Lec 3
Liver Diseases (1)

- Hepatic Injury patterns
- Mechanisms of Injury and Repair
- Injured hepatocytes may show several potentially reversible changes, such as
- accumulation of fat (steatosis) and bilirubin (cholestasis); when injury is not
- reversible, hepatocytes die by necrosis or apoptosis. Necrosis is commonly seen
- following hepatic injury caused by hypoxia and ischemia. Apoptotic cell death
- predominates in viral, autoimmune, and drug- and toxin induced hepatitides.

Widespread death of hepatocytes may produce confluent necrosis. With

increasing severity, necrosis “bridges” central veins and portal tracts.

Regeneration to replace lost hepatocytes takes place primarily by mitotic

replication of hepatocytes adjacent to those that have died. Scar formation may

follow severe acute injury but occurs more often as a reaction to chronic injury.

Inflammation and immunologic reactions are involved in many forms of liver

disease. Systemic inflammation alters the metabolic and biosynthetic activities

of the liver, leading to increased secretion of acute-phase reactants such as

C-reactive protein, serum amyloid A protein (a precursor of some forms of

amyloid), and hepcidin, a key regulator of iron metabolism .

Liver Failure

Though the liver has a marked regenerative capacity and a large functional

reserve, hepatic failure may develop from severe acute and fulminant liver

injury with massive necrosis of liver cells (acute hepatic failure), or from

advanced chronic liver disease (chronic hepatic failure).

ETIOLOGY Acute and chronic hepatic failure result from different causes:

Acute (fulminant) hepatic failure occurs most frequently in acute viral hepatitis.

Other causes are hepatotoxic drug reactions (e.g. anaesthetic agents,

nonsteroidal anti-inflammatory drugs, anti-depressants), acute alcoholic

hepatitis, mushroom poisoning and pregnancy complicated with eclampsia.

Chronic hepatic failure is most often due to cirrhosis. Other causes include

chronic active hepatitis, chronic cholestasis (cholestatic jaundice) and Wilson's

disease.

MANIFESTATIONS In view of the diverse functions performed by the liver, the syndrome of acute or chronic hepatic failure produces complex manifestations.

1. Jaundice

2. Hepatic encephalopathy (Hepatic coma) , with symptoms ranging from subtle behavioral abnormalities to confusion, stupor, coma, and death. Hepatic encephalopathy is believed to be caused by elevated ammonia levels, which correlate with impaired neuronal function and cerebral edema

3. Hyperkinetic circulation

4. Hepatorenal syndrome, is a form of renal failure occurring in individuals with acute or chronic liver failure in whom there is no intrinsic renal pathology to account for renal dysfunction. Liver failure results in the production of vasodilators such as nitric oxide that increase blood flow in the abdominal viscera with consequent decreased renal perfusion pressure and reduced glomerular filtration rate. The syndrome's onset begins with a decrease in urine output and rising blood urea nitrogen and creatinine levels (azotemia).

5. Hepatopulmonary syndrome

6. Coagulation defects , The liver produces a number of coagulation factors whose levels decline in liver failure, leading to easy bruising and bleeding

7. Ascites and oedema 8. Endocrine changes 9. Skin changes

CIRRHOSIS

Cirrhosis of the liver is one of the ten leading causes of death in the Western

world. It represents the irreversible end-stage of several diffuse diseases

causing hepatocellular injury and is characterised by the following 4 features:

1. It involves the entire liver.

2. The normal lobular architecture of hepatic parenchyma is disorganised.

3. There is formation of nodules separated from one another by irregular bands

of fibrosis.

4. It occurs following hepatocellular necrosis of varying etiology so that there

are alternate areas of necrosis and regenerative nodules.

PATHOGENESIS

Irrespective of the etiology, cirrhosis involves a combination of a few processes:

FIBROGENESIS Continued destruction of hepatocytes causes collapse of normal

lobular hepatic parenchyma followed by fibrosis around necrotic liver cells.

REGENERATIVE NODULES The surviving hepatocytes act as stimulants for growth and proliferation of more hepatocytes under influence of growth factors. This compensatory proliferation of hepatocytes is restricted within fibrous nodules forming regenerative nodules.

VASCULAR REORGANISATION Due to damaged hepatic parenchyma and formation of fibrous nodules, the new vessels formed in the fibrous septa are connected to the vessels in the portal triad (i.e. branches of hepatic artery and portal vein) and then the blood is drained into hepatic vein. This way, the blood bypasses the hepatic parenchyma.

