PATHOPHYSIOLOGY OF LIVER DISEASES

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https://doi.org/10.5281/zenodo.10667202

Abstract. *Liver diseases remain one of the most difficult areas of internal medicine, despite the achievements of modern science and practice. Their high prevalence, often nonspecific clinical manifestations, and the lack of possibility of etiological verification create difficulties in diagnosis and treatment. Nevertheless, modern hepatology obliges the doctor to know and select the best methods known in the world for examining and treating hepatological patients.*
Keywords: *Dubin-Johnson syndrome, Crigler-Nayar syndrome.*

According to WHO, approximately 30% of the world's adults currently suffer from liver disease. Among liver diseases, viral hepatitis takes first place, both in our country and abroad, causing significant socio-economic damage to society. Currently, at least 9 varieties of viruses are known that have tropism for human liver cells. Some of them have been studied quite fully (A, E), others (F, G, TTV and SEN), relatively recently discovered, require further study. Among viral hepatitis, parenteral hepatitis (HBV, HCV, HDV), which is characterized by severe and chronic forms, leading to liver cirrhosis and hepatocellular carcinoma, deserves special attention. The number of people infected with parenteral hepatitis viruses in the world, according to WHO experts, is about 325 million people. Liver disease will become the leading cause of premature death worldwide by 2020, driven by rising obesity and alcohol abuse. The creation of this textbook was dictated not only by the desire to reflect the diagnostic and therapeutic issues of liver diseases, but also by the rapid development of modern gastroenterology. The format of the textbook made it possible, to a certain extent, to cover almost all sections of modern hepatology from the standpoint of rational pharmacotherapy. The chapters are written within the framework of evidence-based medicine. Compared to the first edition of the manual in 2010, this edition has made changes to all sections due to the active development of clinical hepatology in the current decade.

MORPHOFUNCTIONAL CHARACTERISTICS OF THE LIVER.

The liver is a multifunctional organ, performing various functions in the body. In the prenatal period, the liver serves as a hematopoietic organ; in the postnatal period, it is a depot of blood and an antianemia factor. It is the most important heat-producing organ in the body. The liver produces bile, which plays an important role in the processes of digestion, iron metabolism, and excretion of various substances. Toxins and poisons, as well as a number of medicinal substances, are inactivated in the liver (by oxidation, the addition of other molecules or molecular groups to them - sulfates, glucuronic acid or amino acids, or by deposition or excretion in the bile). In the liver, a number of hormones are destroyed and, therefore, their effect on organs and tissues ceases. The liver is actively involved in the metabolism of proteins, fats, carbohydrates, as well as water and vitamins, being their depot and ensuring their metabolism. The liver is a depot of microelements: iron, copper, etc. Substances involved in blood clotting and the activity of the anticoagulation system are formed in it. The liver is an important organ of the reticuloendothelial (lymphoreticulohistiocytic) system. Thus, the liver is a complex organ with metabolic, excretory and protective functions in the body. From a clinical point of view, such structural elements of the

hepatobiliary system as hepatocytes are of interest; bile ducts; cells lining the sinusoids (endothelial cells, spindle-shaped Kupffer cells, perisinusoidal fat-containing cells, rare pit cells); extracellular matrix. For normal liver function, its blood supply is also extremely important. The listed structural components of the liver in liver diseases are usually involved in the pathological process in a certain way, often with characteristic clinical and biochemical manifestations.

CLINICAL EQUIVALENTS OF FUNCTIONAL LIVER DISORDERS.

Clinical manifestations of liver dysfunction are very diverse. Some pathological symptoms are characteristic of chronic diseases, others are detected in both acute and chronic processes in the liver. Jaundice is a yellow discoloration of the mucous membranes, sclera and skin associated with the accumulation of bilirubin in them. It is a symptom of various diseases. Yellowness of the sclera and skin becomes obvious when the concentration of bilirubin in the blood is more than 30 μmol/l. Metabolism of bilirubin. Bilirubin is a breakdown product of hemoglobin in the cells of the reticuloendothelial system (80%) and, to a lesser extent, of other heme-containing proteins (20%) in the liver. The heme formed during the destruction of hemoglobin in the endoplasmic reticulum of macrophage cells is metabolized under the action of enzymes to indirect (unconjugated) bilirubin. Indirect bilirubin is released into the blood and binds to albumin. This form of bilirubin is toxic in high concentrations, dissolves only in fats, does not pass through the kidney filter and, therefore, does not appear in the urine. Molecules of unconjugated bilirubin are captured by carriers of transport systems localized in the membranes of hepatocytes and transferred to intracellular ligand proteins. In the hepatocyte, the process of conjugation of bilirubin with glucuronic acids occurs using the enzyme uridine diphosphate glucuronyltransferase (UDPGT) with the formation of direct (bound, conjugated) bilirubin to monoglucoronides and, to a greater extent, to diglucoronides. Conjugation converts bilirubin into a non-toxic water-soluble compound, which, when circulating in the blood in high concentrations, can appear in the urine. In some cases, conjugated (direct, bound) bilirubin is not detected in the urine. This phenomenon is due to the partial binding of bilirubin glucuronides to plasma albumin and explains the delayed resolution of jaundice during the recovery period in patients with acute liver diseases. Conjugated bilirubin molecules are actively transported through the canalicular membrane into the bile and then enter the small intestine. In the distal ileum and colon, bilirubin is hydrolyzed by beta-glucuronidases to an unconjugated form, which is converted by intestinal microflora into colorless urobilinogen. A small amount of urobilinogen is reabsorbed and enters the enterohepatic (enterohepatic) circulation, i.e., it is recaptured by hepatocytes and excreted into bile. If the liver is damaged, urobilinogen may appear in the urine. Urobilinogens or their pigmented derivatives urobilin's are excreted in the feces. In healthy individuals, total serum bilirubin is represented mainly by indirect bilirubin (no more than 20 μmol/l), direct bilirubin makes up no more than 25% of the total, stool is colored, and traces of urobilin may be present in the urine.

