Patho 2

Clinical features of liver diseases (think of functions)

Jaundice (not a must, but a major feature)	yellowish discoloration of skin and sclera due to accumulation of bile salts in these areas
hypoalbuminemia→edema	If we do liver tests that usually measures protein levels (major site of protein synthesis), enzymes, clotting factors, sometimes in certain liver diseases we will find the albumin levels decreased
hyperammonemia	Accumulation of AMMONIA from urea cycle, keep in mind it's a toxic substance
fetor hepaticus	Patients might have musty or sweet and sour smell-odor
Palmar erythema (hyper estrogen anemia)	Redness of palms (erythematous palms), due to increased estrogen→ dilatation of capillaries in palms mostly
spider angiomas	Spider like capillaries
hypogonadism and gynecomastia	Especially in chronic MALE patients, due to effect of estrogen→ lower male hormones and enlarged breast

Liver diseases

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: 1-**massive hepatic necrosis**: fulminant viral hepatitis (Hep A, B,D), drugs and chemicals (like acetaminophen, halothane, anti TB drugs CCL 4 poisoning (high exposure) ,mushroom poisoning) ((more information below the table, from the slides)) 2-**chronic liver disease (most common cause of liver failure, particularly cirrhosis)**	Notes: -We can exclude viral hepatitis by serology -Drugs should be noted not only in liver diseases but all diseases - acetaminophen=paracetamol -halothane= anaesthetic agent, patients can react to halothane so suddenly after their exposure - we shouldn't give halothane to patients undergoing short-term surgery to prevent hepatic failure -massive hepatic necrosis usually give rise to ACUTE LIVER FAILURE (patients who are not known to have liver diseases) -Sometimes liver failure can occur without changes, for example acute liver failure patients present with necrosis and chronic liver patients, present with fibrosis BUT in some patients even if we examined their liver, we won't see significant change in their liver, and that group is whom we should keep in mind → liver failure without gross cirrhosis, major death of hepatocytes Okay but how come?? This case is called: **hepatic dysfunction without overt necrosis** hepatocytes may be viable but unable to perform normal metabolic function and this occurred due to certain conditions like Rye syndrome, tetracycline toxicity (tetracycline=antibiotic), acute fatty liver of pregnancy(which can lead to	Consequences of liver failure: 1- MULTIPLE Organ failure (kidney/lung failure) 2- BLEEDING (COAGULOPATHY)and this is a really important feature, (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. (Renal failure due to liver disease)	-

			acute liver failure a few days after onset)(they are healthy patients but due to some changes they develop severe fatty filtration and liver failure) الحل الوحيد هون لانه التغيرات مش كتير واضحة اني احاول اربط حالة المريض بالمضاعفات خاصة RYE SYNDROME		

MASSIVE HEPATIC NECROSIS:

Fulminant HEPATIC failure from the onset of symptoms to hepatic encephalopathy within two to three weeks, it also can be sub fulminant, within three months.

causes viral hepatitis in (50 -65%) of patients especially in (hepatitis B,B-D, C,**A(especially in non-immunized in developing countries although it is benign)**,, drugs and chemicals in 20 to 30% of patients,, 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 (orange – not common causes we consider them when we exclude the major 2 causes)

*Hep B+D can aggravate condition in carriers without symptoms, and if we have a D superimposed on B → v. severe hepatitis associated with necrosis called fulminant hepatitis

