Liver Diseases.

Right upper Quadrant Pain.

Hepatic Injury types

General Features about liver

has many function —> clinical manifestation of its disease is related to its loss of funtion

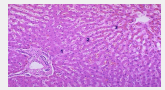
has huge functional capacity —> SO, lost when MOST of the hepatocytes are lost, since if only a few are damaged from injury the other viable cells will increase their function to keep normality

brown in colour & has smooth outer surface

shape changes indicate different diseases

structure (functional unit)

- each lobule is composed of 6 acini
- lobule
- each acinus is composed of 3 zones
  - zone 1 (periportal area)
  - zone 2 (parenchyma between zone 1 & 3)
  - zone 3 (pericentral area)



parenchyma is organized into plates of hepatocytes

- hepatocytes are radially oriented around terminal hepatic vein (central vein) — this plate can be lost during hepatic injury
- hepatocytes show only minimal variation in the overall size, but nuclei may vary in size, number & ploidy (no. of chromosome)
- vascular sinusoids presents between cords of hepatocytes
- hepatocytes are lined with kuppfer cells

exchange between blood and hepatocytes occurs in sinusoids which makes it important as they absorb substances that are brought by hepatic artery and they excrete their products into veins

this exchnage is affected during diseases and manifested as the accumulation of many substances which can be toxic, and loss of substances that are being produced by the liver —> proteins

hepatic injury types

- Inflammation = hepatitis
- Degeneration
  - ballooning degeneration
  - feathery degeneration —> retained biliary material, accumulation of iron & copper
- Steatosis
- Necrosis
- Regeneration
- Fibrosis
- Cirrhosis
- Ductular Proliferation

Clinical Syndromes

the major clinical syndromes of liver disease are

- Hepatic Failure
- Cirrhosis
- Portal Hypertension
- Cholestasis

Ductular Proliferation

abnormal increase in the number of bile ducts within the liver

this proliferation of bile ducts can occur in certain diseases that specifically affect the biliary tract, which includes the structures involved in the production, transport, and excretion of bile

Fibrosis

the formation of excess fibrous connective tissue in response to chronic or sever injury

no organization of the fibrous tissue

CHRONIC & irreversible

types

- Periportal Fibrosis
- Pericentrl Fibrosis
- Bridging Fibrosis
- Pericellular Fibrosis

fibrous tissue deposits diretly within the sinusois around singl or multiple hepatocytes

Regeneration

evidenced by increased mitosis or cell cycle markers

Progenitor cells

- cells of Canal of Herring (located in the small bile ducts)
- have the capacity to differentiate into both: hepatocyte & bile duct cells
- if there is an injury & we lose heptocytes, progenitor cells can be stimulated & start to divide into new hepatocytes

this is normal

mitotic activity of hepatocytes may be increased in disease processes

Necrosis

depending on the type

- Coagulative Necrosis
  - coagulation —> ischemia —> decreased O2 level —> decreased ATP —> decreased pumping of ions —> swelling
  - location: around central vein
  - caused by ischemia
- Councilman bodies
  - individual hepatocytes appears shrinked with prominent eosinophilic pigmented nucle (condensed chromatin)
  - it indicates that the liver has been exposed to injury
  - may present without inflammation
- Lytic Necrosis
  - caused by hydrolytic enzymes
  - infection-associated liqeufactive necrosis

depending on the cause

- Ischemic
- Toxic

depending on the location

- Centrilobular bodies
  - location: around central vein
- Mid zonal
- Periportal (interface hepatitis)
  - T-cell induced hepatocyte apoptosis
  - location: zone 1
  - seen in viral hepatitis
- Focal
  - peice meal necrosis
    - if mild & reversible inflammation — necrosis is limited to the periportal area
    - if more severe inflammation — necrosis extends to the adjacent parenchyma
  - bridging necrosis
    - necrosis connects between 2 sites in the liver (e.g central vein & portal area)
    - indicats that the process is severe
    - can heal by fibrosis, which is something very ominous in the liver, since it indicates that the process is goning into the chronic process, which can develop into cirrhosis

- Diffuse
  - if 90% of hepatocytes are damaged — massive necrosis
  - less than 90% — sub-massive necrosis
  - classified depeding on the amount of hepatocytes that is destroyed

Inflammation = Hepatitis

can be chronic or acute

presented by infiltration of parenchyma by inflammatory cells

Degeneration, Ballooning Degeneration

swelling of the hepatocytes due to injury

irregularly clumped cytoplasm, showing large clear spaces

substance may accumulate in hepatcytes

- fat
- iron
- copper
- retained biliary material — will appear as a brown pigment within the hepatocyte

Steatosis

description

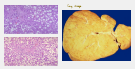
- fat accumulation within the cytoplasm of hepatocyte
- fat accumulation begins in zone 3

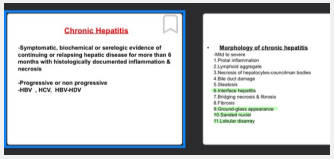
forms

- Microvesicular
  - the cytoplasm of hepatocytes is filled with tiny lipid droplets, and the nucleus is located centrally in the cell
  - conditions associated with it
    - Reye's syndrome
    - ACUTE fatty change or pregnancy
    - ALD (alcohol liver disease)
- Macrovesicular
  - a single large fat droplet or smaller well-defined fat droplets occupy the cytoplasm of hepatocytes, pushing the nucleus to the periphery
  - conditions associated with it
    - DM
    - obese

morphology

- colour change to yellow
- soft greasy consistency





Hepatic Failure

→ Due to chronic more than Acute.

