Liver Cirrhosis

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Liver cirrhosis

- Chronic progressive liver disease characterized histologically by:
  - Necroinflammatory reaction
  - Fibrosis
  - Loss of the lobular and vascular architecture of liver lobules
  - Regenerating nodules with disturbed architecture (non-functioning).
Causes of liver cirrhosis

- Viral hepatitis: B and C
- Alcohol
- Biliary diseases: primary or secondary
- Autoimmune hepatitis
- Vascular causes: CHF, Budd-Chiari syndrome (thrombosis in the hepatic vein → congestion and cirrhosis), Veno-occlusive disease
- Drugs and toxins (mainly those used in chemotherapy and immuno-suppression)
- Hereditary and metabolic: hemochromatosis (disturbance in iron metabolism), Wilson’s disease (disturbance in copper metabolism), α1-antitrypsin deficiency
- Non alcoholic liver disease (NASH) (*)
- Cryptogenic liver cirrhosis (no cause is identified)

Non alcoholic Steatohepatitis (NASH)

- Recently, it started to be considered as the most common cause for the Cryptogenic liver cirrhosis.
- In NASH, there is lipid deposition inside the hepatocytes.
- **Causes**: (metabolic syndrome)
  1- Central obesity (el karsh!!)
  2- Uncontrolled diabetes
  3- Hypertriglyceridemia
- >> Those pts may progress to liver cirrhosis, liver failure and HCC.
Pathogenesis of the features of liver cirrhosis

- Features of liver cirrhosis are due to:
  - Portal hypertension
  - Liver cell dysfunction

Portal circulation

* The esophagus is one place where the systemic and the portal circulation connect, as the upper 2/3 is drained to the systemic circulation, and the lower 1/3 is drained to the portal circulation (left gastric vein)

>> Obstruction → enlargement and congestion of the spleen → splenomegaly and hypersplenism
Measurement of Portal pressure

HVPG = WHVP - FHVP

Portal hypertension

- Elevation of portal vein pressure to more than 10 mmHg due to anatomic or functional obstruction to blood flow in the portal venous system
- **Classified** into:
  - Presinusoidal: portal vein thrombosis *(can cause pure portal HTN)*
  - Sinusoidal: cirrhosis
  - Postsinusoidal: Budd chiari syndrome, veno-occlusive disease
- **Consequences:**
  - Esophageal varices
  - Splenomegaly and hypersplenism *(→ anemia, leukopenia and thrombocytopenia)*
  - Ascites
  - Hepatic encephalopathy

>> Those 2 don’t develop in pure portal HTN, there must be a degree of liver dysfunction (need combined defect)
Liver cell failure manifestations

- Fatigue
- Low grade fever
- Fetor hepaticus
- Loss of muscle mass and subcutaneous fat *(thin face caused by the loss of the cheeks’ fat pads)*
- Jaundice
- Coagulopathy *(bleeding tendency)*
- Low albumin *(causes LL edema, ascites)*
- Cardiovascular changes:
  - Hyperdynamic state due to A-V shunts and vasodilators *(that lead to palmar erythema and warm hands)*
  - Cardiac dysfunction

Liver cell failure manifestations

- Skin changes: palmar erythema, spider nevi, leuconychia *(white nails)*
- Endocrine changes:
  - In males: infertility, feminization, decreased potency, testicular atrophy, decreased libido
  - In females: infertility, amenorrhea
- Metabolic changes: impaired glucose tolerance, hypoglycemia
- Bone changes: Osteoporosis
- Pulmonary changes: infections, effusion, pulmonary hypertension, impaired CO diffusion, cyanosis
- Ascites
- Hepatic encephalopathy
- **Note**: clubbing is rare in liver cirrhosis, only 2 types can lead to clubbing: primary biliary cirrhosis and hemochromatosis
Investigations in liver cirrhosis

- **Biopsy** is the gold standard for diagnosis
- **Lab abnormalities:**
  - Mild to moderate rise in AST and ALT
  - Bilirubin and alkaline phosphatase may be mildly elevated
  - Low albumin
  - Prolonged PT
- **Non invasive measures** to evaluate for cirrhosis:
  - Laboratory tests: APRI, Fibrotest
  - Fibroscan: to assess the stiffness of liver tissue by special instrument.
- Investigations to find the cause for cirrhosis

