Hepatic injury:

Inflammations (hepatitis)

Could be acute or chronic
Could be infectious or non-infectious

Degeneration :

1. Ballooning degeneration:
cells increase in size because something (mainly water) enters the cell and make it swell. early manifestation

2. Feathery degeneration:
accumulation of fat, or iron, copper, biliary material accumulation

Steatosis (fatty change) :

Not a diagnosis – it's a description for what is going in the liver, liver changes colour to yellow and it gets greasy, structure become compressed because hepatocytes enlarge, present in two very similar forms:

1. Microvesicular = appears in ALD, Reye syndrome, acute fatty change of pregnancy

2. Macrovesicular= usually related to metabolic diseases or non-alcoholic fatty liver diseases ,e.g.= DM and obesity

Ductular proliferation:

the presence of Duct-like structures from stem cell-mediated regeneration

Cirrhosis :

Micronodules or macronodules

Necrosis = sever injury :

1. Depending on Type
-Coagulative necrosis : vascular problem like thrombus
-Councilman bodies: indicator of injury, due to toxicity, vascular problems
-Lytic necrosis (LIQUIFACTIVE), frequently related to infection

2. Depending on the cause:
- Ischemia (can be systemic vascular problem or due to use of a certain drug),
- shock

3. Depending on location :
-Centrilobular necrosis
-Midzonal
-Periportal: interface hepatitis
-Focal: piece meal necrosis , bridging necrosis
-Diffuse: massive and submassive necrosis, result from exposure to severe toxin , drugs (anesthetics) used in a short period of time , viral diseases (fulminant)

Fibrosis :

portal ,periportal, pericentral, bridging

Regeneration

- By mitosis from the remaining hepatocytes
- By differentiation from stem cells called (cells of canal of herring), they are progenitor for hepatocytes and cholangiocytes

Clinical features of liver diseases :

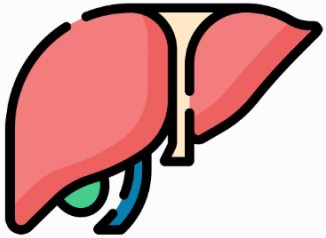
Jaundice:
yellowish discoloration of skin and sclera due to accumulation of bile salts in these areas

fetor hepaticus:
Patients might have musty or sweet and sour smell-odor

spider angiomas :
Spider like capillaries

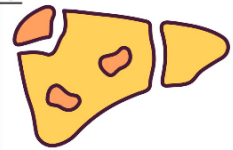
Palmar erythema (hyper estrogen anemia):
due to increased estrogen = dilatation of capillaries in palms mostly

hypoalbuminemia = edema
hyperammonemia
hypogonadism and gynecomastia :
Especially in chronic MALE patients, due to effect of estrogen lower male hormones and enlarged breast



Hepatic failure:

-it's a problem because it can develop in patients who are not really known to have liver disease (it can result from smth acute like exposure to toxins)
-it results when the hepatic functional capacity is almost totally lost (80-90./.) leading to accumulation of toxic substances in blood and development of neurological manifestations
-associated with deterioration of health of patient



-associated with high mortality rate
-its not frequent to have a patient with liver failure however you have to know they can present as emergency.
- present with loss of hepatocytes+ their function

Causes of liver failure:



1. Acute liver failure massive hepatic necrosis:

- Fulminant hepatic failure from the onset of symptoms to hepatic encephalopathy = within 2 to 3 weeks
- it also can be sub fulminant = within 3 months.
- its causes :

viral hepatitis in (50 -65%) of patients especially in (hepatitis B,B-D, C,A (especially in non-immunized in developing countries),
drugs acetaminophen, halothane, anti TB drugs CCL 4 poisoning (high exposure) ,mushroom poisoning
chemicals in 20 to 30% of patients

Or heat stroke, hepatic vein obstruction, Wilson disease, acute fatty liver of pregnancy, massive malignant infiltration, reactivation of chronic HBV hepatitis on HDV superimposed infection, autoimmune hepatitis

2. chronic liver disease

the most common route to hepatic failure, ending in cirrhosis.

3. Hepatic dysfunction without overt necrosis.

- Hepatocytes may be viable but unable to perform normal metabolic function:

1- acute fatty liver of pregnancy (which can lead to acute liver failure a few days after onset)
2- tetracycline toxicity
3- Reye syndrome

Consequences of liver failure:

1- Multiple Organ failure

(kidney/lung failure)

2- bleeding (COAGULOPATHY)

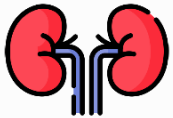
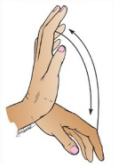
a major complication due to loss of coagulation factors like Factor II,VII,IX,X

3- Hepatic encephalopathy

due to accumulation of toxic substances = neurological manifestations = can be loss of peripheral sensations or low level of conseiousness = rigidity, hyperreflexia, EEG changes (heart would be affected), seizures, asterixis.

4- Hepatorenal syndrome:

renal failure in patients with severe liver disease with no morphologic or functional causes for renal failure.


Alcoholic liver disease :

Hepatic steatosis

- Hepatic steatosis occurs almost in all alcoholic drinkers. (90% -100%)

- occur even in moderate intake of alcohol in form of microvesicula steatosis
- Chronic intake → diffuse steatosis
- Liver is large (4 – 6 kg) soft yellow & greasy
- Continued intake → fibrosis
- fatty change is reversible with complete abstention from further intake of alcohol

- Initially the uptake of alcohol will cause fatty change, this could be reversible when the patient completely stop the uptake of alcohol.

- If the patient continue the uptake of alcohol it would progress to irreversible and develop fibrosis.

*these injuries aren't stages of the development in injury

Alcoholic hepatitis

- patients develop attacks of liver damage

1-Hepatocyte Snelling and necrosis: it is due to accumulation of fat and water and proteinsc, cholestasis and hemosiderin deposition in hepatocytes and Kupffer cells

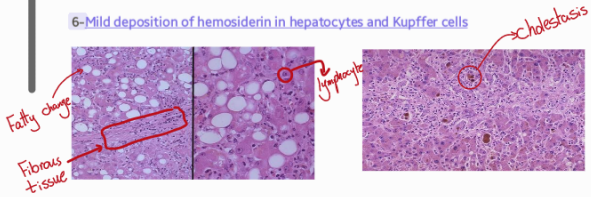
2-Mallory-hayline bodies: characteristic but not pathognomonic of alcohol liver disease, eosinophilic cytoplasmic inclusions (globules) in degenerating hepatocytes formed of collapse of cytokeratin intermediate filaments and other proteins. It can be present in other diseases like primary biliary cirrhosis, Wilson disease, chronic cholestatic syndromes, hepatocellular carcinoma

3-Neutrophilic reaction: inflammatory process (damage >> neutrophils) but as the time pass, chronicity develop and neutrophils will be replaced by other lymphocytes.

