LECTURE 5

Wilson Disease

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

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

↓

Sec. into plasma

(90 – 95% of plasma Cu)

↓

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 ceruloplamin & the biliary excertion of Cu. is ↓**
- **Defective function of ATP-7B →failure of Cu. excretion into bile & inhibits secretion of ceruloplasmin into the plasma →Cu. accumulation in liver**

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

1-Production of free radicals

2-Binding to sulfhydryl groups of cellular proteins

3-Displacement of other metals in hepatic metalloenzymes

-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

-Urinary exc. Of cu. ↑

Morphology

Liver

1-Fatty change
2-Acute hepatitis
3-chronic hepatitis
4-cirrhosis
5-massive hepatic necrosis

(rhodanine stain or orcein stain)

:Brain

Toxic injury to basal ganglia esp. the putamen causing atrophy & cavitation

Eye:

kayser- fleischer rings

green – brown depositis of Cu. in descemet membrane in the limbus of the cornea

(hepatolenticular degeneration)

- **Clinically**

-Presentation > 6 yrs of age

-Most common presentation is acute on chronic hepatitis

-Neuropsychiatric presentation can occur

behavioral changes

Frank psychosis

Parkinson disease- like syndrome

- **DX**

1- ↓ in serum ceruloplasmin level

2- ↑ in urinary exc. Of Cu.

3- ↑ hepatic content of copper

> 250 mg/gm dry wt.

α-1-Antitrypsin Defeciency

-- Aut. Recessive disorder

- 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

-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 in 90% of individuals

-PiZZ genotype →↓ 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 Pizz 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

-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 adolescance

-chronic hepatitis & cirrhosis

-HCC in 2- 3 % of Pizz adults + cirrhosis

Reye's Syndrome

- Fatty change in liver & encephalopathy
- < 4 yr.
- 3 – 5 d after viral illness
- ↑liver & abn. LFT

Vomiting lethargy.

25% may go into coma

Pathogenesis

-Derangement of mitochondrial function along or in combination with viral infection & salicylate

-Microvesicular steatosis

-Brain edema

-Absent inflammation

-Sk. Muscles, heart, kidneys – fatty change

Budd – Chiari Syndrome

-Thrombotic occlusion of the hepatic vein

-Hepatomegaly
-Wt.gain
-Ascitis
-Abd. Pain

Causes:

1-PCV

2-Pregnancy

3-Postpartum

4-Oral contraceptive

5-PNH

7-Mechanical obstruction

8-Tumors as HCC

9-Idiopathic in 30% of the cases

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- **Morphology**

-Swollen liver , red with tense capsule

-centrilobular congestion & necrosis

-Fibrosis

-Thrombi

- Clinically
- Mortality rate is high if not treated