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 INFECTIONOUS ETIOLOGIES OF ACUTE HEPATITIS

- CMV - cytomegalovirus; immunocompromised host
- EPSTEIN-BARR – mononucleosis; lymphadenopathy; splenomegaly
- TB and M. avium intracellulare (MAI)

HUMAN HEPATITIS VIRUSES

<table>
<thead>
<tr>
<th>Virus</th>
<th>Genome</th>
<th>Genomic Size (kb)</th>
<th>Envelope</th>
<th>Family/Genus</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
<td>RNA</td>
<td>7.5</td>
<td>-</td>
<td>Picornaviridae hepatovirus</td>
</tr>
<tr>
<td>HBV</td>
<td>DNA</td>
<td>3.2</td>
<td>+</td>
<td>Hepadnaviridae</td>
</tr>
<tr>
<td>HCV</td>
<td>RNA</td>
<td>9.6</td>
<td>+</td>
<td>Flaviviridae hepacivirus</td>
</tr>
<tr>
<td>HDV</td>
<td>RNA</td>
<td>1.7</td>
<td>+</td>
<td>Unclassified (viroid), delta virus</td>
</tr>
<tr>
<td>HEV</td>
<td>RNA</td>
<td>7.5</td>
<td>-</td>
<td>Unclassified, togavirus and alpha virus-like</td>
</tr>
</tbody>
</table>
SYMPTOMS OF ACUTE VIRAL HEPATITIS

- Fatigue, nausea, anorexia
- Jaundice
  - Low-grade fever, abdominal pain
  - Arthralgia, myalgia, headache

OUTCOMES OF VIRAL HEPATITIS

ACUTE ILLNESS

- CHRONIC HEPATITIS
- CURE
- FULMINANT HEPATITIS

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

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

HAV (Hepatitis A Virus)

Global Prevalence of Hepatitis A Infection

HAV Prevalence
- High
- Intermediate
- Low
- Very Low
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

Typical Serologic Course of Acute Hepatitis A Virus Infection

HAV

- Fecal
- ALT
- IgM anti-HAV

Months after exposure

Symptoms

Total anti-HAV

IgM anti-HAV

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 CLINICAL

- Transmission – parenteral, secretions, sexual, mother to child (vertical)
- 6-8 week incubation
- 20% of 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>
</tr>
</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>

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**Hepatitis C Virus**

- Nucleic Acid: 9.6 kb ssRNA
- Classification: Flaviviridae, Hepacivirus
- Genotypes: 1 to 6
- Enveloped
- In vitro model: primary hepatocyte and T-cell cultures; replicon system
- In vivo replication: in cytoplasm, hepatocyte and lymphocyte; human and other primates

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**Hepatitis C Virus: Genome and Gene Products**

- Core
- Envelope
- Protease
- p7
- NS 2
- NS 3
- NS 4
- NS 4B
- NS 5A
- NS 5B
- RNA polymerase
- Helicase
- Nonstructural protein coding region
- Structural protein coding region

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**Hepatitis C Virus: Gene Products and Functions**

<table>
<thead>
<tr>
<th>Gene Product</th>
<th>Function/Activity</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
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

• Presence of associated autoantibodies – ANA, thyroid antibodies, LKM, smooth muscle

• Diagnostic liver biopsy – interface hepatitis and plasma cell infiltration

• Treatment - steroids and immunosuppressants

END