GIS 13

PATHOLOGY

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♥ Wilson Disease ♥

- An autosomal recessive metabolic disorder of (Cu+2) metabolism.
- It is caused by mutations (>80 mutations) in the ATP7B gene on chromosome 13 which encodes an ATPase metal ion transporter in the Golgi region (in hepatocytes).
- Gene (allele) frequency →1:200 in a population.
- Incidence rate →1:30,000 in a population.

Pathogenesis:

One essential mineral that our body needs to get through the diet is copper. Typically, our intake of copper is about 2-5 mg per day. This amount of copper is obtained from the food we eat (Main source).

The copper from the diet is absorbed$_1$ in the small intestine via enterocytes. It then binds$_2$ to albumin and is passed$_3$ off into the portal vein→to the liver. Once it's in the liver, it's sent to a special transport protein -ATP7B- which binds copper to α-2-globulin protein, which carries the copper in the blood.

This α-2-globulin is responsible for carrying 95% of the copper in blood. After it binds to copper, it is now called ceruloplasmin. So, copper is carried to peripheral organs as ceruloplasmin. Excess ceruloplasmin is taken back by hepatocytes for lysosomal degradation$_1$. This is followed by secretion$_2$ of free copper (Cu+2) into the bile.

With Wilson disease, there's a defect in this ATP7B transport protein, and that means it can't incorporate the copper into ceruloplasmin in hepatocytes. Therefore, absorbed copper fails to enter the circulation in the form of ceruloplasmin. The biliary excretion of free (Cu+2) is also inhibited, in this case. As a result, copper builds up and accumulate inside hepatocytes.

Copper 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.

In Wilson's disease; the liver tends to release accumulated copper that is not bound to ceruloplasmin into the bloodstream. This free copper precipitates

- By the age of five, copper spills over to the circulation, causing hemolysis, as well as the involvement of other organs, such as the brain, cornea, kidneys, bones, joints and parathyroid glands.

- Urinary excretion of copper increases.

- In order to differentiate Wilson's disease from other diseases (particularly chronic hepatitis): Special stains for copper: (rhodanine stain$_1$) or copper-associated protein (orcein stain$_2$) can be used to visualize the abnormal copper stores within hepatocytes.

Morphology

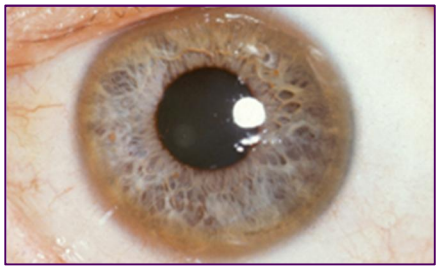
I. Liver

When the amount of copper in the liver overwhelms the proteins that normally bind it, it causes oxidative damage that leads to liver fatty change → acute hepatitis → chronic hepatitis → cirrhosis, and eventually, massive hepatic necrosis.

II. Brain:

Most copper is deposited in the basal ganglia, particularly in the putamen causing atrophy and cavitation of the ganglia. Damage to these areas produces neuropsychiatric symptoms.

III. Eye:



Kayser–Fleischer ring: Green-brown rings that appear to encircle the iris of the eye. They are due to copper deposition in part of the limbus cornea (Descemet's membrane). That's why the other name for Wilson's disease is hepatolenticular degeneration.

Clinically

- Presentation > 6 yrs of age (i.e. people diagnosed with Wilson's disease are older than 6).
- Most common presentation is acute$_1$ or chronic$_2$ hepatitis.
- Neuropsychiatric presentation can occur; behavioral changes, frank psychosis, Parkinson disease-like syndrome…etc.

Diagnosis

- Levels of ceruloplasmin are abnormally low.
- Urine copper is elevated.
- Hepatic content of copper is elevated; a level of 250 mg (or more) of copper per gram of dried liver tissue confirms Wilson's disease.