→ may be a Dysfunction with NO cirrhosis

Description

- results when the hepatic functional capacity is almost totally lost
- is the end result of severe hepatic damage
- most common cause is due to chronic process (much more than acute)
- if the failure is acute, we should think of viral infection
  - fulminant viral hepatitis
  - hepatitis C
  - hepatitis D superimposd in B
  - hepatitis A — particularly if it occurs in adults who are not immunized to A
  - hepatitis E — with pregnant women

Complications

- multiple organ failure: kidneys & lungs
- coagulo-pathy —> def. factors (II, VII, IX, X)
- bleeding
- Hepatic encephalopathy —> ↓ level of consiousness, rigidity, hyperreflexia, EEG [electroencephalogram] changes, seizures & asterixis (Result of Acute)
- Hepato-Renal syndrome

Clinical Features

- Jaundice
- Hypo-albuminemia —> decreased collic pressure —> edema
- Hyper-ammonemia
- Fetor hepaticus (musty Or sweet & sour breathe)
- Palmar erythema
- Hyper-estrogemia
- Spider angiomas
- Hypo-gonadism & Gynecomastia (enlargement of man,s breast)

Categories

1. ACUTE liver failure with massive hepatic necrosis
   - most often caused by drugs or fulminant viral hepatitis
   - denotes clinical hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy within 2 to 3 weeks
   - A course extending as long as 3 months is called SUBACUTE failure
   - The histologic correlate of acute liver failure is massive hepatic necrosis
   - is an uncommon but life-threatening condition that often requires liver transplantation

   → May Result in Hepatic encephalopathy.

2. CHRONIC liver failure
   - the most common route to hepatic failure
   - chronic liver damage ending in cirrhosis
3. hepatic dysfunction, without overt cirrhosis
   - hepatocytes may be viable, but unable to perform normal metabolic function
   - examples
     - Reye's syndrome
     - tetracycline toxicity
     - ACUTE fatty liver of pregnancy

Hepatocytes are still viable, can't work

↳ Acute fatty liver → preg → Reye's → tetracycline toxicity.

can lead to ACUTE liver failure a few days after onset

→ mainly By Hepatitis E

Massive hepatic necrosis

-Fulminant hepatic failure from the onset of symptoms to hepatic encephalopathy (within 2 -3 wks).
Subfulminant (within 3 months).

Causes:

1-Viral hepatitis 50 – 65% (B, B-D, A,C hepatitis)
2-Drugs & chemicals 20 – 30%
3-Heat stroke
4-Hepatic vein obstruction
5-Wilson disease
6-Acute fatty liver of pregnancy
7-Massive malignant infiltration
8-Reactivation of chronic HBV hepatitis on HDV superimposed infection
9-Autoimmune hepatitis

Cirrhosis

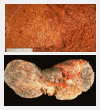
Clinical Features

- silent
- Anorexia (loss of appetite), weight loss, weakness
- progressive hepatic failure
- complications
  - portal hypertension
  - hepatocelular carcinoma

Main Characteristics

- bridging FIBROUS septae
- Parenchymal NODULES encircled by fibrotic bands
- architecture disruption

Types



- MICRO-nodules < 3mm in diameter
- MACRO-nodules > 3mm in diameter

Causes

- CHRONIC alcoholism
- CHRONIC viral infection
  - hepatitis B virus (HBV)
  - hepatitis C virus (HCV)
- biliary disease
- hemochromatosis
- autoimmune hepatitis
- Wilson disease
- α-1- antitrypsin deficiency
- rare causes
  - galactosemia
  - tyrosinosis
  - glycogen storage disease III & IV
  - lipid storage disease
  - hereditary fructose intolerance
  - drug-induced (e.g methyldopa)
  - cryptogenic cirrhosis (10%) — cirrhosis of uncertain etiology

Pathogeneis

cirrhosis requires cell death to occur over long periods of time

1) hepatocellular death

2) regeneration

fibrosis progresses to scar formtion when the injury involves not only the parenchyma, but also the Supporting Connective tissue (

the ECM collagen (types I, III, V, XI) is present only in (liver capsule, portal tracts & around central vein)

- in normal liver: delicate framework of type IV collagen & other proteins lie in SPACE OF DISSE
- in cirrhosis: types I & III collagen & others are deposited in the SPACE OF DISSE

3) progressive fibrosis

the stimuli for the activation of Stellate cells & production of collagen are

- ROS
- Growth factors
- cytokines, TNF, IL-1, lymphotoxins

4) vascular changes consisting of

loss of sinusoidal ENDOthelial cell fenestrations

development of vascular shunts that contribute to defects in liver function

- portal vein-hepatic vein shunt
- portal vein-hepatic artery shunt

Vascular shunts create abnormal connections between arteries and veins in the liver → bypass the normal liver circulation → inadequate blood supply to the liver tissue → liver tissue damage → fibrosis → cirrhosis.

• ← NOTE

Portal Hyper-tension

Description

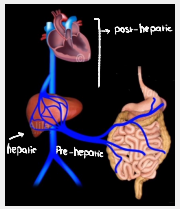
- increased blood pressure in the portal venous system

Pathogenesis

- ↑ resistance to portal blood flow at the level of SINUSOIDs
  - compression of central veins by (peri-venular fibrosis) & (parenchymal nodules)
  - Arterial–portal anastomosis develops in the fibrous bands → increase the blood pressure in portal venous system

Causes

- PRE-hepatic
  - portal vein thrombosis
  - massive splenomegaly
- POST-hepatic
  - severe RIGHT sided heart failure
  - constrictive Peri-Carditis
  - hepatic vein outflow obstruction
- hepatic
  - cirrhosis
  - schistosomiasis (infection)
  - massive fatty change
  - diffuse granulomatosis as: sarcoidosis (inflammatory disease), TB
  - disease of portal microcirculation as: nodular regenerative hyperplasia



Clinical Consequences

Ascites

- collection of excess fluid in peritoneal cavity —> it becomes clinically detectable when at least 500ml have accumulated
- Features (fluid composition)
  - serous fluid
  - contains as much as 3g/ml of protein (albumin)
  - it has the same concentration as blood of glucose, Na+ & K+
  - MESOthelial cells & lymphocytes
  - neutrophils = inflammation
  - RBCs = disseminated cancer
- Pathogenesis
  - SINUSOIDAL increased blood presure
  - hypo-albumin-emia
  - leakage of hepatic lymph into the peritoneal cavity
    - normal thoracic duct lymph flow = 800-1000 ml/day
    - in cirrhosis, it may approach 20L/day
  - renal retension of Na+ & water due to secondary hyper-aldosteronism

