MEIN CLINICAL AND LABORATORY MANIFESTATIONS OF CHRONIC HEPATITIS AND LIVER CIRRHOSIS

Independent study manual for medical students

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

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ОСНОВНІ КЛІНІЧНІ І ЛАБОРАТОРНІ ПРОЯВИ ХРОНІЧНИХ ГЕПАТИТІВ ТА ЦИРОЗІВ ПЕЧІНКИ

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BASIC CLINICAL AND LABORATORY MANIFESTATIONS OF CHRONIC HEPATITIS AND LIVER CIRRHOSIS

The liver is the central organ of chemical homeostasis, which provides metabolism of proteins, fats, carbohydrates, enzymes, vitamins, minerals, pigments, as well as the secretion of bile and detoxification of the body. Chronic liver damage leads to scarring (cirrhosis), as well as the development of liver failure. Therefore, liver disease is one of the most important medical problems worldwide.

CHRONIC HEPATITIS

Chronic hepatitis is a diffuse polyetiological inflammatory liver disease caused by a primary lesion of hepatocytes of varying severity, lasting for at least 6 months, which is able to transform into cirrhosis of the liver.

Etiological factors:

– acute hepatitis B, C, D, G, F;

– toxic factors:

a) endogenous – toxins resulting from burns, infections (malaria, brucellosis, leishmaniasis, tuberculosis, syphilis);

b) exogenous: alcohol, pesticides, drugs (anti-tuberculosis drugs, tetracycline, aminazine, elenium, sulfonamides, peopirin, synestrol, nerobol, narcotic substances, fluorotane, hexenal, phenobarbital, allopurinol, 6-mercaptopurine, methotrexate, xenobiotics, alcohol;

– ionizing radiation;

– hereditary factors and metabolic disorders (Konovalov-Wilson's disease, hemochromatosis, a1-antitrypsin deficiency);

– severe damage of the digestive system;

– Collagenoses: “disseminated lupus erythematosus”, periarteritis nodosa, systemic scleroderma.

Pathogenesis. The leading role in the development of chronic inflammatory liver disease belongs not to an etiological factor, but to a condition of an organism as a whole, its adequate immune response to the action of the virus, toxin or alcohol. The pathogenesis of chronic hepatitis is based on autoimmune processes, which result in the formation of immune complexes of autoantigen-autoantibody, which settle on cell membranes, cause their damage, the migration of granulocytes and monocytes, and then cell death.

Classification of chronic hepatitis

(A. Loginov, Y. Blok, 1987)

1. Etiology
   1.1. Viral.
   1.2. Autoimmune.
   1.3. Alcoholic.
   1.4. Cholestatic (precedes primary biliary cirrhosis).
   1.5. Drug-induced
   1.6. Hepatitis with Wilson disease.
   1.7. Hepatitis with alpha-1-antitrypsin deficiency.
   1.8. Reactive.

2. Morphology:
2.1. Active (aggressive).
2.1.1. With moderate activity.
2.1.2. With pronounced activity.
2.1.3. Necrotizing form.
2.1.4. With intrahepatic cholestasis.
2.2. Persistent
3. Phases:
3.1. Exacerbation
3.1.2. Remission

Classification of chronic hepatitis

(International Congress of Gastroenterology, Los Angeles, 1994)

By etiology and pathogenesis:

1. Chronic viral hepatitis B (CVHB)
2. Chronic viral hepatitis D (XVHD)
3. Chronic viral hepatitis C (CVH)
4. Uncertain chronic viral hepatitis (F, G, TiTi)
5. Autoimmune hepatitis (type 1, type 2, type 3)
6. Drug-induced chronic hepatitis
7. Toxic hepatitis
8. Alcoholic hepatitis
9. Cryptogenic hepatitis

According to clinical, biochemical and histological criteria:

1. The degree of activity, determined by the severity of the non-inflammatory process:

a) minimal;
b) moderate;
c) severe

2. Stage, determined by the prevalence of fibrosis and the development of liver cirrhosis: 0,1,2,3,4.

Features of chronic hepatitis can have a number of other diseases:

– primary biliary cirrhosis;
– Wilson's disease;
– primary sclerosing cholangitis;
– α-1-antitrypsin liver failure.

Clinical features

Clinical manifestations of chronic hepatitis depends on the stage of the disease and the activity of the process. In evaluating complaints, the following clinical syndromes are distinguished.

