

Министерство здравоохранения республики Беларусь
Учреждение образования
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии
Обсуждено на заседании кафедры
Протокол №7 от 30.08.2017

МЕТОДИЧЕСКАЯ РАЗРАБОТКА

Для проведения занятия со студентами
3 курса ФПСЗС, обучающихся на английском языке
по патологической физиологии

Тема: **Патофизиология печени**

Theme: **Pathophysiology of liver**

Время 3 ак. часа

1.Actuality of the theme. The diseases of liver and bile excretory system take considerable specific weight in a general morbidity of the population, and last decade the further growth of them was increased. Technological revolution and associated with it the negative ecological shifts have resulted in useful increase of frequency and spread spectrum of diseases of liver and cholic tracts. In connection with urbanisation of life, hypokinesia, and also such negative phenomenon as alcoholism, morbidity the hepatitises and cirrhosis of liver, cholelithiasis and cholecystitis considerably has increased. The chemicalization of effecting, agriculture, mode of life activities and medicine promoted growth of frequency of toxic and medicamental damages of liver. Sharp increase of medical manipulations, blood transfusion have stimulated useful increase of morbidity by serumal hepatitis.

Learning goals of the lesson: to study etiology and pathogenesis of liver failure.

Educational goals of the lesson: formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

Objectives of the lesson:

1. To know etiology, pathogenesis and complications of liver pathology.
2. To be able to explain changes in exchange of bile pigments in various pathological processes in liver.
3. To know principles of diagnosis of liver functional state.

To repeat the following questions from related disciplines to ensure absolute mastery of the material:

1. Structure of liver acinus (histology, cytology, embryology disciplines).
2. Genetic apparatus of cell (medical biology and genetics discipline).
3. Peroxide oxidation of lipids (biochemistry discipline).
4. Scheme of erythropoiesis (histology, cytology, embryology disciplines).
5. Quantitative parameters of red blood. Methods of determination of erythrocytes count, hemoglobin content (normal physiology discipline).

Control questions of the lesson:

1. General etiology and pathogenesis of liver diseases.
2. Violations of portal blood circulation, arterial blood supply of liver.
3. Parenchymal liver damage. Disorders of biliary excretion.
4. Hepatic insufficiency: types, causes, mechanisms of development, manifestations.
5. Hepatic coma, etiology, pathogenesis, clinical manifestations.
6. Jaundice: types, mechanisms, manifestations.
7. Syndromes in liver diseases and their pathogenetic evaluation.
8. Principles of prevention and therapy of main liver syndromes and diseases.

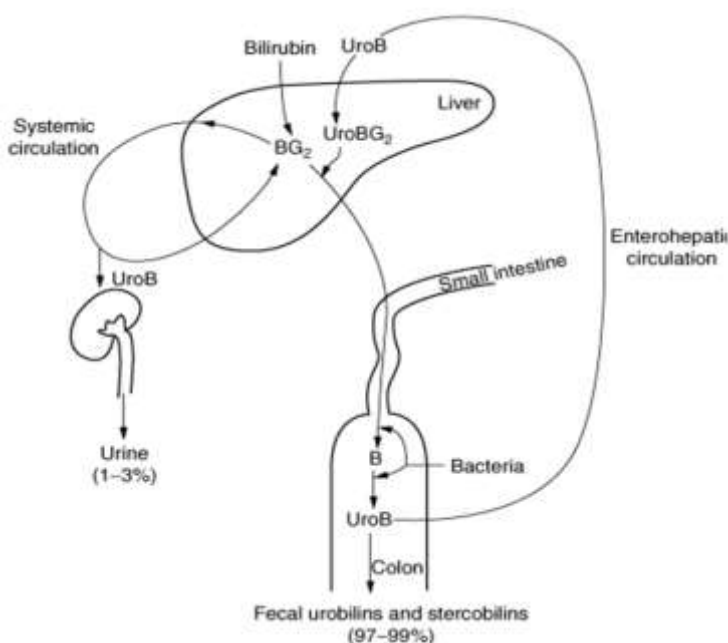
Calculation of study time

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

Anatomy of the liver

80 per cent with glucuronic acid to form bilirubin glucuronide, about 10 per cent with sulfate to form bilirubin sulfate, and about 10 per cent with a multitude of other substances. In these forms bilirubin is



excreted from the hepatocytes by an active transport processes into the bile canaliculi and then into the intestines.

