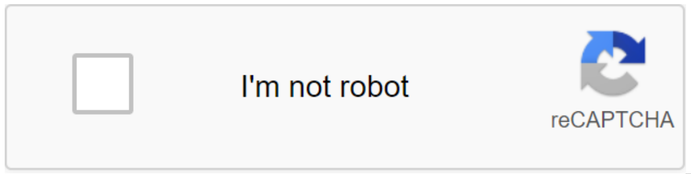

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Bilirubin metabolism and jaundice pdf

li-11-1 BILIRUBIN METABOLISM Dr. E. Orfei Physiology and Pathology 1-Bilirubin production. 2-Transport in the blood. 3-Hepatocellular absorption. 4-Intracellular transport in hepatocytes. 5-Conjugation with glucuronic acid. 6-Secretation in bile ducts. 7- Intestinal metabolism. 8- Renal release of bilirubin 9- Kidney selection of urobilinogen 1-BILIRUBIN PRODUCTION Bilirubin is an incurable product of heme metabolism. Heme is present in hemoglobin and in other oxidative compounds such as pe michotical and microsomal cytochromes (P-450). Thus, plasma bilirubin is part of the erythropoietic and partially non-erytropoetic. Approximately 85% erythropoietics and 15% non-erythropoetics. Erythropoetic fraction comes from two sources: circulating normal aging red cells and immature defective red bone marrow cells. The daily production of bilirubin is between 250 and 350 mg. and non-hemoglobin heme compounds, especially from hepatic cytochromes and from myoglobin. These two fractions were detected by labeling hemoglobin with radioactive glycine, and observing that one fraction (78%) of the Bilirubin is excreted in feces for 120 days, and the other fraction is released within 10 days or less. The first was called a late marked bilirubin, the second was called an early marked bilirubin or bypass bilirubin. The bypass bilirubin can be markedly elevated in some pathological conditions: sideroblastic anemia, megaloblastic anemia, eritroleukemia, lead poisoning and a congenital disorder called idiopathic dysteritropoetic jaundice. Patients affected by this condition do not have hemolysis. They have hyperbilirubinemia and jaundice. Giprbilirubinemia due to bypass bilirubin. Bilirubin from erythropoieic heme is produced by monocytic macrophagues, reticulo-endothelial, in every organ, but especially in the spleen, liver and bone marrow in order of importance. Bilirubin from non-erythropoiegic hepatic hemesis is produced in hepatocytes. The tetrapirrolic heme ring is broken by oxygenase on the alpha bridge, the link between the two carbons opposite the gamma bridge, which is between two carbons carrying two propionic acids. The tetrapirrool molecule from the ring turns into a tetrapylic chain without iron. HEME and Heme oxygenase - OXY- HEME (closed tetrapylic ring with iron) OXY- HEME - heme reductase - BILIVERDIN (open tetrapyrol ring without iron) BILIVERDIN - biliverdin reductase - BILIRUBIN (unconjugated) Pathology produced by bilirubin Meets at 1) thalassaemia, spherocytosis), 2) hemolysis (erytroblastosis fetalis, 3) has acquired diseases of red cells (dyserythropoiesis) etc. In an adult, even noticeable hemolysis does not produce a significant increase in serum bilirubin if the clearance of hepatic bilirubin is normal. In a newborn, however, noticeable hemolysis will be catastrophic. At levels 20 mg/d bilirubin serum the baby will be deeply jaundiced and will develop kernicterus (Nuclear jaundice: a serious form of yellow staining and degeneration of the intracranial gray matter, especially the lenticular nucleus, ammonium, horn and subthaladine area). Phototherapy is used to treat hierbilirubinemia in newborns. Bilirubin is a photoreceptor. Blue light turns bilirubin into colorless oxidation products that stand out in the urine. Synthetic porphyrins, containing tin or zinc instead of iron, cause a decrease in the formation of bilirubin, competing for the activity of heme oxygenase macrophages. These compounds have been used in the treatment of hyperbilirubinemia in animals and humans (e.g. Gilberts syndrome) with limited success. 