Liver Diseases

ALCOHOLIC LIVER DISEASE

- Alcohol is the most widely abused agent, it is the 5th leading cause of death in USA due to: 1) Accidents, 2) Cirrhosis

- 80 – 100 mg/dl is the legal definition for driving under the influence of alcohol >> 44 ml of ethanol is required to produce this level in 70kg person
- 50 – 60gm/day → borderline effect
- Ethanol toxicity is dose dependant
  - — Short term ingestion of 80 gms/d of ethanol (8 bears) >> fatty change in liver/mild reversible hepatic changes
  - — Long term ingestion (10-20yrs) of 160gm of ethanol per day >> severe hepatic injury
  - — In occasional drinkers, blood level of 200 mg/dl >> produces coma & death. At 300-400 mg/dl >> Resp. failure
  - — Habitual drinkers can tolerate levels up to 700 mg/dl without clinical effect due to metabolic tolerance explained by 5-10X induction of cytochrome P-450 and system that includes enzyme CYP2E1 which increases the metabolism of ethanol as well as other drugs as cocaine & acetominophen
- Women are more susceptible to hepatic injury due to ↓ gastric metabolism of ethanol

■ Ethanol Metabolism:

- — Primarily in liver by enzymes.
- — Ethanol is Absorbed → Acetaldehyde → Acetic Acid

- — After absorption, ethanol is distributed as Acetic acid in all tissues & fluid in direct proportion to blood level
- — less than 10% of absorbed ethanol is excreted unchanged in urine, sweat & breathe
- — Women have ↓ gastric alcohol dehydrogenase enzyme activity than men → They develop ↑ blood alcohol levels after drinking the same quantity
- — There is genetic polymorphism in aldehyde dehydrogenase that affect ethanol metabolism
  e.g 50% of chinese , vietnamase & Japanese have lowered enzyme activity due to point mutation of the enzyme → accumulation of acetaldehyde → facial flushing, tachycardia & hyperventilation

■ Mechanism of ethanol toxicity:

1. Fatty change
   - Shunting of lipid catabolism toward lipid bio-synthesis due to excess production of NADH over NAD in cytosol & mitochondria
   - Acetaldehyde forms adducts with tubulin & ↓ function of microtubules → ↓ in lipoprotein transport from liver
   - ↑ peripheral catabolism of fat → ↑ FFA (Free fatty acids) delivery to the liver
   - ↓ secretion of lipoproteins from hepatocytes
   - ↓ oxidation of FFA by mitochondria
2. Induction of cytochrome P-450 enhances the metabolism of drugs to toxic metabolites (e.g acetominophen) → ↑ the injury of the liver
3. Increase free radicals production due to (+) of cytochrome P-450 leads to membrane & protein damage within hypatocytes
4. Alcohol directly affect microtubular & mitochondrial function & membrane fluidity
5. Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes → immune attack
6. Superimposed HCV infection causes acceleration of liver injury (HCV hepatitis occurs in 30% of alcoholics)
7. Alcohol causes release of bacterial endotoxins into portal circulation from the gut → inflammation of the liver
8. Alcohol causes regional hypoxia in the liver due to release of endothelins which are potent vasoconstrictors → ↓ hepatic sinusoidal perfusion
9. Alteration of cytokine regulation: ▼TNF is a major effector of injury ▼IL6 ▼IL8 ▼IL18

Liver Diseases

■ Forms of alcoholic liver disease:

1. Hepatic steatosis (90-100% of drinkers):

- Ethanol causes ↑↑ FA release, or its synthesis → ↑↑ free fatty acids in the blood → accumulate in liver

- Can occur following even moderate intake of alcohol → microvesicular steatosis
- Chronic intake → diffuse steatosis (liver is ◆large (hepatomegaly, 4 - 6 kg), ◆soft yellow & greasy)
- Continued intake → fibrosis
- Fatty change is reversible with complete absention from further intake of alcohol

- Clinical features: ◆Enlargement of liver, ◆Increased liver enz. ◆Severe hepatic dysfunction is unusual
- Reversible

2. Alcoholic hepatitis (1-35% of drinkers):

- Characteristic Findings:

1) Hepatocyte swelling (hepatomegaly) & necrosis:
   - Accumulation of fat, water & proteins
   - Cholestasis (reduced flow of bile from liver >> accumulation of bile within the liver in the cytoplasm of hypatocytes & small bile ducts)
   - Hemosiderin deposition in hepatocytes & Kupffer cells

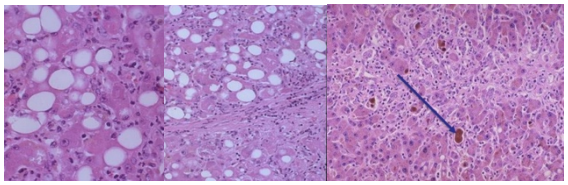
2) Mallory-hyaline bodies:
   - Eosinophilic cytoplasmic inclusions in degenerating hepatocytes formed of cytokeratin intermediate filaments & other proteins
   - Mallory-hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease

3) Neutrophilic reaction: infiltration of inflammatory cells→ further damage (necrosis) to hepatocytes