Clinical picture

- Compensated cirrhosis
- Decompensated cirrhosis
- Cirrhotic patients may develop hepatocellular carcinoma (HCC)
Compensated liver cirrhosis

- Usually asymptomatic
- Fatigue is the commonest symptom
- Signs of chronic liver disease may be present: spider nevi, palmar erythema, nail changes, gynecomastia, testicular atrophy, hepatosplenomegaly
Decompensated cirrhosis

- Jaundice: Bilirubin above 3 mg/dl
- Bleeding esophageal varices
- Ascites
- Hepatic encephalopathy

Esophageal varices

- Due to portal hypertension resulting in increased collateral circulation between high pressure portal venous system and the low pressure systemic venous system.
- Present in lower esophagus, occasionally in gastric fundus.
- May rupture and lead to severe recurrent bleeding which is frequently fatal

>> the bleeding can be massive and lead to death, but sometimes it may stop spontaneously, but with high chance of recurrence!!
Early varices

>> Bluish structures at the lower esophagus

Moderate varices
Advanced esophageal varices

They can occlude the lumen of the esophagus, and they are prone to rupture at any time

Treatment of esophageal varices

- Resuscitation and blood transfusion as needed
- Use of somatostatin, octreotide or glypressin (to decrease the portal blood flow)
- Variceal band ligation (VBL)
- Sclerotherapy
- Drugs to lower portal pressure: B-blockers, nitrates, carvidolol
- TIPS (a shunt between the portal and systemic circulations inside the liver, to decrease the portal pressure)
- Surgical shunt operations

>> In the shunting, the incidence of hepatic encephalopathy increases, as more toxins are being shunted to the systemic circulation through these shunts
Transjugular Intrahepatic Portosystemic shunts (TIPS)
Ascites

• In cirrhosis, ascites results from 2 main pathogenic mechanisms:
  – sinusoidal hypertension
  – sodium retention (secondary to systemic and splanchnic vasodilatation)

• Other causes:
  – Hypoalbuminemia
  – Lymphatic exudation
  – Cardiac dysfunction
  – Peritoneal infection or malignancy
  – Nephrotic syndrome
Stages of ascites

– Preascites stage.
– Diuretic responsive ascites
– Refractory ascites (requiring multiple paracentesis)
– Ascites with Hyponatremia
– Hepatorenal syndrome

Treatment of ascites

• Sodium restriction and bed rest
• Spironolactone
• Loop diuretics

• Albumin infusion
• Large volume paracentesis
• TIPS
• Peritoneovenous shunts
• Liver transplantation
Pathogenesis and treatment of ascites

Dilational hyponatremia, mainly attributable to impaired free water excretion through the nonosmotic release of vasopressin
- occurs in patients with cirrhosis and ascites
- it is usually asymptomatic because it develops slowly.
- May lead to hepatic encephalopathy, increased mortality pre and post transplantation
- Treatment:
  - Fluid restriction to less than 1L/day
  - Plasma expansion with IV Albumin infusion (do NOT give saline)
  - Vasopressin receptor antagonists

Hyponatremia

*Furosemide should only be used in conjunction with spirolactone.
Hepatorenal syndrome (HRS)

- Development of renal failure in patients with refractory ascites
- Due to decreased renal perfusion
- Kidneys are histologically normal
- **2 Types:**
  - **Type 1:** Rising serum creatinine to more than 2.5 mg/dl within 2 weeks
  - **Type 2:** Slowly rising creatinine: more than 1.5 in more than 2 weeks
- Sodium in urine less than 10 mmol/L.
- Ascites and hyponatremia usually present
- Carries very poor prognosis:
  - Mortality in type 1: 50% in 1 month
  - Mortality within 6 months in type 2

Pathophysiology of the HRS
Treatment of HRS

>> Make sure that it is HRS, not RF caused by the drugs or hypovolemia.

