**Acute and Chronic Hepatitis**

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**Conflicts of interest disclosures**

- Consultant: Gilead Sciences, Vertex Pharmaceuticals

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**Review Goals**

- Understand the meaning of hepatitis  
- Be able to differentiate between acute and chronic hepatitis  
- Understand important features of a select number of causes of hepatitis

**Inflammation directed at hepatocytes**

- **Hepatitis**  
  - Pathologic target is hepatocytes  
  - ALT and AST >> Alk Phos  
  - Can be acute with insult usually less than 6 months in duration

- **Cholangitis**  
  - Target is mostly biliary ductal cells  
  - Alk Phos >> ALT/AST  
  - Can also be acute or chronic

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**Sleuthing the cause**

- **Acute hepatitis**
  - Toxins (e.g. acetaminophen)
  - Viral: A-E, CMV, EBV, HSV, VZV
  - Autoimmune hepatitis
  - Vascular compromise
  - Fulminant Wilson’s

- **Chronic hepatitis**
  - Toxins
  - Viral: B and C
  - Metabolic: NAFLD, Glycogenic hepatopathy
  - Genetic
    - Hemochromatosis
    - Wilson’s Disease
  - Immune
    - Autoimmune hepatitis
    - Celiac sprue
  - Vascular
    - Balo-Chiari
    - Rt. Sided Heart failure
    - VOD

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**Viral Hepatitis**

- **Hepatotrophic Viruses:**  
  - Hepatitis A-E

- **Non hepatotrophic Viruses:**  
  - CMV, EBV, HSV
Hepatitis A Virus (HAV)

- A single-stranded RNA virus. Causes mostly acute and occasionally relapsing episodes of hepatitis.
- Responsible for between 20 and 40% of acute hepatitis in the U.S.
- Fulminant liver failure is very rare but possible, particularly in setting of pre-existing chronic liver disease. At least one study has reported high mortality rates in the setting of chronic HCV infection.
- Fecal-oral route with incubation period ranging from 2 to 8 weeks with an average of 4 weeks.

HAV con’t

- Presence of IgM antibodies to HAV signifies acute infection
- IgG antibodies suggest prior infection or vaccination and thus immunoprotection
- Post-exposure treatment with IgG effective if given within 2 weeks
- Post-exposure IgG treatment does not decrease effectiveness of vaccination

Hepatitis B Virus (HBV)

- Double stranded DNA virus
- Cause of both acute and chronic hepatitis
- Common disease, with an estimated worldwide prevalence of 350 million and 250,000 annual deaths. Most prevalent in Asia and Sub-Saharan Africa
- Modes of transmission are blood borne and sexual

HBV con’t

- Acute infection is characterized by the presence of HBsAg and HBV DNA. IgM HBeAb also develops early in the infection and may be the only serologic marker during the “window period”.
- Presence of HBsAg for greater than 6 months implies chronicity
- HBeAg suggests a highly infectious state and correlates with high levels of HBV DNA and hepatocellular damage.
- The presence of HBsAb signifies immunity, either from vaccination or prior infection

Serologic Patterns in Acute HBV infection

HBV con’t

- Age of infection is important determinant of chronic state.
  - Early childhood infection >90%.
  - Adult infections ~5%
- Chronic HBV infection may be asymptomatic, or cause cirrhosis and/or hepatocellular carcinoma (HCC)
- Cirrhosis does not have to be present for HCC to develop.
- Extrahepatic manifestations related to circulating immune complexes:
  - Rashes, arthralgias, glomerulonephritis and polyarteritis nodosa occur in 20% of patients
HBV con’t

- Treatment with interferon alpha, pegylated interferon, lamivudine, adefovir, entecavir or tenofovir can normalize aminotransferases in chronically infected patients, and lead to loss of HBeAg. Loss of HBsAb is seen in only a minority of patients.
- Liver transplantation is indicated for fulminant liver failure (acute infection) and for decompensated cirrhosis (chronic infections).