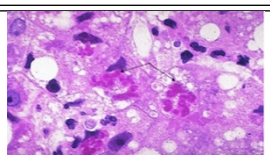
4) Fibrosis: (depends on the duration of alcohol intake)
   - Sinusoidal & perivenular fibrosis
   - Periportal fibrosis

5) Cholestasis: ↓↓ flow of bile from liver

6) Mild deposition of hemosiderin in hepatocytes & Kupffer cells



Alcoholic hepatitis
Fig. 1+2) Inflammatory infiltration.
Fig. 3) Cholestasis



Mallory-hyaline bodies
The arrows >> cytoplasmic granules

Mallory-hyaline bodies are also seen in:
- ▲Primary biliary cirrhosis
- ▲Wilson disease
- ▲Chronic cholestatic syndromes
- ▲Hepatocellular carcinoma

- Clinical features: ◆15-20 years of excessive drinking & presence of injury, ◆Non-specific symptoms, malaise, anorexia, weight loss, ◆Enlargement of the liver & spleen, ◆increased LFT (liver function test)
- Each bout of hepatitis: ◆carries a 10-20% risk of death ◆With repeated bouts, cirrhosis appears in 1/3 of patients in few years.

Steatosis & hepatitis may develop independently

3. Cirrhosis (14% of drinkers/Only 8 - 20% of alcoholics):

- After chronic ingestion of alcohol → Liver toxicity
- Usually it develops slowly, but can develop rapidly in the pressure of alcoholic hepatitis (within 1-2 yrs)

- Clinical features: ◆Portal hypertension
- Initially the liver is enlarged yellow but over years it becomes brown shrunken non-fatty organ s.t < 1 kg in weight, There's bile stasis
- Mallory bodies are only rarely evident at this stage
- Laennec cirrhosis = liver appears as scar tissue
- Irreversible

Liver with Alcoholic Cirrhosis
with micronodules (small nodules)

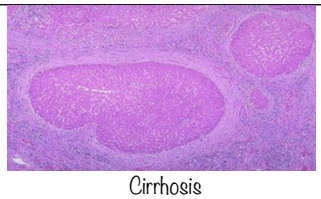
■ Causes of death in alcoholic liver disease: ◆Hepatic failure ◆Massive GI bleeding ◆Infections ◆Hepatorenal syndrome (Multiorgan failure) ◆HCC (hypatocellular carcinoma) in 3-6% of cases

Liver Diseases

CIRRHOSIS

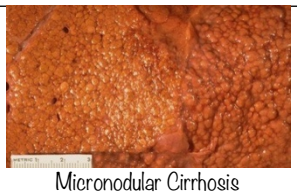
- It is a diffuse process characterized by fibrosis & the conversion of liver parenchyma into nodules.
- Main characteristics: ▲Bridging fibrous septae ▲Parenchymal nodules encircled by fibrotic bands ▲Diffuse architecture disruption

- Types (Depending on the diameter of the nodule):
  1. Micronodules < 3mm in diameter
  2. Macronodules > 3 mm in diameter
     - In alcoholic cirrhosis, micronodular → or mixed micro & macronodular



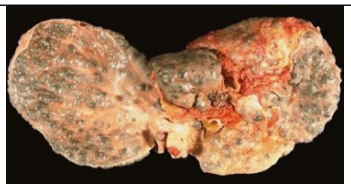
Cirrhosis

The normal liver parenchyma is replaced by parenchyma encircled with fibrous tissue that could be infiltrated by lymphocytes



Micronodular Cirrhosis

The liver surface is normally smooth, after cirrhosis it is changed into nodular one by a diffused process



Macronodular Cirrhosis

- Causes:
  - Common: ◆Chronic alcoholism (the most common cause in Western world) ◆Chronic viral infection HBV& HCV ◆Biliary disease ◆Hemochromatosis (Excessive deposition of iron in liver tissue) ◆Autoimmune hepatitis ◆Wilson disease ◆α-1-antitrypsin deficiency
  - Rare: ◆Galactosemia ◆Tyrosinosis ◆Glycogen storage disease III &IV ◆Lipid storage disease ◆Hereditary fructose intolerance ◆Drug induced e.g methyldopa
  - Cryptogenic cirrhosis: The underlying cause is unknown (10% of cases)

- Pathogenesis of cirrhosis:

- The mechanism of cirrhosis involves:
  1. Hepatocellular death (#Occurs over a long period of time #Accompanied with fibrosis #Regardless of the initial cause)
  2. Regeneration of hepatocytes
  3. Progressive fibrosis
  4. Vascular changes

- Cell death should occur over a long period of time & accompanied by fibrosis

Effect of Cirrhosis on ECM components and stellate cells		
	Normal	Cirrhosis
ECM Collagen (types I, III, V& XI)	Present only in: 1. Liver capsule 2. Portal tracts 3. Around the central vein	Deposited in the space of Disse → This interferes with the exchange function of hepatocytes
Delicate framework of type IV collagen & other proteins	Lie in the space of Disse.	
Perisinusoidal cells / stellate cells / Ito cells (Lie in the space of Disse)	Act as storage cells for: 1. Vitamin A 2. Fat	- The major source of collagen in cirrhosis. (How?↓) - Transforming growth factor β (TGF-β) stimulates these stellate cells (they're myofibroblast-like cells) to produce collagen - The stimuli for the activation of stellate cells & production of collagen: ▲Reactive oxygen species (Produced during inflammatory process) ▲Growth factors ▲Cytokines: TNF, IL-1, lymphotoxins