Pain syndrome: persistent or intermittent pain (sometimes feeling of heaviness) in the right hypochondrium or epigastric region, of a different nature and intensity, aggravated after a slight physical exertion, errors in diet

Astheno-vegetative syndrome: weakness, fast fatigability, decreased performance, depressed mood, irritability, headaches, cardialgia, weight loss.

Dyspeptic syndrome includes:

1) gastric dyspepsia: loss of appetite, bitter and dry mouth, heaviness in epigastria, belching, poor tolerance to fatty foods, nausea, and sometimes vomiting;

2) intestinal dyspepsia: stubborn bloating, diarrhea, constipation, often combined with weight loss, up to cachexia.

Hemorrhagic syndrome: fragility of blood vessels, hemorrhages on the body, slight vulnerability of the gums, bleeding (uterine, nasal, etc.).

Ascitic-Edematous Syndrome: abdominal enlargement (ascites), lower extremity edema

Disandocrine syndrome: decreased libido, gynecomastia in men, amenorrhea in women.

Articular syndrome: pain in the joints, their deformity, the formation of ankylosis, muscle pain.

Cholestasis syndrome (insufficient secretion of all or the main components of bile, primarily bile acids): persistent or intermittent jaundice, pruritus, especially at night, darkening of urine, discolored feces.

Fever: An increase in body temperature can be remitting or even hectic, with chills and sweating.

Hepatic encephalopathy syndrome: memory loss, impaired thinking, drowsiness, inadequate behavior, disorientation in time and space, hepatic coma (the most severe stage of hepatic encephalopathy).

Physical data

The general condition is from relatively satisfactory to severe (depending on the stage and activity of the process).

Consciousness: not disturbed, disturbed (euphoria, delirium, hepatic coma during intoxication of the central nervous system).

Position: active, passive (with coma), forced.

Appearance (habitus) - the patient looks older than the passport age, especially in case of alcoholic hepatitis.

Pallor of the skin with a grayish tinge, local or diffuse hyperpigmentation is observed in chronic liver diseases, severe pallor due to hemolytic or posthemorrhagic anemia – in liver cirrhosis.

Jaundice is first detected on the sclera and mucous membrane of the soft palate, sometimes in the area of the nasolabial triangle, the forehead, and the palms. With intense jaundice, the skin color may become greenish-yellow due to the oxidation of bilirubin to biliverdin. Sometimes it may be missing.

Scratches and abrasions on the skin, which are the result of pruritus caused by irritation of the nerve endings of the skin with bile acids, impaired biliary excretion during the development of cholestasis. Itching may occur in the absence of jaundice.

"Hepatic palms" (tenar and hypotenar hyperemia), ***"liver tongue"*** (raspberry), ***"spider naevi"*** (telangiectasia or stellate angiomas, which are raised above the skin formations from 1 mm to 1–2 cm, resembling asterisks, often located on the neck, face, shoulders, back, hands, when pressed with a glass slide you can see their pulsation) - skin symptoms due to the expansion of the subcutaneous vessels under the influence of an excess amount of estrogen in the blood and changes in receptor sensitivity.

Hemorrhagic syndrome in the form of petechiae, bruises, hemorrhages - manifestations of hemorrhagic diathesis, observed in severe lesions of the hepatic parenchyma.

Xanthomas are intradermal plaques, most often located on the eyelids (xanthelasma), hands, elbows, knees, feet, buttocks, in the axillary areas, the origin of which is associated with an increased content of lipids in the blood.

"Raspberry tongue", hair loss in the armpits and pubic are characteristic of chronic liver diseases.

White nails in chronic liver disease are caused by metabolic disorders and the accumulation of estrogen and serotonin.

Atrophy of the muscles of the shoulder girdle, caused by a impaired protein metabolism and hormonal imbalance.

"Clubbing fingers"– a thickening of the distal phalanges of the fingers, due to severe dysproteinemia.

Swelling of the joints ("biliary rheumatism") is observed mainly in biliary cirrhosis.

Endocrine disorders:

– *gynecomastia and female type of hair* condition of the integuments, atrophy of the testicles of men associated with hyperestrogenemia, are observed with severe liver damage;

– *Loss of pubic and axillary hair*, hypertrophy of the parotid salivary glands – with alcoholic hepatopathy;

– *infantilism* (underdevelopment of secondary sexual characteristics) is observed in chronic liver diseases developing in childhood or adolescence due to impaired steroid hormone synthesis.