Porto-Systemic shunts

Because of ↑ portal venous pressure —> bypasses develop wherever the systemic & portal circulation share capillary beds

- Gastro-Esophageal junction —> Varices
  - appear in 65% of patients with advanced cirrhosis
  - cause death in 50% of them due to UGI bleeding
- sites
  - around & within the rectum —> Hemorrhoids
  - Retro-Peritoneum
  - Falciform ligament of the liver (Peri-Umbilical & abdominal wall collaterals) —> Caput Medusae

Hepatic Encephalopathy

a complication of ACUTE & CHRONIC hepatic failure

- disturbance in brain function ranging from
  - behavioural changes
  - marked confusion & stupor
  - coma & death
- the changes may progress over hrs or days
- Neurological signs
  - rigidity
  - hyper-reflexia
  - non-specific EEG (electro-encephalo-gram)
  - seizures
  - asterixis (non-rhythmic rapid extension flexision movements of head & extremities)
- brain signs
  - edema
  - astrocytic reaction
- Pathogenesis
  - I/ Severe loss of hepatocellular function
  - 2/ Shunting of blood around damaged liver
  - 3/ Exposure of Brain to toxic metabolic products
  - ↑ NH3 level in blood → generalized brain edema impaired neuronal function — ACUTE insult
  - alteration in central nervous system AA (amino acids) metabolism — CHRONIC insult

Splenomegaly

- normal spleen < 300g
- enlarged spleen: 500-1000g
- not necessarily correlated with other features of portal hypertension
- may result in hyper-splenism

Alcoholic Liver Diseases

General Notes

- alcohol is the 5th leading cause of death due to: accidnts & alcoholic cirrhosis
- causes more than 60% of chronic liver disease
- the legal definition for driving under the influence of alcohol
  - if the blood alcohol levels = 80-100 mg/dl
  - 44ml of ethanolis required to produce this level in 70kg person
- short term ingestion of 80 g/day of ethanol generally produces mild, reversible Hepatic changes
- chronic intake of 50-60gm/day is considered a borderline risk for severe injury
- in occasional drinkers
  - blood level of 200 mg/dl produces: coma
  - blood level of 300-400 mg/dl produces: death & respiratory failure
- habitual drinkers
  - can tolerate levels up to 700 mg/dl without clinical effect
  - this is due to metabolic tolerance explained by 5-10X induction of cytochrome p-450 system that includes enzyme CYP2E1, which increases the metabolism of ethanol & other drugs as cocaine & acetominophen
- women seem to be more susceptible to hepatic injury than are men because of low gastric metabolism of ethanol and differences in body composition
- forms of alcoholic liver disease
  - Hepatic Steatosis (90-100% of drinkers)
  - Alcoholic Hepatitis (1-35% of drinkers)
  - Cirrhosis (14% of drinkers)
  - steatosis & hepatitis may develop independently

Causes of death in alcoholic liver disease

!! Death !!

- hepatic failure
- massive GI bleeding
- infections
- hepato-renal syndrome
- HCC (hepatocellular carcinoma) in 3-6% of cases

Mechanism of Ethanol Toxicity

- Fatty change
  - due to excess production of NADH over NAD in cystol & mitochondria
  - Shunting of lipid catabolism toward lipid bio-synthesis
  - ↑ peripheral catabolism of fat → ↑ FA delivery to the liver
  - Acetaldehyde forms adducts with tubulin (monomer of microtubules) → ↓ function of microtubules → ↓ in lipoprotein transport from liver
  - ↓ secretion of lipoproteins from hepatocytes
  - ↓ oxidation of FFA by mitochondria
- enhances the metabolism of drugs to toxic metabolites (e.g acetominophen)
- CYP2E1 is induced by chronic alcohol consumption
- ↑ free radicals production —> leads to membrane & protein damage
- Alcohol directly affect microtubular & mitochondrial function & membrane fluidity
- Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes → immune attack
- Superimposed HCV infection causes acceleration of liver injury (HCV hepatitis occurs in 30% of alcoholics)
- Alcohol → release of bacterial endotoxins into portal circulation from the gut → inflammation of the liver
- Alcohol → regional hypoxia in the liver due to release of ENDOthelins which are potent vaso-constrictors → ↓ hepatic sinusoidal perfusion
- Alteration of cytokine regulation
  - TNF (a major effector of injury)
  - IL6, IL8, IL18

Ethanol metabolism

- absorbed as ethanol
- Women have lower levels of gastric alcohol dehydrogenase activity than men & they may develop higher blood Levels than men after drinking the same quantity of ethanol
- by alcohol dehydrogenase in the stomach & liver
- Ethanol —> Acetaldehyde
  - by cytochrome P-450 in the liver
  - by catalase in the liver
- Acetaldehyde —> Acetic acid
  - by aldehyde dehydrogenase
- 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
- there is genetic polymorphism in aldehyde dehydrogenase that affect etanol metabolism
- 50% of chinese, vietnamase & Japanese have lowered enzyme activity due to point mutation of the enzyme → accumulation of acetaldehyde → facial flushing, tachy-cardia & hyper-ventilation

1 Hepatic Steatosis

- description
  - liver is enlarged (4-6 kg) soft yellow & greasy
  - fatty change is reversible, with complete abstention from further intake of alcohol
- moderate intake of alcohol —> microvesicular steatosis
- chronic intake —> diffuse steatosis
- continued intake —> fibrosis
- Clinical Features
  - ↑ liver (in size)
  - ↑ liver enzyme
  - severe hepatic dysfunction is unusal

2 Alcoholic Hepatitis

weight loss.