4-Fibrosis: Irreversible, patients are usually in a stage more severe that fatty change alone , they develop fibrosis in all areas that DON'T contain fibrous materials, and this indicated chronicity.
(Sinusoidal and perivenular fibrosis , Periportal fibrosis)

5-Cholestatis: problem in excretion of bile because of hepatocytes' chronic exposure to toxic substances = accumulation of bile salts in hepatocytes.

6-Mild deposition of hemosiderin in hepatocytes and Kupffer cells

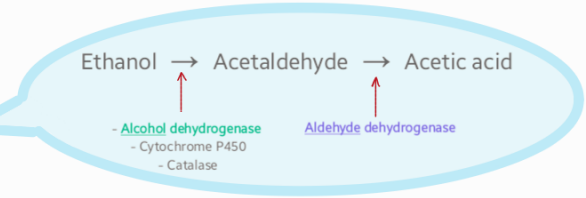


Cirrhosis

- usually it develops slowly, initially the liver is enlarged yellow but over years it becomes brown shrunken and non fatty organ
- s.t<1 kg in wt.
- micronodular after a while = mixed micro and macro nodular (due to cohesion of micronodules)
- Laennec cirrhosis = scar tissue
- Bile stasis : Biliary system is obstructed/filled with bile material
-Mallory bodies are only rarely evident at this stage

-IRREVERSIBLE (the patient have the outcomes of liver failure)
-it can develop rapidly in the presence of alcoholic hepatitis (within 1-2 years)
-related to amount of damage
-patient can present for the first time when he has complications of cirrhosis (no early manifestation, or they can be present but these manifestations would be mild and unspecific)
-pts have enlarged thyroid and fatty changes
- some patients with cirrhosis have no enlargement of liver = ALL the liver is fibrosed and the liver retracted = overall size shrinks

Ethanol metabolism:



- 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 lower levels of gastric alcohol dehydrogenase activity than men & they may develop higher blood Levels than men after drinking the same quantity of ethanol.
- women will develop more severe manifestation due to toxicity
- women are more susceptible to hepatic injury

-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.

Pathogenesis of alcoholic liver disease:

- short term ingestion of 80 gram of ethanol per day(8 beers) = Mild reversible hepatic changes (fatty liver)
- long term ingestion (10-20 years) of 160g of ethanol per day = severe hepatic injury
- 50-60gm/day >> Borderline effect
- only 8 to 20% of Alcoholics develop cirrhosis

Clinical features:

- Hepatic steatosis (reversible)

↑ liver ↑ liver enzymes Severe hepatic dysfunction is unusual

- Alcoholic hepatitis

15-20 yr. of excessive drinking, Non-specific symptoms, malaise, anorexia, weight loss although these symptoms are not specific , Hepatosplenomegaly , ↑ liver function test

Each bout of hepatitis → 10-20% risk of death → cirrhosis in 1/3 in few years.

-Cirrhosis

Portal hypertension

Mechanisms of ethanol toxicity :

1. Fatty change 👴👧

- shutting of lipid catabolism towards lipid biosynthesis due to excess production of NADH over NAD in cytosol and mitochondria.
-Acetaldehyde combine forms adducts with tubulin (protein in hepatocytes)and lower function of microtubules(site of excretion) lowering in lipoprotein transport from liver – subopitimal excretion

-HIGH catabolism of fat High FFA delivery to the liver
-LOW secretion of lipoprotein (imp to form complexes with fat to carry the fat to target organs to be utilized) = increase FFA and deposition
-LOW oxidation of FFA by mitochondria

2. Induction of cytochrome P-450

enhances the metabolism of drug to toxic metabolites like acetaminophen = interfere with drug metabolism = damage effect of drug

3. Higher free radicals production

due to activation of cytochrome P-450 leads to membrane and protein damage

4. acetaldehyde causes lipid peroxidation and antigenic alteration of hepatocytes

lead to immune attack, cells develop new antigens on hepatocytes so they would be recognized with immune cells

5. Alcohol directly affects microtubular and mitochondrial function and membrane fluidity

6. superimposed HCV hepatitis infection

acceleration of liver injury (HCV occurs in 30% of all Alcoholics)

7. release of bacterial endotoxins into portal circulation from the gut

Alcohol = release of bacterial endotoxins into portal circulation from the gut inflammation of liver

8. regional hypoxia in the liver

Alcohol = regional hypoxia in the liver due to release of endothelins which are potent
vasoconstrictors = low hepatic sinusoidal perfusion

9. Alteration of cytokine regulation

TNF is a major effector of injury , we also have IL6/IL8/IL18

Causes of death in alcoholic liver disease

1- hepatic failure
2- Massive GI bleeding
3- Infections
4- Hepatorenal syndrome
5- HCC in 3-6% of cases

Definition:

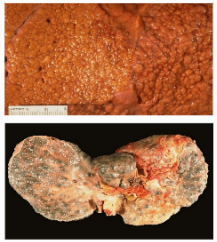
Chronic, Diffuse (INVOLVE WHOLE LIVER), characterized by fibrosis and the conversion of liver parenchyma into nodules.

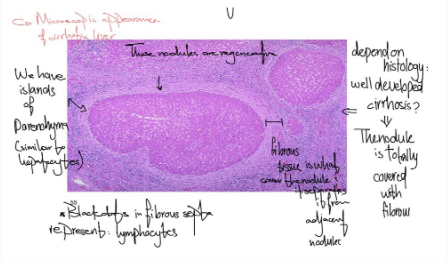
Main characteristics :

bridging fibrous septa, parenchymal nodules circled by fibrotic bands, diffuse architecture disruption. (that's why when we take small biopsies the whole nodule may not be presented, so we need to ask the radiologist to make sure it is DIFFUSE)

Types :

- Micronodules < 3mm in diameter
- Macronodules> 3mm in diameter





Cirrhosis

Causes:

1- chronic alcoholism (main cause in developed countries),
2- chronic viral infection (HBV and HCV)
3- biliary disease.

if we excluded the causes up, we must look for metabolic diseases although they are not common:

4- hemochromatosis (most common metabolic cause),
5- autoimmune hepatitis.
6- Wilson disease.
7- A1 antitrypsin deficiency.

