COMPLETE EXACT LIVER PATHOLOGY ORGANIZED SHEET

Organized from the original slides - complete content, same slide wording preserved as much as possible

WILSON DISEASE

Definition / Genetics

• 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 - normal copper pathway

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

Pathogenesis - Wilson disease defect

• 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 sec. 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

Spillover / other organs

• 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

Site	Original slide details
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 degenceration)

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 DEFICIENCY

Definition / genetics / function

• Aut. Recessive disorder

• freq. 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 pi. Is located on chr.14

Gene mutations / genotypes

• 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 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 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 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

No.	Cause
1	PCV
2	Pregnancy
3	Postpartum
4	Oral contraceptive
5	PNH

No.	Cause
7	Mechanical obstruction
8	Tumors as HCC
9	Idiopathic in 30% of the cases

Morphology

• Swollen liver , red with tense capsule
• centrilobular congestion & necrosis
• Fibrosis
• Thrombi

Clinically

• Mortality rate is high if not treated

BILIARY DISEASES

Primary sclerosing cholangitis

• Inflammation , obliterative firosis, & segmental dilation of the obstructed intra hepatic & extra hepatic bile ducts
• In PSC, UC coexists in 70% of patients
• in patients of UC, 4% develop PSC
• 3-5 the decades
• M: F 2:1

PSC clinical / antibodies

• asymptomatic pts.
• persistent ↑ serum alkaline phosphatase
• fatigue, pruritis, jaundice, wt loss, ascitis, bleeding, encephalopathy
• antimitochondrial Abs < 10% of cases
• Antinuclear cytoplasmic Abs in 80% of cases

PSC Morphology

• Concentric periductal onion-skin fibrosis & lymphocytic infilrate
• Atrophy & obliteration of bile ducts
• Dilation of bile ducts inbetween areas of stricture
• Cholestasis & fibrosis
• Cirrhosis, cholangiocarcinoma (10 - 15%)

PSC Pathogenesis

• Exposure to gut derived toxins
• Immune attack
• Ischemia of biliary tree

Secondary biliary cirrhosis

• Prolonged obst. To extrahepatic biliary tree

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
• Age 20-80yrs (peak 40-50yrs)
• F>M
• Insidious onset
• Pruritis, jaundice
• Cirrhosis over 2 or more decdes

PBC labs / antibodies / associations

• ↑Alkaline phosphatase & cholesterol
• Hyperbilirubinemia = hepatic decompansation
• Antimitochondrial Abs > 90%
• Antimitochondrial pyruvate dehydrogenase
• Associated conditions: sjogern synd. Scleroderma thyroiditis, RA, Raynauds phenomenon. MGN, celiac disease.

PBC Morphology

• interlobular bile ducts are absent or severely destructed (florid duct lesion)
• intra epithelial inflammation
• Granulomatous inflammation
• Bile ductular proliferation
• Cholestesis
• Necrosis of parenchyma
• Cirrhosis

PSC vs PBC fast comparison

Feature	Primary sclerosing cholangitis	Primary biliary Cirrhosis
Main lesion	Inflammation , obliterative firosis, & segmental dilation	Non-suppurative granulomatous destruction of medium-sized intrahepatic bile ducts
Ducts	intra hepatic & extra hepatic bile ducts	intrahepatic bile ducts
Association	UC coexists in 70%	sjogern synd. Scleroderma thyroiditis, RA, Raynauds phenomenon. MGN, celiac disease.
Antibodies	antimitochondrial Abs < 10%; Antinuclear cytoplasmic Abs in 80%	Antimitochondrial Abs > 90%
Morphology clue	onion-skin fibrosis	florid duct lesion / Granulomatous inflammation

SINUSOIDAL OBSTRUCTION SYNDROME (VENO-OCCLUSIVE DISEASE)

• Originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloids
• This occurs in the first 20-30 days after bone marrow transplantation
• Which is caused by:
1- Drugs as cyclophosphamide
2- Total body radiation

Incidence / clinical presentation

• 20% in recepients of allogeneic marrow transplant
• Clinical presentation Mild - severe
• Death if does not resolve in 3 months

Mechanism

Toxic injury to sinusoidal endothelium

↓

emboli

↓

blockage of bl. Flow

↓

Passage of blood into space of Disse

↓

↑stellate cells → fibrosis

PELIOSIS HEPATIS

• sinusoidal dilatation

Causes

1- anabolic steroids
2- oral contraceptive
3- danazol

Pathogenesis

• Unknown

Clinical

• Asymptomatic
• Intra abdominal hemorrhage
• Liver failure
• reversible

LIVER TUMORS - BENIGN / NODULES

Benign

• Most common is cavernous hemagioma
• Usually <2cm
• Subcapsular
• Liver cell adenoma
• Young female
• Hx of oral contraceptive intake
• May rupture esp. during pregnancy causing severe intraperitoneal hemorrhage
• Rarely may contain HCC
• Misdx. Of HCC