- Characteristic Findings
  - Hepatocyte swelling & necrosis
    - accumulation of fat, water & proteins
    - Cholestasis (impaired production, secretion, or outflow of bile)
    - Hemosiderin (is a brown iron-containing pigment) deposition in hepatocytocytes & kupffer cells
  - Mallory-hayline bodies
    - description
      - easinophilic cytoplasmic inclusions
      - in degenerating hepatocytes
      - formed of cytokeratin intermediate filaments & other proteins
    - NOTE: Mallory-hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease
    - they are also seen in
      - primry biliary cirrhosis
      - Wilson disease
      - CHRONIC cholestatic syndromes
      - hepatocellular carcinoma
  - Neutrophilic reaction
  - Fibrosis (as a remodeling)
    - Sinusoidal & peri-venular fibrosis
    - Peri-portal fibrosis
  - Cholestasis
- Clinical Features
  - 15-20 years of excesive drinking
  - non-specific symptoms: malaise, anorexia, weight loss
  - ↑ liver & spleen (in size)
  - ↑ LFT (liver function test)
  - Each bout of hepatitis → 10-20% risk of death → cirrhosis in 1/3 in few yrs

3 Alcoholic Cirrhosis

Mixed Macro and Micro

- usually it develops slowly
- initially, the liver enlarged & became yellow —> but over years it becomes brown, shrunken & non-fatty organ
  - enlargement followed by shrinkage.
- it can develop rapidly in the presence of alcoholic hepatitis (within 1-2 years)
  - Rapid after
- !! irreversible
- ★★★ mallory bodies are rerely evident at this stage
- Portal Hypertension
- bile stasis
- Laennec cirrhosis = scar tissue
  - cirrhosis associated with → scar tissue.
- Clinical Feature
- micronodules
- mixed micro & macronodules

Non-alcoholic Fatty liver Disease (NAFLD)

Types

- Steatosis (abnormal fat accumulation in liver)
- Steato-Hepatitis (hepatic inflammation due to fat)
  - hepatocyte destruction
  - parenchymal inflammation
  - progressive peri-cellular fibrosis

Predisposing Factors

- type 2 DM (insulin resistance)
- obesity
- dys-lipidemia (↑ TG, ↑ LDL, ↓ HDL)

Mechanism of Fatty Accumulation

- impaired oxidation of fatty acids
- synthesis & uptake of FA
- decreased hepatic secretion of VLDL

Fat accumulation —> ↑ TNF, IL6, chemokine —> liver inflammation & damage

Clinically

- NAFLD is the most common cause of incidental increase in TRANSAMINASEs
- most patients are asymptomatic
- non-specific symptoms
  - fatigue
  - malaise
  - RUQ (right upper quadrant) discomfort
- severe symptoms
- liver biopsy is required for Dx
- NAFLD is a significant contributer to Cryptogenic Cirrhosis

Drug-Induced liver disease

Drug-induced CHRONIC hepatitis

drug-induced chronic hepatitis is clinically and histologically indistinguishable from chronic viral hepatitis or autoimmune hepatitis and hence serologic markers of viral infection are critical for making the distinction

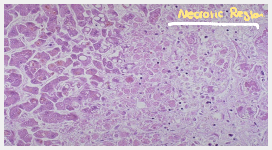
Drugs that may cause ACUTE liver failure

about 60% of these are a consequence of accidental overdosage

- the most common cause (46% of cases) Acetaminophen
- Halothane
- Antituberculosis drugs (Rifampin, Isoniazid)
- Antidepressant Monoamine Oxidase inhibitors
- Toxins as: CCl4 & mushroom poisoning

Patterns of injury

Pattern of Injury	Morphology	Examples
Cholestatic	Bland hepatocellular cholestasis, without inflammation	Contraceptive and anabolic steroids
Cholestatic hepatitis	Cholestasis with lobular necroinflammatory activity	antibiotics; phenothiazines
Hepatocellular necrosis	Spotty hepatocyte necrosis	Methyldoya, phenytoin
	Submassive necrosis, zone 3	Acetaminophen, halothane
	Massive necrosis	Isoniazid, phenytoin
Steatosis	Macrovesicular	Ethanol, methotrexate, corticosteroids, total parenteralnutrition
Steatohepatitis	Microvesicular Mallory bodies	Amiodarone, ethanol
Fibrosis and cirrhosis	Periportal and pericellular fibrosis	Methotrexate, isoniazid enalapril
Granulomas	non-caseating	Sulfonamides
Vascular lesions	Sinusoidal obstruction syndrome (veno-occlusivedisease)	High-dose chemotherapy bush teas
	Budd-Chiari syndrome	Oral contraceptives(OCP)
	Sinusoidal dilatation Peliosis hepatis (blood-filled cavities)	Oral contraceptives (OCP) Anabolic steroids tamoxifen
Neoplasms	Hepatic adenoma	OCP anabolic steroids
	HCC	Thorotrast
	Cholangiocarcinoma	Thorotrast
	Angiosarcoma	Thorotrast, vinyl chloride



Morphology

Drugs Reactions

- Predictable (intrinsic)
  - may occur in anyone who accumulates a sufficient dose (Dose-Dependent)
  - drugs
    - Acetaminophen
    - Tetracycline
    - Antineoplastic agents
    - CCl4
    - Alcohol
- Un-predictable (idiosyncratic = unique to an individual)
  - depends on idiosyncrasies of the host
    - the host's propensity to mount an immune response to the antigenic stimulus
    - the rate at which the host metabolizes the agent
  - drugs
    - Chlorpromazine
    - Halothane
    - Sulfonamides
    - Methyldopa
    - Allopurinol

Mechanisms of drug injury

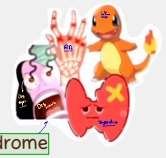
- Direct Toxic damage
  - drugs
    - Acetaminophen
    - CCl4
    - Mushroom toxins
- Immune-mediated damage
- the injury may be immediate or take weeks to months to develop

picture
Alcoholic liver Dis.

