Pathophysiology of the liver: 
Hepatitis & Liver cirrhosis

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Liver and bile system

Diaphragm 
Liver 
Gallbladder 
Cystic duct 
Common bile duct 
Ampulla of Vater 
Sphincter of Oddi 
Duodenum 

Spleen 
Hepatic duct 
Tail of the pancreas 
Pancreatic duct 
Head of the pancreas
Architectonics of the Liver

Etiology

- Infectious agents
- Hepatotoxins
  - Alcohol
  - Drugs
- Alimentary factors
13.4.2016

**Hepatic syndromes**

- Jaundice
- Portal hypertension
- Ascites
- Portosystemic shunt (PSS)
JAUNDICE

Yellowish discoloration of the skin, the conjunctival membranes over the sclerae and other mucous membranes caused by hyperbilirubinemia

- Ludwig Courvoisier (1843-1918)
  - 'Courvoisier's law' is named after him stating that 'if in the presence of jaundice the gallbladder is palpable, then the jaundice is unlikely to be due to a stone.'

Jaundice (Icterus)
Bilirubin Metabolism

- Bilirubin formation
- Transport of bilirubin in plasma
- Hepatic bilirubin transport
  - Hepatic uptake
  - Conjugation
  - Biliary excretion
- Enterohepatic circulation

Pathophysiologic classification of Jaundice

- Hemolytic Jaundice
- Hepatic Jaundice
- Obstructive Jaundice (Cholestasis)
- Congenital Jaundice
Portal Hypertension

- It is a high blood pressure in the portal vein and its tributaries (portal venous system).

- It is defined as a portal pressure gradient (the difference in pressure between the portal vein and the hepatic veins) of 8-10 mm Hg or higher.

Causes of portal hypertension

- **Intrahepatic causes**: liver cirrhosis and hepatic fibrosis (e.g., due to Wilson's disease, hemochromatosis, or congenital fibrosis).

- **Prehepatic causes**: portal vein thrombosis or congenital atresia.

- **Posthepatic obstruction**: occur at any level between liver and right heart.
Hepatic vascular blocks

- Posthepatic block
- Postsinusoidal block
- Intrahepatic block
- Presinusoidal block
- Prehepatic block
- A-V anastomoses

Ascites

- accumulation of fluid in the peritoneal cavity 90% of the cases secondary to chronic liver condition (cirrhosis)
Pathogenesis of ascites

Ascites and caput medusae

- Elevated hydrostatic pressure in v. portae
- Decreased oncotic pressure (hypoproteinemia)
- Increased capillary permeability
- Delayed lymph flow
Patient with Ascites

Portosystemic shunts (PSS)

- Bypass of the liver due to inability of the blood to circulate in the branches of portal vein (also known as a liver shunt)

Most common PSS
- Oesophageal varices
- Dilation of abdominal veins (Caput medusae)
- Hemorrhoidal venous collaterals
13.4.2016 г.

Oesophageal varices

The term HEPATITIS usually refers to a group of viral infections that affect the liver as well as the consequences of that infection.

- Acute
- Chronic
  - Chronic active hepatitis
  - Chronic persistent hepatitis

Hepatitis
### Type of Hepatitis

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of virus</td>
<td>feces</td>
<td>blood/ blood-derived body fluids</td>
<td>blood/ blood-derived body fluids</td>
<td>blood/ blood-derived body fluids</td>
<td>feces</td>
</tr>
<tr>
<td>Route of transmission</td>
<td>fecal-oral</td>
<td>percutaneous mucosal blood borne yes</td>
<td>percutaneous mucosal blood borne yes</td>
<td>percutaneous mucosal blood borne yes</td>
<td>fecal-oral</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>Prevention</td>
<td>pre/post-exposure immunization</td>
<td>pre/post-exposure immunization</td>
<td>blood donor screening; risk behavior modification</td>
<td>pre/post-exposure immunization; risk behavior modification</td>
<td>ensure safe drinking water</td>
</tr>
</tbody>
</table>