Figure: bilirubin metabolism

In the intestine about half of the conjugated bilirubin is covered by bacterial action into the substance urobilinogen, which is highly soluble. Some of the urobilinogen is reabsorbed through the intestinal mucosa back into the blood.

After exposure to air in the urine, the urobilinogen becomes oxidized to urobilin; alternatively, in the feces, it becomes oxidized to stercobilin.

Pathogenesis of hepatocyte injury

1. Direct damage

- cytolytic effect (total destruction of cell)
- cytopathic effect (damage of cell organelles without destruction of cell)

2. Immune-mediated:

- activation of liver macrophages (Kupffer cells, endothelial cells of hepatic sinusoid)
- activation of CTL (CD8 +, CD4 +) to destructed hepatocytes containing viral Ag
- activation of the HIR (synthesis of IgM, IgG)

3. Autoimmune mechanism

4. Induction of apoptosis in hepatocytes:

- CTL by bounding with Fas-receptor of infected hepatocytes)
- by viral proteins (X-protein of hepatitis B virus);
- by ↑ sensitivity of infected hepatocytes to cytokines in the immune or autoimmune reactions.

5. Effect of toxic agents

- direct damage
- ↑ LP → damage of membranes, transmembrane transport, cellular receptors, membrane enzymes
- disorders of mitochondrial functions (reduces the activity of Mt enzymes, uncoupling of OXPHOS, ↓ ATP synthesis)
- inhibition of DNA repair and activate apoptosis
- drugs as haptens converted hepatocyte proteins into immunogens

Experimental modeling of liver pathology

1. Ekk's fistula (1877)

Postcava portal vein anastomosis is in a dog. Portal vein is ligatured above the anastomosis. So, blood from the abdominal cavity flows into the postcava. Object: detoxication, urea formation

2. Inverse Ekk-Pavlov's fistula (1983)

Postcava portal vein anastomosis. Postcava is ligatured. So, blood from the gastrointestinal tract and back part of the body flows into the liver. Object: functional liver state in different conditions

3. Angiostomic method of E.S. London (1919)

Metallic cannula is imposed to the wall of portal vein and hepatic vein → their free ends are placed out through the abdominal wall. Object: functional role of the liver in norm and pathology; the role of the liver in carbohydrate, protein, lipid, pigment and mineral metabolism.

4. Method of isolated liver perfusion

Laboratory animals are the donors of the liver (rats, rabbits, cats). The liver of jumbo is also used (dogs, pigs, calve). Object: the metabolic role of the liver; transplantation

5. Extirpation of the liver

Extirpation of the liver is an experimental model of the hepatic coma. The partial extirpation of the liver does not results in severe metabolic impairments → the intact part of the liver preserve functions and compensation abilities.

6. Administration of infectious and toxic agents

Parenteral administration (injection) of hepatic toxins. Object: CCl₄ → alteration, necrobiosis in the central zone of liver acinus; salt hydrazine → fat hepatitis; alcohol → local dystrophic destructive changes in parenchyma, vascular impairments; chloroform, heliotrope seeds

Juandice

Jaundice is a syndrome, which refers to the yellowing of the body tissues, including a yellowish skin as well as deep tissues. The usual cause of jaundice is large quantities of bilirubin in the extracellular fluids, either non-conjugated bilirubin or conjugated bilirubin.

Bilirubin is easily bound with the elastic tissue. Elastic tissue in large quantity presents in sclera, vascular wall, the skin. An increase in bilirubin level results in sclera, vascular wall and the skin yellowing.

