



Pathology of Chronic Hepatitis

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Pathological Types of Chronic Hepatitis .-

- ✓ **Viral Hepatitis**
- ✓ **Alcoholic Hepatitis**
- ✓ **Non alcoholic steatohepatitis**
- ✓ **Wilson' s Disease**
- ✓ **Haemochromatosis**
- ✓ **Alpha 1 Anti-trypsin deficiency**
- ✓ **Drug-induced hepatitis**

Alcoholic Hepatitis.-

Metabolism of Alcohol

Alcohol is absorbed from GIT, distributed to the tissues, oxidized predominantly in liver:

Alcohol dehydrogenase pathway: acetaldehyde + H₂ which reduces NAD (nicotineamide adenine dinucleotide) into NADH + acetaldehyde, The excess NADH in the cytosol leads to increase lactate:pyruvate ratio

The microsomal ethanol-oxidizing system: cytochrome P-450 dependant pathway

Catalase pathway: plays a minor role

Metabolic disturbances ass. with alc. metabolism .-

Increase lactate:pyruvate ratio: lactic acidosis, decrease renal capacity for uric acid excretion

Impaired carbohyd. metabolism:↓gluconeogenesis from a.a., may produce hypoglycaemia

Impaired fat metabolism:H⁺ ions replace 2 carbon fragments derived from fatty acids as the main energy source of hepatocyte mitochondria, ↓fatty acid oxidation, ↑αglycerophosphate which leads to ↑trapping of fatty acids, ↑synthesis of triglycerides, retention of lipoproteins

Impaired metabolism of serotonin, galactose

Fatty Change.-

Fatty change(Steatosis)occurs mainly in perivenular zone, can be seen in all zones as the injury progress

Initially fat droplets are membrane bound, as the droplets enlarge, they fuse forming non-membrane bound vesicles

Rupture of distended hepatocyte leads to release of fat and inflammatory response

Microvesicular steatosis (foamy degeneration) describes severe liver injury occurring in fatty liver in the absence of alcoholic hepatitis

Alcoholic Hepatitis .-

Non specific digestive symptoms, hepatomegaly, raised liver enzymes

Histopathology: fatty change (steatosis), liver cell necrosis, neutrophil infiltrate, mallory bodies, minimal pericellular fibrosis

Other features: lipogranuloma, bile stasis, Kupffer cell proliferation

Sclerosing hyaline necrosis: perivenular liver cell necrosis associated with deposition of fibrous tissue, occluded hepatic vein, portal hypertension

Alcoholic Cirrhosis.-

Features at risk of progression to cirrhosis: severity of fatty change and hepatic necrosis, widespread obliteration of hepatic venules and Mallory bodies.

WHO definition: diffuse process characterized by fibrosis and the conversion of liver architecture into structurally abnormal nodules

Micronodular cirrhosis: nodules less than 3mm in diameter in a background of alcoholic hepatitis. Hepatic veins are not recognized but new vessel formation is apparent

Non Alcoholic Steatohepatitis .-

NASH: alcoholic hepatitis like pattern of injury occurring in livers of non drinkers

Risk factors: F gender, obesity, hyperlipidaemia, rapid weight loss, type II DM, some drugs

Histopathology: macrovesicular steatosis, focal inflammatory infiltrate (monocytes, polymorphs), pericellular fibrosis, Mallory bodies, focal hepatocyte necrosis, fibrosis

Pathogenesis of NASH.-

Induction of CYP2E1, lipid peroxidation, endotoxins, cytokines are involved in the pathogenesis

Oxidative stress due to lipid peroxidation products

Activated Kupffer cell by endotoxins, is chemoattractant for neutrophil

Increase production of proinflammatory cytokines: TNF alpha, IL-1, IL-6

Humoral immunity: increase gamma globulins, perisinusoidal deposition of IgA, low titre of autoantibodies IgG, IgA LMA Antibodies

Wilson's Disease.-

What is Wilson's disease

It is a genetic disorder in which copper builds in the body mainly in the liver, named after Dr. Samuel Wilson (1912).

It is an autosomal recessive disease, the defective gene is an ATP-ase dependent, P-type copper transporter localized to chromosome 13q-14.3

The symptoms & signs are the result of copper overload in various tissues and organs.