Liver Diseases

■ The vascular changes include:

- Loss of sinusoidal endothelial cell fenestration (normally responsible for the exchange between hepatocytes & the blood) → Associated with the loss of function of hepatocytes
- Development of vascular shunts as ▲Portal vein - hepatic vein ▲Hepatic artery – portal vein
  → That will result with defect in liver function in exchanging substances between blood & hepatocytes
- Loss of microvilli from hepatocytes → decreased transport capacity of the cells
  - Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma & hepatocytes to higher pressure, fast-flowing vascular channels without such solute exchange.
  - The movement of proteins (e.g., albumin, clotting factors, lipoproteins) between hepatocytes & the plasma is markedly impaired.
  - These functional changes are aggravated by the loss of microvilli from the hepatocyte surface, which diminishes the transport capacity of the cell.

■ Clinical features of Cirrhosis: ◆Silent, asymptomatic (due to the functional capacity of the parenchymal hepatocytes), ◆Minimal non-specific symptoms: Anorexia, Weight loss, Weakness

■ Complications: ▼Progressive hepatic failure ▼Hepatocellular carcinoma ▼Portal hypertension

Portal Hypertension

■ Develops because of:

1. Increased resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules (which is characteristic for cirrhotic lesion)
2. Arterial-portal anastomosis in the fibrous bands → increase in the blood pressure in portal venous system (imposing arterial pressure on the normally low-pressure portal venous system)

■ Causes:

1. Prehepatic: ◆Portal vein thrombosis ◆Massive splenomegaly
2. Post hepatic: ◆Severe Rt. sided heart failure ◆Constrictive pericarditis ◆Hepatic vein out flow obstruction
3. Hepatic: ◆Cirrhosis ◆Schistosomiasis ◆Massive fatty change ◆Diffuse granulomatosis as sarcoidosis, TB ◆Disease of portal microcirculation as nodular regenerative hyperplasia

■ Clinical consequence of portal hypertension: ◆Ascitis ◆Portosystemic shunts ◆Splenomegaly ◆Hepatic encephalopathy

➢ Ascitis

- Collection of excess fluid in peritoneal cavity
- Dx: It becomes clinically detectable when at least 500 ml have accumulated

■ Features: ◆Serous fluid ◆Contains as much as 3g/ml of protein (albumin) ◆It has the same concentration as blood of glucose, Na+, & K+ ◆Contains mesothelial cells & lymphocytes ◆Presence of Neutrophils = indicates that there is infection ◆Presence of RBCs = DISSEMINATED CANCER

■ Pathogenesis: Causes:

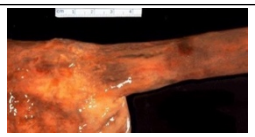
- Sinusoidal increase of blood pressure
- Hypoalbuminemia: decrease in synthesis of albumin in the liver → decrease the osmotic pressure → ascites
- Leakage of hepatic lymph into the peritoneal cavity (due to increase in duct flow)
- Renal retention of Na+ & water due to secondary hyperaldosteronism (↑ blood volume & the hydrostatic pressure → leakage of fluid to extra vascular space)

Normal thoracic duct lymph flow is 800-1000 ml/d
in cirrhosis is 20L/d

Liver Diseases

➢ Portosystemic Shunt

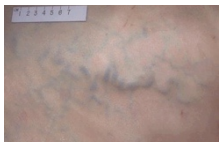
- Because of ↑ portal venous pressure bypasses develop wherever the systemic & portal circulation share capillary beds (Where blood chooses to flow in less resistant circulation)



Esophageal varicies
(The dark linear areas)

■ Sites:

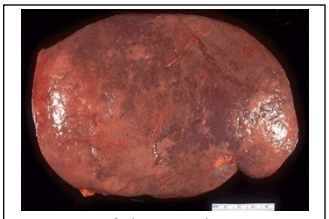
1. Around and within the rectum → Hemorrhoids
2. Gastroesophageal Junction → Varices (Gastroesophageal varicies = appears in 65% of patients with advanced cirrhosis and causes death in 50% of them due to upper GI bleeding)
3. Retroperitoneum
4. Falciform ligament of the Liver (Between the paraumbilical & abdominal wall collaterals) → Caput medusae



Caput medusae
The anterior abdominal wall for a patient with portosystemic shunt showing the dilated tortious veins

➢ Splenomegaly

- Weight of the spleen: ◆Normal: <300grams, ◆Cirrhosis: 500-1000 grams
-Not necessarily correlated with other features of portal hypertension
-May result in hypersplenism (Excessive removal & destruction of RBCs or other blood elements in the spleen (which is enlarged & filled with blood) → resulting in thrombocytopenia)



Splenomegaly

➢ Hepatic Encephalopathy

- It is a complication of acute & chronic hepatic failure
- Disturbance in brain function ranging from behavioural changes to marked confusion & stupor to deep coma & death
- The changes may progress over hours, days, or weeks.

