LIVER DISORDERS

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Liver failure

- Portal hypertension
- Esophageal varices
- Ascites
- Icterus
- Liver failure – hepatic encephalopathy

LIVER FAILURE

- Definition: inability of the liver to fulfill normal functions
- Causes:
  - inflammation – persistent viral hepatitis;
  - alcohol abuse, the most common cause;
  - side effects of - folic acid antagonists,
  - impairment of venous return - right heart failure
  - cholestasis
- Consequences:
  - Plasma proteins – hypoalbuminemia, complement, coagulation factors
  - Avitaminoses of fat soluble vit. (vit. K - II, VII, IX, and X)
  - Detoxication – hyperammonemia, bilirubin-jaudice etc.
  - Alkalosis, hypokalemia.
  - Portal hypertension, ascites, encephalopathy

Contents

1 Liver failure
Portal hypertension

Introduction

- History: 17th century - structural changes in the portal circulation cause gastrointestinal bleeding, 1902 - Gilbert and Carnot introduced the term "portal hypertension.
- Definition: pressure in the portal venous system that is at least 5 mm Hg higher than the pressure in the inferior vena cava; most serious sequelae of chronic liver disease
  - Normal: 4–8 mmHg (1–4 mmHg higher than the hepatic vein free pressure, and not more than 6 mm Hg higher than right atrial pressure)
  - Hypertension: > 10 mmHg
- Cause: obstruction to blood flow from any point in the portal system's origin (in the splanchnic bed) through the hepatic veins (exit into the systemic circulation) or increase in blood flow in the system

Portal system

- Liver receives 1.5 l/min of blood
- Hepatic vascular system is less influenced by vasodilation and vasoconstriction
- Hepatic artery blood flow is inversely related to portal vein flow (hormonally mediated)
- Portal vein system:
  - Supplies 70% of the blood flow to the liver, but only 40% of the liver oxygen supply (remainder hepatic artery), blood mixes in the sinusoids
  - Spleen, Pancreas, Stomach, Bowels, Rectum
  - Liver: sinusoids, central vein, hepatic veins
CAUSES 1

Supraventricular causes
- cardiac disease, inferior vena cava thrombosis or webs.
- Hepatic vein thrombosis, or Budd-Chiari syndrome, has multiple etiologies - hypercoagulable state.
- Liver fibrosis can result from supraventricular disease.

Infrahepatic causes
- Arteriovenous malformation of the splenic vasculature.
- Splenomegaly.
- Portal vein thrombosis.

PORTAL HYPERTENSION - CAUSES 2

Hepatic causes
- Cirrhosis - most common cause of portal hypertension.
  - Chronic viral hepatitis C - the most common cause of cirrhosis.
  - Alcohol-induced.
  - Cholestatic.
  - Hemochromatosis.
  - Alpha 1 antitrypsin deficiency.
  - Drug-induced liver disease.
  - Hepatitis B.
  - Schistosomiasis, cancer.

cytokines as TNF-alpha - stimulate endothelial vasodilators (NO, PGI) + non-endothelial vasodilators (glucagon) -> pressure and flow in the splanchnic vasculature.

PORTAL HYPERTENSION - TYPES

<table>
<thead>
<tr>
<th>Type</th>
<th>Pressure</th>
<th>Location</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presinusoidal</td>
<td>O</td>
<td>N</td>
<td>Prehepatic, blockade of portal, mesenterial or spleen veins (tumors, neonatal umbilical sepsa, thrombophlebitis, polycytemia - viscosity)</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>N or O</td>
<td>Hepatic, congenital fibrosis, schistosomiasis, viral hepatitis, alcoholic &amp; biliary fibrosis, thrombosis, non-alcoholic cirrhosis</td>
</tr>
<tr>
<td>Postsinusoidal</td>
<td>O or N</td>
<td>N</td>
<td>Hepatic, alcoholic cirrhosis, Budd-Chiari sy.</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td>Posthepatic, block of hepatic veins / thrombosis, right heart failure, constrictive pericarditis, etc.</td>
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PORTAL HYPERTENSION - CONSEQUENCES