2-BILIRUBIN TRANSPORT In BLOOD Bilirubin is toxic to tissues, so it is transported in blood associated with albumin. Only a minute's amount of free form is present in the blood. Pathology of transporting bilirubin in the blood. If the free faction increases, bilirubin invades and damages the tissue. It will cross the hem-brain barrier and cause kernicterus in newborns. Free plasma bilirubin can increase in the fallow of pathological conditions: -1- overproduction. -2- defective conjugation in hepatocyte. -3 - the presence of substances that interfere with the binding of bilirubin-albubin: sulfonamides, long-legged fatty acids from breast milk, saicilates, contrast agents, etc. These agents compete for sites binding albumin. 3-HEPATOCELLULAR ABSORPTION OF BILIRUBIN. Bilirubin is taken by hepatocytes on their sinusoidal surface. The album is broken. Albumin remains in plasma. The free molecule bilirubin gets into hepatocyte. This takeover is very fast. Pathology of the absorption of bilirubin hepatocytes. Disruption of absorption will result in unconjugated hyperbilirubinemia. Appearance: 1) Male fern jaundice oil. This oil was used to treat tapeworms. (Aspidium). 3) Jegzichte Sheep. 4-INTRACELLULAR TRANSPORT OF BILIRUBIN IN HEPATOCYTES. In hepatocy, bilirubin is associated with cytoplasmic proteins: ligandyns and protein. Ligandins are a group of enzymes that make up 2% of cytosol proteins. Proteins bind fatty acids. The main function of these proteins is to avoid reflux-free bilirubin in the bloodstream. Apparently, the time between bilirubin absorption and cojugation is relatively long. Pathology of intracellular transport. No lsterbilirubinemia and jaundice known for deficiency 5-CONJUGATION With GLUCURONIC ACID One way for cell cells Unwanted compounds are conjuging them with modified sugar, glycozil. The sugars used for this reaction are xylosis, glucose or glucuronic acid. Glucose is usually present in cell juice, xylocosis and glucuronic acid are formed from glucose dehydrogenase UDP-glucose. Xyloside is prevalent in plants, glucosidization in bacteria and glucuronides in mammals. Unconjugated bilirubinin is lipophilic. Its conjugation with glucuronic acid makes it hydrophilic so it can be eliminated in bile. Many other agents are eliminated by conjugating glucuronic acid: steroids, thyroid hormone, catecholamines, estradiol, testosterone, bile acids, phenols, morphine, which can be conjugated by cells other than hepatocytes. Glucuronidization of bile occurs in two stages: the first glucuron aid (GA) is synthesized from cytosolized glucose, which is complex with uridininedhosphata (UDP) inferno forms udpsulcuronic acid (UDPGA). From this compound, glucuronic acid is transferred to blirubine. The first reaction is catalyzed by UP-glucose dehydrogenate, the second reaction is catalyzed bilirubin-DUGAN-carriers, which are synthesized by microsomes. Any deficiency of these two enzymes will result in defective conjugation and elimination of bilirubin. On the other hand, the administration of microsomal enzyme inductors such as phenobarbital, glutethimide and antipyretic benefits of bilirubin conjugation and elimination by increasing the activity of blarubin transferase. Conjugation occurs in the endoplasmic cytoulum and consists of the formation of ester between glucuronic acid and one or both propionic side circuits of bilirubin. The result will be the formation of bilirubin mono and di-glucuronids. In general, about 80% of di and less than 20% of mono are formed. Human bile cotains are also a small amount of unconjugated bilirubin. Thus: GLUCOS - UDP-Glucoza-dehydrogenase - UDP-GLUCURONIC ACID (UDPGA) UDPGA - BILIRUBIN - glucurnil-transferase - BILIRUBIN MONO - DI-GLUCURONIDES. The pathology of the BILIBUBIN BILirubine GILBERT'SYNDROME condition is due to very mild insufficiency of glucuronyl-transvaza. It's a very common disorder. It affects between 5 and 7% of the population as a whole. It is more common in men. It consists of mild oscillating jaundice due to non-concoticaled hyperbilirubinemia in the range of 5 to 7 mg/dL or rarely higher. The