### Hepatitis A (HAV)

- worldwide distribution
- risk of ALF 0.01-0.1%
- usually hyperacute
- risk:
  - > 40 yrs
  - IVDU
  - homosexual
  - CHB or CHC or alcoholic liver disease
- anti-HAV IgM 95%
- spontaneous survival relatively high (40-60%)
Clinical Features

- Low mortality in healthy people
  - High mortality when older than age 60
  - High in presence of chronic liver disease
- High morbidity
  - Around 20% need hospitalization
  - Lost work days
  - Most become jaundiced

Hepatitis B (HBV)

- A DNA virus that infects only humans
- Belongs to the family Hepadnaviridae
- Knowledge of the *viral proteins* that are perceived by the immune system as "antigens" aids understanding of the various tests used to diagnose acute, chronic, and resolved infection and verify response to immunization
HBV Antigens

- Outer envelope contains a surface protein called hepatitis B surface antigen (HBsAg)
- HBsAg is a marker of viral replication
- Inner core contains the genome, the DNA polymerase w/ reverse transcriptase activity, hepatitis B core antigen (HbcAg) particles. This antigen is not detectable in serum
- A truncated form of the major core polypeptide known as hepatitis e antigen (HbeAg) is the third antigen generated by virus activity. Marker of high infectivity

Hepatitis B Antibodies

- Hepatitis B surface antibody is the antibody to surface antigen. HBsAb is protective and indicates either resolved infection or immunization
- HbcAb is the antibody to core antigen. This is not a protective antibody. Only those who have been exposed to the virus will have this antibody
- HbcAb is measured in serum as:
  - Anti Hbc IgM (usually indicates new infection)
  - Anti Hbc IgG (appears later)
- HBeAb is the antibody to e antigen. Loss of e antigen w/ gain of e antibody is called seroconversion. Not a protective antibody
Epidemiology

- Prevalence of HBV varies markedly around the world, with > 75% of cases in Asia and the Western Pacific.

- Vaccine available > 20 years, but perinatal and early life exposure continue to be a major source of infection in endemic areas.

- Worldwide, chronic HBV and its complications including hepatocellular carcinoma account for > 1 million deaths each year.

Prevalence of Hepatitis B carriers

(Courtesy Centers for Disease Control and Prevention, Atlanta.)
Signs and Symptoms

- Incubation period: a few weeks to 6 months
- About 30% develop jaundice
- 10% to 20% of patients develop serum sickness, i.e., fever, arthralgias, rash
- Fatigue
- Fulminant hepatitis B occurs in < 1% of cases. 80% mortality without liver transplantation
- Enzyme elevations of 1,000-2,000 typical

Clinical outcomes of Hepatitis B

Cirrhosis

Gradually developing chronic disease of the liver, which always involves the organ as a whole. It is the irreversible consequences and final stage of various chronic liver diseases of different etiology or the result of long-term exposure to various noxae.
Liver cirrhosis is characterized by the following 5 criteria:

- Pronounced, insufficiently repaired necrosis of the parenchyma (with or without inflammatory process)
- Diffuse connective tissue proliferation
- Varying degrees of nodular parenchymal regeneration
- Loss and transformation of the lobular structure within the liver as a whole
- Impaired, intrahepatic and intra-acinar, vascular supply with consecutive formation of arterio-venous and porto-venous anastomoses.

Cirrhosis - pathophysiology

(A) Normal sinusoidal architecture
Low matrix density

(B) Liver injury
- Stellate cell proliferation
- Increased density of matrix
- Shrinkage of cilia and canaliculi
- Loss of fenestration

Anatomical types of regenerating nodules

- Micronodular
- Macronodular
- Mixed cirrhosis

Micronodular cirrhosis

- Features: Thick regular septa
  Regenerating small nodules (<3mm)
  Involvement of every lobule

- Alcoholism
- Malnutrition
- Biliary obstruction
- Hemochromatosis
- Venous outflow obstruction
Macronodular cirrhosis

