Patho 5

Wilson disease

Definition	aut. 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)
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 sec. of ceruloplasmin into the plasma →Cu. accumulation in liver
Result of accumulation of copper	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. (why the age of 5-6? Because Cu needs time → 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 exc. 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 (when we suspect Wilson disease, we use this stain to detect copper in liver because it is not stained by protein 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)

	These rings are present in patients who fully developed Wilson disease and is seen by an ophthalmoscope
Clinically	-Presentation > 6 yrs. 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 (CONFIRMATIVE THING however its hard and not practical, why? We have to have liver tissue , dry it in a certain way, then measure amount of copper) > 250 mg/gm dry wt.

a-1 Antitrypsin defeciency

Definition	aut. Recessive disorder, primary disease of lung
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 N. American white population carriers PiMZ : have decreased levels of enzyme level how ever they can be protected from disease (in other words it is manageable)
What is a1-antitrypsin	a1-antiryrpsin is a protease inhibitor as (elastase, cathepsinG, proteinase 3) which are released from neutrophils at the site of inflammation at the lung. --enzyme important to control enzymes secreted during inflammation of lung, that's why its important in order to prevent excessive damage of lung so its deficiency→ damage to lung But what does it have to with the liver? The a1-antitrypsin 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)
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 (why is it associated with liver injury? Because of the auto phagocytosis of proteins) -8-10% of patients develop significant liver damage (NOT ALL patients develop SIGNIFICANT damage because of degree of autophagocytic effect)
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)
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)

Reye syndrome

Definition	-Fatty change in liver & encephalopathy -< 4 yr. (typically young) -3 – 5 d after viral illness (mostly after respiratory viral illnesses) - HIGH liver & abn. LFT (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 (previously it was though, because of the viral infection + young = fever and adults would give them salicylate → Reye syndrome It was thought it was secondary to drug reaction but now it is believed to be because of malfunction of mitochondria and not because of the drug itself) -Microvesicular steatosis -Brain edema (that's why the developed encephalopathy) -Absent inflammation (if we looked at their brain no inflammation) -Sk. Muscles, heart, kidneys – fatty change - if we don't think of this problem apparently we might miss it.