Rare causes:

1. Inherited causes related to enzyme deficiencies (Galactosemia, tyrosinosis, Glycogen storage, diseases III/ IVglycogen deposition in liver, Lipid storage disease, Hereditary fructose intolerance (we have to break it)

2. drug induced
methyldopa

3. cryptogenic cirrhosis.

Pathogenesis:

1. Hepatocellular death
2. Regeneration
3. Progressive fibrosis

Cell death should occur over a long period of time & accompanied by fibrosis
-In normal liver the ECM collagen = (types I, III,V& XI) only in Liver capsule, Portal tracts, Around central vein. delicate framework of type IV collagen & other proteins lies in space of Disse.

-In cirrhosis the ECM collagen = (types I & III collagen & others) are deposited in the space of Disse,
- the major source of collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells) which lie in space of, act normally as storage cells for vit A & fat stimulation due to diseases >> myofibroblast like cells produce TGFB >> stimulate cells to synthesize collagen and deposit it.

The stimuli for the activation of stellate cells & production of collagen are :
reactive oxygen species, Growth factors, cytokines (TNF, IL-I, lymp)

4. Vascular changes

A. Loss of sinusoidal endothelial cell fenestration
B. development of vascular shunts as
- Portal vein - hepatic vein
- Hepatic artery – portal vein → defect in liver function
C. Loss of microvilli from hepatocytes →decrease transport capacity of the cells

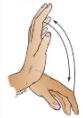
• Collagen deposition converts sinusoids with fenestrated endothelial channels that allow free exchange of solutes between plasma and hepatocytes to higher pressure, fast-flowing vascular channels without such solute exchange.
• the movement of proteins (e.g., albumin, clotting factors, lipoproteins) between hepatocytes and 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

cirrhosis is a chronic process that takes years to develop

1. silent (asymptomatic)

2. anorexia + weight loss + weakness (non-specific)



3. complications (the most common form)

A. progressive hepatic failure
many patients present for the first time with hepatic failure if they had infection or bleeding

B. portal hypertension

C. hepatocellular carcinoma
conventional type of liver cancer has a background of cirrhosis

Portal hypertension:

- high resistance to portal blood flow at the level of sinusoids & compression of central veins by perivenular fibrosis & parenchymal nodules
- Arterial – portal anastomosis develops in the fibrous bands → increase in the blood pressure in portal venous system

- 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.

Causes:

A. Prehepatic (before they reach liver)

1. portal vein thrombosis
2. massive splenomegaly

(liver and spleen share circulation, that's why any problem can be reflected)

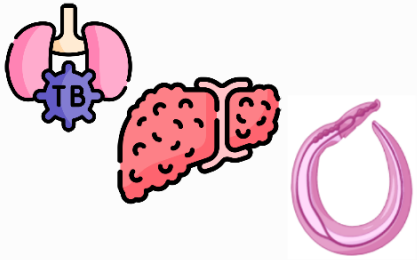
B. Post hepatic (after they leave liver)

1. severe right sided heart failure
2. constrictive pericarditis (heart contraction problem)
3. hepatic vein outflow obstruction (problem outside like a tumor)

Problems in heart and IVC. Heart failure indicate abnormal blood flow that will cause pressure on portal veins.

C. Hepatic

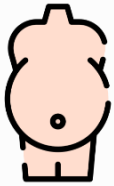
1. cirrhosis (most important + common)
2. shistosomiasis (bilharzia)
3. massive fatty change
4. diffuse granulomatosis as sarcoidosis, TB
5. disease of portal microcirculation as nodular regenerative hyperplasia



Clinical consequences:

Ascites:

collection of excess fluids in intra abdominal cavity it becomes clinically detectable when at least 500 ml have accumulated and they have distended abdomen
features:



1. serious fluids (loss of proteins)
2. contains as much as 3 g/ml of protein(albumin)
3. it has the same concentration as lot of glucose and K+
4. Asctic fluid usually contains no cells but we may see mesothelial cells (which are sense lining the cavity) and lymphocytes
5. neutrophils = infection
6. RBC = disseminated cancer

Pathogenesis:
fluid will be pushed out of the sinusoids and fluid accumulate on the surface of the liver

1. sinusoidal high blood pressure
2. hypoalbuminemia = low osmotic pressure = edema
3. leakage of hepatic lymph into the peritoneal cavity
4. renal retention of Na+ and water due to secondary hyperaldosteronism

At the end increase fluid in circulation >> increase BV >> increase hydrostatic pressure >> fluid is pushed outside (with low osmotic pressure more fluid gets pushed)

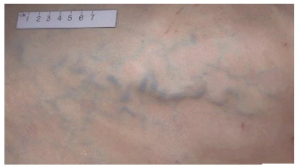
Portosystemic shunt

Because of high portal venous pressure
bypasses develop wherever the systemic & portal circulation share capillary beds

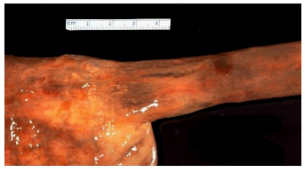
Sites:
1. Around & within the rectum (Hemorrhoids)
2. Gastroesophageal junction (varicies)
3. Retroperitoneum
4. Falciform ligament of the liver (periumbilical & abdominal wall collaterals) → caput medusae

- Gastroesophageal varicies appear in 65% of pts. with advanced cirrhosis & cause death in 50% of then due to UG1 bleeding

caput medusae



Esophageal varicies



Clinical consequences:

Hepatic encephalopathy:

Depending on the amount of toxins produced they develop this case

- It is a complication of acute and chronic hepatic failure
- disturbance in brain function ranging from behavioral changes to marked confusion and stupor to deep coma and death
- these changes may progress over hours or days

Neurological signs:
depend on which part of brain is affected

Rigidity, hyper reflexia, nonspecific EEG, seizures, Asterixis, green chose edema and astrocytic reaction.
Brain shows edema & astrocytic reaction

Pathogenesis:
Physiologic factors important in development of hepatic encephalopathy:

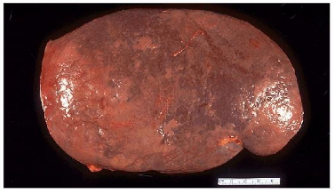
1. Severe loss of hepatocellular function
2. Shunting of blood around damaged liver with no detoxification↓↓

- Exposure of Brain to toxic metabolic products like ammonia which passes BBB
- ↑ NH3 level in blood → generalized brain edema impaired neuronal function
-Chronic insult: alteration in central nervous system AA metabolism

Splenomegaly:

Deviation of blood due to resistance of liver to spleen, usually 500-1000 g (N<300 g) which lead to enlarged spleen full of blood

-not necessarily correlated with other features of portal increased blood pressure
-may result in hypersplenism



Drug induced liver disease

Classification of drug reactions:

1. Predictable (intrinsic):

These reactions are dose and duration dependent,
more exposure >> increase likelihood to develop injury, so these patients after wrong administration to a certain drug +for long time (weeks, months, or years after chronic use) >> liver injury that would be resembled by high liver function test.