■ Neurological signs: ◆Rigidity ◆Hyper-reflexia ◆Non-specific EEG ◆Seizures ◆Asterixis (Non-rhythmic, rapid extension-flexion movements of the head & extremities) ◆Brain shows edema & astrocytic reaction ◆no brain inflammation

■ Pathogenesis:

- Physiologic factors important in development of hepatic encephalopathy:

1. Severe loss of hepatocellular function
2. Shunting of blood around damaged liver

} Exposure of Brain to toxic metabolic products that accumulated in the blood especially ↑ NH3 level in blood → generalized brain edema impaired neuronal function, alteration in central nervous system amino acid metabolism

- In this condition, the liver is unable adequately remove toxins from the blood → This causes a buildup of toxins in your bloodstream, which can lead to brain damage.
- It's a terminal stage of portal hypertension & may lead to the death of the patient.

نتفة فراغ هدية الك قبل ما نبلش بالمحاضرة الرابعة
اذكروا الله فيها وادعولنا

Liver Diseases

DRUG – INDUCED LIVER DISEASE

- Most of the drugs are metabolized in the liver, that's why chronic drug usage will be associated with chronic liver injury and disease process

■ Drug reactions are divided into:

1. Predictable (intrinsic)
   - depends on the dose (dose-dependent)
2. Unpredictable (idiosyncratic)
   - depends on:
   a-The immune response of the host to the antigenic stimulus (the drug)
   b-The rate at which the host metabolizes the agent

Predictable drugs	Unpredictable drugs
Acetaminophen	Chlorpromazine
Tetracycline	Halothane
Antineoplastic agents	Sulfonamides
CCL4	Methyldopa
Alcohol	Allopurinol

- Injury could be immediate or could take weeks to months after the drug uptake.
- Drug-induced chronic hepatitis is clinically & histologically indistinguishable from chronic viral or autoimmune hepatitis.

■ Mechanism of drug injury:

1. Direct toxic damage of hepatocyte
   - Examples: ▲Acetaminophen ▲CCl4 ▲Mushroom toxins
2. Immune-mediated damage
   - the drug acts as a hapten to convert a cellular protein into an immunogen
   (A drug that acts as an antigen → The antigen stimulates the immune reaction that targets the hepatocytes causing their damage)

■ Patterns of injury within the liver: ⭐Hepatocellular necrosis, ⭐Cholestasis ⭐Steatosis, ⭐Steatohepatiti, ⭐Fibrosis, ⭐Vascular lesions, ⭐Granuloma, ⭐Neoplasms benign & malignant

■ Drugs that may cause acute liver failure: (important to recognize because they can be associated with severe liver damage & failure)

1. Acetaminophen: most common
   - it's the precursor of Paracetamol
   - Used in suicidal attempts
2. Halothane:
   - Anesthetic drug that can be associated with severe injury (even on first exposure) and it can progress into acute liver failure.
3. Antituberculosis drugs (Rifampin, Isoniazid)
4. Antidepressant monoamine oxidase inhibitors
5. Toxins such as CCL4 & mushroom poisoning

■ Morphology: ▲Massive necrosis → 500 – 700 gm liver ▲Submassive necrosis ▲Patchy necrosis

NOTE: The doctor deleted Fulminant hepatitis & Chronic Hepatitis from our slides & our recorded lectures

AUTOIMMUNE HEPATITIS

- It's one important form of hepatitis
- Chronic hepatitis with immunologic abnormalities
- Histologic features are similar to chronic viral hepatitis → that's why chronic viral & autoimmune hepatitis should be considered as cases of chronic hepatitis. Also, both of them should be differentiated from each other because their treatment differs.
- It can have either an Indolent or a severe course

Liver Diseases

- Dramatic response to immunosuppressive therapy (A very important characteristic of autoimmune hepatitis, Therefore, we need to differentiate between different causes chronic hepatitis as the treatments vary)

- Characteristic features of autoimmune hepatitis: (when they are present, we should consider disease process):
  - Female predominance (70%)
  - Negative serology for viral Antigens.
  - ↑ serum Immunoglobulins (>2.5 g/dl)
  - High titers of autoantibodies (80% of cases)
  - The presence of other autoimmune diseases as RA, thyroiditis, Sjogren syndrome, Ulcerative Colitis in 60% of the cases.

- Types of autoantibodies that can be found in these patients are:
  1. Anti-smooth muscle antibodies: 🔻Anti actin 🔻Anti-troponin 🔻Anti-tropomyosin
  2. Liver/kidney microsomal antibodies: 🔻Anti-cytochrome P-450 components 🔻Anti UDP-glucuronosyl Transferases
  3. Anti-soluble liver/pancreas antigen (the least common)

- Outcome: 🔷Mild to severe chronic hepatitis 🔷Full remission is unusual 🔷Risk of cirrhosis is 5% (which is the main cause of death)

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

- Types:
  1. Steatosis (fatty liver)
  2. Steatohepatitis: 🔶Hepatocyte destruction 🔶Parenchymal inflammation 🔶Progressive pericellular fibrosis

- Predisposing factors for nonalcoholic liver disease:
  1. Type 2 DM
  2. Obesity : body mass index (BMI)
     > 30 kg /m2 in Caucasians
     > 25 kg /m2 in Asians
  3. Dyslipidemia: ↑TG (triglycerides), ↑LDL, ↓HDL

- Pathogenesis

- Fat accumulation in the liver can be due to a metabolic syndrome such as: 🔺Insulin resistance, 🔺Obesity, 🔺Dyslipidemia

- Mechanism of fatty accumulation:

1. Impaired oxidation of fatty acids, 2. Increased synthesis & uptake of FFA, 3. Decreased hepatic secretion of VLDL → All these are associated with increasing free FA in the circulation and their deposition in the liver

- In addition, presence of any chronic anti-inflammatory process is associated with increase in inflammatory mediators such as: ↑TNF, IL6, chemokine → liver inflammation & damage to liver parenchyma.

