LECTURE 4

Drug – Induced liver disease

-Drug reactions:

1-Predictable (intrinsic)

2-Unpredictable (idiosyncratic)

-**Predictable drug reactions depend on the dose (dose-dependent)**

-Unpredictable drug reactions depend on:

a-The immune response of the host to the antigenic stimulus

b-The rate at which the host metabolizes the agent

- Injury may be immediate or takes weeks to months
- Drug-induced chronic hepatitis is clinically & histologically indistinguishable from chronic viral or autoimmune hepatitis

Predictable drugs:

Acetaminophen
Tetracycline
Antineoplastic agents
CCL4
Alcohol

Unpredictable drugs

Chlorpromazine
Halothane
Sulfonamides
Methyldopa
Allopurinol

-Mechanism of drug injury :

1-Direct toxic damage

e.g acetaminophen
CCl4
mushroom toxins

2-Immune-mediated damage

-Patterns of injury

1-Hepatocellular necrosis
2-Cholestasis
3-Steatosis
4-Steatohepatitis
5-Fibrosis
6-Vascular lesions
7-Granuloma
8-Neoplasms benign & malignant

Drugs that may cause acute liver failure

1-acetaminophen most common

2-Halothane

3-antituberculosis drugs (rifampin, isoniazid)

4-antidepressant monoamine oxidase inhibitors

5-toxins as CCL4 & mushroom poisoning

Morpholagy:

Massive necrosis → 500 – 700 gm liver

Submassive necrosis

Patchy necrosis

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. Increased 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 patients are asymptomatic

-Non-specific symptoms

Fatigue, malaise, RUQ discomfort

-Severe symptoms

-Liver Biopsy is required for diagnosis.

-NAFLD may be a significant contributer to cryptogenic cirrhosis

Hemochsomatosis

- Excessive accumalation of body iron (liver & pancreas)
-1ry or 2ry (genetic or acquired)

:Causes of acquired hemosidrosis

multiple transfusions-1

ineffective erythropoiesis (thalassemia)-2

increased iron intake (Bantu sidrosis)-3

chronic liver disease-4

-**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