Liver Diseases.

Hepatic Injury types

General Features about liver

has many function —> clinical manifestation of its disease is related to its loss of funtion

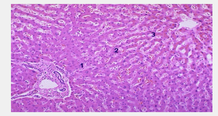
has huge functional capacity —> SO, lost when MOST of the hepatocytes are lost, since if only a few are damaged from injury the other viable cells will increase their function to keep normality

brown in colour & has smooth outer surface

shape changes indicate different diseases

structure (functional unit)

- lobule
  - each lobule is composed of 6 acini
  - each acinus is composed of 3 zones
    - zone 1 (periportal area)
    - zone 2 (parenchyma between zone 1 & 3)
    - zone 3 (pericentral area)



parenchyma is organized into plates of hepatocytes

- hepatocytes are radially oriented around terminal hepatic vein (central vein)
  - this plate can be lost during hepatic injury
- hepatocytes show only minimal variation in the overall size, but nuclei may vary in size, number & ploidy (no. of chromosome)
- vascular sinusoids presents between cords of hepatocytes
- hepatocytes are lined with kupffer cells

exchange between blood and hepatocytes occurs in sinusoids which makes it important as they absorb substances that are brought by hepatic artery and they excrete their products into veins

this exchnage is affected during diseases and manifested as the accumulation of many substances which can be toxic, and loss of substances that are being produced by the liver —> proteins

hepatic injury types

- Inflammation = hepatitis
- Degenertaion
  - ballooning degeneration
  - feathery degeneration — retained biliary material, accumulation of iron & copper
- Steatosis
- Necrosis
- Regeneration
- Fibrosis
- Cirrhosis
- Ductular Proliferation

Inflammation = Hepatitis

can be chronic or acute

presented by infiltration of parenchyma by inflammatory cells

Degeneration

Ballooning Degeneration

swelling of the hepatocytes due to injury

irregularly clumped cytoplasm, showing large clear spaces

substance may accumulate in hepatcytes

- fat
- iron
- copper
- retained biliary material — will appear as a brown pigment within the hepatocyte

Steatosis

description

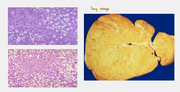
- fat accumulation within the cytoplasm of hepatocyte
- fat accumulation begins in zone 3

forms

- Microvesicular
  - the cytoplasm of hepatocytes is filled with tiny lipid droplets, and the nucleus is located centrally in the cell
  - conditions associated with it
    - Reye's syndrome
    - ACUTE fatty change or pregnancy
    - ALD (alcohol liver disease)
- Macrovesicular
  - a single large fat droplet or smaller well-defined fat droplets occupy the cytoplasm of hepatocytes, pushing the nucleus to the periphery
  - conditions associated with it
    - DM
    - obese

morphology

- colour change to yellow
- soft greasy consistency



Necrosis

depending on the type

- Coagulative Necrosis
  - coagulation —> ischemia —> decreased O2 level —> decreased ATP —> decreased pumping of ions —> swelling
  - location: around central vein
  - caused by ischemia
- Councilman bodies
  - individual hepatocytes appears shrinked with prominent eosinophilic pigmented nuclei (condensed chromatin)
  - it indicates that the liver has been exposed to injury
  - may present without inflammation
- Lytic Necrosis
  - caused by hydrolytic enzymes
  - infection-associated liqeufactive necrosis

depending on the cause

- Ischemic
- Toxic

depending on the location

- Centrilobular bodies
  - location: around central vein
- Mid zonal
- Periportal (interface hepatitis)
  - T-cell induced hepatocyte apoptosis
  - location: zone 1
- peice meal necrosis
  - seen in viral hepatitis
  - if mild & reversible inflammation
    - necrosis is limited to the periportal area
  - if more severe inflammation
    - necrosis extends to the adjacent parenchyma
- bridging necrosis
  - necrosis connects between 2 sites in the liver (e.g central vein & portal area)
  - indicats that the process is severe
  - can heal by fibrosis, which is something very ominous in the liver, since it indicates that the process is goning into the chronic process, which can develop into cirrhosis

types: Focal

classified depeding on the amount of hepatocytes that is destroyed

- Diffuse
  - if 90% of hepatocytes are damaged — massive necrosis
  - less than 90% — sub-massive necrosis

Regeneration

evidenced by increased mitosis or cell cycle markers

Progenitor cells

- cells of Canal of Herring (located in the small bile ducts)
- have the capacity to differentiate into both: hepatocyte & bile duct cells
- if there is an injury & we lose heptocytes, progenitor cells can be stimulated & start to divide into new hepatocytes

this is normal — mitotic activity of hepatocytes may be increased in disease processes