Basic mechanisms of jaundice

- an increase d bilirubin overload on hepatocytes
- impairment of bilirubin transport into hepatocytes
- impairment of bilirubin conjugation
- impairment of bilirubin excretion into bile through canal membrane
- impairment of bile circulation in bile ducts

Jaundice classification

1. prehepatic jaundice (hemolytic)
2. hepatic jaundice
3. posthepatic (obstructive or cholestatic) jaundice

Types of primary (hereditary, enzymopathic, metabolic) jaundice

Type of pathology	Manifestations
Gilbert's syndrome	Mild decrease in UDP-glucuronide transferase activity and transport of unconjugated bilirubin into the liver cell; mild asymptomatic increase in the blood level of unconjugated bilirubin.
Crigler-Najar syndrome type I	Absence of UDP-glucuronide transferase activity in the liver cells; very high unconjugated bilirubin levels in the serum (340–770 $\mu\text{mol/L}$); no conjugated bilirubin is formed - colorless bile; severe neurologic complications.
Crigler-Najar syndrome, Type II	Partial deficiency of UDP-glucuronide transferase; high unconjugated bilirubin levels in the serum (103–340 $\mu\text{mol/L}$); neurologic complications are uncommon.
Dubin-Johnson syndrome	A defect in biliary excretion of bilirubin, cholephilic dyes, porphyrins; high bilirubin levels in the serum (51–257 $\mu\text{mol/L}$), predominantly of the conjugated type; patients are asymptomatic or have vague constitutional or GI symptoms; liver cells contain dark pigment
Rotor syndrome	Similar to the Dubin-Johnson syndrome but the defect of biliary excretion of dyes is not as diffuse; high bilirubin levels in the serum, predominantly of the conjugated type; there is no dark pigment in the liver cells.

HEPATIC FAILURE

Etiology:

- infections (hepatotropic viruses - A, B, C, D, E, F, G, TTV, smaller role EBV, CMV, HSV)
- acute or chronic alcohol intoxication
- parasitic, neoplastic lesions of liver
- violation of the outflow of bile
- circulatory disorders: prolonged venous congestion in the liver
- inherited disorders of metabolism (Wilson's disease, hemochromatosis, α 1-antitrypsin deficiency).
- Hepatotoxic xenobiotics:
 - ✓ industrial poisons (benzene derivatives, lead, Hg, toluene, chloroform...)
 - ✓ drugs (antibiotics, sulfonamides, sleeping pills, indomethacin, paracetamol...)
 - ✓ mushroom poison - phalloidin, contained in Amanita phalloides
 - ✓ aflatoxins (molds)
 - ✓ dyes, household chemicals

Classification of hepatic failure

Liver damage can be:

- primary (in viral hepatitis)
- secondary (due to generalized disease - alcoholism, sepsis)

On the scale of damage:

- partial
- total

By origin:

- hepatocellular (hepatic) - primary hepatocyte injury and failure of their functions
- shunt (bypass) - violations of blood flow in the liver and its shunting by anastomoses into the general circulation
- cholestatic (excretory) violation of formation and excretion of bile
- mixed

By speed of emergence and development:

- lightning (a few hours)
- acute (a few days)
- chronic (several weeks, months, years)

By the reversibility of hepatocyte injury:

- reversible
- irreversible (progressive)

Pathogenesis of hepatic failure

General pathogenesis of HI can be presented as the following chain of changes: action of damage factor → change of molecular architectonics of membranes of hepatocytes → increase free oxidization of lipids → partial or complete destruction of membranes + increase of their permeability → exit from lysosomes different enzymes → deep damage of cells → liberation IL-1 by macrophages → development of inflammatory and immune reaction in a liver → formation of autoantibodies and auto T-killers → additional autoallergic damages of hepatocytes. Each of the pathogenetic links can become dominant in development of hepatic failure.

Manifestations of HF

- disorders of metabolism
- syndrome of antitoxic dysfunction
- hemorrhage syndrome
- hepatic coma
- parenchymatous jaundice
- cholemic syndrome
- acholic syndrome

Disorders of carbohydrate metabolism

- suppression of glycogen synthesis and splitting
- disorders of glyconeogenesis
- hypoglycemia (on an empty stomach), hyperglycemia (after a meal)
- non-oxidized metabolites accumulation (metabolic acidosis).
- suppression of glucuronic acid synthesis