- Discontinue diuretics and expand the intravascular volume with IV albumin.
- Factors known to precipitate renal failure in cirrhosis (infection, fluid or blood loss, hypotension) need to be investigated, and if present, should be treated.
- Vasoconstrictors and albumin infusion may be helpful
- Transplantation is the only definitive therapy

Spontaneous Bacterial Peritonitis (SBP)

- SBP is the most common bacterial infection in hospitalized cirrhotic patients, and it leads to a deterioration of the pt’s condition.
- Bacterial invasion through translocation from intestine
- Usually monomicrobial
- Should be suspected if:
  - Fever, abdominal pain, tenderness, leucocytosis
  - Unexplained encephalopathy, jaundice or worsening renal
- Diagnosis of SBP should be established with an ascites polymorphonuclear cell count > 250 cells/mm3
- **Treatment**
  - should be initiated before obtaining bacteriological culture results.
  - The third-generation cephalosporins (cefotaxime, ceftriaxone) are the agents of choice
  - Daily norfloxacin, ciprofloxacin or DS Co-trimoxazole are effective in preventing SBP recurrence
Hepatic encephalopathy (HE)

- Neuropsychiatric syndrome in patients with advanced liver disease.
- Due to the toxic effect of substances normally metabolized by the liver on the brain, mainly ammonia.
- **Features:**
  - Deterioration in level of consciousness
  - Behavioral and psychiatric changes
  - Lack of concentration
  - Sleep disturbances
  - Flapping tremors *(before losing consciousness)*

The pathogenesis of HE

- Ammonia is released by the action of the colonic bacteria on the dietary proteins, and then absorbed to the portal circulation.
- When the liver is functioning properly, it will take the ammonia and will transfer it to urea, which is easily excreted by the kidneys.
- In liver cirrhosis, the hepatocytes are damaged and cannot deal with ammonia, and because of the collaterals and the blood shunting *(that is caused by the portal HTN)* it will reach the systemic circulation, and the pt will get HE because of the action of the ammonia on the brain.
Classification of HE

- **Type A**: associated with **Acute liver failure**.
- **Type B**: associated with (Bypass) portosystemic shunts without cirrhosis
- **Type C**: caused by **Cirrhosis**:
  - Minimal, subclinical HE
  - Persistent HE
  - Episodic, recurrent HE

Precipitating factors for hepatic encephalopathy
### Treatment of HE

- Identify and treat underlying cause.
- **Lactulose** therapy: (v. imp.)
  - Give sufficient dose to have 2-3 loose motions/day
  - Mechanism of action:
    - Osmotic laxative
    - Stimulant laxative in colon
    - Lowers pH of colon leading to
      - Suppression of ammonia producing bacteria
      - Decrease in the absorption of ammonia
      - Encouragement of growth of lactobacillus species
- **Antibiotics** (non-absorbable, that acts locally on the colonic bacteria): Neomycin, metronidazole, rifaximin
- Drugs that metabolize ammonia:
  - To hippuric acid: sodium benzoate
  - To glutamine: L-aspartate, L-ornithine (LOLA)
- Extracorporeal albumin dialysis.
- Liver Transplantation is the definitive treatment

### Screening for Hepatocellular carcinoma (HCC)

- Cirrhotic patients are at increased risk for HCC especially:
  - Hepatitis B and C
  - Alcoholic cirrhosis
  - Genetic hemochromatosis
  - Primary biliary cirrhosis
- Screening is by:
  - serum alpha-fetoprotein (AFP) testing
  - ultrasonography
- Screening to be done at intervals of 6 or 12 months.
Liver transplantation

- The development of decompensation (ascites, variceal hemorrhage, HE) in patients with cirrhosis is associated with a median survival of only 1.5 years, so liver transplantation should be considered in these patients.
- In order to assess the priority of patients for liver transplantation from cadavers, 2 scoring systems are present:
  - The Child, Tuctotte, Plough (CTP) score is based on 5 parameters:
    - Encephalopathy
    - Ascites
    - Bilirubin
    - Albumin
    - Prothrombin time.
  - The MELD score: Depends on 3 objective variables: creatinine, prothrombin time international normalized ratio, and bilirubin.
- Transplantation from a Living donor: The Right lobe of liver from the donor transplanted in the patient.