NASPGHAN Physiology Education Series

Hepatophysiology

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Anatomy and blood supply of the liver (slides 1-4)

The anatomy of the liver is typically classified segmentally using the Couinaud system, which is based on an imaginary tranverse plane through the bifurcation of the main portal vein. The functional lobes are divided in 8 subsegments: caudate (1), lateral (2,3), medial (4a, 4b), and right (5,6,7,8). The caudate lobe is separate, as it receives blood flow from right- and left-sided vasculature.

The blood supply of the liver is provided by the hepatic artery (25%) and the hepatic portal vein (75%) . Blood supplied by the hepatic artery is oxygenated and blood supplied by the portal vein is primarily deoxygenated, but nutrient-rich. Oxygen comes equally from both vessels and the terminal branches of the hepatic cportal vein and hepatic artery empty together and mix entering the liver. Blood then flows through the liver sinusoids and empties into the central vein of each liver lobule. The central veins then coalesce into hepatic veins. Blood exits the liver via the hepatic vein and returns to the heart via the inferior vena cava, deoxygenated and detoxified.

Until 32 weeks of gestation, hematopoiesis occurs primarily in the liver (and also the spleen).

Physiologic immaturity of hepatic function (slides 5-7)

At birth, hepatocytes are specialized with two surfaces. The sinusoidal surface absorbs a mixture of oxygenated blood and nutrients from the portal vein. The other surface delivers bile and products of conjugation and metabolism to the bile canaliculi. With interruption of the umbilical supply at birth, there is a rapid induction of transamination, synthesis of glutamyl transferase, synthesis of coagulation factors, and production and transport of bile.

The hepatic acinus can be divided into 3 distinct zones. Zone 1 consists of the periportal hepatocytes which are involved with hepatocyte regeneration, bile duct proliferation and gluconeogenesis. Zone 2 has mixed function between zones 1 and 3. Zone 3 borders the central vein and is responsible for detoxification, aerobic metabolism, glycolysis and hydrolysis.

It takes 2 years after birth to achieve full maturity of biliary excretion and involves normal expression of signaling pathways, including JAG1 genes, amino acid transport and insulin growth factors. Preterm infants have immaturity and delay in achieving normal detoxifying and synthetic function, in addition to a risk of hypoxia and sepsis. These factors place them at risk for hepatic decompensation.

Mechanisms of hepatic regeneration (Slides 8-9)

In the fully developed liver, only 1/10-20,000 hepatocytes is dividing. As little as 25% of the liver has the capability of regenerating to a full liver. Several conditions such as viruses, cirrhosis, ischemia, trauma and even a partial hepatectomy can stimulate the liver to regenerate rapidly. Hepatic regeneration requires new hepatocyte and extracellular matrix restoration. IL-6, epidermal growth factor (EGF), TGF-alpha, and TGF beta hepatocyte growth factor are involved in initiation and regulation of regeneration. EGF, in conjunction with insulin and glucagon promotes DNA synthesis of hepatocytes.

Hepatic serum protein synthesis (slides 10-11)

The liver is responsible for synthesis of many proteins. Plasma proteins include albumin, alpha-feto protein, fibronectin, C-reactive protein, opsonin, globulins and other acute phase proteins. Proteins of hemostasis and fibrinolysis include those of the coagulation cascade (except factor VIII which is produced by the endothelium), alpha 1 antritrypsin, antithrombin III, protein C and S, plasminogen and components of the complement cascade. Other important proteins produced by the liver include hormones, prohormones, carrier proteins and apolipoproteins (except apo B48, produced by the intestine).

Taurine is a conditionally essential amino acid in early. Taurine is involved in bile acid conjugation and cholestasis prevention. Populations such as preterm infants, patients who are on chronic TPN and also those with hepatic, cardiac and renal failure, are at risk of taurine deficiency and need supplemenation. Diet is the usual source of taurine but in the presence of vitamin B6 it is synthesized by methionine and cysteine.

Hepatic carbohydrate metabolism (slide 12)

The liver is involved with gluconeogenesis, the synthesis of glucose from amino acids, lactate and glycerol; glycogenolysis, the breakdown of glycogen into glucose; and glycogenesis, the formation of glycogen from glucose.

Hepatic fatty acid metabolism (slide 13)

Dietary triglycerides are absorbed as free fatty acids, packaged into chylomicrons/liposomes, and released through the lymphatic system into the blood and binding to hepatocytes. The liver processed chylomicron remnants and liposomes into VLDL and LDL. Fatty acids which are synthesized by the liver get converted to triglycerises and are transported into the blood as VLDL. In peripheral

tissue, lipoprotein lipase converts VLDL to LDL and free fatty acids by removing trigylcerides. The remaining VLDL then becomes LDL, absorbed by LDL receptors. LDL is then converted into free fatty acids and cholesterol. The liver controls serum cholesterol concentration by removal of LDL. HDL carries cholesterol from the body back to the liver to be broken down and excreted.