Swollen lower limbs, lymphadenopathy, as a result of impaired protein metabolism. Ascites (accumulation of fluid in the abdominal cavity) may appear, as a result of both severe hypoalbunemia and the development of portal hypertension with damage to the liver parenchyma.

Hepatomegaly is an increase in the size of the liver caused by infiltration of the parenchyma by immunocompetent cells, cholestasis, impaired blood circulation in the portal vein system.

On examination of the abdomen, asymmetry in the epigastric region is sometimes noted, due to the elevation of the right costal arch, extensive tumor-like bulging in the right hypochondrium, displaced during breathing.

By percussion of the liver, there is a shift of the lower border of the liver by 1–6 cm below the edge of the costal arch along all lines. There is a displacement of the left border by 1–3 cm outwards from the left parasternal line with an enlargement of the left liver lobe.

On palpation of the liver, the lower edge is firm, blunt, tender due to stretching of the fibrous capsule, the surface of the liver is smooth.

Progressive liver size reduction is an unfavorable prognostic sign.

Splenomegaly is observed in 10–25 % of patients with hepatitis. The increase is insignificant – 1–2 cm.

Laboratory diagnosis

A general (clinical) blood test expresses signs of mesenchymal inflammation characterized by:

– leukocytosis;

– acceleration of ESR;

– eosinophilia;

– increase in blood platelet count;

– bilirubin and urobilinogenic bodies.

General (clinical) analysis of urine manifested "urinary syndrome", due to impaired renal hemodynamics:

– microhematuria;

– moderate proteinuria;

– leukocyturia;

– Cylindruria).

Biochemical blood test

• *Cytolysis syndrome* - an increase of serum levels of intracellular enzymes, reflecting the severity of the inflammatory process in the liver:

– transaminases (ALAT, ASAT)

– dehydrogenases (glutamate dehydrogenase (GDH), lactate dehydrogenase (LDH);

– urokinase;

– increased serum levels of iron and vitamin B_{12}

• *Cholestasis syndrome* – an impairment of the synthesis, secretion or outflow of bile, which is not an analogue of jaundice. It is observed in inflammatory and neoplastic diseases of the hepatobiliary system and is associated with the accumulation of substances in the blood serum which are usually extracted with bile:

– enzymatic indicators of cholestasis (alkaline phosphatase, gammaglutamine transpeptidase (γ-GTP), 5-nucleotidase, leucine aminopeptidase (LAP);

– total bilirubin due to its conjugated fraction (direct);

– bile acids;

Cholestasis may be accompanied by an increase in cholesterol in the blood. Serum transaminases may be normal, moderately, or significantly elevated.

• *Syndrome of an immune inflammation* is shown by increase of following markers in blood serum:

– total protein content due to increase of globulins, especially β- and γ-globulins;

– levels of immunoglobulin A, M, G;

– the appearance of positive sedimentary samples (thymol, formol, sublimate).

• *Hepatocellular insufficiency syndrome* (3 stages: initial, compensation stage, stage of severe decompensation):

– a decrease in the level of enzymes synthesized in the liver (transaminases, aldolases, oxidases);

– an increase in the level of unconjugated bilirubin;

– reduction of total serum protein, albumin (hypoalbuminemia), blood coagulation factors;

– relative hyperaldosteronemia;

– hypokalemia;

– change in acid-base balance.

• *Renal failure syndrome* due to reduced renal blood flow, cortical perfusion, glomerular filtration which is manifested in:

– decrease in concentration function;

– increase in blood concentration of urea, creatinine;

– electrolyte imbalance**.**

CIRRHOSIS OF THE LIVER

Liver cirrhosis is a progressive polyetiological diffuse chronic liver disease, characterized by a significant decrease in the mass of functioning hepatocytes, marked fibrosis with impaired structure of the hepatic lobe and the vascular system of the liver.

Mortality from cirrhosis in developed countries ranges from 13 to 80 per 100,000 population.

Etiological factors:

– viral hepatitis B, C, D (hepatitis C leads to the development of cirrhosis in 97 % of cases);

– chronic alcohol intoxication;

– long-term use of hepatotoxic drugs;

– various chemical intoxications;

– diseases of the biliary tract (intra - and extrahepatic);

– congestive heart failure;

– hereditary factors and metabolic disorders (hemochromatosis, alpha-1-antitrypsin deficiency, tyrosinosis, galactosemia, etc.);

– occlusive processes in the portal vein system (phleboportal cirrhosis;

– unclear etiology (primary biliary cirrhosis).

