VIRAL AND AUTOIMMUNE HEPATITIS

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WHAT IS HEPATITIS?
• Inflammation of the liver
• Almost always, inflammation implies elevation in liver enzymes
• AST and ALT are the key liver enzymes
• Other Liver Function Tests (LFTs) which can be abnormal in hepatitis include:
  • Bilirubin, albumin, alkaline phosphatase, gamma glutamyl transpeptidase

CAUSES OF ACUTE HEPATITIS
• Viral hepatitis
• Other infectious etiologies e.g. CMV, EBV, TB
• Alcoholic hepatitis
• Drug hepatitis
• Ischemic hepatitis
• Choledocholithiasis

OTHER INFECTIOUS ETIOLOGIES OF ACUTE HEPATITIS
• CMV - cytomegalovirus; immunocompromised host
• EPSTEIN-BARR – mononucleosis; lymphadenopathy, splenomegaly
• TB and M. avium intracellulare (MAI)

SYMPTOMS OF ACUTE VIRAL HEPATITIS
• Fatigue, nausea, anorexia
• Jaundice
• Low-grade fever, abdominal pain
• Arthralgia, myalgia, headache
SIGNS OF ACUTE VIRAL HEPATITIS

- Fever – low grade
- Jaundice
- Hepatomegaly with RUQ tenderness
- Splenomegaly - infrequent

LIVER BLOOD TEST ABNORMALITIES IN ACUTE VIRAL HEPATITIS

- AST AND ALT - 1000-5000 IU
- Bilirubin – generally elevated – both conjugated and unconjugated
- Alkaline Phosphatase – minimally elevated
- Bilirubin and urobilinogen increased in urine

OUTCOMES OF VIRAL HEPATITIS

ACUTE ILLNESS

CURE

FULMINANT HEPATITIS

CHRONIC HEPATITIS

HEPATITIS A

- Oral fecal route of transmission
- Excreted in stool about 2 weeks prior to clinical illness
- 1 month incubation period
- Children often asymptomatic
- Never causes chronic hepatitis

HAV - Epidemiology

Global Prevalence of Hepatitis A Infection

HEPATITIS A Virus

- Nucleic Acid: 7.5 kb ssRNA
- Classification: Picornaviridae, Hepatovirus
- One serotype and multiple genotypes
- Nonenveloped, acid and heat stable
- In vitro model: monkey and human cell cultures
- In vivo replication: in cytoplasm of hepatocyte; human and other higher primates
Typical Serologic Course of Acute Hepatitis A Virus Infection

- Symptoms
- ALT
- Total anti-HAV
- Fecal HAV
- IgM anti-HAV

Months after exposure

HAV

PREVENTION AND TREATMENT

- No treatment of infection available
- Passive immunity with gamma globulin can ameliorate disease in early stages of the infection
- Gamma globulin can prevent disease pre-exposure
- Vaccine available to induce active immunity

Hepatitis B Virus

- Nucleic Acid: 3.2 kb DNA
- Classification: Hepadnaviridae
- Multiple serotypes and genotypes A-F
- Enveloped
- In vitro model: primary hepatocyte culture and transfection of cloned HBV DNA
- In vivo replication: in cytoplasm, cccDNA in nucleus, hepatocyte and other tissues, human and other primates

Hepatitis B Virus - Replication

Viral entry

Nuclear import

Repair Transcription

cccDNA

5' 3'

3.5 kb RNA

Viral entry

2.4/2.1 kb RNA

Positive strand synthesis

Removal of pregenome

Negative strand synthesis

Translation

Encapsidation
HEPATITIS B VIRUS
NATURAL HISTORY
- Transmission – parenteral, secretions, sexual mother to child (vertical)
- 6-8 week incubation
- 20% pf patients have serum sickness prodrome
- 4% of patients develop chronic hepatitis
- Treatment and vaccine available
Serological Markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Clinical Significance</th>
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<tbody>
<tr>
<td>HBsAg</td>
<td>Acute/Chronic infection</td>
</tr>
<tr>
<td>Anti-HBc IgM</td>
<td>Acute infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>High infectivity</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>Low infectivity</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Immunity</td>
</tr>
<tr>
<td>Anti-HBc IgG and HBsAg</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>Anti-HBc IgG and anti-HBs</td>
<td>Resolved infection</td>
</tr>
</tbody>
</table>