liver is morphologically normal. Health and life expectancy are normal. Hemolysis, low-calorie diet, nicotinic acid will increase jaundice. The lipid diet will reduce jaundice. Phenobarbital and other enzyme-producing agents are useful. Some people with this syndrome near the bilirubin defect CRYGLER-NAJJAR SYNDROME, TYPE I due to severe deficiency of glucuronyl tranferase. Deep Jaundice Develops Tattoo Birth, High Grey hypbilirubinemia, 20 mg/d., not reacting to phenobarbital. Missing digluculonides. Death is usually in the first year or two with kernicterus. Phototherapy, plasmapheresis and albumin metabolism are beneficial. A liver transplant can save a life. Histole's liver is logically normal. A similar condition exists in Gunn rats. Fortunately, this syndrome is rare. Only 100 or more cases have been described. This seems to be a hereditary autosomal recessive trait. CRYGLER- NAJJAR SYNDROME TYPE II due to moderate insufficiency of glucuronyl transferase. Soft non-conjugated hyperbilirubinemia that responds to enzynent agents: phenobarbital, gltetimide, phenazone, chlorpromazine. Mono- and digluculonides are formed. Patients develop normally, but some may suffer from bilirubin encephalopathy, kernicterus. They will have relentless jaundice for life. It's a family breakdown. The method of genetic transmission is not clear. The conjugation defect may have a related defect in the absorption of bilirubin by hepatocytes. THE BABY'S PYSYLOLOGICAL JAUNDICE. This is due to a very transient insufficiency of glucuronyl transferase. During the first few days of life there is an overproduction of bilirubin and an underdeveloped liver mechanism to remove bilirubin. In addition to insufficient conjugation, bilirubin production, blood transport, absorption and secretion are insufficient. Sometimes to exacerbate the situation there are extrahepathic factors: infections, drugs competing for mandatory areas of bilirubin and, above all, breastfeeding. Long chains of breast milk fatty acids interfere with bilirubin-albumin-binding areas. 6- BILE SECRETION from HEPATOCYTES The liver is an endocrine and exocrine gland. It secretes synthesized foods inside the bloodstream through the sine-soid surface, such as blood proteins, clotting factors, etc., and secretes the outer in the bile tract and bile of the intestine and many other substances terminally products of detoxification function. The mechanism of this external secretion is the least clear in the physiology of the liver. It seems that many cellular organelles are involved in this process: bubbles, Golgi complexes, lysosomes, plasma membranes, mitochondria, cytoskkelet, plasma membranes, canal celli. However, the consequences of a malfunction of this device are clear, especially in the secretion of bile, which will lead to conjugated hyperbilirubinemia. DubIN-JOHNSON SYNDROME Bile Secretion Pathology. The syndrome consists of chronic benign jaundice due to conjugated hyperbilirubinemia without itching or the height of alkaline serum phosphate, nor histological evidence of cholestasis. Hepatocytes contain an abundance of coarse dark brown pigment similar to melanin. The liver is black, but normal. Serum bilirubin ranges from 2 to 20 mg/dL, 60% conjugated. jaundice appears in the first 3 decades of life and intermittent. onset acute, mimicking hepatitis. The forecast is excellent. The disease is inherited as an autosomal recessive trait. The diagnosis is made with a biopsy of the needle. Corridale sheep have similar black liver disease. Click on the photos to increase Fig.11-1-1 Dubin-Johnson Syndrome. The liver is brown-black due to the large number of brownish coarse pigments stored in hepatocytes. Normally, there is no intraheptic cholestasis in this state. The pigment predominates in the centrolobular area. Figure 11-1-2 Dubin-Johnson Syndrome. Older patients may have moderate portal fibrosis. The pigment