Section 23

LECTURE

Pathophysiological Consequences of Cirrhosis

Pathophysiologic Consequences of Cirrhosis: Portal Hypertension, Ascites, Hepatic Coma, Hepatorenal Syndrome

I. Anatomical Considerations

A. *Portal venous blood goes through two capillary beds*

1. Gastric, intestinal pancreatic or splenic
2. Hepatic (sinusoidal)

Thus, most absorbed nutrients, drugs and potential toxins pass through the liver *en route* to the systemic circulation. Regeneration of hepatic tissue dependent on hormones (and nutrients?) from gastrointestinal tract.

B. *Lack of valves in portal venous system*

1. Bi-directional flow possible
2. Retrograde flow via surgically-created anastomoses can relieve portal hypertension

C. *Flexible capacity of hepatic sinusoidal bed:* Expansion with increased central venous pressure, contraction with blood loss

D. *Measurement of portal venous pressure:*

1. Normal up to 10 mm Hg (higher than vena caval pressure)
2. Portal hypertension: > 10 mm Hg
3. Techniques for measuring portal pressure:

   a. Percutaneous portal vein puncture or splenic pulp pressure
   b. Transvenous wedged hepatic vein pressure: wedged catheter or inflatable balloon reflects hepatic capillary (sinusoidal) pressure and, hence, portal vein pressure if no block exists proximal to hepatic sinusoids
   c. Combining a & b can suggest site of obstructed flow in patients with portal hypertension:

	Wedged Hepatic Vein Pressure	Splenic Pulp Pressure
Sinusoidal-postsinusoidal disease (cirrhosis)	Increased	Increased
Pre-sinusoidal venous obstruction (may be prehepatic or involve portal triads)	Normal	Increased

Largely a pedagogical exercise, but if "presinusoidal", liver function and resistance to injury generally well preserved.

E. *Arterial flow to the liver:*

1. Normally 20-30% of hepatic blood flow
2. Anastomoses exist with terminal portal venous system at the hepatic sinusoidal level; such connections may become larger in cirrhosis, thus contributing to elevated portal pressure. These anastomoses are found in the immediate periportal part of the lobule.

II. Mechanisms of Portal Hypertension

A. *Increased portal flow* (Normal = 1.5 liters/minute)

1. Massive splenomegaly: 2-3x normal flow
2. Fistula

B. *Increased resistance* (much more commonly seen)

1. *Pre-sinusoidal* (normal wedged hepatic vein pressure)

a. Thrombosed portal vein

1. Post-surgery
2. Post-trauma
3. Neoplastic invasion
4. Hypercoagulable states (e.g. polycythemia vera)
5. Neonatal phlebitis

a. Omphalitis of the newborn
b. Post-exchange transfusion

b. Intrahepatic portal venule obstruction

1. Schistosomiasis - eggs implanted in portal venules lead to fibrosis and granuloma, not cirrhosis

2. Portal venule fibrosis - "Idiopathic portal hypertension"

a. More common in developed countries
b. Role of heavy metals

2. *Sinusoidal:* cirrhosis

a. Interference with sinusoidal flow by pressure of regenerating nodules against scarring of cirrhotic liver. Wedged hepatic vein pressure increased.

b. Swollen cells (fat) may also narrow sinusoidal channels.

c. Formation of arterio-venous and veno-venous channels in intralobular connective tissue.

3. *Post sinusoidal*

a. *Intrahepatic* - in cirrhosis, scarring may occur, especially about the terminal hepatic vein (central vein) where oxygenation is least. Especially true in the alcoholic, putting fibrous "basket" about hepatic cells.

b. *Post hepatic* - site of obstruction in draining hepatic veins or beyond

1. *"Budd-Chiari syndrome"*: hepatic vein thrombosis of any cause leading to portal hypertension, ascites, tender hepatomegaly

a. Tumor (i.e. hepatoma, hypernephroma)
b. Myeloproliferative disorders (e.g. polycythemia vera)
c. Hypercoagulable disorders (e.g., Factor V Leiden)
d. Sepsis
e. Pregnancy
f. The "pill"
g. Plant-alkaloids (senecio and crotolaria), "bush-tea disease"
h. Congenital webs

2. a. Severe R-sided CHF (e.g., constrictive pericarditis)

b. Endomyocardial fibrosis

III. Consequences of Portal Hypertension

A. Development of collateral circulation, from portal venous to low pressure vena caval system, thus bypassing liver

1. Communicating veins between short gastric and azygous systems: *esophageal varices* (see B below)

2. Perirectal hemorrhoidal channels

3. Recannulation of obliterated umbilical vein leading to abdominal wall veins: *caput medusa*

4. Minor retroperitoneal and transdiaphragmatic channels - artificial stomas

B. *Esophago-gastric varices* - major clinical importance

1. Life-threatening: Variceal hemorrhage often *coup de grace* in history of chronic liver disease

2. Demonstration: By UGI series, endoscopy, angiography

3. Rupture - "Explosive vs Erosive" theories: Most commonly increased portal pressure $\rightarrow$ inc. wall tension (LaPlace's Law $T = P \times R$) $\rightarrow$ congestion and tear

4. Survival: 1-year survival as low as 30% - Survival is a function of the severity of underlying liver disease (i.e., adequacy of clotting factors, ability of liver to withstand shock, etc.). A less catastrophic event with presinusoidal block, when the liver is relatively healthy.