Classification of liver cirrhosis

According to etiology:

– viral (B, C, D);
– alcoholic;
– toxic, including drug-induced;
– non-alcoholic steatohepatitis;
– Wilson's disease;
– due to a deficiency of α-1-antitrypsin;
– primary biliary cirrhosis;
– secondary biliary cirrhosis.

By morphology:

– micronodular (diameter of nodes is from 1 to 3 mm);
– macronodular (diameter of nodes more than 3 mm);
– mixed;
– incomplete septal.

By the stage of the disease:

– compensation;
– subcompensation;
– decompensation;
– terminal stage.

The severity of the clinical course of cirrhosis is determined by clinical and laboratory data and is assessed according to the Child-Pugh Score (Table 1).

Table 1

Parameter	Points		
	1	2	3
Ascites	None	Mild to Moderate	Severe
Encephalopathy, stage	None (grade 0)	Mild to Moderate (Grade I–II)	Severe (Grade III–IV)
Bilirubin, mcmol/L	< 34	34–51	> 51
Albumin, g/L	> 35	28–35	< 28
Prothrombin index, %	> 70	70–40	< 40

Clinical picture

Clinically, liver cirrhosis manifests with the following syndromes:

– asteno-vegetative;
– dyspeptic;
– pain;
– cholestatic;
– hemorrhagic;
– dishormonal;
– articular;
– fever.

The severity of clinical manifestations depends on the stage of the disease, as well as the activity of the pathological process. Specific for liver cirrhosis are portal hypertension syndrome and hepatocellular insufficiency.

Portal hypertension syndrome is caused by an increase in pressure in the portal vein system and manifests itself as hepatosplenomegaly, ascites, and expansion of the saphenous veins. Four stages of portal hypertension are described.

Enlarged saphenous veins on the anterior abdominal wall of the abdomen are anastomoses between the portal vein system and the inferior and superior vena cava in portal hypertension syndrome. Anastomoses around the navel are called "caput medusa." The collateral abdominal wall located above the navel, blood from the portal vein enters the superior vena cava, the collateral below the navel – into the inferior vena cava. If blood flow is impeded, collaterals between the inferior and superior vena cava systems located in the lateral sections of the abdominal wall develop along the inferior vena cava.

Ascites (accumulation of fluid in the abdominal cavity) is a manifestation of portal hypertension and damage of the liver parenchyma in the form of a uniformly enlarged abdomen, with a smoothed or protruding navel, thinned skin, changeable in shape (with a change in the position of the patient's body) by relatively thin and not swollen lower limbs. In the case of compression of the inferior vena cava, edema of the lower limbs can occur along with ascites. Ascites is caused by hypoalbuminemia, a decrease in the osmotic pressure of plasma, portal hypertension, an increase in aldosterone levels with sodium and water retention in the body, and an increase in the permeability of vascular membranes.

Ascites of varying severity can be observed in all forms of cirrhosis. Ascites can have acute or gradual, within a few months, manifestation. In 25 % of patients with cirrhosis ascites can be a first sign of the disease.

Early signs of ascites are an increase in body weight, a negative balance of diuresis. Percussion reveals a dull percussion tone over the flanks and in the lower abdomen (depending on the position of the body). The abdominal wall is stretched and thinned, white streaks appear on it, the navel bulges outward. Increased intra-abdominal pressure contributes to the formation of hernias – umbilical and femoral. Large ascites raises the diaphragm, which leads to heart rotation and displacement of apical impulse to the left as well as to increased pressure in the pulmonary circulation with swelling of the cervical veins. Dispersion of ascitic fluid into the pleural cavity through the cracks in the tendon of the diaphragm can cause hydrothorax, usually right-sided.

Splenomegaly is an enlargement of the spleen, as a result of a compensatory immune response and congestive venous hypertrophy due to portal hypertension. Splenomegaly is a common sign of cirrhosis of the liver. The size of the liver and spleen can vary from small to significant increase.

Hypersplenism syndrome - increased and distorted function of enlarged spleen resulting in anemia, leukopenia with neutropenia, lymphocytopenia and thrombocytopenia, compensatory activation of the bone marrow with an increase in the number of cells, immature predecessors of erythrocytes and platelets.

Hepatocytic syndrome, or hepatocellular insufficiency, manifests with a decrease in appetite, nausea, intolerance to alcohol, tobacco, emaciation, dry scaly skin, hypovitaminosis, fever, parenchymal jaundice, and hepatic smell from the mouth. The severity of this syndrome depends on the stage (compensated, subcompensated, decompensated).