Ex :

- Acetaminophen
- Antineoplastic agents
- CCL4
- Alcohol
- Tetracycline

2. Unpredictable drug depend on :

- The immune response of the host to the antigenic stimulus
- The rate at which the host metabolizes the agent

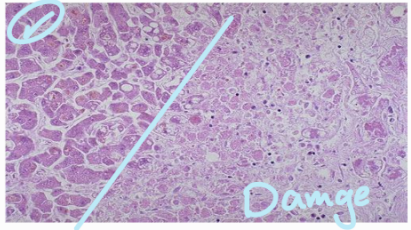
-The injury m.b immediate or takes weeks to months
-Drug-induced chronic hepatitis is clinically & histologically indistinguishable from chronic viral or autoimmune hepatitis

Ex:

- Chlorpromazine
- Halothane
- Sulfonamides
- Methyldopa
- Allopurinol

Morpholagy:

Massive necrosis → 500 – 700 gm liver
Submassive necrosis
Patchy necrosis



Mechanism of drug injury:

1. Direct toxic damage
e.g. acetaminophen, CCl4, mushroom toxins
2. Immune-mediated damage
Drugs are known to produce haptens. Haptens are small molecules that bind to cell surface, and may play a role in changing the antigenicity, which would stimulate immune attacks.

Patterns of injury

1. Hepatocellular necrosis
2. Cholestasis
3. Steatosis
4. Steatohepatitis5-Fibrosis
6. Vascular lesions
7. Granuloma
8. Neoplasms benign & malignant

Drugs that may cause acute liver failure

1. Acetaminophen (most common)
2. Halothane
3. Antituberculosis drugs (rifampin, isoniazid)
4. Antidepressant monoamine oxidase inhibitors
5. Toxins as CCL4 & mushroom poisoning

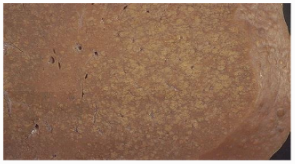
Fulminant hepatitis

Definition:

• severe hepatitis = is associated with necrosis, Hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy in 2-3 weeks.
• Sub fulminant = (up to 3 months).

Causes:

1. viral hepatitis (50-60%) B, C, E (HBV x2> HCV) +HDV superimposed on HBV.
2. drugs and chemicals (25-50%)
3. Obstruction of hepatic vein
4. Wilson's disease
5. acute factor change of pregnancy
6. massive tumor infiltration
7. reactivation of chronic hepatitis B
8. acute immune hepatitis

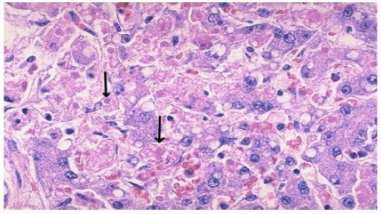


Morphology:

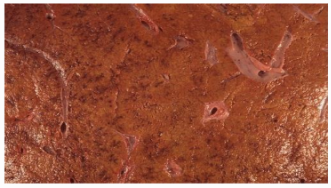
- ↓ liver size (500 – 700 gm)
- Necrosis of hepatocytes
- Collapsed reticulin tissue (fibres seen in liver by a special stain)
- Inflammatory infiltrate
- Regenerative activity of hepatocytes
- Fibrosis

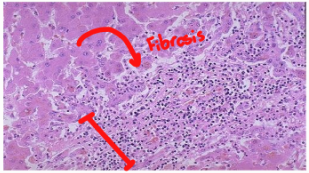
Chronic hepatitis

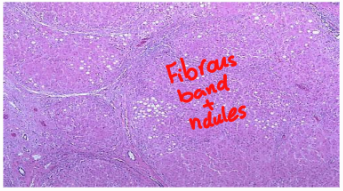
- Symptomatic, biochemical or serelogic evidence of continuing or relapsing hepatic disease for more than 6 months with histologically documented inflammation & necrosis
- Progressive or non progressive
- HBV , HCV, HBV-HDV

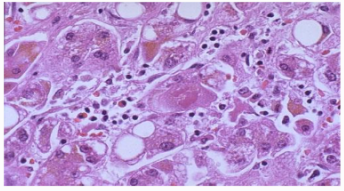


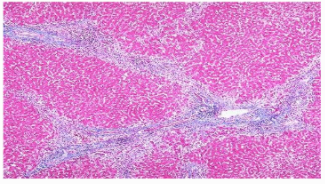
Morphology: Mild to severe
1.Protal inflammation
2.Lymphoid aggregate
3.Necrosis of hepatocytes-councilman bodies
4.Bile duct damage
5.Steatosis
6.Interface hepatitis
7.Bridging necrosis & fibrosis
8.Fibrosis
9.Ground-glass appearance
10.Sanded nuclei
11.Lobular disarray











Autoimmune hepatitis

Definition:

Chronic hepatitis with immunologic abnormalities
- Histologic features are similar to chronic viral hepatitis-Indolent or severe course
- Dramatic response to immunosuppressive therapy.
-Takes years to develop damage, lifelong disease with no cure, treatment is to prevent complications and control the symptoms

Features:

1. Female predominance (70%)
2. Negative serology for viral antigens (NOT A VIRAL DISEASE).
3. increase serum Ig (>2.5 g/dl)
4. High titers of autoantibodies (80% of cases)
5. The presence of other autoimmune diseases as RA, thyroiditis (Graves, Hashimoto thyroiditis), Sjogren syndrome, UC in 60% of the cases)

Type of autoantibodies:

We can find many types with different titters.

1. Antismooth muscle antibodies(most common):
anti actin, antitroponin, anti-tropomyosin
2. liver/kidney microsomal antibodies
(anti cytochrome P-450 components, anti UDP-glucuronosyl transferases)
3. Anti – soluble liver / pancreas antigen

Outcome:

Mild to severe chronic hepatitis
Full remission is unusual.

