PATHOLOGY OF THE GALLBLADDER, BILE DUCTS AND EXOCRINE PANCREAS
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LIVER
BACKGROUND
Liver functions include:
- Production of most serum proteins including albumin and other binding proteins, coagulation factors, acute phase reactants including complement
- Metabolism and excretion of constituents of bile (conjugated bilirubin, bile salts, cholesterol etc)
- Storage e.g. iron, glycogen
- Glucose and lipid metabolism
- Catabolism of various endogenous and exogenous substances
Weight: about 1500gm
Histological structure:
- One cell thick plates of hepatocytes radiate between portal tracts (containing branches of hepatic artery, portal vein and bile ductules) and central veins
- Between the plates of hepatocytes run the sinusoids from which the hepatocytes are separated by the space of Disse and endothelial cells. Within the space of Disse are the phagocytic Kupffer cells, and stellate (Ito) cells
- Between adjacent hepatocytes are tiny bile canaliculi. Tight junctional complexes between adjacent hepatocytes prevent leakage of bile from the canaliculi
- Classic liver lobule: central vein in centre
- Liver acinus: centred on terminal branches of the hepatic artery and portal vein that carry oxygen and nutrient rich blood that then flows through the sinusoids to the terminal hepatic (central) veins. Hepatocytes in zone 1 around the hepatic artery and portal vein branches receive blood that is richest in oxygen and nutrients and those in zone 3 receive blood that is oxygen and nutrient poor. The zones not only reflect differences in blood flow but also differences in metabolism.

GALLBLADDER AND GALLSTONES
BACKGROUND
Gallbladder
Stores and concentrates bile that is produced in the liver.
Volume of about 50ml
Releases stored bile into the duodenum for fat digestion: presence of food in the duodenal lumen stimulates the release of cholecystokinin from enteroendocrine cells in the small intestinal epithelium, which stimulates contraction of the gallbladder and relaxation of the sphincter of Oddi. Neural stimulation contributes.
Histological structure
Layers:
- Folded simple columnar mucus secreting epithelium
- Lamina propria
- Single muscle layer
- Subserosal fat
- Peritoneum covers the undersurface, the upper surface attaches to the liver
Bile contains:
- Bile salts
  - Derivatives of cholesterol important in digestion of fats
    - Most are actively reabsorbed into blood in terminal ileum and returned to liver: enterohepatic circulation
    - Aid fat digestion via detergent action, and fat absorption via formation of micelles
- Cholesterol
  - Waste product
    - Maintained in solution in bile by the action of bile salts and lecithin, forming micelles
- Lecithin: contributes to micelle formation
- Bilirubin: waste product
- Water, electrolytes, fatty acids
Review of bilirubin metabolism

Senescent rbcs (average life span 120 days) are phagocytosed by macrophages, particularly in the spleen, where the haemoglobin is broken down and the heme component is converted to bilirubin, which is released into the blood. This unconjugated bilirubin is not soluble in aqueous solution, binds strongly to plasma albumin and is carried to the liver. In the liver, bilirubin is released from albumin and enters hepatocytes where it is conjugated to glucuronic acid to become water soluble conjugated bilirubin which is actively secreted from hepatocytes into bile. In the intestine, this is then converted by bacteria to urobilinogen, some of which is converted to stercobilinogen, which gives faeces their brown colour. Some urobilinogen is reabsorbed by the intestine and then re-excreted by the liver or excreted in urine. In the urine, urobilinogen becomes oxidised to urobilin, which gives the urine its yellow colour.

CHOLELITHIASIS/GALLSTONES

Very common in developed countries
Cholesterol, pigmented and mixed stones
Majority develop in the gallbladder but occasionally may form in the bile ducts