- Venostasis - impaired secretion, absorption in GUT
- Splenomegaly - enlargement of spleen - hemolysis
- Collateral circulation - opening and dilation of shunts
  - varices (esophageal veins)
  - haemorrhoides (rectal veins)
  - superficial veins (umbilical, paraumbilical - Caput medusae)
- Ascites - lymphatic fluid that leaks across hepatic sinusoidal endothelium due to high hepatic sinusoidal pressure
  - O&U hydrostatic pressure + ò degradation of aldosteron, AHD
- Hepatic encephalopathy (ammonium + toxins bypassing liver)

Complications:
- haematemesis (vomiting of blood) rupture of esophageal varices
- melena (black tarry stool - upper tract bleeding)

PORTAL HYPERTENSION

Esophageal varices

- varicose veins in the esophagus or stomach
- rupture – complication in 40%, danger is low if hepatic ven. pressure < 12 mm Hg

Therapy:
- Medicaments:
  - beta-blockers (decrease resting heart rate by 25%)
  - vasopressin - decreasing splanchnic blood flow (central venous access)
  - Somatostatin – vasoconstrictor in splanchnic bed

Varices

Duodenum

Stomach

Esophageal varices

Thermography of caput medusae

Common tests that are used to evaluate liver function include:
albumin, ALP, ALT, AST, bilirubin; urine GGT, LDH, PT, total cholesterol, total protein

Therapy

- Sclerotherapy - 1–10 mL of sclerosing agent (sodium morrhuate, sodium tetradecyl sulfate, ethanolamine olate, or absolute alcohol) into and around the varices. Common side effects include tachycardia, chest pain, fever, and ulceration at the injection site.
- Banding small elastic rings over a suctioned varix. Banding has fewer side effects than sclerotherapy
- Balloon tamponade is useful to control variceal bleeding through compression high risk of complications, especially aspiration.
The Transjugular Intrahepatic Portosystemic Shunt (TIPS) stent (a tubular device) is placed in the middle of the liver to reroute the blood flow.

**Introduction**

- **Definition:** presence of excess fluid in the peritoneal cavity; frequently develops in chronic liver disease, but may be due to a wide range of causes.
- **Types:**
  - Transudative ascites (low protein) hepatic congestion – from hepatic sinusoids into interstitium, liver capsule, peritoneum
  - Exudative ascites (higher protein) from the peritoneum
- **Mechanisms:**
  1. Blood hydrostatic pressure (Portal hypertension)
     - Reasons: liver disease, abdominal tumors, heart failure, constrictive pericarditis
  2. Osmolarity of plasma
     - Reasons: liver diseases, malnutrition, renal failure, nephrotic sy.
  3. Lymphathetic pressure
     - Reasons: abdominal tumors, cirrhosis
  4. Retention of water
     - Reasons: cirrhosis (Ü breakdown of ALDO -> Na⁺ ADH ð H₂O)

**Ascites**

- **Symptoms:**
  - asymptomatic
  - symptomatic
    - early satiety, abdominal girth, or respiratory distress,
    - acute oliguria, abdominal distention, tympany of the top, bulging flanks, puddle sign, fluid wave, or shifting dullness on physical examination.
  - side effects - hyponatremia, hyperkalemia, hypokalemic, dehydration, hypotension, and azotemia.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Pathogenesis</th>
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<tbody>
<tr>
<td>Portal hypertension</td>
<td>Non-portal hypertension</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Tuberous</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Pancreatic ascites</td>
</tr>
<tr>
<td>Liver tumors</td>
<td>Carcinomatoid</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Lymphatic obstruction</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
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Oncotic pressure – decrease splanchnic lymph - increase intra-abdominal fluid is normally absorbed by the peritoneum, high intraperitoneal pressure results in net increase in absorption.
Ascites

- Treatment:
  - Diuretic therapy, to reduce sodium retention by kidneys, (blocking aldosterone effects. Restrict Na to less than 2 g per day, water restriction (1.5 liters per day) adequate but not necessary unless patients develop hyponatremia.
  - Abdominal paracentesis – sterile aspiration of ascites; large-volume paracentesis -> intraperitoneal pressures drop -> rapid reaccumulation of ascites.