Fibrosis

the formation of excess fibrous connective tissue in response to chronic or sever injury

no organization of the fibrous tissue

CHRONIC & irreversible

types

- Periportal Fibrosis
- Pericentrl Fibrosis
- Bridging Fibrosis
- Pericellular Fibrosis
  - fibrous tissue deposits diretly within the sinusois around singl or multiple hepatocytes

Ductular Proliferation

abnormal increase in the number of bile ducts within the liver

this proliferation of bile ducts can occur in certain diseases that specifically affect the biliary tract, which includes the structures involved in the production, transport, and excretion of bile

Clinical Syndromes

the major clinical syndromes of liver disease are

- Hepatic Failure
- Cirrhosis
- Portal Hypertension
- Cholestasis

Hepatic Failure

Description

- results when the hepatic functional capacity is almost totally lost
- is the end result of severe hepatic damage
- most common cause is due to chronic process (much more than acute)
- if the failure is acute, we should think of viral infection
  - fulminant viral hepatitis
  - hepatitis C
  - hepatitis D superimposd in B
  - hepatitis A — particularly if it occurs in adults who are not immunized to A
  - hepatitis E — with pregnant women

Categories

1. ACUTE liver failure with massive hepatic necrosis
   - most often caused by drugs or fulminant viral hepatitis
   - denotes clinical hepatic insufficiency that progresses from onset of symptoms to hepatic encephalopathy within 2 to 3 weeks
   - A course extending as long as 3 months is called SUBACUTE failure
   - The histologic correlate of acute liver failure is massive hepatic necrosis
   - is an uncommon but life-threatening condition that often requires liver transplantation
2. CHRONIC liver failure
   - the most common route to hepatic failure
   - chronic liver damage ending in cirrhosis
3. hepatic dysfunction, without overt cirrhosis
   - hepatocytes may be viable, but unable to perform normal metabolic function
   - examples
     - Reye's syndrome
     - tetracycline toxicity
     - ACUTE fatty liver of pregnancy — can lead to ACUTE liver failure a few days after onset

Complications

- multiple organ failure: kidneys & lungs
- coagulo-pathy —> def. factors (II, VII, IX, X)
- bleeding
- Hepatic encephalopathy —> ↓ level of consiousness, rigidity, hyperreflexia, EEG [electroencephalogram] changes, seizures & asterixis
- Hepato-Renal syndrome

Clinical Features

- Jaundice
- Hypo-albuminemia —> decreased collic pressure —> edema
- Hyper-ammonemia
- Fetor hepaticus (musty Or sweet & sour breathe)
- Palmar erythema
- Hyper-estrogemia
- Spider angiomas
- Hypo-gonadism & Gynecomastia (enlargement of man,s breast)

Alcoholic Liver Diseases

General Notes

- alcohol is the 5th leading cause of death due to: accidnts & alcoholic cirrhosis
- causes more than 60% of chronic liver disease
- the legal definition for driving under the influence of alcohol
  - if the blood alcohol levels = 80-100 mg/dl
  - 44ml of ethanolis required to produce this level in 70kg person
- short term ingestion of 80 g/day of ethanol generally produces mild, reversible Hepatic changes
- chronic intake of 50-60gm/day is considered a borderline risk for severe injury
- in occasional drinkers
  - blood level of 200 mg/dl produces: coma
  - blood level of 300-400 mg/dl produces: death & respiratory failure
- habitual drinkers
  - can tolerate levels up to 700 mg/dl without clinical effect
  - this is due to metabolic tolerance explained by 5-10X induction of cytochrome p-450 system that includes enzyme CYP2E1, which increases the metabolism of ethanol & other drugs as cocaine & acetominophen
- women seem to be more susceptible to hepatic injury than are men because of low gastric metabolism of ethanol and differences in body composition
- forms of alcoholic liver disease
  - Hepatic Steatosis (90-100% of drinkers)
  - Alcoholic Hepatitis (1-35% of drinkers)
  - Cirrhosis (14% of drinkers)
  - steatosis & hepatitis may develop independently

Hepatic Steatosis

- description
  - liver is enlarged (4-6 kg) soft yellow & greasy
  - fatty change is reversible, with complete abstention from further intake of alcohol
- moderate intake of alcohol —> microvesicular steatosis
- chronic intake —> diffuse steatosis
- continued intake —> fibrosis
- Clinical Features
  - ↑ liver (in size)
  - ↑ liver enzyme
  - severe hepatic dysfunction is unusal

