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Differences in Immuno-Biochemical Diagnosis of Suprahepatic and Subhepatic Jaundice

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Abstract: Jaundice is the yellow color of skin and mucous membranes due to accumulation of bile pigments in blood and their deposition in body tissues. Jaundice should be distinguished from cholestasis, which refers to a decreased rate of bile flow. Depending on the clinical situation, jaundice and cholestasis may coexist or each may exist without the other. Although many sources confidently say that jaundice can be recognized when the serum bilirubin rises to 2 to 2.5 mg/dl, experienced clinicians often cannot see a yellow skin coloration until the serum bilirubin is at least 7 to 8 mg/dl.

Keywords: hyperbilirubinemia, immune, suprahepatic, subhepatic, jaundice.

Introduction

Jaundice, also known as hyperbilirubinemia,[1] is a yellow discoloration of the body tissue resulting from the accumulation of an excess of bilirubin. Deposition of bilirubin happens only when there is an excess of bilirubin, a sign of increased production or impaired excretion. The normal serum levels of bilirubin are less than 1mg/dl; however, the clinical presentation of jaundice as scleral icterus (peripheral yellowing of the eye sclera), is best appreciated only when the levels reach more than 3 mg/dl. Sclerae have a high affinity for bilirubin due to their high elastin content.[2] With further increase in serum bilirubin levels, the skin will progressively discolor ranging from lemon yellow to apple green, especially if the process is long-standing; the green color is due to biliverdin.[3]

Bilirubin has two components: unconjugated (indirect) and conjugated (direct), and hence elevation of any of these can result in jaundice. Icterus acts as an essential clinical indicator for liver disease, apart from various other insults.[4]

Yellowing of skin sparing the sclerae is indicative of carotenoderma which occurs in healthy individuals who consume excessive carotene-rich foods.[5]

CONJUGATED HYPERBILIRUBINEMIA [6]

- Defect of canalicular organic anion transport [7]
- Dubin-Johnson syndrome
- Defect of sinusoidal reuptake of conjugated bilirubin
- Rotor syndrome
- Decreased intrahepatic excretion of bilirubin[8]
- Hepatocellular disease - Viral hepatitis A, B, D; alcoholic hepatitis; cirrhosis, nonalcoholic steatohepatitis, EBV, CMV, HSV, Wilson, autoimmune
- Cholestatic liver disease-Primary biliary cholangitis, primary sclerosing cholangitis

- Infiltrative diseases (e.g., amyloidosis, lymphoma, sarcoidosis, tuberculosis)
- Sepsis and hypoperfusion states
- Total parenteral nutrition
- Drugs & Toxins - oral contraceptives, rifampin, probenecid, steroids, chlorpromazine, herbal medications (e.g., Jamaican bush tea, kava kava), arsenic
- Hepatic crisis in sickle cell disease
- Pregnancy
- Extrahepatic cholestasis (biliary obstruction)[9]
- Choledocholithiasis
- Tumors (e.g., cholangiocarcinoma, head of pancreas cancer)
- Extrahepatic biliary atresia
- Acute and chronic pancreatitis
- Strictures
- Parasitic infections (e.g., Ascaris lumbricoides, liver flukes)

UNCONJUGATED HYPERBILIRUBINEMIA

- Excess production of bilirubin
- Hemolytic anemias, extravasation of blood in tissues, dyserythropoiesis
- Reduced hepatic uptake of bilirubin
- Gilbert syndrome [10]
- Impaired conjugation[11]
- Crigler–Najjar syndrome type 1 and 2
- Hyperthyroid
- Estrogen
- Epidemiology
- The prevalence of jaundice differs among patient populations; newborns and elderly more commonly present with the disease.[12]

The causes of jaundice also vary with age, as mentioned above. Around 20 percent of term babies are found with jaundice in the first week of life, primarily due to immature hepatic conjugation process.[13] Congenital disorders, overproduction from hemolysis, defective bilirubin uptake, and defects in conjugation are also responsible for jaundice in infancy or childhood. Hepatitis A was found to be the most afflicting cause of jaundice among children.[14][15] Bile duct stones, drug-induced liver disease, and malignant biliary obstruction occur in the elderly population.

Men have an increased prevalence of alcoholic and non-alcoholic cirrhosis, chronic hepatitis B, malignancy of pancreas, or sclerosing cholangitis.[16] In contrast, women demonstrate higher rates of gallbladder stones, primary biliary cirrhosis, and gallbladder cancer.[17]

Kernicterus or Bilirubin-induced neurologic dysfunction (BIND), a complication of severe jaundice is a very rare cause of death in neonates with a death rate of 0.28 deaths per one million live births.[18]

PREHEPATIC

Production - Bilirubin is the end product of heme, which is released by senescent or defective RBCs. In the reticuloendothelial cells of spleen, liver and bone marrow, heme released from the RBC undergoes a series of reactions to form the final product bilirubin:

HEPATIC

Hepatocellular uptake - The bilirubin released from the reticuloendothelial system is in an unconjugated form (i.e., non-soluble) and gets transported to the hepatocytes bound to albumin which accomplishes solubility in blood. The albumin-bilirubin bond is broken, and the bilirubin alone is then taken into the hepatocytes through a carrier-membrane transport and bound to proteins in the cytosol to decrease the efflux of bilirubin back into the plasma.