Biochemical parameters of hepatic integrity (slide 14)

With hepatocellular injury, hepatocyte membranes become damaged and permeable and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) escape into the bloodstream.

With cholestasis, obstructed and/or damaged intra- and extra- hepatic bile ducts lead to induction of alkaline phosphatase and gamma glutamyl transferase (GGT)

Pathways of hepatic drug metabolism (slides 15-17)

Hepatic drug metabolism occurs mostly in the smooth endoplasmic reticulum of the liver and occurs in 2 phases.. Factors that increase and decrease drug metabolism affect enzymes in the cytochrome P450 monooxygenase system. Phase 1 of drug metabolism involves oxidation (cytochrome P450, aldehyde dehyrogenase), reduction (NADPH P450) and hydrolysis (esterase, amidase). Phase 1 metabolism is utilized by paracetamol and steroids. Phase 2 is the detoxifying phase and involves conjugation reactions (methylation, glucuronidation).

Bilirubin uptake, metabolism, excretion (slides 18-26)

Bilirubin is formed by breakdown of heme (80% from hemoglobin, 20% from other hemoproteins). Heme is broken down to biliverdin by heme oxygenase and to bilirubin IX alpha by biliverdin reductase. Heme oxygenase, found in Kupffer cells of the liver and the reticuloendothelial cells of the spleen) is the rate-limiting step in bilirubin production. Albumin binds to bilirubin (reversible process except in bilirubin obstruction) and this complex dissociates in liver sinusoids where bilirubin is taken up by hepatocytes. This process is bidirectional and occurs via facilitated diffusion. Defects in transporters at these steps cause unconjugated hyperbilirubinemia (eg Gilbert's Sydnrome). Unconjugated hyperbilirubinemia also results from cirrhosis when bilirubin produced from the spleen bypasses the liver via portosystemic collaterals.

Bilirubin is poorly water-soluble because of internal hydrogen bonding. Thus it can build up in the body and cause toxicity. Conjugation of bilirubin makes it water-soluble and excretable into bile. For neonatal indirect hyperbilirubinemia, the process of phototherapy produces configurational and structural photoisomers, excreted into bile without further metabolism. Bilirubin conjugation is mediated by a family of enzymes called uridine-diphosphoglucuronate glucuronosyltransferase (UGT) with UGTIA1 being the main enzyme of conjugation. UGT1A1 deficiency results in Gilbert's and Crigler-najjar syndromes. Inhibition of UGT1A1 can occur via a factor in breast milk (breast milk jaundice) and an inhibitory factor from maternal

plasma can even be transferred to the fetus transplacentally (Lucey Driscoll synrdome).

Conjugated bilirubin is secreted in bile across the bile canalicular membrane via active transport. There are 4 types of transports (eg MRP2, ABCC2). Conjugated bilirubin excretion can be impaired by viral hepatitis, cholestatsis of pregnancy Dubin-Johnson and Rotor syndromes).

98% of the bile pigment in bile is conjugated and water-soluble and will not be absorbed across the lipid membrane of small intestinal epithelium. The unconjugated fraction is partially reabsorbed through enterohepatic circulation. Bilirubin is reduced by bacterial enzymes in the colon to urobilinoids (urobilinogen and stercobilinogen). Intestinal microflora influence serum bilirubin levels and antibiotic use can increase serum bilirubin levels.

Infants are generally not jaundiced at birth because the placenta can clear bilirubin well from the fetal circulation. However, they can easily develop jaundice for several reasons. Bilirubin production in term neonates is 2-3 time higher than adults because they have more red blood cell volume than adults and the red blood cells have a shorter life span than in adults. Bilirubin clearance is decreased in neonates because of UGT1A1 deficiency and does not achieve adult levels until 14 weeks of age. Neonates have an increase in the enterohepatic circulation of bilirubin.

Portal hypertension (slides 27-31)

Portal hypertension results from a combination of increased portal resistance and/or increased portal blood flow. Splenomegaly is a result of congestion. Decompression through portosystemic collaterals results in esophageal and rectal varices. Decompression also leads to hepatic encephalopathy and hepatopulmonary syndrome. Ascites from portal hypertension can lead to peritonitis and hepatorenal syndrome.

Hepatic encephalopathy is a reversible impairment in neuropsychiatric function. Although a frequent complication of portal hypertension, the pathogensis is largely unclear and is likely from a combination of factors including an increase in ammonia concentration, inhibitory neurotransmitters through GABA receptors in the CNS and changes in central neurotransmitters and amino acids.

Hepatopulmonary syndrome is diagnosied by the triad of liver disease, impaired oxygenation and intrapulmonary vascular dilatations.

Hepatorenal syndrome is a diagnosis of exclusion but a cause of acute renal failure in patients with portal hypertension, associated with a poor prognosis. It is an end-stage process resulting from a sequence of reduction in renal perfusion.