GIS

# Pathology

|Modified slides

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**Autosomal recessive** is one of several ways that a **trait**, **disorder**, or **disease** can be passed down through families.

# Wilson Disease

- **Autosomal** Recessive disorder of **Cu** metabolism
- Caused by **Mutation** in **ATP7B** gene on **chromosome 13** "which "encodes an ATPase metal ion transporter in the Golgi region
- They are more than 80 mutations
- Gene frequency 1:200 individuals
- Incidence of the disease 1:30000 individuals

# Pathogenesis

- **The main cause of Wilson disease is the increase in Cu deposition**

**Main source of Cu is from diet**

↓

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

↓

**Absorption Cu form Complexes with albumin**

transported

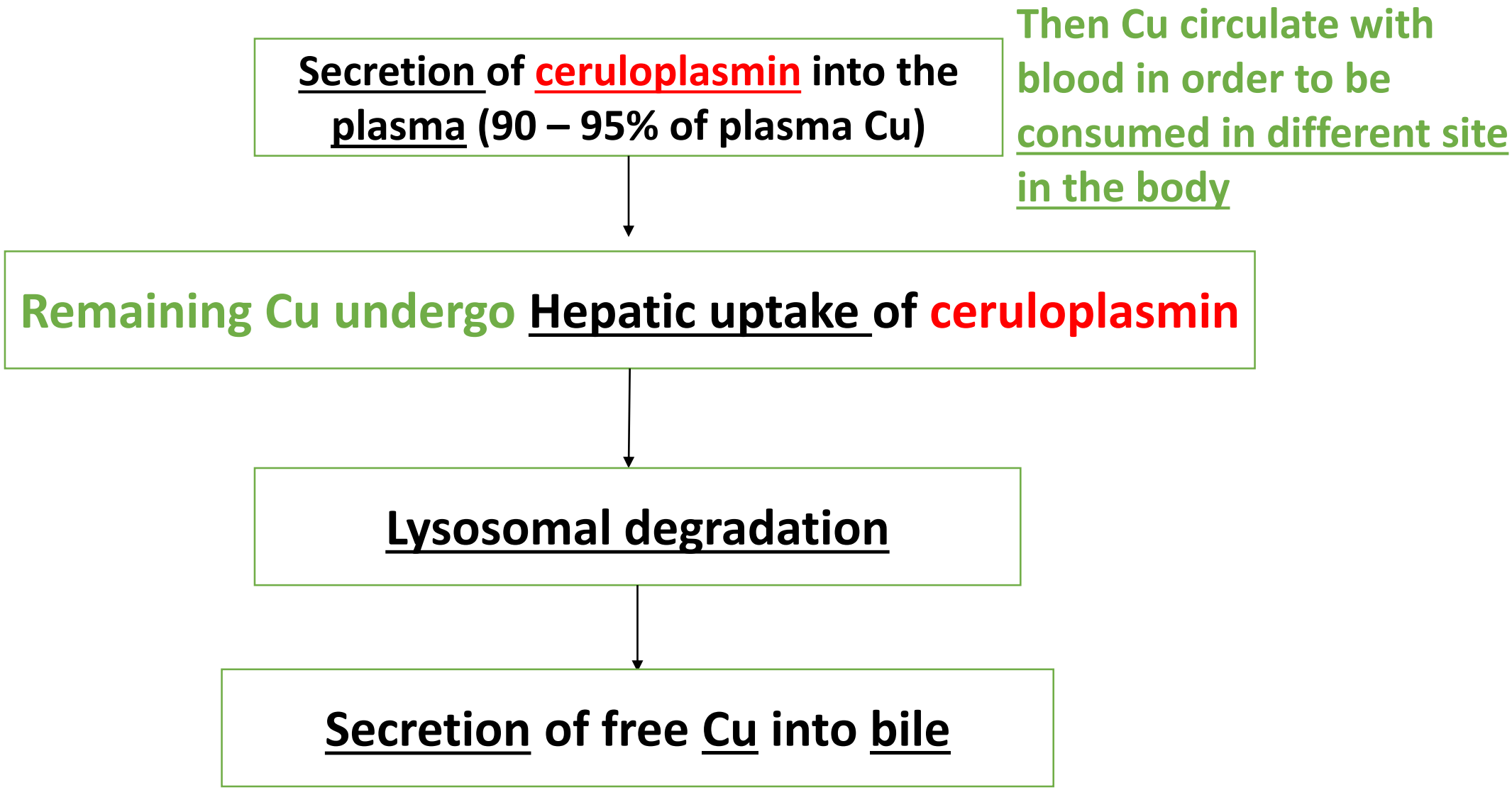
↓

**Hepatocellular uptake in the liver**

↓

**In liver Cu molecules Incorporation with α-2-globulin to form Ceruloplasmin** →

Ceruloplasmin is **a protein in your liver**. binds to copper and carries it throughout your body. If you have low ceruloplasmin, it can point to a genetic condition called Wilson disease


Secretion of ceruloplasmin into the plasma (90 – 95% of plasma Cu)
Then Cu circulate with blood in order to be consumed in different site in the body
Remaining Cu undergo Hepatic uptake of ceruloplasmin
Lysosomal degradation
Secretion of free Cu into bile

- In Wilson disease absorbed Cu. fails to enter the circulation in the form of ceruloplasmin & the biliary excretion of Cu is ↓ because of the accumulation of Cu in hepatocytes

- Occurs because of Defective function of ATP-7B gene that results in →failure of Cu. excretion into bile & inhibits secretion of ceruloplasmin into the plasma leading to →Cu. accumulation in liver

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

**1-Production of free radicals** which has toxic and damaging effects on hepatocytes

**2-Binding to sulfhydryl groups of cellular proteins** leading to their damage

**3-Displacement of other metals in hepatic metalloenzymes** leading to a decrease in their"metalloenzymes" efficiency

## EFFECTS OF CU BY THE AGE OF 5 :

- **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 which can produce manifestations related to the organ damage**

- Urinary excretion Of Cu. Increase because the spilled Cu in the blood can appear within the urinary excretion