Alcoholic Hepatitis

- Characteristic Findings
  - Hepatocyte swelling & necrosis
    - accumulation of fat, water & proteins
    - Cholestasis (impaired production, secretion, or outflow of bile)
    - Hemosidrein (is a brown iron-containing pigment) deposition in hepatocytocytes & kupffer cells
  - Mallory-hayline bodies
    - description
      - easinophilic cytoplasmic inclusions
      - in degenerating hepatocytes
      - formed of cytokeratin intermediate filaments & other proteins
    - NOTE: Mallory-hayline inclusions are characteristic but not pathognomonic of alcoholic liver disease
    - they are also seen in
      - primry biliary cirrhosis
      - Wilson disease
      - CHRONIC cholestatic syndromes
      - hepatocellular carcinoma
  - Neutrophilic reaction
  - Fibrosis (as a remodeling)
    - Sinusoidal & peri-venular fibrosis
    - Peri-portal fibrosis
  - Cholestasis
- Clinical Features
  - 15-20 years of excesive drinking
  - non-specific symptoms: malaise, anorexia, weight loss
  - ↑ liver & spleen (in size)
  - ↑ LFT (liver function test)
  - Each bout of hepatitis → 10-20% risk of death → cirrhosis in 1/3 in few yrs

Alcoholic Cirrhosis

- usually it develops slowly
- initially, the liver enlarged & became yellow —> but over years it becomes brown, shrunken & non-fatty organ
- it can develop rapidly in the presence of alcoholic hepatitis (within 1-2 years)
- irreversible
- mallory bodies are rerely evident at this stage
- Clinical Feature
  - Portal Hypertension
    - bile stasis
    - Laennec cirrhosis = scar tissue
    - micronodules
    - mixed micro & macronodules

Ethanol metabolism

- absorbed as ethanol
- by alcohol dehydrogenase in the stomach & liver
  - Women have lower levels of gastric alcohol dehydrogenase activity than men & they may develop higher blood Levels than men after drinking the same quantity of ethanol
- Ethanol —> Acetaldehyde
  - by cytochrome P-450 in the liver
  - by catalase in the liver
- Acetaldehyde —> Acetic acid
  - by aldehyde dehydrogenase
- After absorption ethanol is distributed as Acetic acid in all tissues & fluid in direct proportion to blood level
- less than 10% of absorbed ethanol is excreted unchanged in: urine sweat & breathe
- there is genetic polymorphism in aldehyde dehydrogenase that affect etanol metabolism
  - 50% of chinese, vietnamase & Japanese have lowered enzyme activity due to point mutation of the enzyme → accumulation of acetaldehyde → facial flushing, tachy-cardia & hyper-ventilation

Mechanism of Ethanol Toxicity

- Fatty change
  - due to excess production of NADH over NAD in cystol & mitochondria
  - Shunting of lipid catabolism toward lipid bio-synthesis
  - ↑ peripheral catabolism of fat →↑ FA delivery to the liver
  - ↓ secretion of lipoproteins from hepatocytes
  - Acetaldehyde forms adducts with tubulin (monomer of microtubules) →↓ function of microtubules →↓ in lipoprotein transport from liver
  - ↓ oxidation of FFA by mitochondria
- CYP2E1 is induced by chronic alcohol consumption
  - enhances the metabolism of drugs to toxic metabolites (e.g acetominophen)
  - ↑ free radicals production —> leads to membrane & protein damage
- Alcohol directly affect microtubular & mitochondrial function & membrane fluidity
- Acetaldehyde causes lipid peroxidation & antigenic alteration of hepatocytes → immune attack
- Superimposed HCV infection causes acceleration of liver injury (HCV hepatitis occurs in 30% of alcoholics)
- Alcohol → release of bacterial endotoxins into portal circulation from the gut → inflammation of the liver
- Alcohol → regional hypoxia in the liver due to release of ENDOthelins which are potent vaso-constrictors → ↓ hepatic sinusoidal perfusion
- Alteration of cytokine regulation
  - TNF (a major effector of injury)
  - IL6, IL8, IL18

Causes of deth in alcoholic liver disease

!! Death !!

- hepatic failure
- massive GI bleeding
- infections
- hepato-renal syndrome
- HCC (hepatocellular carcinoma) in 3-6% of cases

Cirrhosis

Clinical Features

- silent
- Anorexia (loss of appetite), weight loss, weakness
- progressive hepatic failure
- complications
  - portal hypertension
  - hepatocelular carcinoma

Pathogeneis

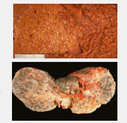
- cirrhosis requires cell death to occur over long periods of time
  - 1) hepatocellular death
  - 2) regeneration
  - 3) progressive fibrosis
    - the ECM collagen (types I, III, V, XI) is present only in (liver capsule, portal tracts & around central vein)
      - in normal liver
        - delicate framework of type IV collagen & other proteins lie in SPACE OF DISSE
      - in cirrhosis
        - types I & III collagen & others are deposited in the SPACE OF DISSE
    - fibrosis progresses to scar formtion when the injury involves not only the parenchyma, but also the Supporting Connective tissue (Laennec cirrhosis)
    - the stimuli for the activation of Stellate cells & production of collagen are
      - ROS
      - Growth factors
      - cytokines, TNF, IL-1, lymphotoxins
  - consisting of 4) vascular changes
    - loss of sinusoidal ENDOthelial cell fenestrations
    - development of vascular shunts that contribute to defects in liver function
      - portal vein-hepatic vein shunt
      - portal vein-hepatic artery shunt

Vascular shunts create abnormal connections between arteries and veins in the liver → bypass the normal liver circulation → inadequate blood supply to the liver tissue → liver tissue damage → fibrosis → cirrhosis.