Hepatitis B Key Concepts

- Double stranded DNA virus
- HBsAg indicates active infection
- HBsAb indicates protective immunity
- Presence of HBsAb and HBeAb indicates protective immunity through prior exposure not through vaccination (HBsAb only). HBcAb is not protective!
- Less than 5% of adult-acquired HBV becomes chronic, whereas 90% of perinatally-acquired HBV becomes chronic
- 100 fold increase risk of HCC with chronic HBV infection

Hepatitis C Virus (HCV)

- Previously known as Non-A, Non-B hepatitis, HCV is an RNA virus
- Approximately 1.8% of U.S. population is HCV antibody positive, 1.3% are HCV RNA positive. HCV RNA should be evaluated in HCV antibody positive persons before a diagnosis is rendered
- Antibodies to HCV do not confer protective immunity
- Responsible for both acute (rare) and chronic (common) hepatitis
- Less than 20% of infected patients are symptomatic during acute infection

HCV con’t

- Variable natural history, but rate of fibrosis affected by alcohol intake
- HCV genotype 1a and 1b are most common in the U.S., but genotypes 2 and 3 are more easily treated with currently available therapies
- Progression to cirrhosis in 20%-30% after 20 years
- HCV is currently the most common indication for liver transplantation in the U.S.

HCV con’t

- The modes of transmission are both percutaneous and sexual. IV drug use is the most common mode of acquisition in the USA
- An estimated 80-85% progress to chronic hepatitis
- Extrahepatic manifestations:
  - cryoglobulinemia with palpable purpura, arthralgias, leukocytoclastic vasculitis and glomerulonephritis.
  - Porphyria cutanea Tarda (PCT), a blistering rash most prominent in the sun exposed areas of the body

HCV con’t

- Therapy for HCV Genotype 1 is combination of pegylated interferon, ribavirin and protease inhibitor for 6 to 12 months
- Therapy for HCV Genotype 2 and 3 is combination of pegylated interferon and ribavirin
- Potential side effects of treatment are numerous and include fever, nausea, myalgias, depression, leukopenias, hemolytic anemia and teratogenic effects
HCV Key Concepts
- 80-85% progress to chronic HCV
- 1.8% of the population have been exposed to HCV, while 1.3% are infected
- Antibodies to HCV do not signify immunity
- Percutaneous and sexual transmission
- Variable disease progression, but alcohol clearly increases risk of progression
- 20% progress to cirrhosis over 20 years
- Leading indication for liver transplantation

Hepatitis D (Delta) Virus
- A defective RNA virus that is dependant upon coinfection with HBV
- Transmitted percutaneously or sexually
- May be transmitted with HBV (co-infection) or during active HBV (superinfection)
- Acute HDV may result in rapid progression in hepatitis leading to fulminant hepatitis

HDV con’t
- Superinfection leads to chronic HDV in 70% of cases
- Diagnosis is made by anti-HD antibodies. Antibody is not protective
- No effective specific therapy HDV infection
- Treatment of the underlying HBV

Hepatitis E Virus
- RNA virus
- Fecal oral transmission
- Highest prevalence in Asia, Central America, Africa
- Clinical disease similar to Hepatitis A
- Incubation period of 2 weeks to 2 months
- Fulminant hepatitis common during pregnancy with mortality rates reported at 15-25%

Metabolic causes of chronic hepatitis
- Iron Overload (specifically genetic Hemochromatosis)
- NAFLD specifically NASH
- Glycogenic Hepatopathy
- Wilson’s Disease
- α1-antitrypsin Deficiency

Hemochromatosis
- Autosomal recessive disease with increased iron absorption through the GI tract
- Most common inherited disease among Caucasians, with a gene frequency of 1:12. The prevalence of homozygosity approaches 1:200
- Extrahepatic iron accumulation in heart, skin and pancreas may result in cardiomyopathy, bronze discoloration of skin, and diabetes
- Other extrahepatic manifestations include arthralgias, testicular atrophy and impotence
Hemochromatosis cont’d