- Laboratory analysis:
  - Protein content, cytological analysis, cultures (infections), Albumin gradient greater than 1.1 g/dL between serum and ascitic fluid → portal hypertensive origin of ascites

- Complication:
  - Spontaneous bacterial peritonitis (SBP) is very high (low oncotic pressure), difficult to diagnose, pain is often absent, 70% Gram-negative bacilli (Streptococcus, Staphylococcus) PMN counts that exceed 250/ml

(3) Icterus - Manifestations

- Definitions:
  - Icterus - symptom - visible yellow coloring of tissues (eyes, skin, mucosa, organs) due to accumulation of lipophilic pigment - bilirubin in membranes of cells in tissues
  - Hyperbilirubinaemia - always present in icterus; however icterus not always accompany it

- Normal bilirubin: < 20 µmol/l
- Hyperbilirubinaemia: > 20 µmol/l
- Icterus: usually > 30-35 µmol/l
- in many cases > 300 µmol/l
- Subicterus: transient reaction (e.g. reabsorption of haematomas)

Icterus

Bilirubin Metabolism

1. Cleavage of the heme ring by a microsomal heme oxygenase
2. Reduction of biliverdin to bilirubin

- Only endogenous source of CO
**BILIRUBIN METABOLISM**

**High lipid solubility of bilirubin**
- Soluble in the lipid bilayers of cell membranes - toxic effect
- Transported in the blood by serum proteins

**Conjugation to a water-soluble substance**
- Decreases its lipid solubility
- Eases its excretion
  Executed in liver microsomes by attachment of 2 molecules of glucuronic acid in 2 steps: substrate is bilirubin (or bilirubin monoglucuronide)

Van Der Bergh reaction
  Coupling of bilirubin with a diazonium salt to form a colored complex. *Water soluble forms react directly,* to measure water insoluble form bound to albumin, alcohol is added to release it into solution, i.e. react indirectly

<table>
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<tr>
<th>Unconjugated bilirubin</th>
<th>Indirect (Bi-Albumin, Bi-prealbumin)</th>
</tr>
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<tbody>
<tr>
<td>Conjugated bilirubin</td>
<td>Direct (Bi-monoglucuronide, Bi-diglucuronide)</td>
</tr>
</tbody>
</table>

**BILIRUBIN & BILE ACIDS**

**Urine bile pigments**
- Urobilinogen
  - 1-4 mg (2.7 µmol) water soluble - source: enterohepatic circulation
  - Hemolytic anaemia, hepatocellular disease
  - Hepatobiliary obstruction

**Conjugated bilirubin**
- Normally only traces
  - Hepatocellular disease, Bile obstruction

**HPQL Bi fractions in plasma (at 450 nm)**
- Alpha fraction: > 90% indirect (u Bi) (water soluble, albumin-bound), < 10% direct
- Beta fraction: Bi-monoglucuronide
- Gamma fraction: Bi-diglucuronide
- Delta fraction: direct Bi + indirect Bi

**Bile salts** - cholate, taurocholate

**ICTERUS AND HYPERBILIRUBINEMIA**

- **Prehepatic (haemolytic)**
  - Increased bilirubin production

- **Hepatic (hepatocellular)**
  - Decreased uptake into the liver cells
  - Impaired conjugation
  - Impaired secretion of conjugated bilirubin

- **Posthepatic (obstructive)**
  - Increased bilirubin production
  - Decreased conjugation
  - Impaired secretion

- **Specific syndromes**
  - (Gilbert, Crigler-Najjar, Dubin-Johnson,Rotor)
  - Acute and chronic liver damage
  - Drug side effects

- **Estrogens, cystic fibrosis, etc.**

- **Blood**
  - Hemolysis etc.
  - Bilirubin

- **Jaundice**
  - Prehepatic
  - Intrahepatic
  - Posthepatic

- **Liver**
  - Conjugated bilirubin
  - Cholestasis
  - Outflow

- **Gall stones, tumors, etc.**
  - Extrahepatic outflow
CAUSES OF ICTERUS

Prehepatic (haemolytic)
- Unconjugated bilirubin

Hepatic (hepatocellular)
- Unconjugated bilirubin
- Conjugated bilirubin

Premicrosomal
- Unconjugated bilirubin

Microsomal
- Unconjugated bilirubin

Postmicrosomal
- Conjugated bilirubin

Prehepatic (haemolytic)
- Conjugated bilirubin

1 - PREHEPATIC ICTERUS

PREHEPATIC ICTERUS - PRINCIPLES

- Bi production exceeds liver’s capacity to conjugate
  - Unconjugated Bi
  - Conjugated Bi
- AST, ALT normal
- γGT normal or
- Stool: dark
- Urine: O urobilines, dark orange
- Anaemia: Ery, Hb, Ret