- Clinical features:
  - NAFLD is the most common cause of incidental increase in transaminases that are produced by the liver.
  - Most patients are asymptomatic
  - Non-specific symptoms: Fatigue, malaise, RUQ (right upper quadrant) discomfort
  - Severe symptoms may present.
  - Dx: Liver biopsy is required for diagnosis.
  - NAFLD may be a significant contributor to cryptogenic cirrhosis that is associated with undefined reason for cirrhosis.

Liver Diseases

HEMOCHROMATOSIS

- Excessive accumulation of body iron (liver & pancreas).
- Normally, the total body iron 2-6gm in adults , 0.5gm in liver mostly in hepatocytes .
- In disease, total iron may exceed 50 gm → 1/3 accumulate in the liver

■ Features of hemochromatosis: ◆Micronodular cirrhosis (all patients) ◆D.M (75 – 80%) ◆Skin pigmentation (75-80%) ◆Cardiomegaly, joints disease, testicular atrophy

- skin pigmentation in patients with liver disease along with DM >> we should think of hemochromatosis as a possible disease

■ Types: Primary or secondary (genetic or acquired)

— Causes of acquired hemosiderosis: ◆Multiple transfusions, ◆Blood condition that is characterized by the presence of ineffective erythropoiesis (thalassemia), ◆Increased iron intake (Bantu sidrosis), ◆Chronic liver disease

— Genetic hemochromatosis (4 variants): The most common form: is autosomal recessive disease of adult onset caused by mutation in the HFE gene on chromosome number 6.

■ Pathogenesis:

- Primary defect in hemochromatosis in intestinal absorption of dietary iron.
- In herediatary hemochromatosis (whatever the underlying defect/mutation), there is a defect in the regulation of intestinal absorption of dietary iron → increase in intestinal absorption of dietary iron → leading to net iron accumulation of 0.5-1 gm/yr (that's why the disease is usually after the age of 40)

- The gene responsible is HFE gene located on chromosme 6 close to HLA gene complex.
  - — HFE gene regulates the level of hepcidin hormone synthesized in liver
  - — Hepcidin → inhibition of Fe absorption from intestinal enterocytes.
  - — HFE gene deletion → decreasing the hepcidin in the blood and causing iron overload due to the increased absorption of iron.

■ Two mutation can occur in HFE gene:

1. Mutation at 845 nucleotide → tyrosine substitution for cystine at AA 282 site (C282 Y)
2. Aspartate substitution for histidine at AA 63 (H63D) (less common) [AA refers to Amino Acid]

— 10% of the patients have other gene mutations

- Carrier rate for C282Y is 1/70 cases
- Homozygosity is 1/200 cases
- 80% of patients are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation
- 10% of patients are either homozygous for H63D mutation or compound heterozygous for both types of gene mutations (C282Y/H63D mutation)

■ Excessive Fe deposition in the tissues particularly in the liver → toxic to tissues & damage to hepatocytes due to: ◆Lipid peroxidation ◆Stimulation of collagen formation ◆DNA damage

■ Morphological changes:

1. Deposition of iron in the form of hemosiderin in different organs like: Liver, Pancreas, Myocardium, Pituitary, Adrenal, Thyroid & parathyroid, Joints, Skin
2. Cirrhosis
3. Pancreatic fibrosis associated with damage to the islets of Langerhans and development of DM

Liver Diseases

■ Examination of these tissues will show: ▼No inflammation, ▼Fibrosis, ▼Cirrhosis in liver, ▼Joint involvement (Synovitis), ▼Polyarthritis (pseudogout), ▼Pigmentation of liver & skin, ▼Fibrosis of pancreas & myocardium, ▼Atrophy of testes because of excessive deposition of iron & tissue damage.

■ Clinical presentation: ◆Hepatomegaly ◆Abdominal pain ◆Skin pigmentation ◆D.M ◆Cardiac dysfunction ◆Atypical arthritis ◆Hypogonadism ◆↑ Serum Fe ferritin
◆These patients can have HCC (hepatocellular carcinoma) 200x higher risk compared to normal individuals

■ Epidemiology: ▲M:F 5-7:1 ▲5th-6th decades & not before age of 40

WILSON DISEASE

- Autosomal Recessive disorder of Cu metabolism
- Mutation in ATP7B gene on chromosome 13 which encodes an ATPase metal ion transporter in the Golgi region
- more than 80 mutations
- Gene freq. 1:200 individuals
- Incidence: 1:30000 individuals