- More than 50% of patients asymptomatic at presentation. Fasting transferrin saturation (Fe/TIBC) is preferred screening test over ferritin
- Gene responsible, HFE, isolated in 1996. Mutations, C282Y and H63D identified
- C282Y homozygote present in 85% of affected US residents of Western European extraction
- Diagnosis either by total iron content of liver tissue on biopsy (next slide) or by HFE genotype

Wilson’s Disease cont’d

- Decreased level of serum ceruloplasmin, a circulating protein carrier of copper
- Increased hepatic copper on biopsy
- Kayser-Fleischer rings (Fig D, next slide) on slit lamp exam represent copper deposition in the cornea
- Treatment is copper chelation, usually with Penicillamine or Trientine
- Decreased GI copper absorption with oral zinc is another therapeutic modality

Wilson’s Disease

- A disease impaired biliary copper excretion
- Autosomal recessive disorder with prevalence of 1:30,000. Gene is a Cu ATPase.
- Neurological, especially extrapyramidal features, or psychiatric manifestations may dominate presentation
- Liver disease may present as “fulminant Wilson’s” associated with massive hemolysis, high transaminases(AST>ALT), low alkaline phosphatase, jaundice and liver failure.
- Most often a disease of teenagers, rare >40 yrs.

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Wilson’s Disease

α1-Antitrypsin Deficiency

- An autosomal recessive disease.
- Most common in people of Northern European descent.
- Emphysema occurs most commonly in the 4th and 5th decades, as a result of unopposed activity of leukocyte elastase. Smoking accelerates lung disease.
- Liver disease due accumulation of mutant protein in the endoplasmic reticulum.

α1-Antitrypsin Deficiency cont’d

- Diagnosis is through serologic evaluation of antitrypsin levels followed by Pi typing.
- Histological diagnosis shows characteristic PAS positive, diastase resistant globules in hepatocytes (next slide).
- No effective therapy for liver disease.
- Recombinant α1-AT in emphysema.
- Transplantation for advanced cirrhosis.

α1-antitrypsin deficiency
Courtesy J. Glickman, BWH Pathology

Non-alcoholic Steatohepatitis

- Part of a spectrum of diseases called non-alcoholic fatty liver disease: NAFLD.
- NAFLD includes simple steatosis (fatty liver) and steatosis with inflammation (non-alcoholic steatohepatitis).
- Fatty accumulation in hepatocytes, often macrovesicular on histology specimens (next slide).
- No alcohol intake.
- Inflammation +/- fibrosis on biopsy.
- Presenting findings may include hepatomegaly and elevated aminotransferases.

Histology in NAFLD
(Courtesy of Dr Hema Khurana, BWH Pathology)

Simple Steatosis
NASH
- steatosis
- lobular inflammation
- Ballooning degeneration

Fibrosis
zone 3
peri sinusoidal
- cirrhosis
- nodule formation
- fat may be absent
Non-alcoholic Steatohepatitis cont'd

- Obesity, hyperlipidemia and insulin resistance or frank diabetes are common
- Ultrasound, CT or MRI findings are suggestive, although biopsy is necessary to confirm diagnosis and distinguish simple steatosis from steatohepatitis.
- Natural history is unclear. At least 15-20% of patients have fibrosis on initial biopsy.
- Cirrhosis is less common but estimates range from 0% to 38% of cases.