Non-alcoholic fatty liver disease

Types:

1. Steatosis (Fatty liver) (mild form)
2. Steatohepatitis: (more severe because we have inflammation +fatty change) associated with hepatocyte destruction, parenchymal inflammation, progressive pericellular fibrosis

Predisposing factors:

1. Type 2 DM
2. Obesity: body mass index > 30 kg /m2 in Caucasians
   body mass index> 25 kg /m2 in Asians
3. Dyslipidemia (↑ TG, ↑ LDL, ↓ HDL)

Pathogenesis:

- Metabolic syndrome
- Insulin resistance (type 2 diabetes), Obesity, Dyslipidaemia (can be diagnosed by blood's lipid test)

Mechanism of fatty accumulation:

1. Impaired oxidation of fatty acids
2. synthesis & uptake of FFA
3. Decreased hepatic sec. of VLDL,++increase TNF, IL6, chemokine liver inflammation & damage

Clinically:

-NAFLD is the most common cause of incidental increase in transaminases.
- Most pts. are asymptomatic
- Non-specific symptoms: Fatigue, malaise, RUQ discomfort
- Severe symptoms (related to liver injury)
- Liver biopsy is required for confirmatory
- biopsy is to evaluate the presence of fatty infiltration and its degree
- NAFLD m.b a significant contributor to cryptogenic cirrhosis

Hemochromatosis

Definition:

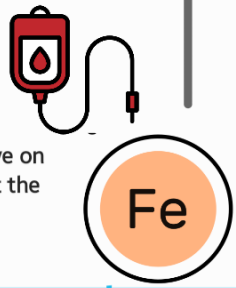
- Excessive accumulation of body iron (liver & pancreas or other organs)
- Forms primary or secondary (genetic or acquired)

Genetic hemochromatosis: (4 variants)

-The most common form is autosomal recessive disease of adult onset caused by mutation in the HFE gene on chr.6, (site of mutation differs in patients)

Acquired hemosiderosis causes:

1- multiple transfusions
2- ineffective erythropoiesis (thalassemia), patients how survive on repeated blood transfusion, receive chelating agents to prevent the deposition of iron
3- increased iron intake in food and drink (Bantu siderosis)
4- chronic liver disease



Pathogenesis:

- primary defect in intestinal absorption of dietary iron.
-Total body iron 2-6gm in adults 0.5gm in liver mostly in hepatocytes, we can also find it in the bone marrow because bone marrow synthesizes RBC which contains iron (specifically heme)
- In disease >50gm Fe accumulated 1/3 in liver

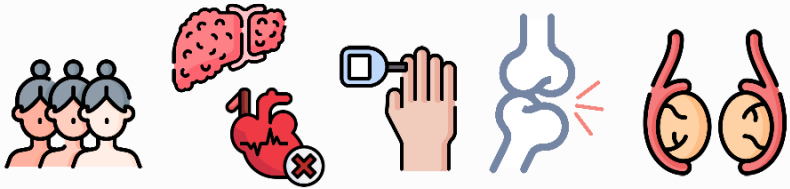
- In herediatary hemochromatosis there is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5 – 1 gm/yr

- The gene responsible is HFE gene located on chr.6 close to HLA gene complex
-HFE gene regulates the level of hepcidin hormone

Features :

1. Micronodular cirrhosis (all patients)
2. D.M (because pancreas is damaged) (75 – 80%)
3. skin pigmentation (75-80%)
4. cardiomegaly, joints disease, testicular atrophy (associated with infertility)

-Symptoms appear 5th – 6th decadesnot before age 40
-M:F ratio 5 - 7: 1,
(women usually shed iron during their menstruation, so the iron deposited amount is less)



hepcidin

is a hormone synthesized in the liver it works by preventing excess Iron absorption by controlling the ion channels, and when the person has low iron levels (due to bleeding or anemia) it will lower its levels so the iron can enter the channels.

-Hepcidin >> (-) Fe absorption from intestine by increasing the closure of the channels.
-Hepcidin is lowered in cases of anaemia for example because the body needs iron

-HFE gene deletion >> low hepcidin >>causes iron overload

Mutations in the HFE gene :

1. Mutation at 845 nucleotide >> tyrosine substitution for cystine at AA 282 (C282 Y)
2. aspartate substitution for histidine at AA 63 (H63D) 10% of pts. have other gene mutations

- Carrier rate for C282Y is 1/70
- Homozygosity is 1/200 (common)
- 80% of pts. are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation
-10% of pts. are either homozygous for H63D mutation or compound heterozygous for C282Y/H63D mutation

---

Excessive Fe deposition:

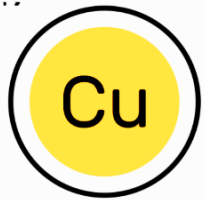
Toxicity of the tissues
Lipid peroxidation, stimulation for collagen formation (iron is a stimulant for FIBROSIS), DNA damage.

Morphological changes:

1-Deposition of hemosiderin in different organs (Liver, Pancreas, Myocardium, Pituitary Adrenal Thyroid & parathyroid, Joints, Skin)
2-Cirrhosis
3-Pancreatic fibrosis
-No inflammation, Fibrosis, Cirrhosis, Synovitis, Polyarthritis(pseudogout), Pigmentation of liver (very dark), fibrosis of pancreas & myocardium
-Atrophy of testes

Definition:

Autosomal Recessive disorder of Cu metabolism that present in early and late adulthood.



Mutation

- mutation in ATP7B gene on chr. 13 which encodes an ATPase metal ion transporter in Golgi region.
- > 80 mutations can affect this gene that result in this disease
- Gene freq. 1:200
- Incidence is 1:30000 (not common, however if you missed it = big problem)

Wilson disease

Normal metabolism of Cu:

Any alteration of these steps leads to accumulation of copper in the body.

Main source of Cu is from diet.

↓

Absorption of ingested Cu (2-5 mg/d) is by the intestine (MAIN ABNORMALITY)

↓

Complex with albumin to reach the liver

↓

Hepatocellular uptake

↓

Incorporation with α-2-globulin (protein) to form Ceruloplasmin.

↓

Copper is complexed with ceruloplasmin and secreted into plasma (90 – 95% of plasma Cu) >> circulates and get utilized.

↓

Hepatic uptake of ceruloplasmin

↓

Lysosomal degradation of ceruloplasmin

↓

Secretion of free Cu into bile

↓

Eliminated from body

Pathogenesis

- In Wilson disease absorbed Cu. Fails to enter the circulation (because there is no ceruloplasmin + or we have low levels) in the form of ceruloplasmin & the biliary excretion of Cu. is LOW

- Defective function of ATP-7B >> failure of Cu excretion into bile & inhibits secretion of ceruloplasmin into the plasma >> Cu accumulation in liver

The Result :

1. Production of free radicals
2. binding to sulfhydryl groups of intracellular proteins
3. displacement of other metals in hepatic metalloenzymes system

-By the age of 5yrs. (Cu needs time to accumulate and show its complications) Cu Spills over to circulation causing haemolysis & involvement of other organs as brain & cornea also kidneys, bones joints & parathyroid glands.