Alcoholic liver disease	-alcohol is most widely abused agent -it is the 5th leading cause of death in USA due to #1 accident #2 cirrhosis	-causes: excessive//continuous ethanol consumption (causes more than 60% of chronic liver disease in most western world countries in accounts for 40% to 50% of deaths due to cirrhosis) -pathogenesis: Short term ingestion of as much as 80g per ethanol per drink (8 beers or 7 ounces of 80 proof liquor) generally produces mild reversible hepatic changes (fatty changes) but chronic intake of 50 to 60g per day is considered a borderline risk for severe injury(women seem to be more susceptible to hepatic injury than men because of low gastric metabolism of ethanol and differences in body composition)	-Although cirrhosis is not so common in alcoholics (14-15./.) of them develop cirrhosis, the likely hood of development of cirrhosis is related to AMOUNT AND DURATION OF CONSUMPTION -80 to 100 Mg/dl is the legal definition for driving under the influence of alcohol, we don't mention a certain number of cups for example because at the end each beverage has different percentage of alcohol. -44 ML of ethanol is required to produce this level in 70 Kg person There are differences between occasional drinkers and habitual drinkers: - occasional drinkers bl. level of 200 milligram per deciliter produces, in death in respiratory failure at 300 to 400 mg/dl. (low level in blood→ severe manifestations) -habitual drinkers can sustain higher levels than occasional drinkers in form of clinical presentation, these levels are up to 700mg/dl without clinical effect due to metabolic tolerance explained by 5 to 10 x induction of cytochrome P-450 system that includes enzyme CYP 2E1 which increases the metabolism of ethanol as well as other drugs as cocaine and acetaminophen (SOME PEOPLE CLEAR THE DRUG RAPIDLY FROM THEIR BODY SO THEY NEED A HIGHER DOSE). -CYP2E1 =enzyme responsible for dealing and clearing of ethanol -ACTIVE CYP2E1 (CYTP450 SYSTEM) → rapid clearing→ reach excretory form of ethanol quickly -IF IT WAS NOT ACTIVE → clearing and metabolism takes longer time→ ethanol stays in the body for a longer time→body deals with the damaging effect that results from the metabolism by product because they are not excreted quickly - we also have racial differences regard the manifestation of toxicity	We have 3 **forms** of alcoholic level disease (IMP THEY ARE NOT STAGES OF THE DISEASE meaning that the patient can present with any one of these forms) = 1-hepatic steatosis (90-100% of drinkers) 2-alcoholic hepatitis (1/3) (1-35% of drinkers) 3-cirrhosis (14% of drinkers, steatosis and hepatitis may develop in independently) -Cirrhosis is strongly dependent to alcohol consumption in developed countries where it is strongly dependent to viral disease in places that have viral endemics

-HEPATIC STEATOSIS: (MODERATE-> SEVERE) can occur following even moderate intake of alcohol in form of microvesicular steatosis, chronic intake leads to diffuse steatosis (involve large area of liver). liver becomes LARGE (due to fat infiltration) (4KG->6KG) and SOFT YELLOW AND GREASY. These patients can develop other forms of liver disease (more severe forms).

Important, fatty changes are INITIALLY reversible with complete abstention from further intake of alcohol BUT If the patient continues to take alcohol this would lead to fibrosis.(FIBROSIS IS AN INITIAL SIGN OF IRREVERSIBILITY EVEN IF THE PATIENT QUITS).

ALCOHOLIC HEPATITIS: (fatty change + inflammation)

CHARACTERISTIC FINDINGS: these patients develop attacks of liver damage

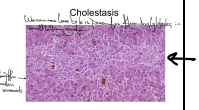
1-HEPATOCYTE SWELLING AND NECROSIS: it is due to accumulation of fat and water and proteins→ CHOLESTASIS and hemosiderin deposition in hepatocytes and Kupffer cells

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 (usually this carcinoma is related to cirrhosis→ cirrhosis in western countries→ alcohol so its like an indirect relation).

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

4-Fibrosis: patients are usually in a stage more severe that fatty change alone → they develop fibrosis, actually patients who develop attacks of alcoholic hepatitis are liable to have more damage that would lead to fibrosis. Fibrosis is in all areas that DON'T contain fibrous materials, and this indicated chronicity.

-Sinusoidal and perivenular fibrosis -Periportal fibrosis

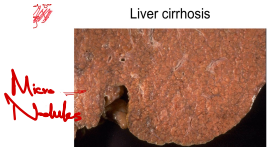


5-Cholestatis: problem in excretion of bile because of hepatocytes' chronic exposure to toxic substances→ subnormal function of hepatocytes + damage in Kupffer cells

6-Mild deposition of hemosiderin in hepatocytes and Kupffer cells

-ALCOHOLIC CIRRHOSIS (chronic)

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 (when the liver changes to fibrous tissue, no hepatocytes) = scar tissue
- Bile stasis : Biliary system is obstructed/filled with bile material
usually, the last part of the liver to disappear are the bile ducts (damage start in hepatocytes).
-Mallory bodies are only rarely evident at this stage (we always look for them)
-IRREVERSIBLE (no way the liver can go back to normal, and 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 (liver is not palpable) → this means ALL the liver is fibrosed and the liver retracted → overall size shrinks

Ethanol metabolism

ETHANOL → ALCOHOL DEHYDROGENASE (LIVER/STOMACH)→ ACETYLDEHYDE

CYT P450 // CATALASE (LIVER)

ACETYLDEHYDE → ALDEHYDE DEHDROGENASE → ACETIC ACID

Q; Why do we need to change ethanol into acetic acid? Because it is the excretory form of ethanol, and it's the form that is absorbed and distributed in the body, can be detected in body fluids and breath.