Mortality in NAFLD

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Study size</th>
<th>Cirrhosis</th>
<th>Liver death</th>
<th>All deaths</th>
<th>F/u (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>14 (35%)</td>
<td>9.6</td>
</tr>
<tr>
<td>Steatosis</td>
<td>68</td>
<td>0</td>
<td>0</td>
<td>7 (10.1%)</td>
<td>13.7</td>
</tr>
<tr>
<td>Steatosis</td>
<td>170</td>
<td>2 (1.2%)</td>
<td>1 (0.6%)</td>
<td>48 (28.2%)</td>
<td>20.7</td>
</tr>
<tr>
<td>Steatosis</td>
<td>74</td>
<td>42 (56.8%)</td>
<td>22.7%</td>
<td>42 (56.8%)</td>
<td>18.5</td>
</tr>
<tr>
<td>Total</td>
<td>342</td>
<td>2 (0.7%)</td>
<td>3 (0.9%)</td>
<td>111 (32.5%)</td>
<td>15.6</td>
</tr>
<tr>
<td>NASH</td>
<td>26</td>
<td>1 (4%)</td>
<td>0</td>
<td>4 (15.4%)</td>
<td>8.7</td>
</tr>
<tr>
<td>NASH</td>
<td>71</td>
<td>10 (14.1%)</td>
<td>2 (2.8%)</td>
<td>19 (26.8%)</td>
<td>13.7</td>
</tr>
<tr>
<td>NASH</td>
<td>57</td>
<td>NR</td>
<td>10 (17.5%)</td>
<td>56 (63.2%)</td>
<td>18.5</td>
</tr>
<tr>
<td>NASH</td>
<td>31</td>
<td>3 (9.8%)</td>
<td>5 (9.8%)</td>
<td>24 (74.1%)</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>205</td>
<td>16 (10.8%)</td>
<td>15 (7.5%)</td>
<td>83 (40.5%)</td>
<td>15.5</td>
</tr>
</tbody>
</table>

Therapy Guidelines

<table>
<thead>
<tr>
<th>Modality</th>
<th>Summary</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss</td>
<td>Hypocaloric diet or physical activity.</td>
<td>3%-5% decrease body weight improves steatosis. ~10% improves inflammation.</td>
</tr>
<tr>
<td>Metformin</td>
<td>No effect on liver histology.</td>
<td>Not recommended as specific treatment for NAFLD.</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Effective in NASH.</td>
<td>Long term safety in NASH not known. Data from trials all in non-diabetic patients.</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Effective in NASH.</td>
<td>Considered first line therapy in non-diabetic, non cirrhotic NASH.</td>
</tr>
<tr>
<td>Ursodeoxycholic acid</td>
<td>Not effective.</td>
<td>Not recommended.</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>May be effective for treatment of hypertriglyceridemia.</td>
<td>No clear data as yet for role in NAFLD or NASH.</td>
</tr>
<tr>
<td>Statins</td>
<td>Can be used to treat dyslipidemia in NAFLD patients.</td>
<td>No significant evidence to suggest enhanced liver disease in patients with liver disease.</td>
</tr>
<tr>
<td>Bariatric Surgery</td>
<td>Effective in Obese individuals with NASH.</td>
<td>No clear recommendation to use as specific treatment for NASH.</td>
</tr>
</tbody>
</table>

Key Concepts

- **Hemochromatosis**
  - Transferrin saturation is best screening test.
  - High risk of hepatocellular carcinoma in cirrhosis.
  - Phlebotomy in non-anemic patients is standard of care.

- **NAFLD**
  - Risk factors: Obesity, hypertriglyceridemia and diabetes.
  - Must eliminate alcohol use as possible cause.
  - Normalize LFTs by weight loss, decreased triglycerides and euglycemia. Vitamin E is first line agent in new guideline.

- **Wilson’s Disease**
  - Autosomal recessive.
  - Copper accumulation in liver and brain.
  - Corneal Kayser-Fleischer rings.
  - Rarely presents after age 40.
  - May present as fulminant hepatitis or cirrhosis.