is stored in lysosomes such as lipofusin. Bile canals do not contain bile. According to studies conducted in Corridale sheep, the pigment contains a melanin-like component and its formation is associated with a defect in the secretion of epinephrine metabolites. ROTOR SYNDROME. This condition is similar to Dubin-Johnson. There is intermittent jaundice with conjugated hyperbilirubinemia, similar to the clinical course, an excellent prognosis, but without pigment in the liver tissues. BENIGN RECURRENT INTRAHEPATHIC CHOLESTASE. Syndrome, characterized by periodic attacks of quite severe jaundice. Attacks usually begin before puberty, but they can begin later. They are preceded by 2-4 weeks of itchy malaise, anorexia followed by an increase in jaundice without pain or fever and an average duration of 2-3 months during each attack. This can last from towing for weeks to two years. Nausea, vomiting, abdominal pain and skin rash occur in some cases. An injured person can have up to 30 attacks during his lifetime. Biochemically, these patients have elevated serum bilirubin, 10 to 20 mg/dL, mostly conjugated, elevated alkaline phosphatases and bile acids. The Alpa-glutamic transferase (GGT) has been upgraded. Whey bile acids are increased by 2-30 times. Transaminease is sometimes noticeably elevated. These anomalies and clinical symptoms completely disappear at disease-free intervals. In the cholestatic phase there is an acinar zone 3 cholestasis with bile corks and mononuclear penetration of cells in the cholestatic area. In some cases, there may be mild hepatocytic damage and a portal of mono-nuclear penetration. These changes do not produce any fibrosis or cirrhosis of the liver. The liver biopsy, taken within clear intervals, was normal. The disorder is quite rare and appears to be family-friendly with an autosomal recessive nature. FAMILY RECURRENT INTRAHEPETIC CHOLESTASIS PREGNANCY. This disorder is clinically and biochemically similar to benign intragepathic cholestasis. This occurs in the third trimester of pregnancy, when estrogen levels are highest and disappear after childbirth. The affected subjects appear to belong to families with a benign intragepetic trait The Gonad steroid appears to be plying a defining role in the cause of this syndrome. Liver histology shows cholestasis is similar to benign intragepical cholestasis. Most commonly found in Scandinavia (1/100), Bolivia and Chile (1/10). The disorder is safe for the mother, but not for the fetus, which will suffer premature birth and stillbirth due to a placental heart attack. Mothers have a higher incidence of gallstones. Sometimes the disorder occurs only in the presence of itching without jaundice. (Prurit gravidarum). Patients are not very sick, as in the fatty liver of pregnancy, hepatitis, obstructive jaundice. DRUG-INDUCED INTRAHEPETIC CHOLESTASE. Many drugs produce cholestasis. The first cases have been reported due to chloromasin and synthetic steroids currently out of the market (Nilavara). Synthetic oral contraceptives are at a high level on the list. They appear to be sensitive and affect only sensitive people. Many seem to impair the secretory function of hepatocytes. And the list is growing with the advent of new drugs. The liver in these cases can show noticeable and deadly necrosis. POST-OPERATIVE INTRAHEPATIC CHOLESTASIS This is due to the combined effect of bilirubin overload, flowing from blood transfusions and defects in hepatocytic secretory function. Usually jaundice appears in 1-2 postoperative days and disappears in one or two weeks, Hyperbilirubinemia is predominantly conjugated with a rate of normal alkaline phosphatase and transaminase. BACTERIAL INFECTIONS is a form of intraheptic cholestasis. Hyperbilirubinemia is conjugated in all cases. Increased whey alkaline phosphate in some cases. Hepatocellul hepatocellal histology without special hepatocellular damage. Three types of morphological changes have been described: 1-canalicular cholestasis, the most common, mostly pericentral without hepatocellul damage. 