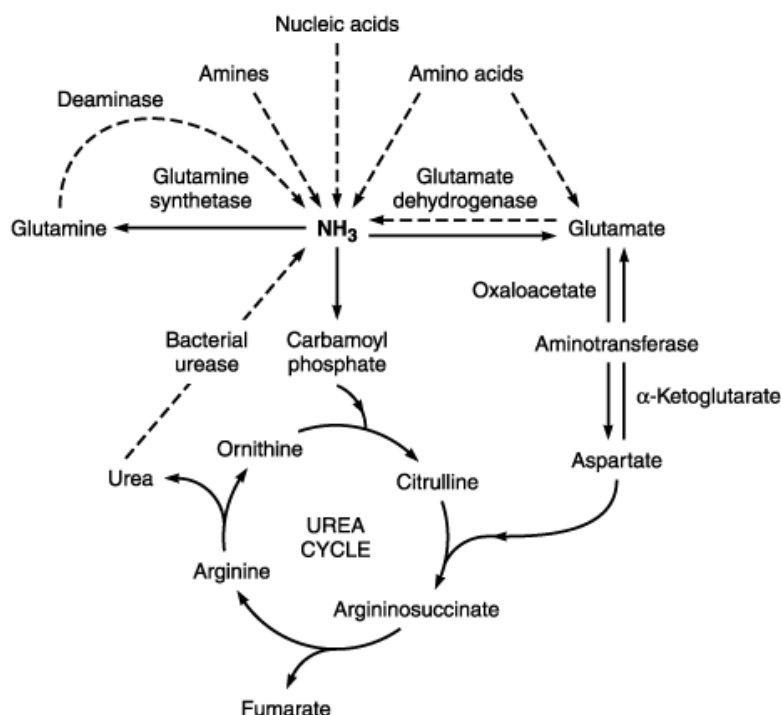
Disorders of lipid metabolism

- lipolysis (for energy)
- hyperlipemia, hyperlipoproteinemia (accumulation of lipids out of adipose tissue)
- incomplete oxidation of triglycerides and FA with accumulation of intermediate products (ketone bodies)
- accumulation of POL products
- ↓ synthesis of phospholipids

Disorders of protein metabolism

- Proteins synthesized exclusively in the liver: albumin; blood coagulation factors: I (fibrinogen), II (prothrombin), III, V, VII, IX, X, XI; transport proteins: haptoglobin, transferrin, ceruloplasmin, LDLP, proteins that transport a hormones
- hypoproteinemia
- disproteinemia (↓albumins and ↑globulins)
- ↓ oncotic pressure (edema)
- disorder of intermediate aminoacids catabolism → metabolic acidosis
- reduced of urea synthesis → ammonia accumulation in blood (hyperazotemia)

Urea cycle



Disorders of hormone metabolism

↓ inactivation of insulin, thyroxin, aldosterone, sexual hormones → excess of hormones
dismetabolism of steroid hormones.

Disorders of acid-basic balance

accumulation of incompletely oxidized products → metabolic acidosis.

Disorders of vitamin metabolism

inhibited formation of active form of Vit: D3, retinol (carotene), coenzyme A (from B5)

depot of vitamin B12 and folic acid
↓ absorption of fat-soluble Vit (A, D, E, K)

Syndrome of antitoxic dysfunction:

- intestinal poisons: phenolic aromatic connections (phenol, indole, scatole) biogenic amines (cadaverine, putrescine), ammonia;
- poisonous metabolites: some fat acids (valerianic, kapron); sulphureous amino acid (taurine, cystine, metionin); toxic derivative of pyruvate;
- exogenous poisons (mushroom, microorganism or parasite origin and other);

Violation of disintoxication function of liver is accompanied development of syndrome of hepatocerebral insufficiency, which shows up the complex of psychical and neurotic disorders up to the loss of consciousness and development of the comatose state.

Hepatic encephalopathy

Hepatic encephalopathy (hepatolenticular syndrome) – neuro-psychiatric disorder with disturbance of intelligence, consciousness, reflex activity and function of vital organs.

Distinguish acute and chronic hepatic encephalopathy.

Stages of hepatic encephalopathy:

Stage I - prodromal. Appear initial mental changes - slowing of thinking, behavior disorder, disorientation of the patient in reality, sleep disorder (sleepiness during the day, insomnia at night), tearfulness. Patients may fall into periods stupor with the fixation look. Characteristic and quite early symptom is a change in handwriting (dysgraphia). EEG is usually not changed.

Stage II - beginning coma. Exacerbated symptoms of I stage. In some patients appear seizures and psychomotor agitation. Formed stereotyped movements such as flapping tremor of the hands (asterixis), stupor. Patients may become untidy, familiarity. Often, the body temperature rises, there is hepatic breath. EEG revealed minor initial changes.