Liver Nodules - Focal noudular hyperplasia

• Well demarcated hyperplastic hepatocytes with central scar.
• Non-cirrhotic liver
• Not neoplasm but nodular regeneration
• Local vascular injury
• Females of reproductive age
• No risk of malignancy
• 20% of cases have cavernous hemagnioma

Macroregenerative Nodules

• Cirrhotic liver
• Larger than cirrhotic nodules
• No atypical features,
• Reticulin is intact
• No malignant potential

Dysplastic nodules

• Larger than 1 mm
• Cirrhotic liver
• Atypical features, pleomorphism and crowding
• High proliferative activity
• High or low dysplasia
• Precancerous (monoclonal, +ve gene mutations

Types

1- Small - cell dysplastic nodules
2- Large - cell dysplastic nodules

Nodules comparison

Lesion	Original high-yield identifiers
Focal noudular hyperplasia	Non-cirrhotic liver; Not neoplasm but nodular regeneration; central scar; No risk of malignancy
Macroregenerative Nodules	Cirrhotic liver; Larger than cirrhotic nodules; No atypical features; Reticulin is intact; No malignant potential
Dysplastic nodules	Larger than 1 mm; Cirrhotic liver; atypical features, pleomorphism and crowding; Precancerous

HEPATOCELLULAR CARCINOMA

Incidence / demographics

• 5.4% of all cancers
• Incidence: <5/100000 population in N&S America N& central Europe Australia
• 15/100000 population in Mediterranean
• 36/100000 population in Korea, Taiwan mozambique, china
• Blacks > white
• M:F ratio 3:1 in low incidence areas. >60yr
• 8:1 in high incidence areas. 20-40yr

Predisposing Factors

1- Hepatitis carrier state
vertical transmission increases the risk 200X
cirrhosis mau be absent
young age group (20-40yr)
2- >85% of cases of HCC occur in countries with high rates of chronic HBV infection
3- Cirrhosis
In western countries cirrhosis is present in 85-90% of cases
>60yr
HCV & alcoholism
4- Aflatoxins
5- Hereditary tyrosinemia (in 40% of cases)
6- Hereditary hemochromatosis

Pathogenesis

1- Repeated cycles of cell death & regeneration
HBC, HCV, gene mutations, Genomic instability

2- Viral integration
HBV DNA intergration which leads to clonal expansion

3- HBV DNA intergration which leads to genomic instability not limited to integration site.

4- HBV
X-protein which leads to transactivation of viral & cellular promoters,
Activation of oncogenes,
Inhibition of apoptosis

5- Aflatoxins (fungus Aspirgillus flavus)
mutation of p53

6- Cirrhosis
HCV
Alcohol
Hemochromatosis
Tyrosinemia (40% of pts. Develop HCC despite adequate dietary control

Morphology

1- HCC

2- CC

3- Mixed

• Unifocal
• Multfiocal
• Diffusely infiltrative
• Vascular invasion is common in all types.
• Well ---- Anaplastic

Fibrolamellar carcinoma

• 20-40 yr. M=F
• No relation to HBV or cirrhosis
• better prognosis
• single hard scirrhous tumor

Cholangiocarcinoma

• Cholangiocarcinoma are desmoplastic

metastasis

• Vascular - lungs, bones, adrenals, brain, in 50% of cholagiocarcinoma

C/P

• abd. Pain, malaise, wt. loss
• increase α-feto protein in 60 - 75% of pts.

α-feto protein increases also with:

1- yolk sac tumor

2- cirrhosis,

3- massive liver necrosis,

4- chronic hepatitis,

5- normal pregnancy,

6- fetal distress or death

7- fetal neural tube defect.

Prognosis

• Death within 7 -10 months

Causes

1- Cachexia

2- GI bleeding
3- Liver failure
4- Tumor rupture and hemorrhage

THE END

ONE-PAGE FINAL REVIEW TABLES

Storage / metabolic diseases

Disease	Key gene / defect	Classic clues
Wilson Disease	ATP7B gene on chr. 13; Cu metabolism	Kayser- fleischer rings; ↓ ceruloplasmin; ↑ urinary Cu.; hepatic Cu > 250 mg/gm dry wt.
α-1-Antitrypsin Deficiency	gene pi. on chr.14; PiZZ genotype	PAS-+ve & diastase resistant inclusions; neonatal hepatitis; cirrhosis; HCC

Vascular / sinusoidal disorders

Disorder	Main definition	Key morphology / mechanism
Budd - Chiari Syndrome	Thrombotic occlusion of the hepatic vein	centrilobular congestion & necrosis; fibrosis; thrombi
Sinusoidal Obstruction Syndrome	Veno-occlusive disease after bone marrow transplantation	Toxic injury to sinusoidal endothelium → emboli → blockage → fibrosis
Peliosis Hepatis	sinusoidal dilatation	Pathogenesis Unknown; intra abdominal hemorrhage; reversible