# Liver diseases (2)
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HYPERBILIRUBINAEMIA (CHOLESTASIS) This form of hyperbilirubinaemia is defined as failure of normal amounts of bile to reach the duodenum. Morphologically, cholestasis means accumulation of bile in liver cells and biliary passages. The defect in excretion may be within the biliary canaliculi of the hepatocyte and in the microscopic bile ducts (intrahepatic cholestasis or medical jaundice), or there may be mechanical Obstruction to the extrahepatic biliary excretory apparatus (extrahepatic cholestasis or obstructive jaundice).

1. INTRAHEPATIC CHOLESTASIS Intrahepatic cholestasis is due to impaired hepatic excretion of bile and may occur from hereditary or acquired disorders.

i) Hereditary disorders producing intrahepatic obstruction to biliary excretion are characterised by ‘pure cholestasis’.

ii) Acquired disorders with intrahepatic excretory defect of bilirubin are largely due to hepatocellular diseases and hence are termed ‘hepatocellular cholestasis’ e.g. in viral hepatitis, alcoholic hepatitis, and drug-induced cholestasis such as from administration of oral contraceptives. The features of intrahepatic cholestasis include: predominant conjugated hyperbilirubinaemia due to regurgitation of conjugated bilirubin into blood, bilirubinuria, elevated levels of serum bile acids and consequent pruritus, elevated serum alkaline phosphatase and hyperlipidaemia . ‘Pure cholestasis’ can be distinguished from ‘hepatocellular cholestasis’ by elevated serum levels of transaminases in the latter due to liver cell injury.

2. EXTRAHEPATIC CHOLESTASIS Extrahepatic cholestasis results from mechanical obstruction to large bile ducts outside the liver or within the porta hepatis. The common causes are gallstones, inflammatory strictures, carcinoma head of pancreas, tumours of bile duct, sclerosing cholangitis and congenital atresia of extrahepatic ducts. The features of extrahepatic cholestasis (obstructive jaundice), like in intrahepatic cholestasis, are: predominant conjugated hyperbilirubinaemia, bilirubinuria, elevated serum bile acids causing intense pruritus, high serum alkaline phosphatase and hyperlipidaemia. However, there are certain features which help to distinguish extrahepatic from intrahepatic cholestasis. In obstructive jaundice, there is malabsorption of fat-soluble vitamins (A,D,E and K) and steatorrhoea resulting in vitamin K deficiency. Prolonged Prothrombin time in such cases shows improvement following parenteral administration of vitamin K.

VIRAL HEPATITIS The term viral hepatitis is used to describe infection of the liver caused by hepatotropic viruses. Currently there are 5 main varieties of these viruses causing distinct types of viral hepatitis:

1. Hepatitis A virus (HAV), causing a faecally-spread self-limiting disease.
2. Hepatitis B virus (HBV), causing a parenterally transmitted disease that may become chronic.
3. Hepatitis C virus (HCV), previously termed non-A, non-B (NANB) hepatitis virus involved chiefly in transfusion-related hepatitis.
4. Hepatitis delta virus (HDV) which is sometimes associated as superinfection with hepatitis B infection.
5. Hepatitis E virus (HEV), causing water-borne infection.

While HBV is a DNA virus, all other human hepatitis viruses are RNA viruses.

CLINICOPATHOLOGIC SPECTRUM Among the various etiologic types of hepatitis, evidence linking HBV and HCV infection with the spectrum of clinicopathologic changes is stronger than with other hepatotropic viruses. The typical pathologic changes of hepatitis by major hepatotropic viruses are virtually similar. HAV and HEV, however, do not have a carrier stage nor cause chronic hepatitis. The various clinical patterns and pathologic consequences of different hepatotropic viruses can be considered under the following headings:

i) Carrier state

ii) Asymptomatic infection

iii) Acute hepatitis: The most common consequence of all hepatotropic viruses is acute inflammatory involvement of the entire liver. In general, type A, B, C, D and E run similar clinical course and show identical pathologic findings. Clinically, acute hepatitis is categorised into 4 phases:

incubation period, pre icteric phase, icteric phase and post-icteric phase.

1. Incubation period It varies among different hepatotropic viruses: for hepatitis A it is about 4 weeks (15-45 days); for hepatitis B the average is 10 weeks (30-180 days); for hepatitis D about 6 weeks (30-50 days); for hepatitis C the

mean incubation period is about 7 weeks (20-90 days) , and for hepatitis E it is 2-8 weeks (15-60 days).