Stage III - stupor. Patients are in a prolonged sleep interruptible occasional revivals. In the neurological status marked muscle rigidity, mask-like face, slow voluntary movements, gross violations of speech (dysarthria), hyperreflexia, clonus of the patella, etc. The EEG shows profound disturbances.

Stage IV - coma. Lost consciousness, no response to pain stimulus, in the initial phase marked pathological reflexes. In the future, pupils dilate, reflexes fade, falling blood pressure, may appear breathing Kussmaul or Cheyne-Stokes, and death.

Hepatic coma

Hepatic coma - this is the end stage of hepatic encephalopathy, characterized by loss of consciousness, lack of reflexes and violation of basic functions of the organs.

Factors that trigger the rapid development of coma: protein foods, diuretics (not sparing potassium), sedatives. Mortality of patients in stage IV, reaches 80-90%.

Etiology distinguish 4 **types of coma**:

- 1) **endogenous** (true) develops with massive necrosis of hepatocytes in cases of acute liver failure, with the typical violation of numerous liver functions patients experienced severe bleeding, increased levels of free bilirubin in the blood, liver hyperasotemia type hepatic breath. Amenable to treatment with difficulty.
- 2) **exogenous** (shunt, bypass) occurs in case of the development of powerful systems collaterals between the portal vein and inferior vena cava during cirrhosis. Can also occur when the artificial imposition of portocaval anastomoses that carry blood from the intestines, rich BAS (ammonia, cadaverine, putrescine, etc.), bypassing the liver, flows into the bloodstream and has a toxic effect on the brain. This form is easier to therapy (blood dialysis, purgation, broad-spectrum antibiotics), has a more favorable prognosis.
- 3) **mixed** in advanced liver cirrhosis with the deaths of large numbers of hepatocytes and the presence of portocaval anastomoses
- 4) **electrolyte** associated with the development of hypokalemia. In the pathogenesis play a role secondary aldosteronism, use of diuretics (potassium not sparing), frequent vomiting, diarrhea, which leads to electrolyte imbalance (hypokalemia, alkalosis). Manifested severe weakness, decreased muscle tone, weakness, twitching calf muscle, cardiac dysfunction (tachycardia, a "woodpecker" rhythm), respiratory failure. Electrolytic treatment of coma - the use of drugs potassium.

Pathogenesis of hepatic coma.

The followings mechanisms matter in development of hepatic coma:

- 1) Violation of synaptic transmission, as a number of toxic matters (low molecular weight fat acids, tyramine and other) is unreal neuromediators, which bring to violations transmissions over of nervous impulses, violations of co-operations of interneurons and disorders of integrative functions of CNS. In addition, maintenance of gamma aminobutyric acid, GABA increase – inhibition mediators of the central nervous system, which appears in bowels under the action of microflora[*gut organisms*] and don't inactivate in a liver.
- 2) Violations of power metabolism – the deficit of ATP. A leading role in development of such violations belongs to the ammonia. Binding of some acids to the ammonia conduces to violation functioning of metabolic way of cycle of Krebsa and, as a result, to violation of reactions of resynthesis of ATP. Diminishing of maintenance of ATP in nervous cells results in disorders of processes of active transport of cations, violation of generation of nervous impulses, changes of size of diaphragm potential.
- 3) Enhanced GABAergic transmission. At pathology there is disturbed clearance of GABA in the liver (GABA produced in the decarboxylation of glutamic acid). GABA accumulates in brain tissue, exerting an inhibitory effect on neurons, impairing their function, resulting in the development of hepatic encephalopathy.
- 4) Violation of function of cellular membranes as a result of direct action on them of cerebral toxic matters, which shows up disorders of function of Na-K-pumps, as a result of what diaphragm potential diminishes and a generation and conducting of nervous impulses become impossible.
- 5) Development of metabolic acidosis and violations of exchange of electrolytes.