- Urinary excretion Of cu increases

Morphology:

Liver:

1. Fatty change (young age group, children 5+(especially at 7)
2. Acute hepatitis
3. chronic hepatitis (when he turns 10-12, this form is not explained by other diseases)
4. cirrhosis
5. massive hepatic necrosis and hepatic failure

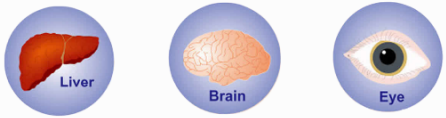
*Seen by rhodanine stain or orcein stain

Brain:

Toxic injury to basal ganglia esp. the putamen causing atrophy & cavitation

Eye

kaiser- Fleischer rings, green – brown deposits of Cu In Descemet membrane in the limbus of the cornea (Hepatolenticular degeneration)



Clinically:

- Presentation > 6 years of age (enough copper should be deposited)
- Most common presentation is acute on chronic hepatitis
- In young patients, it's a matter of suspension >> Neuropsychiatric presentation can occur.
• behavioural changes (kids 6 or more develop abnormal behaviours)
• Frank psychosis
• Parkinson disease- like syndrome

Diagnosis:

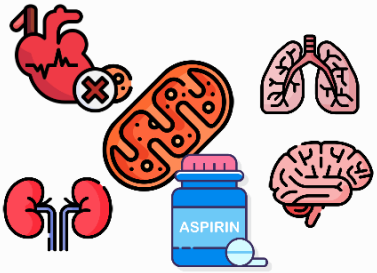
LOW serum ceruloplasmin level
HIGH urinary exc. Of Cu.
HIGH hepatic content of copper
> 250 mg/gm dry wt.

Definition:

• Fatty change in liver & encephalopathy
• - < 4 yr. (typically young)
• 3 – 5 day after viral illness (mostly after respiratory viral illnesses)
• HIGH liver & abnormal Liver function test, Vomiting lethargy, 25% may go into coma (1/3 of patients)

Pathogenesis:

- Derangement of mitochondrial function along or in combination with viral infection& salicylate
- Microvesicular steatosis
- Brain edema = encephalopathy
- Absent inflammation
- Skeletal muscle , heart, kidneys – fatty change



Reye's syndrome

a-1 Antitrypsin defeciency

Definition:

Autosomal Recessive disorder, primary disease of lung
a1-antiryrpsin is a protease inhibitor as (elastase, cathepsinG, proteinase 3) which are released from neutrophils at the site of inflammation at the lung.
- important to control enzymes secreted during inflammation of lung, in order to prevent excessive damage of lung so its deficiency >> damage to lung. It is synthesized and secreted in the liver, and because its found there it may induce damage at the liver (due to mutation in the gene responsible for the enzyme (Pi gene)

Mutation:

The gene pi Is located on chr. 14

- At least 75 forms of gene mutation are present
- The most common genotype is pi.MM present normally in 90% of individuals

- PiZZ genotype (homozygous, abnormal form) LOW level of a-1-antitrypsin in blood (only 10% of normal) are at high risk of developing clinical disease

- freq. 1:7000 in North American white population
- carriers PiMZ : have decreased levels of enzyme level how ever they can be protected from disease

Morphology

-Intracytoplasmic globular inclusions in hepatocytes which are acidophilic in H&E sections
-The inclusions are PAS-+ve & diastase resistant
-Neonatal hepatitis cholestasis & fibrosis
Chronic hepatitis, Cirrhosis (not so frequent)
Fatty change, Mallory bodies (we usually check for hep and if we see them we should think of a1 patients)

Pathogenesis:

- The mutant polypeptide (PiZ) is abnormally folded in the liver& polymerizes in the hepatocytes causing its retention in the ER of hepatocytes
-Although all individual with Pizz genotype accumulate a1-AT-Z protein in the liver >> only 10% of them develop clinical liver disease.
This is due to lages in ER protein degradation pathway

The accumulated a-1-AT-Z is not toxic but the autophagocytic response stimulated within the hepatocytes appear to be the cause of liver injury by auto phagocytosis of the mitochondria

- 8-10% of patients develop significant liver damage (NOT ALL patients develop SIGNIFICANT damage because of degree of autophagocytic effect)

Clinical features

-neonatal hepatitis with cholestatic jaundice appears in 10 – 20% of newborns with the disease (rare)
-Attacks of hepatitis in adolescence
- chronic hepatitis & cirrhosis
-HCC (hepatocellular carcinoma) in 2- 3 % of Pizz adults (with severe defeciency) plus minus having cirrhosis

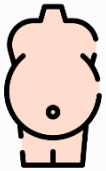
(this is not common so if we exclude all the other causes we should think of A1 antitrypsin)

Budd Chiari syndrome

Definition:

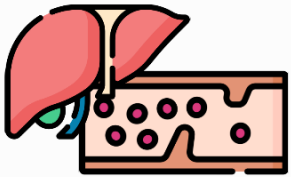
Thrombotic occlusion of the hepatic vein, so any condition that has an increased risk of thrombus formation >> pt can develop Budd Chiari

Complaints:



- Hepatomegaly
- Weight Gain
- Ascites
- Abdominal Pain and tenderness

*if its acute = severe symptoms , chronic = mild symp



Diagnosis:

Clinical and suspicion

Because we don't have a specific thing to look for all the symptoms are non-specific

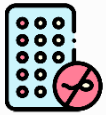
Mortality rate is high if not treated.

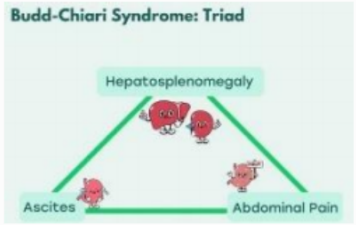
It's a serious disease, if not recognized early = liver failure + death

Causes

all these cases >> increase the risk of a thrombus so eventually, have a risk to develop into the syndrome, cause can be blood diseases, or others.