■ Pathogenesis:
- The main cause of Wilson disease is the increase in Copper (Cu) deposition.
- Main source of Cu is from diet → Absorption of ingested Cu (2-5 mg/d) → Complex with albumin → Hepatocellular uptake in the liver → Incorporation with α-2-globulin to form Ceruloplasmin → Secretion of ceruloplasmin into the plasma (90 – 95% of plasma Cu), so the Cu can be uptaken anywhere in the body → Hepatic uptake of ceruloplasmin → Lysosomal degradation → Secretion of free Cu into bile

- In Wilson disease, absorbed Cu. fails to enter the circulation in the form of ceruloplasmin & the biliary excretion of Cu is decreased (because of the accumulation of Cu in hepatocytes)
- Defective function of ATP-7B gene → failure of Cu. excretion into bile & inhibits secretion of ceruloplasmin into the plasma → Cu. accumulation in liver

- ↑ Cu. Accumulation in the liver results in:
    1. Production of free radicals (which has toxic & damaging effects on hepatocytes)
    2. Binding to sulfhydryl groups of cellular proteins leading to their damage.
    3. Displacement of other metals in hepatic metalloenzymes leading to a decrease in their efficiancy.

- By the age of 5yrs. Cu. Spills over to circulation causing hemolysis & involvement of other organs as brain & cornea also kidneys, bones joints & parathyroid glands which can produce manifestations related to organ damage.
-Urinary excretion of Cu. ↑ because the spilled Cu in the blood can appear within the urinary excretion.

■ Morphology:
    — Liver: ▼Fatty change ▼Acute hepatitis ▼Chronic hepatitis ▼Massive hepatic necrosis ▼Cirrhosis (apparently these manifestations can be caused by other diseases & that's why in proper patients we should include Wilson disease in more differential diagnosis in these conditions)
    — Brain: ▼Toxic injury to basal ganglia esp. the putamen causing atrophy & cavitation (this why the patient may have neurological manifistation)
    — Eye: ▼Kayser-Fleischer rings: Green-brown deposits of Cu. in the descemet membrane in the limbus of the Cornea (hepatolenticular degeneration) (Might be associated with degeneration of the brain)
- Rhodanine stain or orcein stain to see the copper deposition in hepatocytes

Liver Diseases

■ Clinical Presentation: ◆> 6 yrs of age (Because of the increasing amount of Cu within deposited organs) ◆Most common presentation is acute on chronic hepatitis ◆Neuropsychiatric presentation can occur: behavioral changes, Frank psychosis, Parkinson disease-like syndrome

■ Dx: ▲↓ in serum ceruloplasmin level ▲↑ in urinary excretion Of Cu. ▲↑ hepatic content of copper (> 250 mg/gm dry wt. of the liver)

α-1-ANTI-TRYPSIN DEFICIENCY

- Autosomal Recessive disorder
- freq. 1:7000 in native american white population
- α-1-antiryrpsin (α-1-AT) is a protease inhibtor as elastase, cathepsinG , proteinase 3 which are released from neutrophils at the site of inflammation
- The gene pi. is located on chromosome 14
- At least 75 forms of gene mutation are present
- The most common genotype is pi.MM present in 90% of individuals
- PiZZ genotype → ↓ level of circulating α-1-antitrypsin in blood (=only 10% of the normal) >> These individuals are at high risk of developing clinical disease

■ Pathogenesis
- The mutant polypeptide (PiZ) is abnormally folded & polymerizes causing its retention in the ER of hepatocytes
- Although all individual with Pizz genotype accumulate α-1-AT-Z protein, only 10% of them develop clinical liver disease >> This is due to lags in ER protein degradation pathway
- The accumulated α-1-AT-Z is not toxic but the autophagocytic response stimulated within the hepatocytes appear to be the cause of liver injury by autophagocytosis of the mitochondria
- 8-10% of patients develop significant liver damage

■ Morphology: ▼Intracytoplasmic globular inclusions in hepatocytes which are acidophilic in H&E sections ▼The inclusions are PAS-positive & diastase resistant ▼Neonatal hepatitis with cholestasis & fibrosis ▼Chronic hepatitis ▼Cirrhosis (due to the formation of scar tissue in the liver) ▼Fatty change ▼Mallory bodies

■ Clinical features: ◆neonatal hepatitis with cholestatic jaundice appears in 10 – 20% of newborns with the disease ◆Attacks of hepatitis in adolescance ◆chronic hepatitis & cirrhosis in older patients ◆HCC (hepatocellular carcinoma) in 2- 3 % of Pizz adults ± cirrhosis

REYE'S SYNDROME

- Fatty change in liver & encephalopathy

■ Pathogenesis: Derangement of mitochondrial function along or in combination with viral infection & salicylate (used during viral illnesses as an antibiotic agent) - 3–5 days after viral illness

■ Epidemiology: ▲< 4 year-old (in young children)

■ Clinical features: ◆Enlargement of the liver & abnormal LFT (liver function tests), liver enzymes are generally elevated ◆Vomiting ◆lethargy ◆25% may go into coma ◆Microvesicular steatosis ◆Brain edema ◆Absent inflammation ◆Skeletal Muscles, heart, & kidneys show fatty change

Liver Diseases

PRIMARY SCLEROSING CHOLANITIS (PSC)

