portal hypertension
7. Hepatocellular carcinoma is seen with increased frequency in those with cirrhosis
8. Liver biopsy shows PAS-positive, diastase-negative globules in periportal hepatocytes
9. No therapy is available, since liver damage is the result of the deposition of abnormal α_1 -antitrypsin. Liver transplantation will cure the disease

Figure 1: Abnormally folded α_1 -antitrypsin becomes trapped in hepatocytes, leading to inflammation and fibrosis



III. Wilson's Disease - Primary copper overload disorder

- A. Normal copper homeostasis
 1. Copper is ingested in the diet and is found in shellfish, chocolate, nuts, and mushrooms. 50% of ingested copper is absorbed
 2. Absorbed copper is taken up by liver and used in production of ceruloplasmin
 3. Unabsorbed copper excreted in stool
- B. Genetics of Wilson's disease
 1. This defect is inherited in an autosomal recessive fashion. 1/30,000 are homozygous in the US and Asia. This disorder is considered to be rare.
 2. The genetic defect causes decreased hepatic excretion of copper (as opposed to hemochromatosis, where the defect is one of absorption)
- C. Clinical manifestations
 1. Neuropsychiatric: due to copper deposition in the basal ganglia. Kayser-Fleischer rings are ocular copper deposits in Descemet's membrane and are seen on slit-lamp examination
 2. Cardiomyopathy due to copper deposition in heart (rare)
 3. Renal tubular deposition leads to aminoaciduria and glycosuria -> Fanconi's syndrome
 4. Hemolysis is often seen secondary to high levels of unbound copper in serum
 5. Liver disease: variety of presentations: abnormal liver tests, acute hepatitis, fulminant hepatic failure, chronic active hepatitis, cirrhosis
- D. Diagnosis
 1. Lab tests: low ceruloplasmin, high urinary copper excretion
 2. Liver biopsy can be used to determine the quantitative hepatic copper content\
 3. Genetic testing has been limited by large variety of mutations
- E. Therapy
 1. Trientine is first line therapy: chelates copper
 2. D-penicillamine
 - a. also a chelator - falling from favor as first-line therapy
 - b. Side effects: skin rash, lupus-like syndrome (arthralgias, proteinuria)



3. Interruption of chelation therapy can lead to fulminant hepatic failure
3. Oral zinc can be used to diminish copper absorption
4. Liver transplantation is curative
5. First degree relatives should be screened by H&P, serum ceruloplasmin level and slit-lamp examination

Figure 2. Algorithm for diagnosis of Wilson's disease

IV. Primary Biliary Cirrhosis (PBC)

- A. Definition: a chronic cholestatic liver disease characterized by autoimmune destruction of small interlobular and septal bile ducts
- B. Clinical presentation
 - 1. PBC is often insidious in onset
 - 2. The most common presentation is an asymptomatic elevation in serum alkaline phosphatase
 - 3. 90% of PBC patients are women between ages of 35 and 60
 - 4. Early clinical findings include pruritis, fatigue, malabsorption of lipid-soluble vitamins and hypercholesterolemia
 - 5. Later findings include xanthelasmas (subcutaneous lipid deposition), skin hyperpigmentation, osteoporosis, jaundice, ascites and portal hypertension
- C. Diagnosis
 - 1. Increased serum alkaline phosphatase
 - 2. Anti-mitochondrial antibody - present in 95-98% of patients
 - 3. Liver biopsy - chronic non-suppurative destructive cholangitis
- D. Therapy
 - 1. Ursodeoxycholic acid (ursodiol), which is thought to replace endogenous hepatotoxic bile acids, provides symptomatic and biochemical improvement. Recent studies suggest a transplant-free survival advantage
 - 2. Cholestyramine is a resin which binds bile acids. This drug can relieve pruritis, but has no effect on natural history of disease. Furthermore, bile acid binding can worsen fat-soluble vitamin malabsorption
 - 3. Liver transplantation is curative. Optimal timing for transplantation can be based on mathematical models of disease progression

