***L2 Liver pathology أ د محمد القرطاس***

***( Cont... ) Pathophysilogy of alcohol hepatitis :-***

1- increase in lipid formation by increase in lipo-protie degredation

2- free radical

3- affecting mitochondia

4- immunological attack of hepatocytes

5- acetaldyhde activted lipid peroxidase & cytosk. disruption

***Circulatory effect of cirrhosis***

***Portal hypertension***

Increased resistance to portal blood flow may develop from prehepatic, intrahepatic, and posthepatic causes . *The dominant intrahepatic cause is cirrhosis, accounting for most cases of portal hypertension.* Far less frequent are schistosomiasis, massive fatty change, diffuse granulomatous diseases such as sarcoidosis and miliary tuberculosis, and diseases affecting the portal microcirculation, exemplified by nodular regenerative hyperplasia

Portal hypertension in cirrhosis results from increased resistance to portal flow at the level of the sinusoids and compression of central veins by perivenular fibrosis and expanded parenchymal nodules. Anastomoses between the arterial and portal systems in the fibrous bands also contribute to portal hypertension by imposing arterial pressure on the normally low-pressure portal venous system. The four major clinical consequences are (1) ascites, (2) the formation of portosystemic venous shunts, (3) congestive splenomegaly, and (4) hepatic encephalopathy

**Ascites :-**

Ascites refers to the collection of excess fluid in the peritoneal cavity. It usually becomes clinically detectable when at least 500 mL have accumulated, but many liters may collect and cause massive abdominal distention. It is generally a serous fluid having as much as 3 gm/dL of protein (largely albumin) as well as the same concentrations of solutes such as [glucose](mk:@MSITStore:E:\Pathology%20books\Robbins%20Basic%20Pathology%208th%20edition.CHM::/www.studentconsult.com/content/bookcontent.cfm@id=hc016003.htm), sodium, and potassium as in the blood. The fluid may contain a scant number of mesothelial cells and mononuclear leukocytes. Influx of neutrophils suggests secondary infection, whereas red cells point to possible disseminated intra-abdominal cancer. With long-standing ascites, seepage of peritoneal fluid through transdiaphragmatic lymphatics may produce hydrothorax, more often on the right side.

**Pathogenesis of Ascitis :-**

*Sinusoidal hypertension,* alters Starling forces and drives fluid into the space of Disse, which is then removed by hepatic lymphatics; this movement of fluid is also promoted by hypoalbuminemia. *Leakage of hepatic lymph* into the peritoneal cavity: normal thoracic duct lymph flow approximates 800 to 1000 mL/day. With cirrhosis, hepatic lymphatic flow may approach 20 L/day, exceeding thoracic duct capacity. Hepatic lymph is rich in proteins and low in triglycerides, as reflected in the protein-rich ascitic fluid. *Renal retention of sodium and water* due to secondary hyperaldosteronism , despite a total body sodium value greater than normal.

**Portosystemic Shunt:-**

With the rise in portal venous pressure, bypasses develop wherever the systemic and portal circulations share capillary beds. Principal sites are veins around and within the rectum (manifest as hemorrhoids), the cardioesophageal junction (producing esophagogastric varices), the retroperitoneum, and the falciform ligament of the liver (involving periumbilical and abdominal wall collaterals). Although hemorrhoidal bleeding may occur, it is rarely massive or life threatening. Much more important are the *esophagogastric varices* that appear in about 65% of those with advanced cirrhosis of the liver and cause massive hematemesis and death in about half . Abdominal wall collaterals appear as dilated subcutaneous veins extending outward from the umbilicus *(caput medusae)* and constitute an important clinical hallmark of portal hypertension.

**Splenomegaly \_ :-**

Long-standing congestion may cause congestive splenomegaly. The degree of enlargement varies widely (usually ≤1000 gm) and is not necessarily correlated with other features of portal hypertension. Massive splenomegaly may secondarily induce a variety of hematologic abnormalities attributable to hypersplenism

***Metabolic and inherited liver diseases :-***

1. **Wilson s disease :-**

***Pathogenesis:-***

This autosomal recessive disorder of copper metabolism is characterized by the accumulation of toxic levels of copper in many tissues and organs, principally the liver, brain, and eye. The genetic defect responsible for Wilson disease is a mutation in *ATP7B.* This gene, located on chromosome 13, encodes an ATPase metal ion transporter that localizes to the Golgi region of hepatocytes.