- Inflammation, obliterative fibrosis, & segmental dilation of the obstructed intra hepatic & extra hepatic bile ducts

- In PSC, UC (ulcerative colitis) coexists in 70% of patients with PSC
- In patients of UC, 4% develop PSC

■ Epidemiology: ▲3-5th decades of life ▲M:F = 2:1

■ Pathogenesis: underlying causes: ◆Exposure to gut derived toxins ◆Immune attack (By autoantibodies) ◆Ischemia of biliary tree

■ Clinical features: ◆Asymptomatic ◆Persistent ↑ serum alkaline phosphatase ◆Fatigue, pruritis, jaundice, weight loss, ascitis, bleeding, encephalopathy (especially in late stages) ◆Antimitochondrial antibodies < 10% of cases (important to differentiate it from primary biliary cirrhosis) ◆Antinuclear cytoplasmic antibodies in 80% of cases

■ Morphology: ▼Concentric periductal onion-skin fibrosis & lymphocytic infiltrate (surrounding the bile duct) ▼Atrophy & obliteration of bile ducts ▼Dilation of bile ducts inbetween areas of stricture ▼Cholestasis & fibrosis ▼Cirrhosis ▼Cholangiocarcinoma (10-15% of cases)

SECONDARY BILIARY CIRRHOSIS

- Prolonged obstruction to extrahepatic biliary tree

■ Causes: (any condition that causes obstruction of the biliary tree): ◆Cholelithiasis ◆Malignancies ◆Stricutres (the common bile duct is abnormally narrow) ◆Biliary atresia (one or more bile ducts are congenitally narrow, blocked, or absent)

PRIMARY BILIARY CIRRHOSIS

- Chronic, progressive & often fatal cholestatic liver disease
- Non-suppurative granulomatous destruction of medium-sized intrahepatic bile ducts, portal inflammation & scarring

■ Epidemiology: ▲Age: 20-80 years (peak incidence in 40-50 yrs) ▲F>M

- Insidious onset >> When symptoms appear, their onset is insidious, with patients typically complaining of slowly increasing fatigue & pruritus
- Symptoms: Pruritis, jaundice, & Cirrhosis over 2 or more decades (after initial representation)

■ Clinical features: ◆ ↑ Alkaline phosphatase & cholesterol ◆Hyperbilirubinemia ◆Antimitochondrial antibodies (in > 90% of the cases) especially Antimitochondrial pyruvate dehydrogenase
◆Associated conditions: Sjogern syndrome, Scleroderma thyroiditis, RA, Raynaud's phenomenon, MGN, & celiac disease (All of them are autoimmune diseases)

■ Morphology: ▼Interlobular bile ducts are absent or severely destructed (florid duct lesion) ▼Intra epithelial inflammation ▼Granulomatous inflammation (centered around destructed duct) ▼Bile ductular proliferation ▼Cholestasis (due to destruction of biliary tree) ▼Necrosis of parenchyma ▼Eventually, fibrosis & Cirrhosis

Extra note: Florid duct lesion: granulomatous destruction of the bile ducts, it's the histological hallmark of PBC.

Liver Diseases

BUDD – CHIARI SYNDROME

- Thrombotic occlusion of the hepatic vein

■ Causes: 🔷PCV (Polycythemia vera: increased tendency for thrombus formation) 🔷Pregnancy 🔷Postpartum 🔷Oral contraceptive 🔷PNH (Paroxysmal nocturnal hemoglobinuria: a rare blood disease that causes red blood cells to break apart) 🔷Mechanical obstruction 🔷Tumors as HCC 🔷Idiopathic in 30% of the cases

■ Morphology: 🔻Swollen liver, red with tense capsule 🔻centrilobular congestion & necrosis 🔻Fibrosis (if the case was sub-acute or chronic it might be associated with fibrosis) 🔻Thrombi

■ Clinical features: 🔶Hepatomegaly (increased liver size) 🔶weight gain 🔶Ascites 🔶Abdominal Pain

- Mortality rate is high if not treated

SINUSOIDAL OBSTRUCTION SYNDROME (VENO-OCCLUSIVE DISEASE)

- Originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloids
- This occurs in the first 20-30 days after bone marrow transplantation

■ Causes: 🔷Drugs as cyclophosphamide 🔷Total body radiation (like radiation before bone marrow transplantation → resulting in damaging the liver, particularly sinusoidal epithelium)

In other words, it is a complication of radiation to the whole body or high-dose chemotherapy given before a bone marrow transplant.

■ Incidence: 20% in recipients of allogeneic marrow transplant.