V. Primary Sclerosing Cholangitis (PSC)

- A. Definition: a progressive cholestatic disorder characterized by inflammation, obliteration and fibrosis of medium and large sized intra- and extrahepatic bile ducts
- B. Clinical presentation
 - 1. PSC is often seen in the setting of underlying inflammatory bowel disease (IBD)
 - 2. 70% of patients are male; the mean age at diagnosis is 40 years
 - 3. Asymptomatic elevation in alkaline phosphatase, especially in patient with IBD, should prompt an evaluation for this disorder
 - 4. Symptomatic presentations include jaundice, pruritis and fever with abdominal pain due to ascending cholangitis
 - 5. Late presentation of PSC is that of end-stage liver disease and portal hypertension. Patients can also present with cholangiocarcinoma, the incidence of which is significantly increased in this disorder
- C. Diagnosis
 - 1. Serum tests: increased alkaline phosphatase, mildly increased transaminases
 - 2. There is no diagnostic serum marker for PSC
 - 3. Cholangiography, often performed by endoscopic retrograde cholangiopancreatography (ERCP), is diagnostic. Cholangiographic abnormalities include:
 - a) Diffusely distributed, multifocal annular strictures with intervening segments of normal or slightly dilated ducts
 - b) Short band-like strictures
 - c) Diverticulum-like outpouchings
 - 4. Liver biopsy is suggestive, but not diagnostic for PSC
 - a) Periductal inflammation and fibrosis
 - b) Bile duct proliferation
- D. Therapy
 - 1. No currently accepted medical treatment is available
 - 2. Management of PSC hinges on the management of biliary complications such as strictures and cholangitis
 - 3. Liver transplantation is curative. Models of disease progression exist, but are not as widely accepted as those for PBC

Table 2. Comparison of the two major cholestatic liver diseases

PBC vs. PSC		
	PBC	PSC
Demographic	Women	IBD
Lab	↑ Alk Phos	↑ Alk Phos
Serology	AMA	None
Diagnosis	Liver Biopsy	Cholangiogram
Therapy	Ursodiol	none

VI. Alcoholic Liver Disease

A. Demographics

1. The incidence of serious liver disease rises with the greater amounts of ethanol
 - a) short-term use of up to 80 g of alcohol/day generally produces mild hepatic changes
 - b) 100-150 g or more/day is associated more consistently with severe liver disease (alcoholic hepatitis and/or cirrhosis), especially when ingested for ten years or more
2. Women are more susceptible to develop severe alcoholic liver disease than are men

B. Spectrum of Disease

1. Fatty Liver (steatosis):
 - a) The most frequent morphologic abnormality found in alcoholics
 - b) Even brief periods of alcohol ingestion (2-8 days) may result in fatty liver
 - c) Associated with binge drinking interspersed with periods of sobriety
 - d) Usually asymptomatic; hepatomegaly is the most frequent finding
 - e) In approximately one-third of the patients' liver function tests are abnormal
 - f) Fatty liver without hepatocellular injury is reversible; does not progress
 - g) Treatment is alcohol withdrawal and an adequate diet
2. Alcoholic Hepatitis
 - a) Clinical spectrum ranges from the asymptomatic to the critically ill
 - b) Symptoms include weight loss, anorexia, abdominal pain and nausea
 - c) Physical exam may reveal fever, jaundice, ascites, fluid retention, bleeding, or neurological dysfunction
 - d) Laboratory tests are not diagnostic, but suggestive of the diagnosis
 - 1) AST is frequently increased. ALT may be minimally elevated
 - 2) AST/ALT ratio is >1 and frequently >2
 - 3) Bilirubin and alkaline phosphatase may be increased, mimicking biliary obstruction
 - 4) Leukocytosis occurs in most patients
 - e) Liver biopsy confirms the diagnosis: hepatocytes necrosis, Mallory bodies, inflammatory infiltrate with PMNs, fibrosis, fatty change
 - f) Prognosis
 - 1) Depends on the severity of the acute lesion, and the presence or absence of underlying cirrhosis
 - 2) Increased mortality with encephalopathy, high bilirubin, renal failure, prolonged prothrombin time, spider angiomas, and ascites
 - 3) In hospital mortality ranges from 1%-40%
 - g) Therapy
 - 1) Alcohol cessation, adequate nutrition, and general medical support
 - 2) In more severe cases, corticosteroids may improve prognosis
3. Alcoholic Cirrhosis
 - a) Alcoholic cirrhosis is seen in 15% to 20% of chronic alcoholics