♥ α-1-Antitrypsin deficiency ♥

- An autosomal recessive disorder.
- Frequency → 1:7000 in North American white population.
- α-1-antiryrpsin is a protease inhibitor; it inhibits various proteases as elastase, cathepsin G, and proteinase 3 which are released from neutrophils at the site of inflammation.
- The gene Pi. (Peptidase inhibitor) is located on chromosome 14.
- At least 75 forms of gene mutation are present.
- The most common genotype is Pi.MM. It is present in 90% of normal individuals.
- People with Pi.ZZ genotype (~10% of normal individuals), have lower blood levels of alpha-1 antitrypsin, and they are at high risk of developing clinical disease (extra: this is usually sufficient to protect the lungs from the effects of elastase in people who do not smoke).

Pathogenesis

- The mutant polypeptide (PiZ α-1-Anti-trypsin) is abnormally folded, and it polymerizes causing its retention in the ER of hepatocytes.
- Although all individuals with Pi.ZZ genotype accumulate α-1-Anti-trypsin-Z protein, only 8-10% of them develop clinical liver disease (liver damage). This is due to ER protein degradation pathways.
- The accumulated α-1-AT-Z is not toxic, but the auto-phagocytic response stimulated within the hepatocytes (upon its accumulation) appears to be the cause of liver injury by auto-phagocytosis of the mitochondria.

Morphology

1) Intra-cytoplasmic globular inclusions in hepatocytes are acidophilic in H&E sections. These inclusions are PAS-positive and diastase resistant.
   Diastase is an enzyme that digests glycogen (diastase sensitive and PAS-positive) but doesn't alter these inclusions since they're diastase resistant. Therefore, PAS-Diastase procedure doesn't reveal glycogen granules since they will be digested by the enzyme. On the other hand, α-1-AT deficient hepatocytes (having the inclusions) will stain with PAS even after diastase treatment (diastase resistant).
2) Neonatal hepatitis, cholestasis, fibrosis, chronic hepatitis, cirrhosis, hepatic fatty change and Mallory bodies.

Clinical features

1) Neonatal hepatitis with cholestatic (obstructive) jaundice appears in 10-20% of newborns with the disease.
2) Attacks of hepatitis in adolescence.
3) Chronic hepatitis and cirrhosis.
4) HCC (hepatocellular carcinoma) occurs in 2-3 % of Pi.ZZ adults (with or without cirrhosis).

♥ Reye's syndrome ♥

- It typically happens in children < 4 y/o, three to five days after a viral infection.
- It's characterized by fatty liver$_1$ and encephalopathy$_2$. Therefore, liver function tests (LFTs) are abnormal and liver enzymes are generally elevated.

Pathogenesis

Derangement (damage) of mitochondrial function along or in combination with viral infection and salicylate (e.g. Aspirin).

Clinical features

1) Symptoms mainly include vomiting, lethargy, and 25% of the patients may go into coma.
2) Micro-vesicular steatosis.
3) Brain edema.
4) Absent inflammation.
5) Skeletal muscles, heart, and kidneys can also show fatty changes.

♥ Budd–Chiari Syndrome♥

- Occlusion of the hepatic veins that drain the liver.
- It presents with hepatomegaly$_1$, weight gain$_2$, ascites$_3$, and abdominal pain$_4$.
- Causes:
  1. PCV (polycythemia vera); a disease in which the bone marrow makes too many red blood cells.
  2. Pregnancy.
  3. Postpartum state.
  4. Oral contraceptive.
  5. PNH (paroxysmal nocturnal hemoglobinuria).
  6. Mechanical obstruction of hepatic veins.
  7. Tumors as HCC (hepatocellular carcinoma).
  8. Idiopathic in 30% of the cases.

Morphology

1) Swollen liver; red with tense capsule.
2) Centrilobular congestion and necrosis.
3) Fibrosis.
4) Thrombi.

Clinically

- Mortality rate is high if not treated.

