GI
PATHOLOGY

#5

WRITER:
Sana&Faten

CORRECTOR:
Faten&Sana

DOCTOR:
Maha Shomaf

WILSON DISEASE:

-Autosomal Recessive disorder (inherited)**of Cu metabolism.**

-the problem with this disease is the accumulation of the Cu due to **mutation in ATP7B gene on chromosome 13 which encodes an ATPase metal ion transporter in Golgi region.**

-they are more than**> 80 mutations.**

-Gene frequency 1:200 individuals

-Incidence of this disease is 1:30000 (not common, so that you should keep it in your mind when the patient comes with the possibility of Wilson disease, the manifestations need to be looked for and prove them).

-in order to understand what is going on in the disease process we must know the normal Cu metabolism:

The Main source of Cu is from diet.

↓

Absorption of ingested Cu (2-5 mg/d) from enterocytes**.**

↓

The Cu will Complex with albumin and circulate until it reaches the liver.

↓

Hepatocellular uptake of Cu

↓

The Cu will **Incorporate with α-2-globulin to form Ceruloplasmin** (which is complex can reach the target sites where the Cu utilize).

↓

Then secretion **into plasma (90 – 95% of plasma Cu)**

↓

Hepatic uptake of ceruloplasmin (any excess amount of ceruloplasmin will return to the liver).

↓

in order to be degraded by **Lysosomal degradation**

↓

Then **Secretion of free Cu into bile** (and excreted with bile, so the body get rid of excess Cu in normal situations).

- In Wilson disease absorbed Cu. Fails to enter the circulation in the form of ceruloplamin & the biliary excretion of Cu.

-but in patients with Wilson disease, they have a **Defective function of ATP-7B (the function of this enzyme:** delivering copper to the secretory pathway as ceruloplamin and mediating export of excess copper into the bile) **→ as a result, failure of Cu. excretion into bile & inhibits secretion of ceruloplasmin into the plasma →Cu. accumulation in liver** (and in other organs but mainly at liver).

-after accumulation of considerable amount of Cu in the liver, the Cu can spill over the circulation without forming a complex, so that the free Cu levels will increase in the blood and that will lead to excretion of Cu with urine (it is a way for diagnosis and helpful tool for Wilson disease identification).

-↑Cu. Accumulation in the liver results in: -

(Cu accumulation ⟶ cellular damage ⟹ liver damage), the underlying mechanism of damage can be due to:

1-Production of free radicals

2-binding to sulfhydryl groups of cellular proteins (the binding happens in the cell membrane and that will lead to cell damage result in cell death and degradation).

3-displacement of other metals in hepatic metalloenzymes

(metalloenzymes: enzymes in the matrix or tissue that use a metal cation as a cofactor in the enzyme active site and they can suffer from matrix disturbance leading to a decrease in their "metalloenzymes" efficiency).

-By the age of 5yrs. Cu. Spills over to circulation causing hemolysis & involvement of other organs as brain & cornea also kidneys, bones joints & parathyroid glands (so the patient will have multi-systemic manifestations), Urinary **exc. Of cu. ↑**

NOTE: as we said in hemochromatosis, if the patient has liver problem with other systemic manifestations, you should think about these diseases.

Morphology:

1) Liver (different changes of liver that result from Wilson disease can mimic any other types of diseases):

1-Fatty change

2-Acute hepatitis

3-chronic hepatitis

4-cirrhosis (if we exclude the common causes and especially viral hepatitis, we really should think about metabolic diseases like Wilson disease)

5-massive hepatic necrosis (acute hepatic failure).

For diagnosis: intracellular Cu cannot be detected on H&E stain under the light microscope, so if we suspect Cu deposition, we can use **rhodanine stain or orcein stain, these** two stains might show the increase in Cu deposition in the liver, however they should be supported by clinical evidence**.**

2) Brain: (another site which is commonly involved in cases of Wilson disease)

Toxic injury to basal ganglia esp. the putamen (there are 3 ganglia but the deposition happens mainly in putamen ganglia) **causing atrophy & cavitation** (the atrophic area also can get necrosis, necrotic brain tissue usually reserved and the dead cells leaving the cavity, so if the patient has a neurological manifestation and makes brain scan, we can see these cavities).