Autoimmune Hepatitis

Description

- CHRONIC hepatitis with immunologic abnormalities
- Female predominance (70%)
- associated with other autoimmune diseases in 60% of the cases
  - RA
  - Thyroiditis
  - Sjogern sndrome
  - UC (ulcerative colitis)



The Type of Auto-antibodies

- Anti-smooth muscle
  - anti-actin
  - anti-troponin
  - anti-tropomyosin
- liver/kidney microsomal antibodies
  - anti-cytochrome P-450 components
  - anti-UDP-glucuronosyl transferase
- Anti-soluble liver/pancreas antigen

Diagnosis

- NEGATIVE serelogy for viral antigens
- ↑ serum immunoglobulin (>2.5 g/dl)
- high titers of autoantibodies (80% of cases) Antibodies titer test
- Histologic features are similar to CHRONIC viral hepatitis histologically

Clinically

- Indolent or Severe course
- mild to severe CHRONIC hepatitis
- risk of cirrhosis in 5% of cases —> which is the main cause of death

Treatment

- dramatic response to immunosuppressive therapy
- full remission is unusual

Hemochromatosis

Description

- excessive acumulation of body IRON
- Primary or Secondary (genetic or acquired)
- symptoms appear 5th – 6th decades & not before age 40

Causes of ACQUIRED hemochromatosis

- multiple transfusions
- ineffective erythropoiesis (Thalassemia)
- increased iron intake (Bantu Sidrosis)
- CHRONIC liver disease

Pathogenesis

- primary (herediatary) defect in intestinal absorption of dietary iron —> leading to net iron accumulation of 0.5-1 g/year
  - normally: total body iron= 2-6g, 0.5g in the hepatocytes
  - in disease: total body iron > 50g, 1/3 in liver
  - genetic hemochromatosis (4 variants)
  - the most common responsible gene is (HFE gene) —> autosomal recessive (AR, HFE)
    - located on chromosome 6 close to HLA gene complex
    - regulates the level of Hepcidin hormone synthesized in liver
      - Hepcidin → reduces Fe. absorption from intestine
    - HFE gene deletion causes iron overload
    - mutation can occur in HFE gene
      - Mutation at 845 nucleotide → leading to Tyrosine substitution for Cystine at AA 282 (C-282-Y)
        - carrier rate for C282Y = 1/70
        - 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 C282Y/H63D mutation
      - Aspartate substitution for Histidine at AA 63 (H-63-D)
      - 10% of patients have other gene mutations
- Excessive Fe deposition → toxicity of the tissues
  - lipid per-oxidation
  - stimulation of collagen formation
  - DNA damage
  - in the liver

Clinically

- Hepatomegaly
- Abdominal pain
- Skin pigmentation (75-80%)
- DM (due to pancreas fibrosis) (75-80%)
- Cardiac dysfunction
- Atypical arthritis
- Hypo-gonadism
- ↑ serum Fe ferritin
- HCC (hepatocellular carcinoma) x200 ↑ in the risk

Morphological Changes

- deposition of Hemosiderin (iron-containing, granular pigment) in diffrent organs
  - liver
  - pancreas
  - myocardium
  - pituitary
  - adrenal
  - thyroid & parathyroid
  - joints
  - skin
- Cirrhosis (in all patients)
- Pancreatic Fibrosis
- Myocardium fibrosis
- Synovitis
- Polyarthritis (pseudogout)
- Pigmentation of liver
- Atrophy of testes

29/4 Patho 5

Wilson Disease

Description

AR

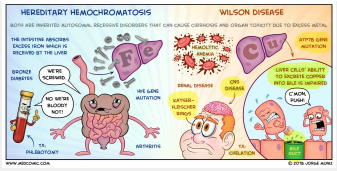
Autosomal recessive disorder of Cu metabolism

mutation in ATP-7B gene on chromosome 13

- this gene encodes an ATPase metal ion transporter in Golgi region
- there are > 80 mutation

gene frequency = 1/200

incidence = 1/30000



Pathogenesis

normally

the main source of Cu is from diet

1) absorption of ingested Cu (2-5 mg/day)

2) complex with albumin

3) hepatocellular uptake

4) incorporation with α-2-globulin to form Ceruloplasmin — ATP7B

5) secretion into plasma (90-95% of plasma Cu)

6) hepatic uptake of Ceruloplasmin

7) lysosomal degradation

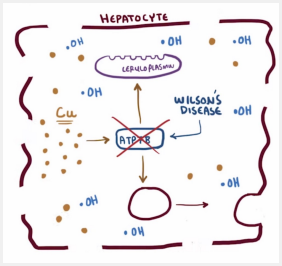
8) secretion of free Cu into bile — ATP7B

in wilson disease

absorbed Cu fails to enter the circulation in the form of Ceruloplasmin & the biliary excretion of Cu is decreased —> Cu accumulation in liver

Cu accumulation results in

- production of free radicals
- binding to Sulfhydryl groups of cellular proteins
- displacement of other metals in hepatic METALLO-enzymes
- by the age of 5 years —> Cu spills over to circulation causing: hemolysis & involvement of other organs as brain, cornea, kidneys, bones, joints & parathyroid glands



so, the urinary excretion of Cu increases (rather than biliary excretion)

Diagnosis

- ↓ in serum ceruloplasmin level
- ↑ in urinary excretion of Cu
- ↑ hepatic content of copper (> 250 mg/g dry weight)