2-protocicular cholestasis, characterized by the presence of a large bile clot in the bile protocules and channels of Goering on the periphery of portal fields. There are no bile ducts in the interclothary bile ducts. 3-Toxic shock syndrome due to staphylococcus aureus infection, producing toxic shock syndrome toxin-1 (TSST-1). This toxin was produced by this organism growing in polyacrylate tampons in menstruating women. The liver suffers from inflammation of the intracetic bile ducts and canaliculi. with rupture of bile ducts and micro-century steatose. There is an inflammatory reaction in the portal area with neutrophils, eosinophils lymphocytes and monocytes. In 50% of cases there is centrolobular cholestasis. 7- INTESTINAL METABOLISM OF BILIRUBIN Bilirubin in the gut is reduced to urobilins according to the following cascade: BILIRUBIN GLUCURONID - bacterial or intestinal beta-glucuronidase - FREE BILIRUBIN - bacterial dehydrogenase - UROBILINOGENEN (colorless) UROBILINOGEN urobilinogen and urobilin is excreted in feces. A small amount of bilirubin and reabsorbed by the intestines and returned to the liver. Bilirubin recunjugated in the liver and re-excreted in the feces. Reabsorbed urobilinogen is excreted in urine, about 4 mg/day and 0.1 to 1 mg in a random urine sample. Pathology of bile secretions in the intestines COMPLETE BILIARY OBSTRUCTION. bile does not reach the intestines, so feces aholika. There is conjugated hyperbilirubinemia and bilirubinuria. Urobilinogen is not formed in the intestines and there is no urobilinogen in the urine. because bile does not reach the intestines, urolyogen is not formed. PARTIAL OBSTRUCTION OF THE BILIARY. Less bile reaches the intestines. Urobilinogen is formed, but in smaller quantities. Less conjuged hyperbilirubinemia, no bilirubinuria and a small amount of urobilinogen in the urine. Hemolysis. Hemolysis causes unconjugated hyperbilirubinemia. There is no bilirubinuria because unconjugated bilirubin is not hydrophilic and cannot be isolated in urine. There is an increase in urobilinogen in the urine because more bilrubine reaches the intestines and more urobilinogen is formed by reabsorbion. 8- RENAL EXCRETION OF BILIRUBIN Only conjuged bilirubin (straight fraction) is excreted in the urine when its plasma level increases above normal. It is not present in the urine of normal subjects and is not eliminated in urine in cases of unconjugated (indirect fraction) of hyperbilirubinemia, for example, in hemolysis. Only a small part of the non-white bilirubin in plasma passes in the urine. Some drugs and bile salts that compete for binding proteins (salicylates, sofosoxazole) increase the degree of release of protein, which varies, and its amount in the urine is not clinical. Conjugated bilirubin can be demonstrated in proximal renal tubes. 9-RENAL EXCRECEY UROBILINOGEN Urobilinogen Urobilinogen is formed by bacteria in the small intestine and colon. It is then absorbed by the small intestine and colon and re-xcreted across the liver in the intestines almost completely. Therefore, a very small amount is released into the urine: 0-4 mg/day. This amount will increase when more urobilinogen is formed or when the liver is sick and unable to re-secrete it. This amount will decrease when its formation in the intestine decreases, for example, in the case of complete obstruction of the bile ducts, when bile cannot flow into the intestines, where urobilinogen is formed by specific bacteria. The urobilinogen, formed by bacteria in the small intestine, is absorbed better than the one that is formed in the colon. CONTENT/ IN THE GALL SYSTEM bilirubin metabolism and jaundice ppt. bilirubin metabolism and jaundice pdf. hereditary jaundice and disorders of bilirubin metabolism