Cholesterol stones
Predominantly composed of cholesterol
Commonest type in developed countries
Single or multiple pale stones
Some may contain variable amounts of calcium carbonate and bilirubin to give them a darker colour, and 10-20% contain sufficient calcium carbonate to make them radio-opaque, whereas most are radiolucent
Pathogenesis is multifactorial
- Supersaturation of bile by cholesterol, which cannot all be maintained in solution by available bile salts and lecithin
- Gallbladder hypomotility permitting formation of biliary sludge
- Excess of factors that promote nucleation e.g. certain proteins, mucin, or deficiency of factors that inhibit nucleation
- Decreased secretion of bile salts
- Cholesterol comes out of solution and crystallizes, crystals become trapped in mucus (-> biliary sludge) enabling growth
Risk factors
- Increased hepatic secretion of cholesterol
  - Increasing age
  - Oestrogen i.e. in females, OCP use and pregnancy
  - Obesity, diet/high blood cholesterol
  - Familial/genetic
  - Certain ethnic groups
  - Certain drugs
  - Other
- Decreased secretion of bile salts e.g. impaired enterohepatic circulation
- Gallbladder hypomotility e.g. related to progesterone in pregnancy

Pigment stones
Mainly composed of calcium bilirubinate, generally multiple
About 50% radio-opaque
Relatively more common in developing countries
Black and brown types
Risk factors and pathogenesis:
- Chronic haemolysis -> excess bilirubin in bile -> typically black stones
- Biliary tract infection -> excessive deconjugation of bilirubin in bile -> typically brown stones
- Cirrhosis, cystic fibrosis, biliary stasis
- Unknown reasons leading to increased amounts of unconjugated bilirubin in bile
Complications/effects of gallstones
- Asymptomatic: most
- Biliary colic: transient steady, rather than colicky, pain/discomfort caused by transient obstruction of the cystic duct
- Cholelithiasis: fine yellow streaks in mucosa related to presence of lipid filled macrophages in lamina propria. No clinical significance
- Chronic cholecystitis: variable fibrosis, muscle hypertrophy, chronic inflammation and development of pouches of epithelium extending into the wall associated with gallstones leading to thickening and sometimes calcification of the gallbladder wall. Clinical features are probably related to the presence of stones rather than the chronic inflammation
- Acute cholecystitis: see later
- Common bile duct obstruction -> obstructive jaundice +/- bacterial cholangitis
- Mucocele of gallbladder: chronic impaction of a stone in the cystic duct may lead to the development of a mucocele or hydrops of the gallbladder: continued secretion of mucus by the lining epithelial cells and absorption of bile pigment results in the accumulation of clear mucinous fluid with distension of the obstructed gallbladder
- Adenocarcinoma of gall bladder: uncommon but gallstones appear to predispose
- Acute pancreatitis: see later
- Internal biliary fistulas: inflammatory adhesions may form between the gallbladder and adjacent structures e.g. duodenum or colon, which when associated with necrosis can lead to the formation of a cholecystenteric fistula. Such fistulae may arise insidiously.
ACUTE CHOLECYSTITIS
Calculus
- >90% of cases
- Gallstone obstructs neck of gallbladder or cystic duct
Acalculous
- Related to infection, severe trauma, burns, major surgery, shock, vasculitis
- Possibly related to ischaemia
Acute calculous cholecystitis
Pathogenesis uncertain but obstruction of the cystic duct or gallbladder neck by stone is present in most. Obstruction -> biliary stasis with alteration of bile constituents by epithelium -> chemical damage to wall -> inflammation. Ischaemia caused by distension and contraction of the gallbladder may contribute. Secondary bacterial infection may occur.
Macroscopically: oedematous erythematous wall, often haemorrhagic, mucosal ulceration
Histologically: neutrophil infiltrate, ulceration, oedema and haemorrhage +/- necrosis. With time – proliferation of fibroblasts (organization) and scarring.
Outcomes
- Spontaneous organization with supportive treatment: most cases. The gallbladder in acute cholecystitis does not become gangrenous and perforate as readily or as early as an appendix in acute appendicitis so there is not as much urgency to remove it. Some cases are removed later electively.
- Empyema: pus filled gallbladder
- Gangrenous cholecystitis (necrosis from release of lysosomal contents of neutrophils +/- secondary bacterial infection) can -> perforation -> generalised acute peritonitis or localised pericholecystic abscess.
- Adhesions and necrosis can -> cholecystenteric fistula