- b) Clinical presentation is variable and may include: fatigue, weight loss, GI bleeding, hepatic encephalopathy, jaundice, increasing abdominal girth
- c) Physical findings: are variable and may include: Dupuytren's contracture, parotid gland enlargement, hepatomegaly, splenomegaly, ascites
- d) Laboratory findings are non-specific and may include: hypoalbuminemia, hypergammaglobulinemia, hyperbilirubinemia, hypoprothrombinemia
- e) Liver biopsy findings of alcoholic cirrhosis
 - 1) Regenerative nodules
 - 2) Fibrous bands linking central and portal zones
 - 3) Fatty change
- f) Prognosis factor is the continuation of alcohol ingestion
 - 1) Five-year survival in patients without ascites, jaundice, or hematemesis was 89% in those who abstained from alcohol, and 65% in those who continued to drink
 - 2) After the onset of any of the above complications, 5-year survival was 60% in abstainers, and 34% in those who continued to drink

VI. References

Cholestatic liver disease

1. Crosignani A, Battezzati PM, Invernizzi P, Selmi C, Prina E, Podda M. Clinical features and management of primary biliary cirrhosis. *World J Gastroenterol* 2008;14:3313-27.
2. Silveira MG, Lindor KD. Primary sclerosing cholangitis. *Can J Gastroenterol* 2008;22:689-98.
3. Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med.* 2006;354:731-9.

Metabolic liver disease

1. Pietrangelo A. Inherited metabolic disease of the liver. *Curr Opin Gastroenterol* 2009;25:209-14.
2. Alexander J, Kowdley KV. HFE-associated hereditary hemochromatosis. *Genet Med* 2009;11:307-13.
3. Teckman JH, Lindblad D. Alpha-1-antitrypsin deficiency: diagnosis, pathophysiology, and management. *Curr Gastroenterol Rep* 2006;8:14-20.
4. Ferenci P. Wilson's Disease. *Clin Gastroenterol Hepatol* 2005;3:726-33.

Alcoholic liver disease

1. Lieber CS. Alcoholic liver disease: new insights in pathogenesis lead to new treatments. *J Hepatology* 2000;32(1 Suppl):113-28.
2. Mendez-Sanchez N, Almeda-Valdes P, Uribe M. Alcoholic liver disease. An update. *Ann Hepatol* 2005 Jan-Mar;4(1):32-42.

Study Questions:

1. A 66 year old asymptomatic woman is noted to have abnormal liver function tests on routine evaluation. Physical examination is notable for no stigmata of chronic liver disease, but a spleen palpable 1 cm below the left costal margin. Lab tests are notable for elevated alkaline phosphatase, and mild thrombocytopenia. Antimitochondrial antibody is detectible.
 - What is the likely diagnosis?
 - Name three other causes of isolated elevation of alkaline phosphatase.
 - Which is more likely to be diagnostic: liver biopsy or cholangiogram?
 - Would you prescribe any medications or further testing?
2. A 35 year old man presents with variceal hemorrhage. He is resuscitated, after which endoscopic hemostasis is achieved. Noting a family history of early cirrhosis, you wish to assess for hereditary causes of liver disease.
 - What tests would you send to screen for hemochromatosis?
 - What tests would you send to screen for Wilson's disease?

- What tests would you send to screen for alpha-1-antitrypsin disease?
- How would you treat these conditions, if diagnosed?