- Features: Septa
  - Nodules of variable size
    (>3mm, even 1~3 cm)
  - Normal lobules in the large nodules

- Two subtypes: postnecrotic, posthepatitic

Mixed cirrhosis

Features:

- Presenting both micro- and macronodules
- From micronodules to macronodules
- Alcoholism
- Antitrypsin deficiency
**Signs and symptoms**

- Hepatomegaly and splenomegaly
- Jaundice
- Cholestasis
- Portal Hypertension
- Oedema and Ascites
- Hepatic Encephalopathy
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Coagulopathy and Hemorrhage

**Cirrhosis - clinical signs**

- [Image of skin lesions]
- [Image of hands with spider naevi]
- [Image of upper body with spider naevi]
Acute Liver Failure - Characteristics

- Impairment of liver functions,
- Jaundice
- Encephalopathy
- Coagulopathy
- Altered mental state → coma

Acute liver failure causes

- Infections (hepatites - 75%)
- Intoxications (fungi, pesticides)
- Medications (paracetamol, extasy, gold salts, NSAIDs, anesthetics, etc.)
- Cardiovascular
- Metabolic
- Other
Metabolic alterations

- **Haemorrhages** – altered vit. K absorption, and thus decreased coagulation factor synthesis, platelets ↓

- **Jaundice** – inability to metabolise bilirubin (bile salts in the skin → itching)

- **Osteoporosis** – altered vit. K and Ca\(^{2+}\) metabolism

Hepatic encephalopathy

Reversible decrease in neurologic function, based upon the disorder of metabolism which are caused by severe decompensated liver disease
Etiology of hepatic encephalopathy

- Fulminant hepatic failure
  - acute severe viral hepatitis, drug/toxin
  - acute fatty liver of pregnancy
  - Due to acute hepatocellular necrosis

- Chronic liver disease
  - cirrhosis of all types (70%), primary liver cancer
  - surgically induced portal-cava shunts
  - Due to one or more potentially reversible precipitating factors

Hepatic encephalopathy (pathogenesis)

Postulated factors/mechanisms:

- Hyperamonemy
- Synergistic effect of neurothropic toxins
  - Amonium
  - Short chain fatty acids
  - Merkaptans
  - Phenols
- Phony neuromediators
  - Octopamin
- gama amino butiric acid (GABA)
Hepatic Encephalopathy
Clinical features

- Reversal of sleep pattern
- Disturbed consciousness
- Personality changes
- Intellectual deterioration
- Fetor hepaticus
- Astrexis
- Fluctuating

Clinical stages of HE

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Intellectual function</th>
<th>Neuromuscular</th>
<th>EEG</th>
</tr>
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<tbody>
<tr>
<td>Stage 1 (Prodromal stage)</td>
<td>Altered judgement, personality and behavior such as apathy, euphoria, lack of awareness</td>
<td>Flapping tremor(±)</td>
<td>Normal</td>
</tr>
<tr>
<td>Stage 2 (Precoma stage)</td>
<td>Mental confusion, drowsiness, poor memory, computation, sleep disorders, disorientation</td>
<td>Flapping tremor (+) (easily elicited)</td>
<td>Abnormal (slower rhythms, triphasic waves)</td>
</tr>
</tbody>
</table>

ataxia
Clinical stages of HE

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<tr>
<td>Stage 3 (Deep somnolence)</td>
<td>Marked confusion, spasticity, extensor plantar response,</td>
<td>Flapping tremor (+)</td>
<td>Abnormal (if patients cooperate)</td>
</tr>
<tr>
<td></td>
<td>stupor/aus, obeying simple commands, somnolence</td>
<td>(Severe slowing with frequencies in the theta and delta)</td>
<td></td>
</tr>
<tr>
<td>Stage 4 (Coma)</td>
<td>Not rousable, coma</td>
<td>Flapping tremor (-)</td>
<td>Abnormal absence of response to painful stimuli</td>
</tr>
</tbody>
</table>

Hepatic transplantation - the radical solution

Between 5 and 10 000 transplantations/year (10 % of patients)
Thank you