CHOLESTASIS
Reduced secretion of bile constituents into the bile canaliculi and/or decreased bile flow through the canaliculi or bile ducts.
Intrahepatic cholestasis: causes include viral hepatitis, alcoholic steatohepatitis, certain drugs, pregnancy, primary biliary cirrhosis, malignancy, intrahepatic biliary atresia
Extrahepatic cholestasis – obstruction of extrahepatic bile ducts: causes include gall stones, carcinoma of the bile ducts or head of the pancreas, external compression by enlarged neoplastic lymph nodes and sclerosing cholangitis.
Consequences: Bile pigment accumulates in hepatocytes and bile canaliculi. Conjugated bilirubin moves from hepatocytes into the bloodstream. Elevation of serum alkaline phosphatase released from canalicular membranes of hepatocytes and GGT from endoplasmic reticulum and bile duct epithelial cells.
When persisting, oedema, inflammation, hepatocyte necrosis, bile duct proliferation and fibrosis and after many years cirrhosis may develop.
Clinically
- Jaundice
- Pale faeces (lack of bile pigment in faeces)
- Dark urine (from presence of conjugated bilirubin in urine)
- Itching (probably from bile salts accumulating in skin)
- Skin xanthomas (focal accumulations of cholesterol related to hypercholesterolaemia) in protracted cases
- Steatorrhoea (from impaired delivery of bile salts to intestine) in protracted cases

SCLEROSING CHOLANGITIS
Autoimmune, sometimes seen in association with inflammatory bowel disease, especially ulcerative colitis
Chronic inflammation and fibrosis of intrahepatic and extrahepatic bile ducts
Causes chronic bile duct obstruction and ultimately cirrhosis
Most patients are male.

PRIMARY BILIARY CIRRHOSIS
Autoimmune inflammation and destruction of intrahepatic bile ducts leading to cirrhosis
Most patients are female

EXOCRINE PANCREAS
ACUTE PANCREATITIS
Inappropriate activation of pancreatic enzymes within the pancreas -> variable, often severe, acute inflammation, oedema, necrosis of pancreas and adjacent fat. In severe cases bleeding occurs within pancreas and surrounding tissues: acute haemorrhagic pancreatitis. In fat necrosis, fatty acids combine with calcium salts -> focal calcification and sometimes hypocalcaemia. Fat necrosis may be widespread throughout the abdominal cavity.
Risk factors
- 80% associated with either gallstones or alcohol.
- Gallstones: obstruction of ampulla of Vater and pancreatic duct by stone
- Alcohol
  - Pathogenesis ? via metabolic injury
  - Often underlying chronic pancreatitis
- Miscellaneous: other cases associated with e.g. hypercalcemia, hyperlipidaemia, certain drugs, certain infections, genetic
Typically severe abdominal pain that is referred to the back. Often nausea, vomiting +/- shock. Elevated serum amylase and lipase

Complications include

- Full-blown acute pancreatitis is a medical emergency – enzymes and cytokines released into circulation -> activation of systemic inflammatory response with complement activation and release of vasoactive agents -> vasodilatation, increased vascular permeability with variable plasma loss into interstitial tissues -> shock +/- disseminated intravascular coagulation and acute respiratory distress syndrome
- Pancreatic abscess from infection of the necrotic pancreas
- Pancreatic pseudocyst: persisting localised collections of necrotic debris that become surrounded by fibrous tissue
- Bowel obstruction from surrounding oedema
- Gastrointestinal, intraperitoneal or retroperitoneal bleeding (uncommon)
- Hypocalcemia
- Pancreatic ascites

CHRONIC PANCREATITIS

Chronic inflammation with destruction and fibrosis of pancreas
Causes exocrine and ultimately endocrine insufficiency
Generally presents with pain and/or malabsorption
Attacks of acute pancreatitis may occur
Most cases associated with alcoholism, other causes include chronic duct obstruction, metabolic and genetic abnormalities
Complications include pancreatic pseudocyst, malnutrition, diabetes mellitus, biliary obstruction, duodenal obstruction

PANCREATIC CARCINOMA

Male predominance, middle age and elderly
Adenocarcinoma, schirrous
60% arise in the head of the pancreas
Risk factors: smoking, ?dietary, ?chronic pancreatitis
Generally poor prognosis
Clinically
- Jaundice from obstruction of common bile duct
- Abdominal +/- back pain
- Palpable non-tender gall bladder (Courvoisier’s sign)
- Migratory venous thromboses (Trousseau sign) due to production of procoagulant substances
- Anorexia, weight loss etc

Metastasises to
- Lymph nodes
- Peritoneum -> ascites
- Liver, bone, lung