3) Eye:

The very characteristic finding in those patients when we suspect Wilson disease, we have to do ophthalmoscope (which is examination of the eye) to detect **Kayser- fleischer rings, they will have green**-yellowish-**brown ring surrounding the cornea due to deposits of Cu in Descemet membrane in the limbus of the cornea, forming hepatolenticular degeneration** (:it is name refers to involvement of cornea in the process).

- **Clinically:**

Patients with Wilson disease are similar of the hemochromatosis disease, because they need enough amount of Cu to produce damage and manifestations:(ex of these manifestations)

1)Presentation > 6 yrs of age

classical patients are around 10-12 years of age (because enough amount of Cu accumulate at in this age also the damage is present).

2)Most common presentation is acute on chronic hepatitis

3)initially presentation might be **Neuropsychiatric presentation can occur behavioral changes and Frank psychosis** (the patient in school age, they have been noticed him with dramatic changes and abnormality in his behavior- strange behavior-).

4) Parkinson disease- like syndrome with tremor (that seen in elderly).

- **In order to diagnosis:**

1- ↓ in serum ceruloplasmin level

2- ↑ in urinary exc. Of Cu.

3- ↑ hepatic content of copper > 250 mg/gm dry weight (it is a definite diagnosis is done by measuring the amount of Cu, which is depositing in the dry weight of liver, but it is too difficult way because we need to have a piece of liver and extract the amount of Cu from it then compare it to the amount of Cu in the total weight).

-so that usually, we depend on the clinical manifestations and serum and urine Cu levels, all these should indicate the presence of Wilson disease.

4) electron microscope examination of the liver tissue might be helpful, however it cannot differentiate or identify the exact type of mineral, which is depositing, so it can mimic iron deposition or something else.

A-1-ANTITRYPSIN DEFECIENCY:

(It is primary a lung disease)

-Autosomal Recessive disorder (not too common, but we should consider it because it can produce different manifestations).

-freq. 1(carriers of the gene)**:7000** (it is less common than the Wilson) **in N. American white population.**

α-1-antiryrpsin(enzyme)**: is a protease inhibitor as elastase, cathepsinG , proteinase3 which are released from neutrophils at the site of inflammation.**

Note: - proteases: enzymes secreted in tissues when there is inflammation in order to destruct the inflamed tissues and they are different types like: elastase, cathepsinG , proteinase3.

-the normal scenario:

Inflamed tissues will release destructive enzymes, after that these enzymes will inactivate by α-1antitripsin enzyme (inhibitory enzyme), so it subasizes the inflammation and the destruction is acceptable and allow regeneration.

-the patients with α-1antitrpsin deficiency:

When they get inflammation, they will experience a very excessive tissue destruction due to active destructive enzymes (proteases), classically it will develop something called emphysema (because the destruction of the air ways wall).

Now, why the liver is involved in this disease?

-Because the α-1antitripsin enzyme synthesizes in the liver, the gene is responsible for encoding this enzyme is **the gene pi. and is located on chr. 14**, in normal individuals both alleles are normal and they refer to PiM **,**so genetically they are **PiMM genotype, The most common genotype is pi.MM present in 90% of individuals** (they have normal α-1antitripsin enzyme levels).

-On the other hand, **at least 75 forms of gene mutation are present,** the mutated gene refers to PiZZ genotype because the disease is autosomal recessive (the patient develops the disease with both mutated alleles).

-PiZZ genotype →↓ level of α-1-antitrypsin in blood (only 10% of normal) are at high risk of developing clinical disease.

Note: carriers have one gene mutation, and they have considerable amount of α-1antitripsin enzyme synthesis, and they don't have a disease, so the patients must be homozygous recessive genotype.

Pathogenesis:

-Individuals with mutated genes can synthesize a certain level of enzyme (as we know the enzymes are a proteins), however these **mutant polypeptide (PiZ) is abnormally folded and polymerizes causing its retention in the ER of hepatocytes** (intracellular inclusions), and it is a way for diagnosis α-1antitripsin enzyme deficiency disease.