C. Treatment of Variceal Hemorrhage

1. Medical emergency

a. Sengstaken-Blakemore or Linton tube. Temporary mechanical tamponade. High complication rate: ulceration, rupture, aspiration
b. Vasopressin or octreotide infusion - decrease splanchnic flow and portal pressure. Former with renal and myocardial problems
c. Angiographic embolization of varices: Percutaneous, transhepatic puncture of portal vein

d. Endoscopic sclerotherapy or band ligation of esophageal varices. Old technique rediscovered and simplified. Chemical or mechanical thrombosis of varix and fibrosis of submucosa. Current treatment of choice
e. Transjugular intrahepatic portosystemic shunt (TIPS). Creation of an intrahepatic portacaval shunt by means of a plastic stent bridging hepatic to portal vein. Effective for refractory hemorrhage, complicated by encephalopathy

2. Medical - Long term

a. Sclerotherapy or band ligation repeated to obliterate varices. Impact on survival is unclear.
b. Beta blockers and other agents to decrease portal pressure. Reduce risk of rebleeding. Portal pressure helps liver perfusion.

3. Surgical approaches

a. Ligation of varices, transection of esophagus or stomach. Varices reform.
b. Decompression of the portal system to prevent variceal hemorrhage
c. Large anastamoses created: porta-caval, spleno-renal, meso-caval, selective spleno-renal
d. Value:

1. Prophylactic (no prior variceal hemorrhage) - no improved survival
2. Therapeutic elective (previous variceal hemorrhage) - probably improves survival slightly
3. Emergency - high risk; value uncertain
4. Results always better in patients with better liver function; best in pre-sinusoidal portal hypertension
5. Effectively control recurrent hemorrhage at expense of complications (proportional to size of shunt):

i. Hepatic encephalopathy. Severe in 20% of post- operative cases. Occurs in 50%. Incidence: ? more frequent but certainly more lethal than in unshunted patients.
ii. Progressive hepatic failure - loss of portal blood supply to liver. Hepatofugal flow in side to side shunts.

6. Attempts to selectively decompress blood supply to varices. Preserve hepatotrophic factors and first-pass clearing of absorbed toxins: Distal spleno-renal shunt (Warren shunt)

i. Separates variceal perfusion from hepatic perfusion
ii. Transient advantage

iii. Formation of secondary collaterals
iv. No effect on survival and effect on encephalopathy

D. *Congestive Splenomegaly*

1. Hypersplenism: thrombocytopenia can increase tendency to bleed. Corrected when spleen removed, and often by other shunts.

E. *Endocrine Effects*

1. Estrogenic effects:

a. "Spiders"
b. testicular atrophy
c. gynecomastia

2. Related to an imbalance between androgens and conjugated estrogens.

F. *Ascites*

1. General considerations: the presence of free fluid in the peritoneal cavity may be a consequence of portal hypertension, but may occur in other situations.

a. Low serum-ascites albumin gradient (< 1.1 g/dL). Exudative ascites, protein content typically greater than 2.5 gm.

1. Peritoneal inflammation (i.e. tumor implants, acute and chronic peritonitis, starch peritonitis, tuberculosis)
2. High grade right-sided heart failure
3. Acute or chronic pancreatitis
4. Lymph leakage from cisterna chyli obstruction (lactescent fluid)

b. High serum-ascites albumin gradient (>= 1.1). Transudative ascites, low protein concentration, most commonly seen in uncomplicated cirrhosis

2. Mechanism of ascites

Major determinants in cirrhosis

a. Portal hypertension - elevations favor transudation of fluid into peritoneal cavity. "Underfill" hypothesis. Usually not sufficient to cause ascites without decreased serum albumin or hepatic lymphatic obstruction.

b. Plasma colloid osmotic pressure - depression favors transudation of fluid into peritoneal cavity
c. Increased hepatic lymph - up to 5x normal. Newly synthesized albumin passes directly to ascites. Blocked lymph absorption in retroperitoneum.
d. Renal sodium + water retention essential to ascites; "Overflow"hypothesis
e. Portal hypertension may lead to nitric oxide-mediated arteriolar vasodilatation, leading to underfilling and stimulation of the renin-angiotensin, sympathetic, and antidiuretic hormone axes. "Vasodilatation" hypothesis.