1. PCV (polycythaemia vera)
2. Pregnancy (due to hormonal changes)
3. Postpartum
4. Oral contraceptive
5. PNH (paroxysmal nocturnal haemoglobinuria)
6. Mechanical obstruction (compression associated with a tumour for example, obstruction + stasis = predispose thrombus formation)
7. Tumors within liver as (HCC) (tumor enlarges and compress the surroundings. If the tumor for example was close to a portal vein and closed it = thrombus) (HCC: this type of cancer tend to infiltrate the vessels tumour growth within a vessel)
8. Idiopathic in 30% of the cases





Morphology:

- Swollen liver, red with tense capsule
- microscopically: centrilobular congestion and necrosis (Because they are tributaries of portal veins)

(congestion: dilated vessels + stuffed with blood.

it is associated with necrosis because once the central vein is filled with blood = compress surrounding hepatocytes = necrosis of hepatocytes, it can be acute or prolonged, if it is prolonged = fibrosis around the central vein)

- Fibrosis
- Thrombi

Primary sclerosing cholangitis

Definition:

Disease that affects biliary tract of liver. Not so frequent but important >> Inflammation, obliterative fibrosis, & segmental dilation of the obstructed intra hepatic & extra hepatic bile ducts
*This fibrosis that surround bile duct >> segmental dilatation that gives significant appearance of hepatocytes

Notes

The importance arises because it is related to other diseases.
(UC: ulcerative colitis, inflammatory bowel disease)
- In PSC, UC coexists in 70% of patients.
-in patients of UC, 4% develop PSC
- 3rd – 5th decade of life
- M: F 2:1

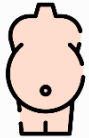
Pathogenesis:

- Exposure to gut derived toxins
(exposure of biliary system by toxins produced by the normal flora)
- Immune attack
- Ischemia of biliary tree

Clinical findings:

- asymptomatic patients.
- persistent ↑ serum alkaline phosphatase (characteristic feature about this disease, this enzyme is a part of the liver function test, and it reflects the biliary system >> this enzyme is excreted by epithelium lining the biliary system)
- fatigue, pruritis (severe itching due to deposition of bile salt), jaundice (obstruction of the biliary system), weight loss, ascitis
- bleeding, encephalopathy (in severe biliary damage and eventually development of fibrosis and cirrhosis)
- This is an autoimmune disease, we would find antibodies like:
• Antinuclear cytoplasmic Abs in 80% or more of cases,
• antimitochondrial Abs < 10% of cases (these antibodies are characteristic of other diseases)





Morphology:

- Concentric periductal onion-skin fibrosis & lymphocytic Infiltrate
(around the bile duct (destructed by inflame. process) fibrosis in layers + presence of lymphatic infiltrate).
This process of fibrosis is segmental, meaning that not all the tube gets fibrosed rather that certain segments. As a result we would have segmental obstruction
- Atrophy & obliteration of bile ducts
- Dilation of bile ducts in between areas of stricture
- Cholestasis (because the biliary system is the target)& fibrosis
- Cirrhosis, cholangiocarcinoma (10 – 15%)

1. Primary Biliary cirrhosis

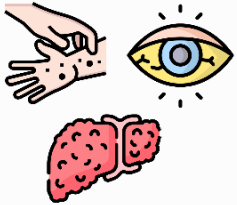
Definition:

Characterized by cirrhosis related to biliary disease (inflammation + destruction).
Chronic, progressive & often fatal cholestatic liver disease, non-suppurative granulomatous destruction (main Characteristic) of medium-sized intrahepatic bile ducts, portal inflammation & scarring.

Presentation

Patient presents late, because the condition takes along time to develop in addition to having non-specific manifestations at the beginning. This process is graded.

- Age 20-80yrs (wide range) (peak 40-50yrs)
- F>M
- Insidious onset
- Patients mostly suffer from: Pruritis, jaundice
- Cirrhosis over 2 or more decades (2-3 yrs. up to decades)



Notes

- ↑Alkaline phosphatase & cholesterol (cholesterol excreted through bile)
- Hyperbilirubinemia = hepatic decompensation
- progression of the disease is inevitable + it can be prolonged that's why they can develop jaundice
- Antimitochondrial Abs > 90%, Antimitochondrial pyruvate dehydrogenase is the characteristic

Associated conditions

High probability of having other autoimmune diseases like:
Sjogren synd., Scleroderma thyroiditis, RA, Raynaud's phenomenon. MGN, celiac disease

Morphology:

-interlobular bile ducts are absent or severely destructed (florid duct lesion)
-intra epithelial inflammation
-Granulomatous inflammation (usually surrounding the biliary system)
-Bile ductular proliferation
-Cholestasis (EXTENSIVE)
-Necrosis of parenchyma (depending on the severity)

2. Secondary biliary cirrhosis

Definition:

Prolonged obst. To extrahepatic biliary tree, so disease affedting the biliav >> 2nd biliay cirhosis.
All these diseases have characteristics of abnormality bile ducts, narrowing of bile ducts, bleeding of hepatocytes due to toxins of bile

causes:

1. cholelithiasis: stone formed in bile ducts, however some stones can be formed in the biliary system, these stones can fall in biliary system and cause obstruction which means all the bile secreted from this system is stagnant = damage hepatocytes , if not treated early = cirrhosis

2. biliary atresia : narrowing of the biliary system, can be intrahepatic- extrahepatic, most common: atresia of bile duct)

3. malignancies : can be primary or secondary and as they grow slowly >> causing pressure from outside = obstruction

4. stricutres : congenital or induced by surgeries >> fibrous band that would eventually contract >> entrap the common bile duct or the hepatic duct

Sinusoidal obstruction syndrome (Veno-occlusive disease)

Notes

- Originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloids.
- Pts with malignancies especially leukemic , because most of them receive bone marrow transplantation. This occurs in the first 20-30 days after bone marrow transplantation.
- Before receiving the new BM they undergo radiation to remove leukemic cells and clear their system, and because the radiation is systemic = can damage the hepatocytes and the sinusoids. It can also be because of chemotherapy.

-Why does it occur 20-30 days after transplantation? Because that's the time needed for the end process of preparation, or in other words the time needed for the cells to damage and cause obstruction of the sinusoids.

Causes

1. Drugs as cyclophosphamide
2. Total body radiation

Incidence:

- 20% in recipients of allogeneic marrow transplant

Clinical Presentation:

- Mild – severe
- Death if does not resolve in 3 months, however if he survived, death is avoided.

Mechanism:

Toxic injury to sinusoidal endothelium = death of the lining endothelial cells = desquamation/separation of these cells forming clusters = emboli blockage of bl. Flow = Passage of blood into space of Disse → ↑stellate cells → fibrosis.