Normal copper physiology involves (1) absorption of ingested copper (2-5 mg/day); (2) plasma transport in complex with albumin; (3) hepatocellular uptake, followed by incorporation into an α2-globulin to form ceruloplasmin; (4) secretion of ceruloplasmin into plasma, where it accounts for 90% to 95% of plasma copper; and (5) hepatic uptake of desialylated, senescent ceruloplasmin from the plasma, followed by lysosomal degradation and secretion of free copper into bile. In Wilson disease, the initial steps of copper absorption and transport to the liver are normal. However, absorbed copper fails to enter the circulation in the form of ceruloplasmin, and biliary excretion of copper is markedly diminished. Defective function of *ATP7B* leads to failure to excrete copper into bile, *the primary route for copper elimination from the body.* The defect apparently also inhibits secretion of ceruloplasmin into the plasma. Copper thus accumulates progressively in the liver, apparently causing toxic liver injury by (1) promoting the formation of free radicals, (2) binding to sulfhydryl groups of cellular proteins, and (3) displacing other metals in hepatic metalloenzymes. Usually by 5 years of age, copper that is not ceruloplasmin bound spills over into the circulation, causing hemolysis and pathologic changes at other sites, such as brain, cornea, kidneys, bones, joints, and parathyroid glands. Concomitantly, urinary excretion of copper increases markedly. *The biochemical diagnosis of Wilson* disease is based on a decrease in serum ceruloplasmin, *increase in hepatic copper content, and increase in urinary excretion of copper.*

**Microscopically:-**

The liver often bears the brunt of injury in Wilson disease, with hepatic changes ranging from relatively minor to massive damage. **Fatty change** may be mild to moderate, with vacuolated nuclei (glycogen or water) and occasional hepatocyte focal necrosis. An **acute hepatitis** can mimic acute viral hepatitis, save possibly for the accompanying fatty change. A **chronic hepatitis** resembles chronic hepatitis of viral, drug, or alcoholic origin but may show such distinguishing features as fatty change, vacuolated nuclei and Mallory bodies. With progression of chronic hepatitis, **cirrhosis** develops. **Massive liver necrosis** is a rare manifestation that is indistinguishable from that caused by viruses or drugs. Excess copper deposition can often be demonstrated by special stains (e.g., rhodanine stain for copper, orcein stain for copper-associated protein). Because copper also accumulates in chronic obstructive cholestasis, and because histology cannot reliably distinguish Wilson disease from viral- and drug-induced hepatitis, demonstration of hepatic copper content in excess of 250 μg/gm dry weight is most helpful for making a diagnosis.

In the **brain,** toxic injury primarily affects the basal ganglia, particularly the putamen, which demonstrates atrophy and even cavitation. Nearly all patients with neurologic involvement develop **eye lesions** called **Kayser-Fleischer rings** (green to brown deposits of copper in Descemet membrane in the limbus of the cornea)-hence the alternative designation of this condition as hepatolenticular degeneration.

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**2- Haemochromatosis :-**

Characterized by excessive accumulation of iron the body , most of which in which deposited in the paranchymal organs ( liver , pancreas , heart ...) , complicated by macronodular type cirrhosis

We have two types:-

1- primary type ( defect in gene on chromosome 6 )

2- secondary type ( paraenteral administration in iron )

**Microscopically:-**

Characterized by (portal fibrosis , heamosidrin deposit in hepatocytes which detected by using prussian blue stain ).

1. **- alpha -1- antitrypsin deficiency** :-

Autosomal recessive disorder characterized by decrease the level of this protease inhibiter enzyme. AAT deficiency is an autosomal recessive disorder marked by abnormally low serum levels of this protease inhibitor. The major function of AAT is the inhibition of proteases, particularly neutrophil elastase released at sites of inflammation. AAT deficiency leads to pulmonary emphysema, because a relative lack of this protein permits the unrestrained activity of tissue-destructive proteases

Morphology :-

Hepatocytes in AAT deficiency contain round to oval cytoplasmic **globular inclusions** of retained AAT, which are strongly positive in a periodic acid-Schiff stain By electron microscopy they lie within smooth, and sometimes rough, endoplasmic reticulum. Hepatic injury associated with PiZZ homozygosity may range from marked **cholestasis** with **hepatocyte necrosis** in newborns, to **childhood cirrhosis,** or to a smoldering chronic inflammatory hepatitis or cirrhosis that becomes apparent only late in life.