Fetor hepaticus is the sweetish characteristic breath of patients caused by a disturbance in the metabolism of amino acids and aromatic compounds, in particular, the products of methionine conversion. With endogenous coma, the smell is similar to the smell of raw liver, with exogenous - with the smell of sulfur or overripe fruit.

Hepatopancreatic syndrome is a reduced pancreatic function

Diagnostics

In the diagnosis of the liver cirrhosis, the same methods are used as in chronic hepatitis (general blood test, general urine test, biochemical blood test).

Ascitic fluid analysis : sterile transudate, relative density less than 1015, protein content – 20–30 g/l, leukocytes – about 280 per μl, including, up to 27 % of stab neutrophils, a small number of lymphocytes and mesothelial cells.

Abdominal x-ray can reveal the elevation of the dome of the diaphragm (in ascites).

Ultrasound examination allows to determine the size of the liver and spleen, the surface and the lower edge of the liver, its capsule thickenning, significant abnormalities of echostructure and vascular structure of the organ.

Ultrasound scanning allows early diagnosis of portal hypertension (the earliest morphological feature is an increase in the diameter of the portal vein more than 15 mm and a diameter of the splenic vein more than 10 mm, recanalization of the umbilical veins, spontaneous vascular shunts), and also to detect the accumulation of ascitic fluid even in a minimal amount - first around the liver, then in the lateral parts of the abdomen and in the small pelvis.

Computed tomogram allows to determine the state and degree of enlargement of the liver and spleen, as well as the presence of portal hypertension and ascites.

Radionuclide study in liver cirrhosis allows to determine significant abnormalities of the main indicators of radiopharmaceutical clearance: the half-time of blood clearance is extended to 10 minutes, maximal concentration in the liver parenchyma – up to 44 minutes, half-time excretion of the pharmaceutical from the liver – up to 200 minutes. There is a significant deformation of the scintigraphic image – the distribution of colloid in the liver

is uneven, the large-focal uneven distribution over the entire contour of the liver (in areas of increased proliferation of connective tissue, the accumulation of the pharmaceutical preparation is reduced). There are often an increase in size and a more intense image of the left lobe are determined, while the right lobe decreases in size and accumulates less pharmaceuticals.

There is often a decrease in the size of the liver due to a decrease in the accumulation of the drug in the marginal zones, in this case the size of the liver, determined by this method and by echosonography do not match. Characteristic is a change in the ratio between the accumulation of radiopharmaceuticals in the liver and spleen, the image intensity of the spleen is often higher than that of the liver. The structure of the spleen becomes heterogeneous, due to thrombosis and focal proliferation. Possible is an accumulation of the drug in the bones of the spine and pelvis.

Complications

1. Bleeding from esophageal varicose veins.
2. Hepatorenal syndrome.
3. Hepatic coma (hepatocerebral insufficiency).
4. Symptomatic ulcers of the stomach and duodenum.
5. Osteoporosis and osteomalacia.

SITUATIONAL TASKS

1. A 34-year-old patient with a 15 years history of alcohol abuse isdmitted to the hospital with general weakness, lack of appetite, pain in the right hypochondrium, vomiting of blood for.

Examination shows weight loss, scleral jaundice, dry skin, presence of "spider nevi" on the skin of the face and shoulder girdle, hyperemia of the palms, "crimson" tongue with flattened papillae. The abdomen is enlarged, the protrusion of the navel is visible, the saphenous veins are dilated.

Percussion shows ascites, the liver is 6 cm below of the right costal arch, the spleen is 5 cm below of the left costal arch.

Which of the following is your preliminary diagnosis?

A. Chronic hepatitis. *C. Liver cancer*. *E. Hemolytic anemia*.
B. Cirrhosis of the liver. *D. Leukemia*.

2. A 34-year-old patient complains of weakness, weight loss, nausea, diarrhea, pain in the right hypochondrium after eating fatty foods.

On examination the skin turgor and elasticity are reduced. Muscle atrophy, jaundice of the sclera are present. The abdomen is soft, the lower edge of the liver is determined 3 cm below the edge of the costal arch along the right midclavicular line.

Which of the following is your preliminary diagnosis?

A. Chronic cholecystitis. *C. Functional dysp epsia*. *E. Chronic pancreatitis*.
B. Chronic hepatitis. *D. Cirrhosis of the liver*.

Навчальне видання

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