Clinical Features. About 40% of individuals with cirrhosis are asymptomatic until

the most advanced stages of the disease. Even at late stages, they present with

nonspecific clinical manifestations, such as anorexia, weight loss, weakness, and

eventually signs and symptoms of liver failure discussed earlier. Jaundice,

encephalopathy, and coagulopathy may result from chronic liver disease, much

the same as in acute liver failure. However, there are some significant additional

features:

1. Chronic severe jaundice can lead to pruritus (itching) . Pruritus is also seen in other disorders associated with cholestasis, suggesting that it is related to the accumulation of bile salts in the body; its precise pathogenesis is unknown.
2.Portal hypertension is more frequent and manifests in more complex ways in chronic liver failure than in acute liver failure . It stems from increased vascular resistance coupled with increased portal blood flow.
3. Portosystemic shunts develop due to sustained portal hypertension. These shunts are produced principally by dilation of collateral vessels.
4. Ascites is the accumulation of fluid in the peritoneal cavity. About 85% of cases of ascites are caused by portal hypertension due to cirrhosis. The fluid is a transudate .
5. Long-standing portal hypertension may cause congestive splenomegaly.
6. Hyperestrogenemia due to impaired estrogen metabolism in male patients with chronic liver failure can give rise to palmar erythema (a reflection of local vasodilatation) and spider angiomas of the skin. Such male hyperestrogenemia also leads to hypogonadism and gynecomastia.
7. Most chronic liver diseases predispose to development of hepatocellular carcinoma .

JAUNDICE

Jaundice or icterus refers to the yellow pigmentation of the skin or sclerae bybilirubin. Bilirubin pigment has high affinity for elastic tissue and hence jaundice

is particularly noticeable in tissues rich in elastin content. Jaundice is the result of elevated levels of bilirubin in the blood termed hyperbilirubinaemia. Normal serum bilirubin concentration ranges from 0.3-1.3 mg/dl, about 80% of which is unconjugated. Jaundice becomes clinically evident when the total serum bilirubin exceeds 2 mg/dl. A rise of serum bilirubin between the normal and 2 mg/dl is generally not accompanied by visible jaundice and is called latent jaundice.

CLASSIFICATION AND FEATURES OF JAUNDICE Based on pathophysiology, jaundice may result from one or more of the following mechanisms:

1. Increased bilirubin production : Hemolytic anemias , Resorption of blood from internal hemorrhage (e.g., alimentary tract bleeding, hematomas) , Ineffective erythropoiesis (e.g., pernicious anemia, thalassemia)
2. Decreased hepatic uptake : Drug interference with membrane carrier systems
3. Decreased hepatic conjugation : Physiologic jaundice of the newborn Diffuse hepatocellular disease (e.g., viral or drug-induced hepatitis, cirrhosis)
4. Decreased excretion of bilirubin into bile : Drug-induced canalicular membrane dysfunction (e.g., oral contraceptives, cyclosporine) , Hepatocellular damage or toxicity (e.g., viral or drug-induced hepatitis) .

Inflammatory destruction of intrahepatic bile ducts (e.g., primary biliary cirrhosis, primary sclerosing cholangitis) , Gallstones , External compression (e.g., carcinoma of the panceas)

Accordingly, a simple age-old classification of jaundice was to divide it into three predominant types: pre-hepatic (haemolytic), hepatic, and post-hepatic cholestatic. However, hyperbilirubinaemia due to first three mechanisms is mainly unconjugated while the last variety yields mainly conjugated hyperbilirubinaemia. Hence, currently pathophysiologic classification of jaundice is based on predominance of the type of hyperbilirubinaemia. The presence of bilirubin in the urine is evidence of conjugated hyperbilirubinaemia

NEONATAL JAUNDICE

Jaundice appears in neonates when the total serum bilirubin is more than

3 mg/dl. It may be the result of unconjugated or conjugated

hyperbilirubinaemia; the former being more common. Important causes of

neonatal jaundice are listed below:

A. UNCONJUGATED HYPERBILIRUBINAEMIA

1. Physiologic and prematurity jaundice : Because the hepatic machinery for conjugating and excreting bilirubin does not fully mature until about 2 weeks of age, almost every newborn develops transient, mild unconjugated hyperbilirubinemia, termed neonatal jaundice or physiologic jaundice of the

newborn. This may be exacerbated by breastfeeding due to the action of bilirubin deconjugating enzymes in breast milk. Phototherapy with blue light (which converts bilirubin to a soluble isomer that is readily excreted in the

urine) is sufficient to keep the levels of bilirubin within a safe range until the

hepatic processes for conjugation mature sufficiently.

2. Haemolytic disease of the newborn and kernicterus
3. Congenital haemolytic disorders
4. Perinatal complications (e.g. haemorrhage, sepsis)
5. Gilbert’s syndrome

B. CONJUGATED HYPERBILIRUBINAEMIA

1. Hereditary
2. Infections (e.g. hepatitis B, hepatitis C , rubella, herpes simplex, syphilis,

toxoplasma, gram-negative sepsis)

3. Metabolic (e.g. alpha-1-antitrypsin deficiency, cystic fibrosis,)
4. Idiopathic (neonatal hepatitis, congenital hepatic fibrosis)
5. Biliary atresia (intrahepatic and extrahepatic)
6. Reye’s syndrome