Autoimmune Hepatitis

- Chronic hepatitis with immunologic abnormalities

-Histologic features are similar to chronic viral hepatitis

-Indolent or severe course

-Dramatic response to immunosuppressive therapy

Features:

1-Female predominance (70%)

2-Negative serelogy for viral Ags.

3-↑serum Ig (>2.5 g/dl)

4-High titers of autoantibodies (80% of cases)

5-The presence of other autoimmune diseases as RA, thyroiditis, sjogern syndrome, UC in 60% of the cases

The type of autoantibodies

1-Antismooth myuscle abs
- anti actin
- anti troponin
- anti tropomyosin

2-liver/kidney microsomal Abs
- anti cytochrome P-450 components
- anti UDP-glucuronosyl transferases

3-Anti – soluble liver / pancreas antigen

Outcome

Mild to severe chronic hepatitis

Full remission is unusual

Risk of cirrhosis is 5% which is the main cause of death

Nonalcoholic Fatty Liver Disease

Types:

1. Steatosis (Fatty liver)
2. Steatohepatitis
   hepatocyte destruction
   parenchymal inflammation
   progressive pericellular fibrosis

Predisposing factors :

1-Type 2 DM
2-Obesity : body mass index
> 30 kg /m2 in caucasians
> 25 kg /m2 in Asians
3-Dyslipidemia (↑ TG, ↑LDL, ↓HDL)

Pathogenesis

. **Metabolic syndrome**
    . Insulin resistance
    . Obesity
    . Dyslipidemia

.

Mechanism of fatty accumulation

1. Impaired oxidation of fatty acids
2. synthesis & uptake of FFA
3. Decreased hepatic sec. of VLDL

. ↑TNF , IL6 , chemokine →liver inflammation & damage

Clinically

- NAFLD is the most common cause of incidental ↑ in transaminases
- Most pts. are asymptomatic
- Non-specific symptoms

  Fatigue, malaise, RUQ discomfort
- Severe symptoms
- Liver Bx is required for dx.
- NAFLD m.b a significant contributer to cryptogenic cirrhosis

Hemochsomatosis

- Excessive accumalation of body iron (liver & pancreas)

-1ry or 2ry (genetic or acquired)

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Causes of acquired hemosidrosis :

1-multiple transfusions

2-ineffective erythropoiesis (thalassemia)

3-increased iron intake (Bantu sidrosis)

4-chronic liver disease

-**Features:**

1-Micronodular cirrhosis (all patients)

2-D.M (75 – 80%)

3-skin prigmentation 75-80%)

4-cardiomegaly , joints disease, testicular atrophy

Symptoms appear 5^{th} – 6^{th} decades
not before age 40

-M:F ratio 5 - 7: 1

-Genetic hemochromatosis (4 variants)

-The most common form is aut. recessive disease of adult onset caused by mutation in the HFE gene on chr.6

Pathogenesis

-1ry defect in intestinal absorption of dietary iron.

-Total body iron 2-6gm in adults 0.5gm in liver mostly in hepatocytes

-In disease >50gm Fe accumulated → 1/3 in liver

-In herediatary hemochromatosis there is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5 – 1 gm/yr

-The gene responsible is HFE gene located on chr.6 close to HLA gene complex

-HFE gene regulates the level of hepcidin hormone synthesized in liver

-Hepcidin → (-) Fe. absorption from intestine

-HFE gene deletion causes iron overload

-Two mutation can occur in HFE gene:

1-Mutation at 845 nucleotide → tyrosine substitution for cystine at AA 282

(C282 Y)

2-aspartate substitution for histidine at AA 63 (H63D)

10% of pts. have other gene mutations

-Carrier rate for C282Y is 1/70

-Homozygosity is 1/200

-80% of pts. are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation

-10% of pts. are either homozygous for H63D mutation or compound heterozygous for C282Y/H63D mutation

Excessive Fe deposition → toxicity of the tissues :

1. **Lipid peroxidation**
2. **Stimulation of collagen formation**
3. **DNA damage**

Morphological changes:

1-Deposition of hemosiderin in diffferent orgens

Liver

Pancreas

Myocardium

Pituitary

Adrenal

Thyroid & parathyroid

Joints

Skin

2-Cirrhosis

3-Pancreatic fibrosis

-No inflammation
-Fibrosis
-Cirrhosis
-Synovitis
-Polyarthritis(pseudogout)
-Pigmentation of liver
-fibrosis of pancreas & myocardium
-Atrophy of testes

Clinical presentation

M:F 5 – 7 :1 5 – 6 the decades
Hepatomegaly
Abdominal pain
Skin pigmentation
D.M
Cardiac dysfunction
Atypical arthritis
Hypogonadism
↑serum Fe ferritin
HCC 200x ↑in the risk

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 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

-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 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 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

-Athoyugh 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'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

-

- **Morphology**

-Swollen liver , red with tense capsule

-centrilobular congestion & necrosis

-Fibrosis

-Thrombi

- Clinically
- Mortality rate is high if not treated

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

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-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

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%)

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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

-↑Alkaline phosphatase & cholesterol

-Hyperbilirubinemia = hepatic decompansation

-Antimitochondrial Abs > 90%

Antimitochondrial pyruvate dehydrogenase

-Associated conditions: sjogern synd. Scleroderma thyroiditis, RA, Raynauds phenomenon. MGN, celiac disease.

- **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**

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

-20% in recepients of allogeneic marrow transplant

-**Clinical presentation**

Mild – severe

Death if does not resolve in 3 months

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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

-Asymptomatic
-Intra abdominal hemorrhage
-Liver failure

-reversible

Liver tumors

- 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

Hepatocellular carcinoma

- **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 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