***Intrahepatic liver Biliary disease :-***

***Biliary cirrhosis***This condition is due to biliary obstruction

There are tow types that may lead to obstruction.

**A- primary biliary cirrhosis:-**

The pathogenesis is due to autoimmune diseaselead todamagemedium size intrahepatic bile ducts.

**B- Secondary biliary cirrhosis :-**

Obstruction that end with cirrhosis.

Cuases:-

{ tumors , gall stones , atresia ....}

***Jaundice and Cholestasis :-***

Jaundice Accumulation of conjugated & unconjugated bilirubin systemically & deposition in tissue giving arise to yellow discoloration.

Types of bilirubin [conjugated , unconjugated }

Jaundice, a common manifestation of liver disease, results from the retention of bile. Hepatic bile formation serves two major functions. Bile constitutes the primary pathway for the elimination of bilirubin, excess cholesterol, and xenobiotics that are insufficiently water soluble to be excreted into urine. Second, secreted bile salts and phospholipid molecules promote emulsification of dietary fat in the lumen of the gut. Because bile formation is one of the most sophisticated functions of the liver, it is also one of the most readily disrupted. Thus, *jaundice,* a yellow discoloration of skin and sclerae *(icterus),* occurs when systemic retention of bilirubin leads to elevated serum levels above 2.0 mg/dL (the normal in the adult is <1.2 mg/dL). *Cholestasis* is defined as systemic retention of not only bilirubin but also other solutes eliminated in bile (particularly bile salts and cholesterol).

***Normal pathophysiology:-***

Unconj. Will change to conj. Bilirubin by bound to glucuronic acide a reaction catalaze by enz. { uridine diphosphate glycuronyl transferase UGT }.

***Causes o Jaundice :-***

**1- increase in bilirubin production .**

**2-Reduce hepatic uptake.**

**3- impair conjugation.**

**4- Decrease hepatocellular excretion.**

**5- Impaired bile flow (obstruction).**

***Jaundice may also result from inborn errors of metabolisms***

***1-Gilbert syndrome*** :-

is a relatively common, benign, somewhat heterogeneous inherited condition presenting as mild, fluctuating unconjugated hyperbilirubinemia. The primary cause is decreased hepatic levels of glucuronosyl transferase. Although this is attributed to a mutation of the responsible gene, additional polymorphisms may play a role in the variable expression of this disorder. Affecting up to 7% of the population, the hyperbilirubinemia may go undiscovered for years and *does not have associated morbidity.*

***2- Dubin-Johnson syndrome***

results from an autosomal recessive defect in the transport protein responsible for hepatocellular excretion of bilirubin glucuronides across the canalicular membrane. These patients exhibit conjugated hyperbilirubinemia. Other than having a darkly pigmented liver (from polymerized [epinephrine](mk:@MSITStore:F:\Desktop\Robbins%20Basic%20Pathology%208th%20edition.CHM::/www.studentconsult.com/content/bookcontent.cfm@id=hc016003.htm) metabolites, not bilirubin) and hepatomegaly, patients are otherwise without functional problems.

***3- Reye s syndrome***

*Reye syndrome is a rare disease characterized by fatty change in the liver and encephalopathy.* The most severe forms are fatal. It primarily affects children younger than 4 years of age, typically developing 3 to 5 days after a viral illness. The onset is heralded by pernicious vomiting and is accompanied by irritability or lethargy and hepatomegaly. Serum bilirubin, ammonia, and aminotransferase levels are essentially normal at this time. Although most patients recover, about 25% progress to coma, accompanied by elevations in the serum levels of un conjugate bilirubin, aminotransferases, and particularly ammonia. Death occurs from progressive neurologic deterioration or liver failure. Survivors of more serious illness may be left with permanent neurologic impairments. The pathogenesis of Reye syndrome involves a generalized loss of mitochondrial function. Reye syndrome is now recognized as the prototype of a wide variety of conditions known as *"mitochondrial hepatopathies."* Reye syndrome has been associated with [aspirin](mk:@MSITStore:F:\Desktop\Robbins%20Basic%20Pathology%208th%20edition.CHM::/www.studentconsult.com/content/bookcontent.cfm@id=hc016043.htm) administration during viral illnesses, but there is no evidence that salicylates play a causal role in this disorder.