- **α1-antitrypsin deficiency**
  - Autosomal recessive.
  - Emphysema and cirrhosis.
  - PAS positive globules in liver, diastase resistant.
Immune Mediated Hepatitis

- Autoimmune Hepatitis
- Celiac Sprue

Autoimmune Hepatitis

- Characterized by the presence of auto antibodies and hypergammaglobulinemia
- Female predominance (3.6:1 Female:Male)
- Typical onset between 10 and 30, although second peak in middle age
- Symptoms include fatigue and RUQ pain
- Hepatomegaly most common finding, Spider nevi in more than 50% of patients.

Autoimmune Hepatitis con’t

- Auto antibodies include ANA, ASMA and anti-LKM
- Hyper gamma globulinemia
- AMA should be negative
- Viral, EtOH and drug/toxin-induced hepatitis must be excluded
- Cirrhosis at time of diagnosis common
- Biopsy necessary for staging
- Immune suppression for treatment

Autoimmune hepatitis

Treatment of AIH

- Prednisone alone or in combination with Azathioprine
- Azathioprine should not be used alone to induce remission
- Azathioprine can be used for maintenance therapy
- Patients should be monitored carefully for side effects of immunosuppressive therapy
Key Concepts

- **AIH**
  - Autoantibodies
  - Increased IgG
  - More common in women
  - Treatment is with immunosuppressives.
  - Induction therapy must include corticosteroids

Conflict of interest disclosures

- Consultant: Gilead Sciences, Vertex Pharmaceuticals

References

- Czaja AJ, Freese DK. Diagnosis and Treatment of Autoimmune Hepatitis. Hepatology 2002

Question 1: A 14 year old female is seen for elevated liver enzymes. ALT is 63 and AST is 78. Albumin is 3.3 and the prothrombin time is 20 seconds with an INR of 2.0. A previous A grade student until the last year, she now fails most courses. She is aggressive, angry, irrational and occasionally violent. Which of the following is true?

- A) She most likely has a defect in the gene for copper transported ATPB7
- B) Slit lamp examination may show Kaiser Fleisher rings
- C) Penicillamine is a good first line therapy
- D) Ceruloplasmin levels are likely to be low
- E) All of the above

The answer is E.

- The patient is young, has neurobehavioral issues along with hepatic impairment. The most likely reason is Wilson’s disease.

Question 2: A 42 year old man is seen for worsening emphysema. He has smoked 2.5 packs of cigarettes per day for 16 years. As part of his pulmonary evaluation he is noted to have an enlarged and nodular liver. A liver biopsy shows PAS positive globules that are diastase resistant. The most likely diagnosis is
Question 2

A) Glycogenic hepatopathy
B) Amyloidosis
C) Alpha-1 antitrypsin deficiency
D) Gaucher’s Disease
E) Idiopathic ductopenia

The correct answer is C.

The patient has alpha-1 antitrypsin deficiency.

Glycogenic hepatopathy is an acquired glycogen deposition disease seen in type 1 diabetics. The glycogen deposits are PAS positive but diastase sensitive (see additional slides for more details). The diagnosis of amyloidosis is made on a Congo red stain.

Gaucher’s disease is a lysosomal storage disorder with deposition of glucocerebrosides in many organs including liver, bone marrow and spleen. Idiopathic ductopenia is a disorder of bile duct loss.


Glycogenic hepatopathy: a type 1 diabetic disorder that may mimic NAFLD

Patients with poorly controlled type 1 diabetes may present with and are often erroneously given a diagnosis of NAFLD:

- Elevated aminotransferases
- Hepatomegaly
- Right upper quadrant pain
- Elevated glycosylated hemoglobin
- Hyperglycemia

Glycogenic hepatopathy (Mauriac’s syndrome)

- Type 1 DM
- RUQ pain, iner lfts, hepatomegaly
- Poor compliance with insulin therapy
- Steatosis unusual
- Marked hepatic glycogen deposition
- No significant fibrosis
- Usually responds to stringent insulin therapy

Rogal S et al. NEJM; 364: 1761-1767