Main Characteristics

- bridging FIBROUS septae
- Parenchymal NODULES encircled by fibrotic bands
- architecture disruption

Types



- MICRO-nodules < 3mm in diameter
- MACRO-nodules > 3mm in diameter

Causes

- CHRONIC alcoholism
- CHRONIC viral infection
  - hepatitis B virus (HBV)
  - hepatitis C virus (HCV)
- biliary disease
- hemochromatosis
- autoimmune hepatitis
- Wilson disease
- α-1- antitrypsin deficiency
- rare causes
  - galactosemia
  - tyrosinosis
  - glycogen storage disease III & IV
  - lipid storage disease
  - hereditary fructose intolerance
  - drug-induced (e.g methyldopa)
  - cryptogenic cirrhosis (10%) — cirrhosis of uncertain etiology

Portal Hyper-tension

Description

increased blood pressure in the portal venous system

Pathogenesis

↑ resistance to portal blood flow at the level of SINUSOIDs

compression of central veins by (peri-venular fibrosis) & (parenchymal nodules)

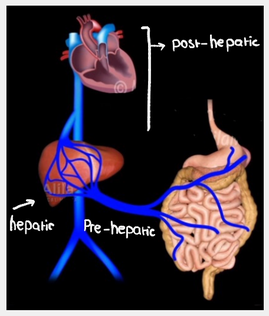
Arterial–portal anastomosis develops in the fibrous bands → increase the blood pressure in portal venous system

Causes

PRE-hepatic (before the liver)
- portal vein thrombosis
- massive splenomegaly → when the spleen enlarges → compresses the portal vein

POST-hepatic (after the liver)
- severe RIGHT sided heart failure
- constrictive Peri-Carditis
- hepatic vein outflow obstruction

hepatic (within the liver)
- cirrhosis
- schistosomiasis (infection)
- massive fatty change
- diffuse granulomatosis → massive as: sarcoidosis (inflammatory disease), TB
- disease of portal microcirculation as: nodular regenerative hyperplasia



Clinical Consequences

① Ascites

collection of excess fluid in peritoneal cavity —> it becomes clinically detectable when at least 500ml have accumulated

Features (fluid composition)
- serous fluid
- contains as much as 3g/ml of protein (albumin)
- it has the same concentration as blood of glucose, Na+ & K+
- MESOthelial cells & lymphocytes
- neutrophils = inflammation
- RBCs = disseminated cancer

Pathogenesis
- SINUSOIDAL increased blood presure
- hypo-albumin-emia
- leakage of hepatic lymph into the peritoneal cavity
  - normal thoracic duct lymph flow = 800-1000 ml/day
  - in cirrhosis, it may approach 20L/day
- renal retension of Na+ & water due to secondary hyper-aldosteronism

Porto-Systemic shunts

Because of ↑ portal venous pressure —> bypasses develop wherever the systemic & portal circulation share capillary beds

appear in 65% of patients with advanced cirrhosis

cause death in 50% of them due to UGI bleeding

sites
- Gastro-Esophageal junction —> Varices
- around & within the rectum —> Hemorrhoids
- Retro-Peritoneum
- Falciform ligament of the liver (Peri-Umbilical & abdominal wall collaterals) —> Caput Medusae

Hepatic Encephalopathy

a complication of ACUTE & CHRONIC hepatic failure

disturbance in brain function ranging from
- behavioural changes ①
- marked confusion & stupor ②
- coma & death ③

the changes may progress over hrs or days

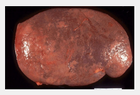
Neurological signs
- rigidity ✓
- hyper-reflexia ✓
- non-specific EEG (electro-encephalo-gram)
- seizures
- asterixis (non-rhythmic rapid extension flexion movements of head & extremities)

brain signs
- edema
- astrocytic reaction

Pathogenesis
- I/ Severe loss of hepatocellular function
- 2/ Shunting of blood around damaged liver
- 3/ Exposure of Brain to toxic metabolic products
- ↑ NH3 level in blood → generalized brain edema impaired neuronal function — ACUTE insult
- alteration in central nervous system AA (amino acids) metabolism — CHRONIC insult

Splenomegaly

- normal spleen < 300g
- enlarged spleen: 500-1000g
- not necessarily correlated with other features of portal hypertension
- may result in hyper-splenism



liver pathology.

* The liver is devided

* Normal liver → shiny smooth surface.

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sinusoid ??