Acute HBV Infection

HBV DNA

HBsAg

Anti-HBs

Anti-HBc

Anti-HBe

HBeAg

Anti-HBc IgM

Acute HBV Infection

HBsAg

Anti-HBs

Anti-HBc

Anti-HBe

HBeAg

Anti-HBc IgM

Months

Years

Hepatitis C Virus

Nucleic Acid: 9.6 kb ssRNA

Classification: Flaviviridae, Hepacivirus

Genotypes: 1 to 6

Envelope

In vitro model: primary hepatocyte and T cell cultures; replicon system

In vivo replication: in cytoplasm, hepatocyte and lymphocyte; human and other primates

Hepatitis C Virus: Morphology and Characteristics

Hepatitis C Virus: Genome and Gene Products

Gene Products and Functions

<table>
<thead>
<tr>
<th>Gene Product</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core (C)</td>
<td>Nucleocapsid</td>
</tr>
<tr>
<td>E1 and E2</td>
<td>Envelope proteins, hypervariable region in E2</td>
</tr>
<tr>
<td>p7</td>
<td>Nonstructural, ion channel (?)</td>
</tr>
<tr>
<td>NS 2</td>
<td>NS 2-3 protease</td>
</tr>
<tr>
<td>NS 3</td>
<td>Protease, nucleotide triphosphatase, and RNA helicase</td>
</tr>
<tr>
<td>NS 4</td>
<td>Cofactor for NS 3 protease activity</td>
</tr>
<tr>
<td>NS 4B</td>
<td>Formation of membranous web</td>
</tr>
<tr>
<td>NS 5A</td>
<td>Interferon sensitivity sequence</td>
</tr>
<tr>
<td>NS 5B</td>
<td>RNA-dependent RNA polymerase</td>
</tr>
</tbody>
</table>
HEPATITIS C CLINICAL

- Most common cause of chronic hepatitis in USA
- 1.5% of population in USA carries the virus
- Parenteral transmission – blood, sexual
- 6-8 week incubation period
- Acute infection generally mild
- 80% of acute develop chronic disease
- No vaccine available
- Treatment – 40-80% cure rate

HEPATITIS D AND E

- HEPATITIS D
  – Also known as delta agent
  – Uses the HBsAg protein coat
  – Hepatitis B must be present – coinfection or preexist

- HEPATITIS E
  – Water borne virus resembling hepatitis A
  – Rarely seen in USA
CHRONIC HEPATITIS

- Fatty liver
- Viral – B and C
- Autoimmune
- Drugs
- Alcohol
- Metabolic
- Others – CHF, hemochromatosis, vasculitis, IBD, celiac disease, neoplasia, etc.

CHRONIC HEPATITIS B AND C

- Cirrhosis develops in 20% of patients
- Liver failure and hepatoma develop in about ½ of cirrhotics
- Diagnosis of chronic hepatitis made on basis of:
  - chronic AST and ALT elevations
  - positive serology
  - positive DNA or RNA in blood
  - some patients have normal liver enzymes
- Treatment available with varying success rates

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AUTOIMMUNE HEPATITIS

- Genetically predisposed host exposed to an environmental agent triggering an autoimmune response directed at liver antigens leading to a necroinflammatory response
- Associated with other autoimmune diseases - thyroid disease, colitis, hemolytic anemia, ITP, diabetes, celiac disease, polymyositis, pericarditis, SLE, MCTD
AUTOIMMUNE HEPATITIS

• Clinical presentation – generally female, fatigue, jaundice, hypergammaglobulinemia, elevated AST and ALT
• Lab - presence of associated autoantibodies – ANA, thyroid antibodies, LKM, smooth muscle
• Diagnostic liver biopsy – interface hepatitis and plasma cell infiltration
• Treatment - steroids and immunosuppressants