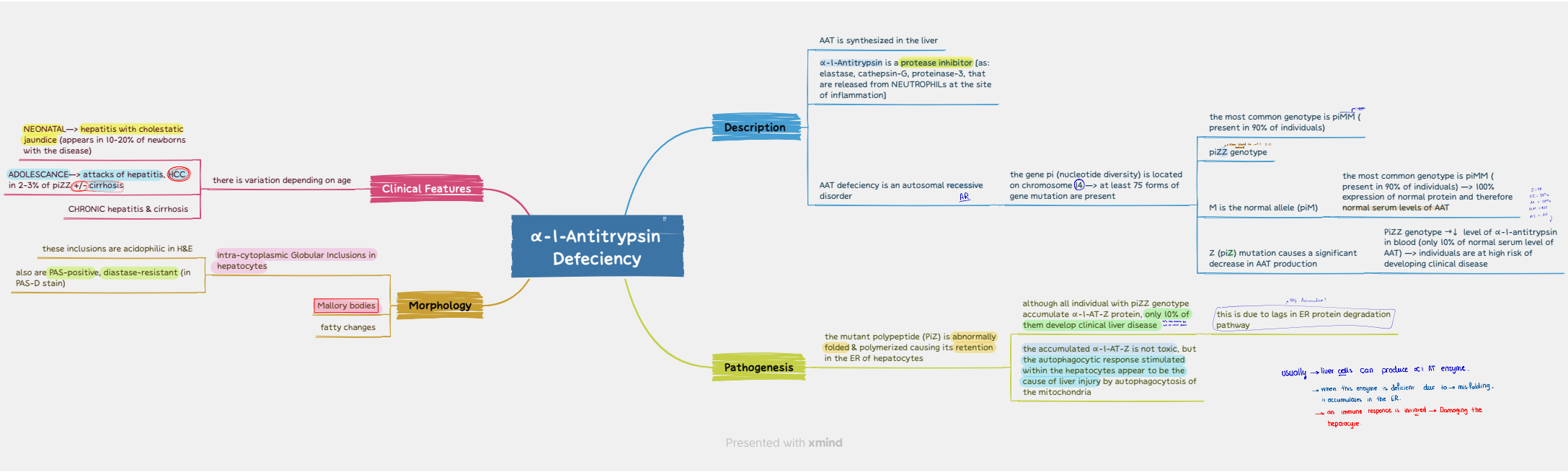
Clinically

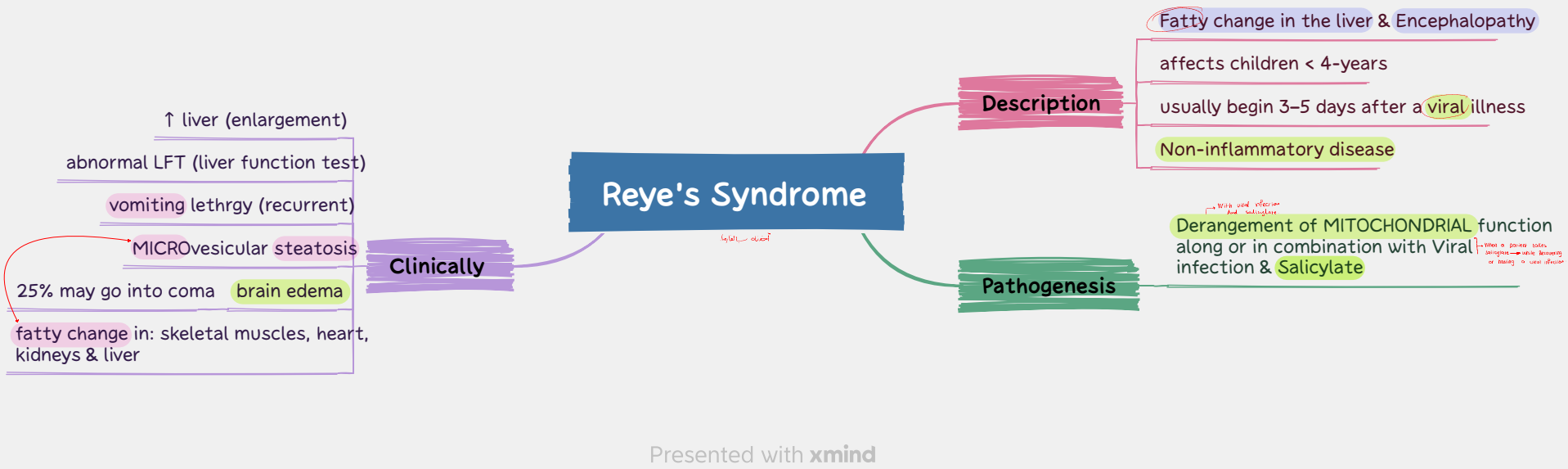
- presentation > 6 years of age
- most common presentation is ACUTE on CHRONIC hepatitis
- neuro-psychiatric presentation
  - behavioral changes
  - frank psychosis
  - parkinson disease-like syndrome