♥ Primary Sclerosing Cholangitis (PSC) ♥

- It is a long-term progressive disease of the liver$_1$ and gallbladder$_2$, characterized by inflammation and obliterative fibrosis$_1$, scarring$_2$, and segmental dilation$_3$ of the obstructed intra-hepatic and extra-hepatic bile ducts (which normally allow bile to drain from the gallbladder).
- Approximately 4% of people with ulcerative colitis (UC) have PSC, and 70% of people with PSC develop UC.
- Diagnosis usually occurs in people in their 3rd-5th decades.
- There is a 2:1 male-to-female predilection in PSC (♂2: ♀1).
- PSC progresses slowly and is often asymptomatic.
- Persistent elevated serum alkaline phosphatase.
- Symptoms include fatigue, pruritus, jaundice, weight loss, ascites, bleeding and encephalopathy
- Anti-nuclear cytoplasmic antibodies are present in 80% of cases.
- Anti-mitochondrial antibodies are present in < 10% of cases.
- Causes
  1) Exposure to gut derived toxins
  2) Immune attack
  3) Ischemia of biliary tree.

Extra: PSC is thought to be an autoimmune disease; it does not demonstrate a clear response to immuno-suppressants. Thus, many experts believe it to be a complex, multifactorial disorder.

Extra: biliary tree is the system which directs secretions from the liver, gallbladder and pancreas through a series of ducts, into the duodenum).

Morphology

1) Concentric peri-ductal onion-skin fibrosis and lymphocytic infiltrate.
2) Atrophy and obliteration of bile ducts.
3) Dilation of bile ducts in between areas of stricture.
4) Cholestasis (blockage of bile flow) and fibrosis.
5) Cirrhosis and cholangiocarcinoma can be seen in 10 –15% of the cases.

♥ Secondary biliary cirrhosis ♥

- Prolonged obstruction to extra-hepatic biliary tree.
- Causes:
    1) Cholelithiasis (The formation of gallstones).
    2) Biliary atresia (One or more bile ducts are congenitally narrow, blocked, or absent).
    3) Malignancies.
    4) Strictures (The common bile duct is abnormally narrow).

♥Primary biliary cirrhosis ♥

- A chronic, progressive and often fatal cholestatic liver disease.
- Characterized by:
    1) Non-suppurative granulomatous destruction of medium-sized intra-hepatic bile ducts.
    2) Portal inflammation and scarring.
- The typical disease onset is between 20 and 80 years (it peaks in the 4th & 5th decades).
- It is much more common in females ♀>>♂.
- Insidious onset.
- Common symptoms are: Pruritus$_1$ and jaundice$_2$.
- It may cause cirrhosis over 2 or more decades.
- Elevated alkaline phosphatase and cholesterol.
- Hyperbilirubinemia; it occurs in advanced stages due to hepatic decompensation (failure of the liver to compensate for the functional overload resulting from disease).
- Anti-mitochondrial antibodies (most common; anti- pyruvate dehydrogenase) are present in more than 90% of the patients.
- Associated conditions: Sjogren syndrome, Scleroderma thyroiditis, RA (rheumatoid arthritis), Raynaud's phenomenon, MGN (membranous glomerulonephritis), and celiac disease.

Morphology

- Interlobular bile ducts are absent or severely destructed (florid duct lesion).
- Intra-epithelial inflammation.
- Granulomatous inflammation.
- Bile ductular proliferation.
- Cholestasis (blockage of bile flow).
- Necrosis of parenchyma.

The florid duct lesion, defined as a granulomatous destruction of the bile ducts, is the histological hallmark of PBC.

♥Cirrhosis Sinusoidal Obstruction Syndrome (Veno-occlusive disease) ♥

- A condition in which some of the small veins in the liver are obstructed.
- Originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloids.
- This occurs in the first 20-30 days after bone marrow transplantation.
- Causes:
  1) Drugs as cyclophosphamide.
  2) Total body radiation.
- Incidence; 20% in recipients of allogeneic marrow transplant.

In other words, it is a complication of radiation to the whole body or high-dose chemotherapy given before a bone marrow transplant.

Clinical presentation

- Mild to severe.
- Death if it is not resolved in 3 months.

Pathogenesis

- Toxic agents (e.g. cyclophosphamide) cause injury to the hepatic venous endothelium (sinusoidal endothelium) → emboli formation → blockage of blood flow → passage of blood into space of Disse → stellate cells activation → fibrosis.

Good luck ♥