*sinusoids are very delicate vascular structures, any collection of cells within >> obstruction >> impede the blood flow

Peliosis Hepatis

Definition: Sinusoidal dilatation (it's a vasculardisease)
Causes: 1. anabolic steroids (taken for muscle building) 2. oral contraceptive 3. danazol
Pathogenesis : Unknown
Features:
-Asymptomatic
-reversible
-Intra abdominal haemorrhage (Due to stagnation of blood flow the fluid >> leaves to abdomen >> its one of the causes of intraabdominal haemorrhage)
-Liver failure

Liver tumours

Liver tumours can be benign or malignant, however most liver tumours are a result of metastasis (secondary tumours).
Our main concern is its presence IN THE LIVER, Any liver mass should be followed up, especially because it's a common site of metastasis + liver plays a big role by carry on body functions
Secondary tumours are the most common tumors of liver
The most common primary tumor is Hepatocellular Carcinoma

Morphology of cancers:

Most common, HCC however we have CC (biliary carcinoma called cholangiocarcinoma, a cancer a rising from biliary epithelium) or mixed.
Tumours are typically unifocal in contrast of that of metastasis which are multifocal. Tumours >> diffusely infiltrative
Does not mean primary tumours are ALWAYS unifocal and secondary tumours always MULTIFOCAL

- Vascular invasion is common in all types.
- Well -- Anaplastic

Cavernous hemagioma

Type /Definition:

Benign (most common benign tumor) tumor of BV

Description:

Made of vessels filled with blood especially because they are Subcapsular (surface of liver) >> they can bleed.
So Any procedure that may irritate these BV >> BLEEDING
They are usually <2cm.

Causes - Prognosis:

Once diagnosed by radiology, biopsy may cause BLEEDING

Liver cell adenoma Benign

Type /Definition:

tumor that produces secretory cells By definition of adenoma: tumor of glands or tumours that produces secretory cells however, liver doesn't have glands that why we didn't say that this type of tumor is tumor of gland, instead we said IT PRODUCES SECRETORY CELLS

Description:

May be misdiagnosed as HCC. But it rarely may contain HCC.
These tumours are also subcapsular so they can be ruptured

Presentation:

Young female on oral contraceptives because they are hormone dependent

Causes - Prognosis:

-Hx of oral contraceptive intake
-May rupture esp. during pregnancy causing severe intraperitoneal haemorrhage

Hepatocellular carcinoma

Type /Definition:

PRIMARY Malignant cancer, it's the faith of many conditions and it forms, makes up 5.4./.of all cancers (tend to metastasize through hematogenous spread that's why it can grow within the hepatic vein or even reach the IVC and causes obstruction)

Incidence:

- -<5/100000 population in N&S AmericaN& central Europe Australia (not frequent)
- -15/100000 population in Mediterranean
- -36/100000 population in Korea, Taiwan Mozambique, China
- Blacks > white
- M:F ratio
- 3:1 in low incidence areas.60yr 8:1 in high incidence areas. 20-40yr

Predisposing factors:

1. Hepatitis (B) carrier state:
vertical transmission (most common CARRIER RATE), increases the risk 200X.
These patients may develop cancer early in life when it gets superimposed by Hep D or when the virus gets reactivated.
This type of cancer is associated with HEP B / C cirrhosis itself regardless the cause increases the risk of cancer and may be absent young age group (20-40yr) (due to high supervision on the transmission of HEP B we reduced the incidence of cirrhosis caused by Hep B however Hep C is HARD to control)

2. >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
4. Aflatoxins(toxins produces by fungi found in improperly stored grains, these toxins can induce gene mutation (immunosuppressant gene) >> imp in carcinogenesis >> In African countries the exposure to these toxins is from early age that's why they have high incidence of cancer

5. Hereditary tyrosinemia (in 40% of cases)(even with the control >> high risk of HCC)
6. Hereditary hemochromatosis

Pathogenesis:

1. Repeated cycles of cell death & regeneration HBC, HCV, gene mutations, Genomic instability

2. Viral integration HBV DNA integration which leads to inducing the synthesis of new protein >> clonal expansion

3. HBV DNA integration which leads to genomic instability not limited to integration site.

4. HBV: X-protein which leads to transactivation of viral & cellular promoters, Activation of oncogenes, Inhibition of apoptosis

5. Aflatoxins (fungus Aspergillus flavus) mutation of p53(tumor suppressive gene)

6. Cirrhosis (itself is a degenerative-regenerative process)
HCV
Alcohol
Hemochromatosis
Tyrosinemia (40% of pts. Develop HCC despite adequate dietary contro)

Fibrolamellar carcinoma

• This tumor is different that primary, its imp bec
• it occur in young individuals. No relation to HBV or cirrhosis
• better prognosis THAN HCC
• Single hard scirrhous tumor.
- Presentation in 20-40 years, M=F

Characteristics:

- large Cells
- eoisinophilic cytoplasm
- fibrotic background (hence its name)

metastasis

Vascular – lungs, bones, adrenals, brain, in 50% of cholangiocarcinoma
C/P
abd. Pain, malaise, wt. loss increase α-feto protein in 60 –75% of pts. BUT ITS TOTALLY UNSPECIFIC
• α-feto protein increases also with:
yolk sac tumor, cirrhosis, massive liver necrosis, chronic hepatitis, normal pregnancy, fetal distress or death, fetal neural tube defect.

Causes OF DEATH :

Cachexia, GI bleeding, Liver failure, Tumor rupture and haemorrhage

Prognosis:

Death within 7 -10 months

Focal nodular hyperplasia

-Well demarcated hyperplastic hepatocytes nodules with central scar.
- Non-cirrhotic background of liver
- Not neoplasm but nodular regeneration

Causes:

Local vascular injury to liver causing arichtecture loss + parenchymal degeneration + fibrosis.
This injury can be because of a vascular problem

Presentation:

- -Females of reproductive age
- -20% of cases have cavernous hemagnioma

Prognosis:

No risk of malignancy

Macro regenerative nodules

Background of Cirrhotic liver
(so, we have cirrhotic nodules and WE FIND AN ENLARGED OUTSTANDING NODULE, So we have to see what caused it to enlarge (to check if its malignant))
- Larger than cirrhotic nodules
- No atypical features (microscopically)
- Reticulin is intact

Prognosis:

No malignantpotential

Dysplastic nodules

- Larger than 1 mm
- Background of a Cirrhotic liver
- Atypical features, pleomorphism and crowdingWith high proliferative activity
- High or low dysplasia
- Has two types:
small – cell dysplastic nodules
Large – cell dysplastic nodules

Prognosis:

Precancerous (monoclonal, +ve gene mutations)
**gene mutations are what makes it precancerous