As we mentioned before, any material which is deposited within hepatocytes can exert injury, and some patients will suffer from damage of hepatocytes, that is why they will have disease in the liver due to **α-1antitripsin enzyme deficiency.**

-Although all individual with Pizz genotype accumulate α-1-AT-Z protein only 10% of them develop clinical liver disease . This is due to lages in ER protein degradation pathway.

-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 auto phagocytosis of the mitochondria (phagocytosis should deal with any deposited material to eliminate it and during this process, it will cause membrane damage, so the hepatocytes that have these inclusions will damage, result in cellular failure).

- 8-10% of patients develop significant liver damage, the damage and severity depend on the enzyme activity and how much precipitation we have .in order to diagnosis, we need to have a liver biopsy, because the diagnosis is rare.

Morphology:

1)Intracytoplasmic globular inclusions in hepatocytes which are acidophilic in H&E. sections

2)The inclusions are PAS-+ve & diastase resistant: Normally in the liver , there are glycogen (carbohydrates)in the cytoplasm that can hide the inclusions and make them not so clear ,in order to be insure that we have these inclusions ,we need to treat the tissue by diastase enzyme (that causes degradation of glycogen in the cytoplasm),that will lead to eliminate the glycogen then the remaining inclusions (they usually eosinophilic in color) they are the deposited malformed enzymes ,finally we can sure that we have α-1antitripsin enzyme deficiency disease.

3)if the α-1antitripsin enzyme deficiency disease happen early it will cause **Neonatal hepatitis cholestasis & fibrosis**

Note: there are different diseases can cause neonatal hepatitis like: α-1antitripsin enzyme deficiency disease, biliary atresia, viral hepatitis).

4)elderly patients with this disease may have **Chronic hepatitis, Cirrhosis Fatty change, Mallory bodies** (similar to alcoholism, because the cytoskeleton of the fibrillary intermediate filaments can collapse due to damage of hepatocytes causing precipitations like Mallory bodies).

Clinical features:

Clinical manifestations depend on the severity and chronicity of the disease:

-neonatal hepatitis with cholestatic jaundice appears in 10 – 20% of newborns with the disease

-Attacks of hepatitis in adolescence

- chronic hepatitis &cirrhosis

- those patients are liable to develop the **HCC** (Hepatocellular carcinoma) **in 2- 3 % of Pizz adults** (especially in patients with homozygous genes) **+ cirrhosis.**

-**Note**: this disease can present at different age groups, at early and late life, so we will keep it as a differential diagnosis throughout different ages.

REYE'S SYNDROME is characterised by:

-Fatty change in liver & encephalopathy and as a result death of the patient.

-< 4 yr. in young children.

-usually comes **3 – 5 d after viral illness.**

-(enlargement of the liver) **↑liver & abnormalities in LFT** (liver function test).

-Vomiting lethargy.

-25% may go into coma, due to total failure of the liver, so we have to prevent it.

-We need liver biopsy for the diagnosis.

Pathogenesis:

-Derangement of mitochondrial function along or in combination with viral infection & salicylate which used during viral illness as an antibiotic agent and it's not used today.

These children patients develop fever after viral infection, and that's why Reye's syndrome was previously thought to be caused by the exposure of salicylate which is used in case of fever. However, this proved to be not

completely correct, because the individuals don't only exposed to salicylate, but also they have some mitochondrial malfunction. As well as, these patients can undergo liver failure and increase in liver enzymes after viral illness.
-the **main** characteristic change in liver is **microvesicular steatosis** (fatty change).

-in **brain only edema** (There's no inflammation).

-Absent inflammation.

-Sk. Muscles, heart, kidneys can show **fatty change.**

BUDD – CHIARI SYNDROME is characterised by:

-Thrombotic occlusion of the hepatic vein (obstruction of the hepatic vein is depending on the size of the formed clot, it will be acute or chronic process, so the clinical manifestation can vary).

-Hepatomegaly (enlargement of the liver because it's filled with blood).

-Weight gain.

-Ascitis (fluid accumulation in the abdomen).

-Abd. Pain.

- What are the **Causes** (predisposing conditions): all causes of Budd – Chiari Syndrome is related to increased tendency for **thrombus formation** as:

1-PCV (polycythemia vera) which is **blood** abnormality for malignancy.