PREHEPATIC ICTERUS - CAUSES

- Reabsorption of hemathoma, hyperthermia, burns
- Immature erythrocytes
- Haemathological disorders (haemolytic anaemia), e.g.
  - β- thalasemia
  - spherocytosis
  - sicle cell anaemia
  - malaria (plasmodium)
- Erythroblastosis fetalis (neonatal icterus)
HEPATOCELLULAR ICTERUS

(a) Bi conjugation is insufficient (b) outflow of bile is blocked within liver
Not uniform laboratory data!
- Unconjugated Bi
- or normal Conjugated Bi
- AST: ALT (> 400 U/l) intrahep. stasis
- γGT
- ALP < 300 U/l
- Stool: light (obstruction)
- Urine: Ū urobilines, Ū c -Bi ß dark yellow

HEPATIC ICTERUS

- Premicrosomal
  Meulengracht-Gilberts' disease inability of the hepatocytes to take up bilirubin from the blood.
  Ū Unconjugated Bi
- NÚ Conjugated Bi
- Lucey-Driscoll sy. (steroid icterus)
- Prolonged neonatal icterus

- Microsomal
  Crigler-Najjar syndrome type I, II conjugation is impaired
  Ū Unconjugated Bi
- Ū Ú Conjugated Bi

HEPATOCELLULAR ICTERUS

Hepatocellular diseases
Viral infections: Hepatitis A, B, C, Epstein-Barr infection, cytomegalovirus, Coxakie
Drugs: amoxicillin, tetracyclines, cytotoxins, isoniazid, procetamol, phenylbutasone, anaesthetic- halothan
Toxins: alcohol, phosphorus, carbon tetrachloride, trichlorethylene, mycotoxins, aflatoxins, toadstool poisoning
Hypoxia: hypotension, shock, hepatic artery thrombosis

Hyperbilirubinaemia + subicterus
- Ū Unconjugated Bi
- Drugs: steroids, phenotiazines, sulphonamides, rifampicin anticonceptives, probenecid

Starvation (24-48 h), congestive heart failure, pulmonary embolism,
HEPATIC ICTERUS

- Postmicrosomal
  Dubin-Johnson-Rotor syndrome
  inability of the hepatocytes to export bilirubin to bile ducts
  ○ Conjugated Bi
  □ Unconjugated Bi

- Intrahepatic cholestasis
  conjugation is impaired
  ○ Unconjugated Bi
  ○ Conjugated Bi

3 - OBSTRUCTIVE ICTERUS
(Hepatobiliary)

OBSTRUCTIVE ICTERUS

- bile outflow into GUT is obstructed
  ○ Unconjugated Bi (sec.)
  ○ ○ Conjugated Bi
  - AST, ALT ○ < 400 U/l
  - γGT ○
  - ALP ○ (300 U/l early indicator of cholestasis)
- Stool: very light (acholic), steatorrhea
- Urine: U urobilines, ○ cBi
- Icterus intensive: ○ Bi > 300 µmol/l
- Pruritus

Causes:
- Intrahepatic - predominantly obstructive (acute) Hepatitis A,C, Ascending cholangitis (chronic) Primary biliary cirrhosis, Sclerosing cholangitis, chronic hepatitis, Weil dis., cholangiocarcinoma
- Intrahepatic obstructive with little damage
  Recidiving cholestasis in pregnancy, Benign idiopathic cholestasis
  Post-operative reflex cholestasis, Steroid, Infections - brucelosis, thyphus
  Budd- Chiari sy., Parasites (amebiasis, bilhariosis), Tumors

Extrahepatic
  bile stones, strictures,carcinomas, pancreatitis, biliary atresia
Consequences of cholestasis