Common Findings in WD.-

Liver findings: Signs of chronic liver disease, Hepatosplenomegaly, rash, +ve antinuclear or anti smooth muscle antibodies

Brain findings: Neuropsychiatric signs, irritability, tremors, gait disturbance

Other findings: ↑ g-globulin levels, arthropathy, cardiac complications, gallbladder stones, renal tubular disease, gynaecomastia, ammenorrhoea, Kayser-Fleisher rings

Diagnosis of WD .-

Serum caeruloplasmin below 20mg/dl

24h urine copper excretion >100µg

Liver copper concentration over 250µg/g dry weight

Copper Metabolism.-

Dietary copper is taken up by intestinal cells

Transported to copper-containing cellular proteins including metallothionin or exported from the cell by P-type ATPase

Copper is rapidly transported to the liver via albumin from the intestinal cells

Following uptake by hepatocytes, copper is either secreted via caeruloplasmin into the blood stream or excreted into the bile

Both physiological mechanisms are defective in WD

Liver Histopathology in WD.-

Acute hepatitis: ballooning of hepatocytes, spotty necrosis, apoptotic bodies, cholestasis, steatosis, periportal cholangiolar proliferation, fibrosis.

Chronic hepatitis: portal inflammation, interface hepatitis, steatosis, presence of Mallory bodies in periportal hepatocytes, +ve copper associated protein granules in hepatocytes, cirrhosis

Haemochromatosis .-

Two specific iron binding proteins

Ferritin: the major storage protein that sequesters iron in tissues (plasma ferritin is a reliable indicator of body iron stores

Transferrin: iron binding protein which maintains iron in a non toxic form during its transport via blood

Haemosiderin: water insoluble deposit of hydrated iron oxide micelles associated with varying amount of denatured protein

Normal iron metabolism.-

Iron absorption: body's needs for iron is exerted at intestinal level, depending on total body iron content, rate of erythropoiesis

Iron transport: iron bound to transferrin is transported from intestine to liver, BM, others

Iron delivery to tissue: binding of iron-transferrin to transferrin receptor, internalization into cell, release of iron in intracellular organelle

Iron storage: Normally iron is stored in the liver as ferritin, few haemosiderin

Classification of Iron Overload.-

Genetic disorders: associated with elevated absorption from a normal diet: hereditary haemochromatosis, autosomal dominant pattern hereditary haemochromatosis

Haematological disorders: thalassaemia major, sideroblastic anaemia

Increased dietary iron: (african iron overload)

Iron via parental route: blood transfusion, parental iron medications

Miscellaneous: end stage cirrhosis, neonatal iron overload, porphyria cutanea tarda

Histological assessment of iron overload.-

The grade (amount) of stainable iron (0-4)

Its distribution in various cell types of parenchyma (0-4)

The presence or absence of fibrosis or cirrhosis (0-4)

Alpha 1 antitrypsin deficiency.-

Mutation in the gene encoding for A1A

protein with no inhibitory activity

accumulation of A1AT in hepatocytes

reduced serum level of A1AT

75 alleles (A-Z) according to their isoelectric points have been described. S (migrate slowly), Z (migrate towards cathode), M (middle).

Histologically, giant cell hepatitis, PAS+, diastase resistant inclusions

Drug- Induced Hepatitis.-

Intrinsic Hepatotoxins (true hepatotoxins)

High incidence of hepatic injury in individuals exposed to it

Produce similar lesions in experimental animals

Dose-dependence of the phenomenon

Direct and indirect hepatotoxins

Idiosyncratic (their toxicity is not predictable, produce hepatic injury in small proportion of exposed individuals)

Pathogenesis .-

CYP3A7, the major cytochrome in the liver is able to metabolize potential hepatotoxins.

Mechanisms of drug reactions:

oxidative stress, chemicals producing free radicals can cause hepatocyte apoptosis and can induce lipid peroxidation of cellular membranes (CCl₄, mushroom intoxication)

immunologic alteration (aflatoxin, sulfonamides, amoxicillin, halothane, chlorofluorocarbons)

Pathological Findings .-

Steatosis: defective disposal of lipids by the liver or impaired oxidation of fatty acids by hepatocytes, defective assembly of triglycerides with apoproteins

Cholestasis: interference with sinusoidal-hepatic uptake, inhibition of excretion of substances into the canaliculus (rifampicin, contraceptive steroids)

Hepatic injury (idiosyncratic): hypersensitivity (immunological) production of antibodies to hepatic proteins, sensitized T cell, metabolic aberration of the host (metabolic)

Morphological forms of toxic hepatitis.-

Acute Hepatitis

Cytotoxic: necrosis, degeneration, steatosis

Cholestatic

Chronic Hepatitis

Inflammatory infiltrate: eosinophils, lymphoid aggregates, granuloma

Cholestasis: hepatocanalicular, canalicular, ductular

Steatosis: mainly microvesicular

Necrosis: bile duct injury, chronic hepatitis injury