# Morphology of Wilson Disease

## 1-In Liver :

1- Fatty change

2- Acute hepatitis

3- Chronic hepatitis

4- Cirrhosis apparently these manifestations can be caused by other diseases and that's why in proper patients we should include Wilson disease in more differential diagnosis in these conditions

5- Massive hepatic necrosis

**rhodanine stain or orcein stain** to see the copper deposition in hepatocytes

## 2- In the brain:

Putamen is **a round structure located at the base of the forebrain (telencephalon)**

- **Toxic injury to basal ganglia esp. the putamen causing atrophy & cavitation** this why the patient may have neurological manifestation

## 3- In Eye:

- formation of Green – brown deposits of Cu. in the descemet membrane in the limbus of the cornea produce a characteristic finding in patient called **Kayser- Fleischer rings**
- **(hepatolenticular degeneration)**

- **Clinically**
- **Presentation > 6 years of age because of increasing in amount of Cu within deposited different organs in order to be damaged and present clinically**
- **Most common presentation is acute on chronic hepatitis**
- **Neuropsychiatric presentation can occur & it can be the first manifestation**

**behavioral changes**

**Frank psychosis** →

> **psychosis** is an abnormal condition of the mind that results in difficulties determining what is real and what is not real

**Parkinson disease- like syndrome**

- **Diagnoses**

**1- ↓ in serum ceruloplasmin level**

**2- ↑ in urinary excretion Of Cu.**

**3- ↑ hepatic content of copper > 250 mg/gm dry wt. Of the liver**

- **Usually diagnosed depend on 1+2**

# α-1-Antitrypsin Deficiency

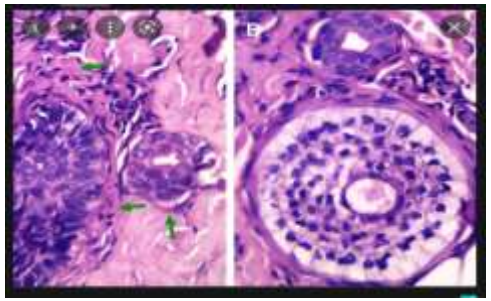
- **Autosomal** Recessive disorder
- Frequency 1:7000 in N. American white population
- **α-1-antiryrpsin** is a **protease inhibitor** as elastase, cathepsinG , proteinase 3 which are released from **neutrophils** at the site of **inflammation**
- **The gene called pi gene** Is located on **chromosome 14**
- At least 75 forms of gene mutation are present
- The most common & normal genotype is pi.MM present in 90% of individuals
- Pi.ZZ genotype there is a mutation in both allele → this associated with decrease level of α-1-antitrypsin in blood (only 10% of normal) are at high risk of developing clinical disease