■ Pathogenesis: Mechanism: Toxic injury to sinusoidal endothelium (due to drugs or irradiation) → emboli formation → blockage of blood Flow → Passage of blood into space of Disse → stellate cells activation → fibrosis

■ Clinical presentation: 🔶Mild to severe 🔶Death if it is not resolved in 3 months

1 Final group of diseases > Liver Nodules & Tumors

2 pages left 🥳

LIVER NODULES

➢ Focal Noudular Hyperplasia

- Well demarcated hyperplastic hepatocytes with central scar, forming localized non-diffused nodules.
- Non-cirrhotic liver
- Not neoplasm but nodular regeneration
- No risk of malignancy (but can be misdiagnosed for malignant nodules)
- 20% of cases have cavernous hemagnioma
- Cause: Local vascular injury
- In females of reproductive age

Liver Diseases

- Macroregenerative Nodules
  - Cirrhotic liver
  - Larger than cirrhotic nodules
  - No atypical features
  - Reticulin is intact (architecture is preserved)
  - No malignant potential

LIVER TUMORS

Benign Neoplasms:

- Cavernous Hemagioma
  - The most common benign liver tumor
  - It's a vascular liver tumor characterized by a collection of dilated blood vessels forming a lesion.
  - Usually <2cm (small)
  - Subcapsular
  - The importance of it: its location in the liver → it can mimic other benign or malignant tumors. Also, it can cause intraperitoneal bleeding

- Liver Cell Adenoma (Hepatocellular Adenoma)
  - Young females with history of oral contraceptive intake.
  - It may rupture, especially during pregnancy (because it may grow rapidly, & this enlargement is due to the hormonal production) → causing severe intraperitoneal hemorrhage
  - Rarely may contain HCC (usually benign)
  - Misdiagnosis Of HCC

> - Extra note: Estrogen stimulates the development of hepatocellular adenoma, thus HA is associated with oral contraceptive intake & pregnancy.

Malignant Neoplasms:

- Primary liver carcinoma could be:
  1. Hepatocellular carcinoma (HCC): origin: hepatocytes
  2. Cholangiocarcinoma (CC): origin: epithelium of biliary duct
  3. Mix of both.

■ Morphology of liver cancer: 🔻Unifocal or Multifocal 🔻Diffusely infiltrative 🔻mode of metastasis: Vascular invasion is common in all types - to lungs, bones, adrenals, & brain, 🔻Well differentiated to highly Anaplastic

■ Clinical presentation of liver cancer: 🔶abdominal Pain, 🔶malaise, 🔶weight loss, 🔶increase α-feto protein in 60-75% of cases.

- Death within 7-10 months.☹️→ Causes: 🔷Cachexia 🔷GI bleeding 🔷Liver failure 🔷Tumor rupture & abdominal hemorrhage

> α-fetoprotein increases also with:
> ⭐yolk sac tumor, ⭐cirrhosis, ⭐massive liver necrosis, ⭐chronichepatitis, ⭐normal pregnancy, ⭐fetal distress or death, ⭐fetal neural tube defect

Liver Diseases

➢ Hepatocellular Carcinoma (HCC)

- 5.4% of all cancers

■ Epidemiology:

- Blacks > white
- Incidence: ▲< 5/100000 population in N&S America, north & central Europe, Australia ▲15/100000 population in Mediterranean ▲36/100000 population in Korea, Taiwan, Mozambique, china
- in low incidence areas: ▲M:F ratio= 3:1 ▲Age: > 60yr
- in high incidence areas ▲M:F ratio = 8:1 ▲Age: 20-40yr

■ Predisposing Factors:

1. Hepatitis carrier state: ◆vertical transmission (HBV) increases the risk 200X ◆cirrhosis may be absent ◆young age group (20-40yr)
2. Chronic hepatitis B infection: ◆>85% of cases of HCC occur in countries with high rates of chronic HBV infection
3. Cirrhosis: ◆In western countries cirrhosis is present in 85-90% of cases ◆> 60yr ◆HCV & alcoholism
4. Aflatoxins (in African countries) (mutagens produced by Aspergillus flavus)
5. Hereditary tyrosinemia: ◆in 40% of cases (extra note: it's a metabolic disorder involves impaired break down of the amino acid tyrosine affects liver & kidneys).
6. Hereditary hemochromatosis (metabolic disorder)

■ Pathogenesis:

1. Repeated cycles of cell death & regeneration HBC, HCV → gene mutations (especially mutations in oncogenes & tumor suppressor genes) & genomic instability
2. Viral integration: HBV DNA intergration → leads to clonal expansion, & to genomic instability not limited to integration site (instability related to sites associated with oncogenes or tumor suppressor genes)
3. HBV: X-protein → leads to transactivation of viral & cellular promoters, Activation of oncogenes (important genes involved in tumors or in developing malignancies), OR Inhibition of apoptosis
4. Aflatoxins (fungus Aspirgillus flavus) → mutation in p53
5. Cirrhosis & its causes; such as ◆HCV, ◆Alcohol, ◆Hemochromatosis, ◆Tyrosinemia (40% of patients develop HCC despite adequate dietary control)

■ Morphology: ▼Unifocal or Multifocal or Diffusely infiltrative ▼metastasis: Vascular invasion ▼Well differentiated to Anaplastic

➢ Cholangiocarcinoma

- Cancer in the epithelial cells of hepatic bile ducts
- Desmoplastic.
- Vascular metastasis to the lungs, bones, adrenals, & brain occurs.

➢ Fibrolamellar Carcinoma

- single hard scirrhous tumor
- Epidemiology: ▲20-40 year-old ▲M=F
- No relation to HBV or cirrhosis
- better prognosis.

خلصتتت الحمدلله

اللّهم إني استودعتك ما قرأت وما حفظت وما تعلمت، فرده لي عند حاجتي إليها إنك على كل شيءٍ قدير، وحسبنا الله ونعم الوكيل

Done by:
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