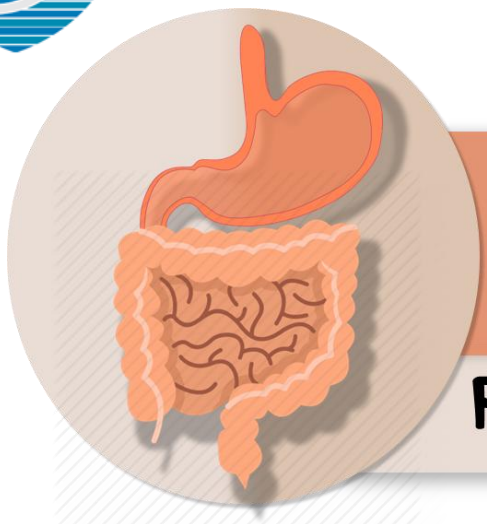

GI system

Pathology

◉Sheet ○Slide

Number:	4
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In the last lecture we have talked about inherited **metabolic liver diseases**, and we started with Hemochromatosis, throughout this sheet we will talk about Wilson's diseases and alpha-1 Antitrypsin deficiency.

In order to save time, as we are running out, I will use the slides and add, explain and illustrate using them. Anything extra will be written in red colour.

Wilson's disease

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

The main outcome of this disease is deposition of copper in the liver.

It is related to a mutation in the *ATPase metal ion transporter, that's why these patients can't deal with copper; due to cerulopalsmin deficiency; thus copper can't be utilized.*

Pathogenesis

Main source of Cu is from diet → Absorption of ingested Cu (2-5 mg/d) → Complex with albumin → Hepatocellular uptake → Incorporation with α-2-globulin to form → Ceruloplasmin → then Ceruloplasmin is secreted from the liver to other organs & any excess will return to the liver to be degraded in the lysozomes and then the copper will be excreted in the bile.

What happens in Wilson Disease patients?

In Wilson disease absorbed Cu. Fails to enter the circulation in the form of ceruloplamin & the biliary excertion of Cu. is decreased

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

And what is the effect of increased copper concentration?

Increased Cu. Accumulation in the liver results in:

1- **Production of free radicals.**
2- **binding to sulfhydryl groups of cellular proteins.**
3- **displacement of other metals in hepatic metalloenzymes.**

What are the other sites that may be affected from the increased copper concentration in the liver?

- **Brain; Toxic injury to basal ganglia esp. the putamen causing atrophy & cavitation.**

- **Eyes; kayser- fleischer rings green – brown depositis of Cu. in descemet membrane in the limbus of the cornea (hepatolenticular degenceration). Which can only be seen using a fundoscope.**

- **Kidney.**
- **Bones.**

Nevertheless, concentration of copper in the urine is a useful diagnostic tool.

What do we see in the liver of a Wilson's disease patient?

Totally non-specific, the presentation and diagnosis is by suspicion, but in general we can see:

1-Fatty change. 2-Acute hepatitis. 3-chronic hepatitis. 4-cirrhosis.

5-massive hepatic necrosis.

As we have previously said, Hemochromatosis presentation is somehow related to middle-aged individuals rather than the extremes. However, manifestations on patients with Wilson disease may start at 10-12 YO, as a result of copper accumulation.

Clinically:

- **Presentation > 6 yrs of age.**
- **Most common presentation is acute or chronic hepatitis**
- **Neuropsychiatric presentation can occur behavioral changes Frank psychosis Parkinson disease- like syndrome.**

If a patient, in his early 20's or even before his 20th birthday, presents to the clinic with a cirrhotic liver, suspicion in a metabolic liver diseases is a must.

Diagnosis:

1- **Decrease in serum ceruloplasmin level; Usually used.**
2- **Increase in urinary exc. Of Cu.**
3- **Increase in hepatic content of copper > 250 mg/gm dry wt; rarely used.**

We have finished talking about Wilson Disease, Nice and sweet.

The third and the final Metabolic disorder of the liver is α-1-Antitrypsin Deficiency.

α-1-Antitrypsin Defeciency

- **Autosomal Recessive disorder.**
- **The usual sites to manifest such a disease are the lungs.**
- **freq. 1:7000 in N. american white population.**
- **α-1-antiryrpsin is a protease inhibtor as elastase, cathepsinG , proteinase 3 which are released from neutrophils at the site of inflammation.**

What is α-1-Antitrypsin enzyme, and what makes it so special?

Well, this enzyme is an inhibitor for a group of enzymes secreted at the site of inflammation, which are called Proteases, any of which acts on the offending agent, and causes it's degradation.