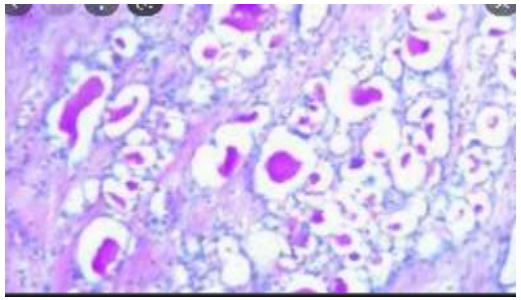
# Pathogenesis

- The mutant polypeptide (PiZ) is abnormally folded & polymerizes causing its retention in the ER of hepatocytes
- Although all individual with Pi.zz genotype accumulate α-1-AT-Z protein only 10% of them develop clinical liver disease.
- This is due to lags 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 autophagocytosis of the mitochondria
- 8-10% of patients develop significant liver damage

# Morphology

- Intracytoplasmic globular inclusions in hepatocytes which are acidophilic in H&E. sections
- The inclusions are **PAS-+ve & diastase resistant**





- This condition can present new porn as **Neonatal hepatitis cholestasis & fibrosis**

It also can present as :

**Chronic hepatitis**

**Cirrhosis**

**Fatty change**

**Mallory bodies**

- **Clinical features**
- These patient can present neonatal hepatitis with cholestatic jaundice appears in 10 – 20% of newborns with the disease
- **Attacks of hepatitis in adolescence**
- **chronic hepatitis & cirrhosis in older patients**
- **HCC in 2- 3 % of Pi.zz adults + cirrhosis**

↓

HEPATOCELLULAR CARCINOMA

# Reye's Syndrome is characterize by

- Fatty change in liver & encephalopathy
- Less than 4 yr. (in young children)
- 3 – 5 d after viral illness
- Enlargement of liver & abnormalities in LFT ( liver function test )
- Vomiting lethargy.
- 25% may go into coma

# Pathogenesis

- Derangement of mitochondrial function along or in combination with viral infection & salicylate which is used during viral illnesses as an antibiotic agent
- Microvesicular steatosis in liver
- Brain edema
- Absent inflammation
- Skeletal Muscles, heart, kidneys can show fatty change

# Budd – Chiari Syndrome

Syndrome characterized by

- **Thrombotic occlusion of the hepatic vein**
- **Hepatomegaly (enlargement of the liver)**
- **Wt. gain**
- **Ascites**
- **Abdominal Pain**

# Causes:

all causes of Budd – Chiari Syndrome is related to increase tendency for thrombus formation as :

1- PCV (Polycythemia vera) which is blood abnormality for malignancy

2- Pregnancy

3- Postpartum

4- Oral contraceptive

5- PNH (Paroxysmal nocturnal hemoglobinuria)

6- Mechanical obstruction

7-Tumors as HCC (Hepatocellular carcinoma)which can grow into hepatic vein

8-Idiopathic (underlaying cause is not clear) in 30% of the cases

# Morphology:

- **Swollen liver , red with tense capsule**
- **Microscopy : centrilobular congestion & necrosis**
- **Fibrosis** if the case was sub-acute or chronic it might be associated with fibrosis of the liver
- **Thrombi in hepatic vein**

- **Clinically**
- **Mortality rate is high if not treated**

# Recommended Videos

- Wilson's disease - causes, symptoms, diagnosis, treatment & pathology – YouTube
- Alpha-1 Antitrypsin Deficiency - causes, symptoms, diagnosis, treatment, pathology - YouTube
- Reye syndrome definition, symptoms & pathophysiology - YouTube

💙 WISH U ALL THE BEST …. 💙