2-Pregnancy

3-Postpartum period

} (females in those conditions have increased possibility to form thrombi)

4-Oral contraceptive

5-PNH (Paroxysmal nocturnal hemoglobinuria) is an another type of hemolytic anemia, these patients have hemolytic anemia due to sensitivity of RBCs to complement, so that they have hemolysis, as well as increase risk of **thrombosis**.

6-Mechanical obstruction.

7-Tumors as HCC (hepatocellular carcinoma) which can grow into hepatic vein and cause compression on it.

8-Idiopathic (underlying cause isn't clear or known) **in 30% of the cases.**

Morphology:

-Swollen liver, red with tense capsule

-microscopically**: centrilobular congestion & necrosis** the affected site is the central vein due to the engorgement of hepatic vein and its tributaries.

-Fibrosis of the liver (with **chronic** budd – chiari), the pressure on central vein can be associated with some degeneration and even fibrosis and therefore the process is considered to be chronic.

-Thrombi in hepatic vein**.**

• **Clinically: Mortality rate is high if not treated** due to liver failure.

PRIMARY SCLEROSING CHOLANGITIS (PSC) is an autoimmune disease characterised by:

-**Inflammation** (that target bile duct [biliary system])**, obliterative fibrosis, & segmental dilation of the obstructed intra hepatic & extra hepatic bile ducts** (not continuous, which creates area of narrowing in the site of obstruction and inflammation, and dilatation at the adjacent area [dilated areas are surrounded by constructed ones]).

- PSC is commonly associated with UC (ulcerative colitis):

-In PSC, UC coexists in 70% of patients, and vice versa but in small percentage as **in patients of UC, 4% develop PSC.**

-Usually at **3rd-5th decades** of life.

-M: F 2:1 (males are affected twice as females).

Clinical presentation:

-asymptomatic pts.

-persistent (elevated) **↑serum alkaline phosphatase** in liver function test, this enzyme is synthesised in the lining epithelium of the biliary system, and when the biliary system is obstructed, it's released in the blood**.**

-Accompanied by: **fatigue, pruritis** (severe itching)**, jaundice, wt loss, ascitis, bleeding, encephalopathy.**

- this condition is characterised by presence of autoantibodies:

-antimitochondrial Abs are found in **< 10% of cases**

-Antinuclear cytoplasmic Abs are found **in 80% of cases**

*This is important in differentiating it from the primary biliary cirrhosis manifestations.

Morphology:

onion-skin appearance📌

-Concentric periductal onion-skin fibrosis & lymphocytic infiltrate (Layers of fibrous tissue are surrounding the bile duct with inflammatory cells).

-Atrophy & obliteration of bile ducts due to their destruction.

-Dilation of bile ducts in between areas of stricture.

-Cholestasis (blockage of bile flow by accumulation of bile salts within small bile duct) **& fibrosis** (it develops over a long period of time)**.**

-Cirrhosis, cholangiocarcinoma (10 – 15%) (increased risk of malignancy for the liver, particularly this type).

*Cholangiocarcinoma: adenocarcinoma that originates from biliary system.

Pathogenesis:

-Exposure to gut derived toxins.

-Immune attack by auto-antibody.

-Ischemia of biliary tree.

*Extra notes from 018 sheet:
-PSC is thought to be an autoimmune disease; it does not demonstrate a clear response to immunosuppressants. Thus, many experts believe it to be a complex, multifactorial disorder.
-biliary tree is the system which directs secretions from the liver, gallbladder and pancreas through a series of ducts, into the duodenum).

SECONDARY BILIARY CIRRHOSIS which can be dealt with, for ex: if the obstruction was due to stones, we can deal with stones.

-Prolonged obstruction to extra hepatic biliary tree ➡ Any condition which is responsible for obstruction of the biliary tree end up with developing of cirrhosis as:

-Causes:

1-cholelithiasis (the formation of gallstones).

2-biliary atresia (one or more bile ducts are congenitally narrow, blocked or absent) which we can deal with it by surgical removal.

3-malignancies primary in biliary system or in the surrounding tissue causing compression on it.

4-strictures (the common bile duct is abnormally narrow) we can remove the cause of it to avoid the damage of hepatocytes.

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