On the contrary, these enzymes cannot discriminate sweet and normal cells; thus causing massive destruction at the action site, in order to prevent this massive destruction, α-1-Antitrypsin is secreted after short period of the lit-up of inflammation in order to inhibit such events.

These patients, however, don't have this protective mechanism and the disease will progress in different organs, one of which are the lungs and so called emphysema.

- The gene is located on chr. 14.
- At least 75 forms of gene mutation are present.
- The most common genotype is pi.MM present in 90% of individuals.
  M allele stands for the normal allele, whenever you see an M allele, that means that the individual is normal.

- PiZZ genotype → decreased level of α-1-antitrypsin in blood (only 10% of normal) are at high risk of developing clinical disease.
- Carrier patients has one normal allele M & the Abnormal Allele Z, yet they will live normal as a single M allele is sufficient to produce the required amount of the enzyme α-1-antitrypsin.

  But still, we have to raise a question about the role of the liver throughout this process:

  Pathogenesis:

- The mutant polypeptide (PiZ) is abnormally folded & polymerizes causing its retention in the ER of hepatocytes.

- Athoyugh all individual with PiZZ genotype accumulate α-1-AT-Z protein only 10% of them develop clinical liver disease.

- The accumulated α-1-AT-Z is not toxic but the autophagocytic response stimulated within the hepatocytes appear to be the

cause of liver injury by autophagocytosis of the mitochondria -8-10% of patients develop significant liver damage.

Well, α-1-antitrypsin is synthesized in the liver, and when the individual acquires such a mutation, they will not be able to synthesize α-1-antitrypsin in the correct form, this will cause a misfolded & unreliable form to accumulate in the hepatocytes, and then autophagocytosis will start to get rid of the misfolded proteins in the cytoplasm of hepatocytes.

What do we expect to see in the clinic?

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 Fatty change Mallory bodies.

Clinical features:

- Neonatal hepatitis with cholestatic jaundice appears in 10 – 20% of newborns with the disease.
- Attacks of hepatitis in adolescence.
- Chronic hepatitis & cirrhosis.
- HCC in 2- 3 % of PiZZ adults + cirrhosis.
- Age presentation is wide.

Clinically we don't expect to see a specific demarcation; as it is not specific.
We must have a biopsy that shows the accumulation of porteinous material within the cytoplasm of hepatocytes. In order not be confused with glycogen, which is mainly found in the cytoplasm of hepatocytes, we often use a diastase enzyme, which causes degradation of glycogen, and any other material that is resistant will remain in the cytoplasm, hence porteinous material.

We have finished talking about α-1-antitrypsin deficiency, buffy and fluffy.

Reye's Syndrome

The presentation is usually misleading, and it is characterized by sudden fatty change in the liver, which is microvesicular, nothing else obvious as an underlying cause.

The patient is prone to develop a liver failure.

During a classical history, the patient's family will usually include a viral infection 3-5 days earlier to the systemic serious symptoms.

- **25% may go into coma, which is a serious condition.**

Pathogenesis

-Derangement of mitochondrial function along or in combination with viral infection & salicylate.
It was previously thought that Aspirin (AKA: salicylate) was the culprit for the development for the disease in children, having known that there is no such a relation keeps in mind that mitochondrial abnormalities is the main cause.
- Microvesicular steatosis.
-Brain edema; without an inflammation, not 2ndry involovment.
-Absent inflammation -Sk. Muscles, heart, kidneys – fatty change.

We have finished talking about Reye's syndrome, Easy-Jappanesy.

Related to vascular diseases in the liver we have:

Budd – Chiari Syndrome

- **Thrombotic occlusion of the hepatic vein.**
- **Patients may develop:**
  1- **Hepatomegaly.**
  2- **Wt.gain.**
  3- **Ascitis; accumulation of fluid in the abdominal cavity**
  4- **Abd. Pain.**

What are the predisposing conditions to develop Budd-Chiari?

1-PCV:
Polycythemia Vera; malignancy of the blood, is a condition characterized by increased RBC count in the blood which indeed will cause stasis, and increase the chance of developing a thrombus or occlusion in the *portal vein*

2- Pregnancy.
3- Postpartum.
4- Oral contraceptive.
5- PNH: Paroxysmal nocturnal hemoglobinuria
6- Mechanical obstruction.
7- Tumors as HCC.
8- Idiopathic in 30% of the cases.