(distribution of acetic acid in fluids and tissues is in direct proportion to blood level)

Q; which gender is promoted to have higher blood levels of alcohol after drinking the same quantity of ethanol? Females, because they have lower levels of gastric alcohol dehydrogenase activity than men. (making them more susceptible to hepatic injury)

-less than 10% of absorbed ethanol is excreted unchanged in urine sweat and breath

Q; what other causes can affect ethanol metabolism other than gender?

Genetic polymorphism (point mutation) present in different races. Different races tend to have difference in the function of aldehyde dehydrogenase and that would affect that it's an old metabolism for example 50% of Chinese Vietnamese and Japanese have lowered enzyme activity due to point mutation of the enzyme→ accumulation of acetaldehyde (toxic substance)→facial flushing (Due to dilatation of BV),tachycardia and hyperventilation

IMPORTANT :females and males have differences in **alcohol dehydrogenase** , while different races have differences in **aldehyde dehydrogenase**

Q; what is the problem with ethanol and fatty change? Ethanol simply interferes with all mechanisms dealing with fat and the outcome→increase in the availability of free fatty acids in the circulation → deposition in other organs mainly liver.

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

-women are more susceptible to hepatic injury due to decreased gastric metabolism of ethanol

-only 8 to 20% of Alcoholics develop cirrhosis

MECHANISM OF ETHNAOL TOXICITY

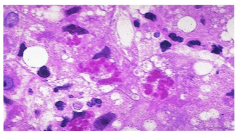
Fatty change	-SHUNTING of lipid catabolism towards lipid biosynthesis due to excess production of NADH over NAD in cytosol and mitochondria. -Acetaldehyde combine forms adducts with tubulin (protein in hepatocytes)and lower function of microtubules(site of excretion)→ lowering in lipoprotein transport 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
Induction of cytochrome P-450 enhances the metabolism of drug to toxic metabolites like acetaminophen	Meaning that → interfere with drug metabolism →damage effect of drug
Higher free radicals production due to activation of cytochrome P-450 leads to membrane and protein damage	FREE RADICALS ARE TOXIC MOLECULES→ DAMAGE
Alcohol directly affects microtubular and mitochondrial function and membrane fluidity	
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
superimposed HCV hepatitis infection	acceleration of liver injury (HCV occurs in 30% of all Alcoholics)
release of bacterial endotoxins into portal circulation from the gut	Alcohol→ release of bacterial endotoxins into portal circulation from the gut→ inflammation of liver
regional hypoxia in the liver	Alcohol→regional hypoxia in the liver due to release of endothelins which are potent vasoconstrictors→low hepatic sinusoidal perfusion
Alteration of cytokine regulation	TNF is a major effector of injury , we also have IL6/IL8/IL18

Clinical features of ethanol toxicity

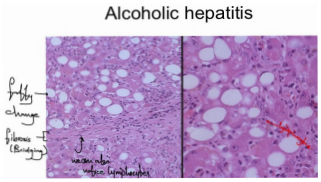
HEPATIC STEATOSIS (REVERSIBLE)	Enlarged liver + high liver enzymes (transaminases) in blood severe hepatic dysfunction is unusual
ALCOHOL HEPATITIS	Related to very long history of alcohol uptake ,chronic process 15 to 20 years of excessive drinking, nonspecific symptoms aggregate in attacks like malaise anorexia weight loss. But with each bout of hepatitis after excessive drinking→aggrevate more damage→ 10-20./. risk of death during attack→ cirrhosis in 1/3 in few years HEPATOSPLEENOMEGALY High LFT
CIRRHOSIS	Portal hypertension

Pictures:

Mallory-hayline bodies



Alcoholic hepatitis



Cholestasis