Morphology

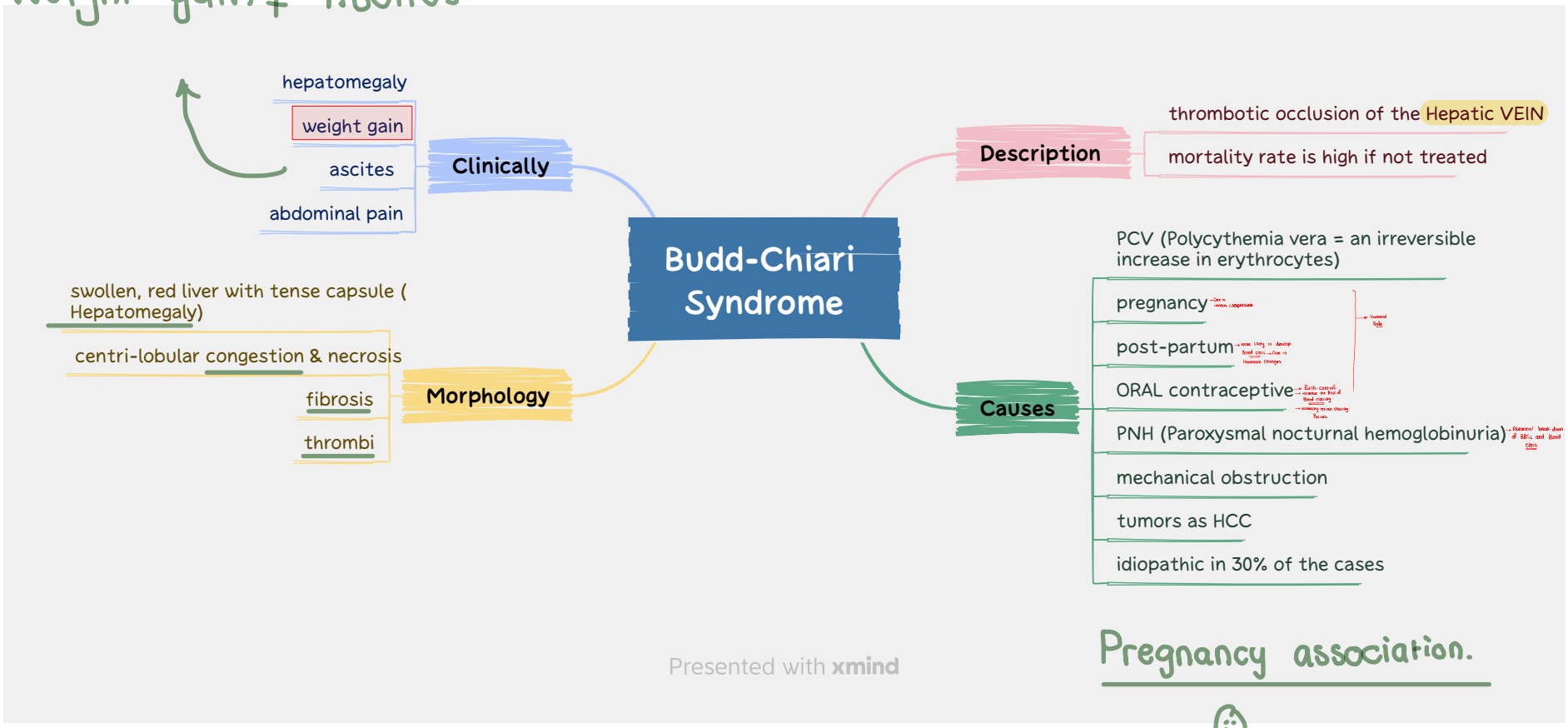
- liver
  - fatty change
  - ACUTE or CHRONIC hepatitis
  - cirrhosis
  - massive hepatic necrosis
- brain
  - toxic injury to Basal Ganglia —> especially the PUTAMEN —> causing atrophy & cavitation
- eye
  - kayser-fleischer rings
    - green-brown deposit of Cu in Descemet membrane in the Limbus of the Cornea
  - Hepato-lenticular degeneration

Rhodanine stain or Orcein stain show Cu deposition

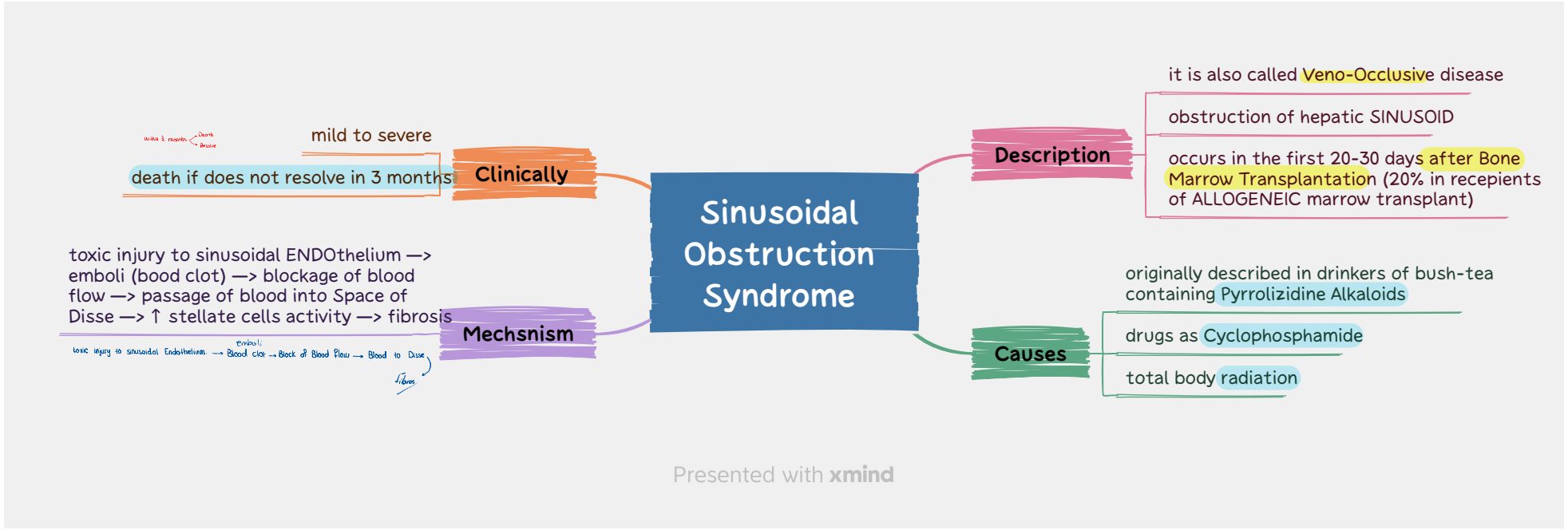




Weight gain + Ascites



Pregnancy association.



Primary Sclerosing Cholangitis (PSC)

Clinically

- asymptomatic
- persistent ↑ serum alkaline phosphatase
- symptomatic
  - fatigue
  - pruritis
  - jaundice
  - weight loss
  - ascites
  - bleeding
  - encephalopathy
- atrophy & oblitration of bile ducts
- dilation of bile ducts inbetween areas of stricture → Segmental Dilation.
- cholestasis
- concentric peri-ductal onion-skin fibrosis

- cirrhosis
- cholangio-carcinoma (10-15%)
- lymphocytic infiltration

Description

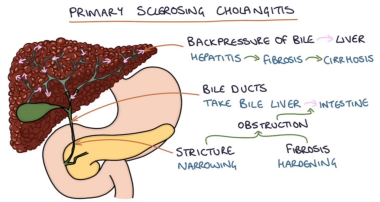
inflammation, oblitrative fibrosis & segmental dilation of the obstructed Intra & Extra hepatic BILE DUCTs

UC (ulcerative colitis) co-exists in 70% of patients → Remember.