The appearance of bilirubinuria indicates an increase in the content of conjugated (direct) bilirubin in the blood. The detection of urobilinogen in the urine is evidence of diffuse liver damage or gastrointestinal bleeding (impaired uptake of urobilinogen from the blood) or hemolysis (increased formation of bilirubin). The absence of urobilinogen in the urine in patients with jaundice is a consequence of blockade of the enterohepatic circulation of bile pigments and occurs with complete obstruction of the common bile duct.

The main factors for the development of jaundice are:

• violation of the uptake of bilirubin and its transport in the hepatocyte;

• defect in bilirubin binding;

• excessive accumulation of bilirubin in the hepatocyte;

• defect in canalicular excretion of bilirubin into bile or obstruction of the main bile ducts, preventing its entry into the small intestine.

There are 3 types of jaundice:

• suprahepatic;

• hepatic (cytolytic, cholestatic and enzymatic);

• subhepatic.

Prehepatic jaundice. Possible causes: increased hemolysis of red blood cells as a result of transfusions of incompatible blood, the development of autoimmune hemolytic anemia, the presence of hereditary hemolytic anemia, the formation of large hematomas, poisoning with certain substances that cause hemolysis, and other causes.

Signs: jaundice has a lemon tint, an increase in bilirubin levels occurs due to the unconjugated (indirect) fraction; The values of serum transaminases and alkaline phosphatase (ALP) are normal, bilirubin is not detected in the urine.

Hepatic jaundice. It usually develops when hepatocytes are damaged by various infectious and toxic agents, with cirrhosis of the liver, as well as with a number of hereditary liver diseases: Dubin-Johnson syndrome, Crigler-Nayar syndrome types 1 and 2, Gilbert. Signs: icteric coloration of the skin, sclera, mucous membranes have varying intensity, which depends on the etiology, stage, and clinical variant of the disease. Hepatic jaundice is often accompanied by intoxication and dyspepsia syndromes, signs of liver failure of varying degrees. In most cases (but not always), the level of serum transaminases in the blood is increased, the content of albumin and some blood coagulation factors is reduced.

Subhepatic jaundice is caused by an obstruction of the flow of bile into the duodenum: cancer of the hepatobiliary system and pancreaticoduodenal zone, cholelithiasis (GSD), some helminthiases, biliary atresia. The main symptoms are progressive jaundice accompanied by skin itching with long-term satisfactory health of the patient.

Clinical and laboratory variants of hyperbilirubinemia.

1. Unconjugated hyperbilirubinemia (bilirubin level, usually less than 5 mg/dL) is associated with excess production and delivery to the liver of such quantities of bilirubin that exceed its ability to accept and conjugate it, for example, with hemolysis, ineffective erythropoiesis, resorption of hematomas. Idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome) is known, associated with a defect in the uptake and conjugation of bilirubin in the liver.

2. Conjugated hyperbilirubinemia has the following options: - Congenital: Dubin-Johnson and Rotor syndromes. — Cholestatic: a) intrahepatic cholestasis (liver cirrhosis, hepatitis, primary biliary cholangitis, drug-induced hepatitis); b) extrahepatic cholestasis (obstruction of the biliary tract as a result of choledocholithiasis, benign strictures of large bile ducts, bile duct atresia, neoplasms of the hepatobiliary system, sclerosing cholangitis).

3. Hyperbilirubinemia with very high bilirubin levels. A bilirubin concentration of more than 30 mg/dL usually indicates a combination of hemolysis with diffuse liver damage or biliary obstruction. In such patients, urinary excretion of conjugated bilirubin prevents even greater accumulation of bilirubin in the blood.

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