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

CHRONIC HEPATITIS  CURE  FULMINANT 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

Global Prevalence of Hepatitis A Infection

- 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
- IgM anti-HAV
- Fecal HAV

Months after exposure:
0 1 2 3 4 5 6 12 24

Hepatitis A 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 - Morphology and Characteristics
- 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
Uncoating
Nuclear import
Transcription
Translation
Positive strand synthesis
Removal of pregenome
Negative strand synthesis
Encapsidation
Nucleus
3.5 kb RNA
2.4/2.1 kb RNA
cccDNA
5' 5' 3' 3'
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 and Clinical Significance

<table>
<thead>
<tr>
<th>Marker</th>
<th>Significance</th>
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</thead>
<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>

### Hepatitis C Virus

**Nucleic Acid:** 9.6 kb ssRNA

- **Classification:** Flaviviridae, Hepacivirus
- **Genotypes:** 1 to 6
- **Structure:** Enveloped
- **In vitro model:** Primary hepatocyte and T cell cultures; replicon system
- **In vivo replication:** In cytoplasm, hepatocyte and lymphocyte; human and other primates

### Gene Products and Functions

<table>
<thead>
<tr>
<th>Product/Site</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</td>
</tr>
<tr>
<td>p7</td>
<td>Hypervariable region in E2</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>

### HBV - Diagnosis

**Clinical Significance of Serological Markers for HBV Infection**

- **HBsAg**
  - Acute/Chronic infection
- **Anti-HBc IgM**
  - Acute infection
- **HBeAg**
  - High infectivity
- **Anti-HBe**
  - Low infectivity
- **Anti-HBs**
  - Immunity
- **Anti-HBc IgG and HBsAg**
  - Chronic infection
- **Anti-HBc IgG and anti-HBs**
  - Resolved infection

### HBV - Replication

- **Structural protein coding region**
- **Nonstructural protein coding region**

**Core**

- Protease
- Protease Cofactor

**Envelope**

- Serine protease
- Helicase

**NS5B**

- RNA-dependent RNA polymerase

**Additional Information**

- Genome and Gene Products
- Hepatitis C Virus: Genome and Gene Products, pt. 2
- Gene Products and Functions
- Hepatitis C Virus: Core (C)
- Hepatitis C Virus: E1 and E2
- Hepatitis C Virus: p7
- Hepatitis C Virus: NS 2
- Hepatitis C Virus: NS 3
- Hepatitis C Virus: NS 4
- Hepatitis C Virus: NS 4B
- Hepatitis C Virus: NS 5A
- Hepatitis C Virus: NS 5B
- Hepatitis C Virus - Replication
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

Serologic events in HBV infection

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>anti-HBs</th>
<th>HBeAg</th>
<th>Anti-HBe</th>
<th>anti-HBc IgM</th>
<th>Anti-HBc IgG</th>
<th>HBV DNA</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HBV Infection</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Normal</td>
<td>11</td>
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<tr>
<td>Vaccine Responder</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Normal</td>
<td></td>
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<tr>
<td>Exposure with Immunity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Normal</td>
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<tr>
<td>Chronic HBV (Wild Type)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Chronic HBV (Precore Mutant)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Normal</td>
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<tr>
<td>Inactive Carrier</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Normal</td>
<td></td>
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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

END