NOTE: in patients of UC, 4% develop PSC

Pathogenesis

- exposure to gut derived toxins
- immune attack
  - anti-mitochondrial antibodies (<10% of cases)
  - anti-nuclear cytoplasmic anibodies (80% of cases) → mainly.
- ischemia of biliary tree



Biliary Cirrhosis

Primary biliary cirrhosis

- Description
  - CHRONIC, progressive & often fatal cholestatic liver disease
  - non-suppurative granulomatous destruction of MEDIUM-sized INTRA-hepatic bile ducts —> portal inflammation & scarring
  - insidious onset
- Cause
  - an autoimmune disease
    - anti-mitochondrial antibodies (>90)
    - anti-mitochondrial pyruvate dehydrogenase
- Associated autoimmune conditions
  - Sjogern syndrome
  - Scleroderma thyroiditis
  - RA
  - Raynauds phenomenon
  - Membranous glomerulo-nephritis (MGN)
  - Celiac disease
- Morphology
  - inter-lobular bile ducts are absent or severely destructed (Florid Duct lesion)
  - intra-epithelial inflammation
  - granulomatous inflammation
  - bile ductular proliferation
  - cholestasis
  - necrosis of parenchyma
  - cirrhosis
- Clinically
  - pruritis
  - jaundice
  - cirrhosis over 2 or more decades
  - ↑ Alkaline phosphatase
  - ↑ cholesterol
  - hyper-bilirubinemia = hepatic decompensation

Mallory Hyaline can be found.

Secondary biliary cirrhosis

- prolonged obstruction to EXTRA-hepatic biliary tree
- Causes
  - cholelithiasis (gall-stone)
  - biliary atresia
  - malignancies
  - strictures


Peliosis Hepatis
Clinically
asymptomatic
Intra-abdominal hemorrhage
liver failure
Pathogenesis
unknown
Description
SINUSOIDAL dilatation
reversible
Causes
anabolic steroids
ORAL contraceptive
Danazol
Presented with xmind

Liver Tumors

Description
- liver tumors may be BENIGN or MALIGNANT
- BENIGN
  - Cavernous Hemangioma
  - Liver Cell Adenoma
- MALIGNANT
  - HCC
  - CC
  - Fibro-lamellar carcinoma

Liver Nodules
- Focal Nodular Hyper-plasia
  - well-demarcated hyper-plastic hepatocytes with (central) scar —> leading to local vascular injury
  - NON-cirrhotic liver
  - not neoplasm —> but nodular regeneration
    - NO risk of malignancy
  - usually affects FEMALE of reproductive age
  - 20% of cases have Cavernous Hemagnioma
- MACRO-regenerative Nodules
  - Cirrhotic liver, but the nodules are larger than cirrhotic nodules
  - NO atypical features —> RETICULIN is intact
  - NO risk of malignancy
- Dys-plastic Nodules
  - the nodules are larger than (1)mm
  - Cirrhotic liver
  - atypical features & high proliferative activity
  - morphology
    - high or low dys-plasia
  - PRE-cancerous (as there are monoclonal, positive gene mutations)
  - Types
    - Small-cell Dys-plastic Nodules
    - Large-cell Dys-plastic Nodules

Cavernous Hemangioma
- most common benign liver tumor
- usually < 2cm (small)
- location: sub-capsular

Liver Cell Adenoma
- this tumor is composed of hepatocytes similar to normal, forming a mass lacking other structure like portal tract
- in FEMALE —> history of ORAL contraceptive
- in MALE —> history of steroids
- may rupture especially during pregnancy, causing severe intra-peritoneal hemorrhage
- rarely may associated with HCC
- misdiagnosis of HCC

Hepatocellular Carcinoma (HCC)
- represents 5.4% of all cancers
- affects blacks > whites
- most commonly is SECONDARY (metastatic)
- Predisposing Factors
  - Hepatitis carrier state —> vertical transmission —> increases the risk 200X
  - CHRONIC HBV & HCV infection
  - Cirrhosis
  - Alcoholism
  - Afla-toxins
  - Hereditary Tyrosinemia (metabolic disease)
  - Hereditary Hemochromatosis
- Pathogenesis
  - any cell under continuous stimulation for division is liable for developing mutations, which is the initial step for carcinogenesis (gene mutations)
  - repeated cycles of cell death & regeneration
  - viral
    - HBV integration leads to
      - clonal expansion
      - genomic instability, that is not limited to integration site
    - HBV X-protein leads to
      - trans-activation of viral & cellular PROMOTERs —> activation of Oncogenes & inhibition of apoptosis
  - Afla-toxins
    - affects the tumor suppressor gene (p53) which results in the loss of cell inhibition
- Morphology
  - mixed
    - HCC (hepatocellular carcinoma)
    - CC (cholangio-carcinoma)
  - Uni-focal
    - primary tumors are usually unifocal " single masses"
  - Multi-focal
    - Metastic /Secondary tumors are usually found as muiltple masses
  - Diffusely Infiltrative
  - Vascular Invasion is common in all types
  - grading is variable (well differentiated to anaplastic)

Cholangio-carcinoma (CC)
- they are Desmoplastic (forming adhesions or fibrous connective tissue within a tumor)
- vascular metastasis (in 50% of cases) —> lungs, bones, adrenals, brain
- Complications
  - Cachexia (metabolic syndrome)
  - GI bleeding
  - liver failure
  - Tumor rupture & hemorrhage
- Clinical Presentation
  - abdominal pain
  - malaise
  - weight loss
  - increased (α-feto protein) in 60-75% of patients
    - NOTE: α-feto protein increases also with
      - yolk sac tumor
      - cirrhosis
      - massive liver necrosis
      - CHRONIC hepatitis
      - normal pregnanvcy
      - fetal distress or death
      - fetal neural tube defect
- Prognosis: death within 7-10 months

Fibro-lamellar Carcinoma
- Single Hard Scirrhous tumor
- NO relation to HBV or Cirrhosis
- better prognosis