Morphology:

- **Swollen liver, because it is engorged with blood.**
- **Development can be acute or chronic.**
- **Acute development usually surrounds the parenchyma around the central vein, which initiate fibrosis around the aforementioned site.**
- **Red with tense capsule.**
- **Centrilobular congestion & necrosis; Thrombi.**
- **Fibrosis.**
- **Clinically: Mortality rate is high if not treated.**

We have finished talking about the liver pathology, in order to grasp it well it needs a bit of revision as a one piece.

Feel free to have a 5 minutes break; try not to look at your bed.

Pathology of the biliary system.

Primary sclerosing cholangitis

- **Abbreviated as PSC.**
- **Classified as autoimmune disease.**
- **Inflammation, obliterative firosis, & segmental dilation of the obstructed intra hepatic & extra hepatic bile ducts.**
  Segmental: not all of the bile duct is affected; alternating affected parts besides a normal tissue.

- **In PSC, UC coexists in 70% of patients.**
- **In patients of UC, 4% develop PSC.**
- **3-5 the decades.**
- **M: F 2:1**

- Asymptomatic pts.
- Persistent increment in serum alkaline phosphatase always points out to a biliary disease; why ?
Well, because the lining epithelium of the ducts is the major site for the secretion of alkaline phosphatase and any inflammation will cause a noticeable increment in the enzyme concentration.

- fatigue, pruritis; itchy skin due to bile salt deposition In the skin, another characteristic of biliary disease, jaundice, wt loss, ascitis, bleeding, encephalopathy.

What is a major characteristic about these patients?

- **They have autoimmune antibodies, Antinuclear cytoplasmic Abs in 80% of cases.**
- **And in less than 10% of the cases antimitochondrial Abs.**

Morphology:

- Concentric periductal onion-skin fibrosis around the bile duct & lymphocytic infiltrate.
- Atrophy & obliteration of bile ducts.
- Dilation of bile ducts in between areas of stricture.
- Cholestasis & fibrosis; generally in all biliary diseases.
- Cirrhosis, cholangiocarcinoma, which is an adenocaricnoma of the biliary system. (10 – 15%).

Pathogenesis:

- Exposure to gut derived toxins.
- Immune attack; due to Ab's.
- Ischemia of biliary tree.

Secondary biliary cirrhosis

- Much more common than primary.
- They can be very serious.
- Prolonged obstruction to extra-hepatic biliary tree is really the main fear, as it will cause stasis in the bile and contribue to cholelithiasis formation.

- Causes: 1-cholelithiasis 2-biliary atresia 3-malignancies 4-stricutres.

Primary biliary Cirrhosis

- Chronic, progressive & often fatal cholestatic liver disease.
- Non-suppurative granulomatous destruction of medium-sized intrahepatic bile ducts, portal inflammation & scarring.
- The granulomas here are not caused by any infectious process.
- Doesn't rise in the background of a secondary cause.

- age 20-80 yrs (peak 40-50yrs)

- F>M -Insidious onset.

- Pruritis.

- jaundice.

- Cirrhosis over 2 or more decades.

- Increased Alkaline phosphatase & cholesterol which is a classical hallmark for biliary diseases.

- Hyperbilirubinemia = hepatic decompansation

- Antimitochondrial Abs > 90% Antimitochondrial pyruvate dehydrogenase, auto-immune antibodies.

- Associated conditions: sjogern synd. Scleroderma thyroiditis, RA, Raynauds phenomenon. MGN, celiac disease.

Morphology:

- Interlobular bile ducts are absent or severely destructed (florid duct lesion).
- Intra epithelial inflammation.
- Granulomatous inflammation; *CHARECTARISTIC MARK*
- Bile ductular proliferation.
- Cholestesis.
- Necrosis of parenchyma.
- Cirrhosis

Sinusoidal Obstruction Syndrome

(Veno-occlusive disease)

- Might be a complication of bone-marrow transplant, This occurs in the first 20-30 days after bone marrow transplantation. Usually patients are under a certain procedure to ensure a successful bone marrow transplantation, that is acheived by:
  1-Drugs as cyclophosphamide.
  2-Total body radiation; to clear all malignant cells in the blood.

And this radiation may cause destruction of the sinusoidal lining; which stimulate the stellate cells to initiate fibrosis, and thus causing Veno-Occlusive disease.

Mechanism

Toxic injury to sinusoidal endothelium →emboli →blockage of bl. Flow Passage of blood into space of Disse →initiate stellate cells → fibrosis

- **Originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloids.**
- **Incidence is about 20% in recepients of allogeneic marrow transplant.**
- **Clinical presentation Mild.**
- **Severe Death if does not resolve in 3 months.**

Unicorns are real … so are your dreams

Please remember that

Love is Wise … Hatred is Foolish