2. Pre-icteric phase This phase is marked by prodromal Constitutional symptoms that include anorexia, nausea, vomiting, fatigue, malaise, distaste for smoking, arthralgia and headache. There may be low-grade fever preceding the onset of jaundice, especially in hepatitis A.

3. Icteric phase The prodromal period is heralded by the onset of clinical jaundice and the constitutional symptoms diminish. Other features include dark-coloured urine due to bilirubinuria, clay-coloured stools due to cholestasis, pruritus as a result of elevated serum bile acids, loss of weight and abdominal discomfort due to enlarged, tender liver.

4. Post-icteric phase The icteric phase lasting for about 1 to 4 weeks is usually followed by clinical and biochemical recovery in 2 to 12 weeks. Up to 1% cases of acute hepatitis may develop severe form of the disease (fulminant hepatitis); and 5-10% of cases progress on to chronic hepatitis

iv) Chronic hepatitis: Chronic hepatitis is defined as continuing or relapsing hepatic disease for more than 6 months with symptoms along with biochemical, serologic and histopathologic evidence of inflammation and necrosis. Majority of cases of chronic hepatitis are the result of infection with hepatotropic viruses—hepatitis B, hepatitis C and combined hepatitis B and hepatitis D infection.

However, some non-viral causes of chronic hepatitis include: Wilson's disease, a-1-antitrypsin deficiency, chronic alcoholism, drug-induced injury and autoimmune diseases.

v) Fulminant hepatitis (Submassive to massive necrosis) In addition, progression to cirrhosis and association with hepatocellular carcinoma are known to occur in certain types of hepatitis.

CHOLELITHIASIS (GALLSTONES) Gallstones are formed from constituents of the bile ( cholesterol, bile pigments and calcium salts) along with other organic components. Accordingly, the gallstones commonly contain cholesterol, bile pigment and calcium salts in varying proportions. They are usually formed in the gallbladder, but sometimes may develop within extrahepatic biliary passages, and rarely in the larger intrahepatic bile duct.

RISK FACTORS These factors which largely pertain to cholesterol stones can be summed up in the old saying that gallstones are common in 4F's acronym for—'fat, female, fertile (multipara) and forty'. Some of the risk factors in lithogenesis are as under:

1. Genetic factors .
2. Age , There is steady increase in the prevalence of gallstones with advancing age which may be related to increased cholesterol content in the bile.
3. Sex , Gallstones are twice more frequent in women than in men.
4. Drugs , Women on oestrogen therapy or on birth control pills have higher incidence of gallstones.
5. Obesity , Obesity is associated with increased cholesterol Synthesis and its excretion .
6. Gastrointestinal diseases Certain gastrointestinal disorders such as Crohn's disease, ileal bypass surgery , etc. are associated with interruption in enterohepatic circulation followed by gallstone formation.
7. Factors in pigment gallstones all the above factors apply largely to cholesterol stones. Pigment stones, whether pure or mixed type, are more frequently associated with haemolytic anaemias which lead to increased content of unconjugated bilirubin in the bile

TYPES OF GALLSTONES As stated before, gallstones contain cholesterol, bile pigment and calcium carbonate, either in pure form or in various combinations. Accordingly, gallstones are of 3 major types—pure gallstones, mixed gallstones and combined gallstones. Mixed gallstones are the most common (80%) while pure and combined gallstones comprise 10% each. In general, gallstones are formed most frequently in the gallbladder but may occur in extrahepatic as well as

intrahepatic biliary passages. Presence of calcium salts renders gallstones radio opaque, while cholesterol stones appear as radiolucent filling defects in the gallbladder.

1. PURE GALLSTONES They constitute about 10% of all gallstones. They are further divided into 3 types according to the component of bile forming them. a) Pure cholesterol gallstones  b)Pure calcium carbonate gallstones . c) Pure pigment gallstones 2. MIXED GALLSTONES Mixed gallstones are the most common (80%) and contain more than 50% cholesterol monohydarate plus an admixture of calcium salts, bile pigments and fatty acids. They are always multiple .

3. COMBINED GALLSTONES They comprise about 10% of all gallstones. Combined gallstones are usually solitary, large and smooth surfaced. It has a pure gallstone nucleus (cholesterol, bile pigment or calcium carbonate) and outer shell of mixed gallstone; or a mixed gallstone nucleus with pure gallstone shell.

CLINICAL MANIFESTATIONS AND COMPLICATIONS In about 50% cases, gallstones cause no symptoms and may be diagnosed by chance during investigations for some other condition (silent gallstones). Symptomatic gallstone disease appears only when complications develop:

1. Cholecystitis
2. Biliary fistula
3. Gallstone ileus
4. Pancreatitis
5. Gallbladder cancer