3. Compartmentalization of ascites

a. Although Na^+ and H_2O seem to be in constant equilibrium with the serum, the ascites compartment is not in equilibrium with other extracellular fluid compartments.
b. Maximal rate of ascites mobilization @ 900cc/day - average 300cc
c. More vigorous diuresis leads to depletion of edema fluid or extracellular (plasma) volume
d. Surgical approach - peritoneo-venous shunting; LeVeen and Denver shunts

G. *Hepatorenal Syndrome*

1. Progressive renal failure in a patient with liver disease characterized by:

a. Severe oliguria
b. Azotemia
c. Urine of high osmolarity and very low sodium concentration (in contrast to acute tubular necrosis)
d. Frequently increased plasma volume and cardiac output

2. Precipitating factors: bleeding, diuresis, paracentesis or none

3. Pathophysiology

a. Altered renal hemodynamics with shunting of blood from renal cortex to medulla
b. ? humoral vs. neural regulators as yet unidentified. A potentially reversible picture without demonstrable intrarenal pathology. Kidneys function if transplanted.
c. High (90%) mortality but varies with prognosis of liver disease.

d. Experimental approaches - vasodilators vs. "false transmitters". Volume repletion.

IV. Hepatic Encephalopathy

A. Description: A state of disordered CNS function associated with severe acute and chronic liver disease

1. *Acute encephalopathy*

   a. Can occur with any form of severe liver disease
   b. Usually reversible and without CNS anatomic pathology
   c. Features include agitation, confusion, drowsiness, stupor, asterixis, fetor hepaticus and a "slow wave" on EEG.

2. *Chronic Encephalopathy*

   a. Usually seen in stable long-surviving cirrhotics, especially post-shunt surgery
   b. Often not reversible with clear-cut CNS pathology: neuronal drop-out, patchy necrosis at the cortico-medullary junction, astrocytic proliferation
   c. Features may include severe personality changes, dementia, memory loss, extrapyramidal signs and, occasionally, spastic hemiplegia.

3. *Determination of Encephalopathy*

   a. Ammonia levels
   b. EEG changes, visual evoked potentials
   c. Perceptive tests

B. Causes of Hepatic Encephalopathy

1. Probably failure of liver to detoxify noxious agents as a result of:

   a. Decreased number of normal hepatic cells
   b. Portal blood shunting away from remaining cells through endogenous or surgically-created channels. Occurrence in shunts even in absence of liver disease.

2. Interaction of protein with intestinal bacteria. Production of potential toxic substances.

   a. Ammonia alone
   b. Ammonia and synergistic compounds -- amines, short-chain fatty acids

c. False neurotransmitters - compete with dopamine and excitatory amino acids
d. Primary inhibitory neurotransmitters - GABA and GABA receptors increased
e. Endogenous benzodiazepine-like compounds – interact with benzodiazepine receptor

3. Ammonia as a marker of protein breakdown

   a. Affected by changes in pH
   b. CNS effects:

      1. changes in cerebral metabolism
      2. do not imitate natural condition
      3. convulsions rare
      4. VEP effect different

   c. Poor correlation with blood levels

4. False Neurotransmitters

   a. Theory of false neurotransmitters:

      1. Provocative but as yet unproved
      2. Flooding of circulation and CNS with protein by-products
      3. Aromatic AA's produce weak imitators of normal neurotransmitters
      4. Accumulation of octopamine, phenylethanolamine in CNS
      5. Increased levels of tryptophan and 5-HIAA

   b. Implications regarding therapy

      1. Branched chain amino acids block CNS entry of aromatics if blood-brain barrier intact
      2. Therapy via infusion of branched chain AA's:
         a. Valine, leucine, isoleucine
         b. Vegetable protein diets

   c. Objections

      1. Octopamine does not reproduce symptoms
      2. Dopinergic drugs - little effect
      3. Noradrenaline and dopamine increased in encephalopathy
      4. Neurophysiologic effects weak

5. Inhibitory neurotransmitters

a. Synthesized by gut bacteria
b. GABA levels and receptors increased
c. Hyperpolarizes neurons - opens chloride channels
d. Imitates VEP of hepatic encephalopathy

6. Factors precipitating hepatic coma

a. GI bleeding - (100 ml blood = 15-20 g protein)
b. Azotemia
c. Constipation
d. High protein meal
e. Cation exchange resins

7. Other clinical problems can decompensate a borderline state:

a. Decompensated CNS
b. Hypokalemic alkalosis - diuresis, renal loss
c. Electrolyte imbalance
d. CNS depressant drugs
e. Hypoxia
f. Sepsis
g. CO_2 narcosis

C. Treatment of Hepatic Encephalopathy

1. Remove precipitating factors, i.e.

a. Control GI bleeding
b. Correct hypokalemia
c. Reduce protein intake - 20-30 gm/day, alternate (vegetable) protein sources
d. Remove sedating drugs

2. Decrease protein catabolism in gut

a. Antibiotics
b. Cathartics, enemas

3. Decreased absorption of protein by-products by acidification of the colon

a. Lactulose - a disaccharide of fructose and galactose, not cleaved in small bowel. Is fermented in colon, producing diarrhea and an acid milieu that converts NH_3 to non-diffusible NH_4^+ ion
b. Other actions: laxative, intrinsic acid pH, change in bowel flora.

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