Conjugation of bilirubin - This unconjugated bilirubin then proceeds to the endoplasmic reticulum, where it undergoes conjugation to glucuronic acid resulting in the formation of conjugated bilirubin, which is soluble in the bile. This is rendered by the action of UDP-glucuronosyl transferase.

POSTHEPATIC

Bile secretion from hepatocytes- Conjugated bilirubin is now released into the bile canaliculi into the bile ducts, stored in the gallbladder, reaching the small bowel through the ampulla of Vater and finally enters the colon.

Intestinal metabolism and Renal transport- The intestinal mucosa does not reabsorb conjugated bilirubin due to its hydrophilicity and large molecular size. The colonic bacteria deconjugate and metabolize bilirubin into urobilinogen's, 80% of which gets excreted into the feces and stercobilin and the remaining (10 to 20%) undergoes enterohepatic circulation. Some of these urobilin's are excreted through the kidneys imparting the yellow pigment of urine.

Dysfunction in prehepatic phase results in elevated serum levels of unconjugated bilirubin while insult in post hepatic phase marks elevated conjugated bilirubin. Hepatic phase impairment can elevate both unconjugated and conjugated bilirubin.

Increased urinary excretion of urobilinogen can be due to increased production of bilirubin, increased reabsorption of urobilinogen from the colon, or decreased hepatic clearance of urobilinogen.

Materials and methods

Liver function tests - to check serum levels of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase, serum albumin, protein and bilirubin

AST, ALT and ALP levels - if the liver transaminase levels increase but ALP levels are low, then the insult is hepatic in origin.

AST/ALT ratio is more than 2 to 1 in alcoholic liver disease.

AST and ALT values are in 1000s; then the hepatocellular disease is likely due to toxins like acetaminophen or ischemia or viral.

If ALP levels are five times elevated than normal and liver transaminases are normal or less than two times normal, then the most likely cause is biliary obstruction. The high serum ALP levels due to a biliary injury can be differentiated from bone disorders by ordering a GGT serum profile, increased levels confirm hepatic origin.

If AST, ALT and ALP levels are normal- then the jaundice is not due to liver or bile duct injury. The cause must probably be pre-hepatic: inherited disorders of liver conjugation or blood disorders or defect in hepatic excretion (Rotor, Dubin-Johnson).

Serum Bilirubin - whether there is a rise in unconjugated or conjugated bilirubin

In addition to the liver panel, all jaundiced patients should have additional tests such as albumin and prothrombin time – which are indicative of chronic and acute liver function, respectively. The inability of prothrombin time to correct with parenteral administration of vitamin K suggests severe hepatocellular dysfunction.

The results of the bilirubin, enzymes, and liver function tests will direct the diagnosis towards a hepatocellular or cholestatic cause and offer some idea of the duration and severity of the disease.

Hepatocellular workup: viral serologies, autoimmune antibodies, serum ceruloplasmin, ferritin.

Cholestatic workup: Additional tests include abdominal ultrasound, CT, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), endoscopic ultrasound (EUS).

Treatment

Treatment of choice for jaundice is the correction of the underlying hepatobiliary or hematological disease, when possible.

Pruritis associated with cholestasis can be managed based on the severity. For mild pruritis, warm baths or oatmeal baths can be relieving. Antihistamines can also help with pruritis.[27] Patients with moderate to severe pruritis respond to bile acid sequestrants such as cholestyramine or colestipol. Other less effective therapies include rifampin, naltrexone, sertraline, or phenobarbital. If medical treatments fail, liver transplantation may be the only effective therapy for pruritis.[28]

Jaundice is an indication for hepatic decompensation and may be an indication for liver transplant evaluation depending on the severity of the hepatic injury.

Differential diagnosis

The differential for yellowish discoloration of the skin is narrow. Healthy individuals with high consumption of vegetables and fruits that contain carotene, such as carrots can present with carotenoderma which classically spares the sclerae.[5]

Quinacrine leads to yellowish discoloration of the skin in up to one-third of patients treated with it.[29]

Complications

Indirect (insoluble) bilirubin is harmful to cells and cellular structures. Due to the physiologic mechanisms that protect against elevated bilirubin, the toxic effects are limited to neonates due to the poorly developed blood-brain barrier. High levels of bilirubin are neurotoxic and can lead to permanent neurologic injury (kernicterus) (Bilirubin-induced neurologic dysfunction).[21]

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