Hepatocellular insufficiency

Syndromes of hepatocellular insufficiency:

- 1) syndrome eating disorders (poor appetite, nausea, abdominal pain, unstable stool, weight loss, anemia appearance). The basis of this syndrome are metabolic disorders;
- 2) syndrome of fever (up to 38 ° C and even to 40 ° C) with leukocyte nuclear shift left. The syndrome is associated with necrosis of hepatocytes entering toxic products in the blood, bacteremia (microorganisms may be received into the bloodstream from the intestine);
- 3) syndrome of jaundice;
- 4) syndrome is an endocrine disorder. Marked decrease in libido, testicular atrophy, infertility, gynecomastia, atrophy of the mammary glands, uterus, menstrual disorders. Perhaps the development of diabetes and secondary aldosteronism;
- 5) syndrome of impaired hemodynamics - the accumulation of histamine and other vasoactive substances leading to vasodilation (compensatory increase in cardiac output combined with hypotension). Decreased synthesis of albumin dropped oncotic pressure, development of secondary hyperaldosteronism cause edematous-ascitic syndrome
- 6) specific liver odor (feto hepaticis) associated with the release of methyl mercaptan. This substance is formed from methionine, due to violation of demethylation in the liver and accumulated, may be contained in the exhaled air;

- 7) "Hepatic signs" - telangiectasia and palmar erythema;
- 8) Syndrome of hemorrhagic diathesis - reduced synthesis of clotting factors and frequent bleeding makes the possibility of DIC

Hepatitis

Is characterized by diffuse inflammation of the liver tissue.

Classification:

primary (independent nosological entity: viral, alcohol, drugs, autoimmune)

secondary (occurring in other diseases)

According to the course:

acute

chronic

Clinical-morphological forms of acute viral hepatitis:

- Cyclic icteric
- Anicteric (80% of hepatitis C and 70% of hepatitis B)
- Subclinical (inapparent)
- Lightning or fulminant (with a massive progressive necrosis of hepatocytes)
- Cholestatic (with involvement in the process of small bile ducts).

Acute hepatitis

Manifest form has for 4 periods:

- Incubation (2-26 weeks).
- Prodromal or preicteric (non-specific symptoms)
- Jaundice (full-scaled picture)
- Convalescence

Outcomes of acute hepatitis

- Full recovery
- Recovery with residual effects
- The transformation to chronic hepatitis
- The development of cirrhosis
- The risk of hepatocellular carcinoma

Chronic hepatitis

Chronic hepatitis — a diffuse inflammatory-dystrophic chronic liver disease, with various etiologies, morphologically characterized by:

- degeneration of liver cells
- histiolymploplasmocytic infiltration
- mild fibrosis of the portal tracts
- hyperplasia of kupffer cells
- maintaining the lobular structure of the liver

Classification of chronic hepatitis

- Viral hepatitis (B, C, D)
- Drug-induced hepatitis
- Toxic hepatitis
- Alcoholic hepatitis
- Genetically determined or metabolic hepatitis (Wilson's disease, hemochromatosis)
- Idiopathic (autoimmune, etc.)
- Nonspecific reactive hepatitis
- Secondary biliary hepatitis with extrahepatic cholestasis.

Variants of chronic viral hepatitis

- Lytic infection (intracellular viral replication with damage and destruction of the hepatocytes; ↑↑↑Ag → autoimmune process)
- Persistence (multiplication of virus particles with hepatocytes, going out of viruses from single cells → smaller amount Ag → less severe autoimmunity).

- Latent (insertion of viral genome into the hepatocyte nucleus → cell division with copies of viral DNA. At a stage of activation of virus replication and releasing, become as lytic.

Phase of chronization is determined by the severity and character of fibrosis:

- with no fibrosis
- portal and periportal subfibrosis
- moderate fibrosis with porto-portal septa
- fibrosis with porto-central septa
- cirrhosis of the liver (irreversible stage)

a) manifestations of portal hypertension

b) with symptoms of hepatic insufficiency

Autoimmune hepatitis

Autoimmune hepatitis is an periportal hepatitis with hypergammaglobulinemia and tissue antibodies. Mostly it regresses under the immunosuppressive therapy.

It is a disease resulting from the impaired immune control.

Types of autoimmune hepatitis

(according to autoantibodies)

Type I

➤ 85% of all autoimmune hepatitis

➤ men:women=8:1

It is mostly observed in old people (lupiform hepatitis in young women is not referred to this type). Anhepatic clinical manifestations are rare, prognosis is good.

➤ antinuclear antibodies AT-ANA

➤ antibodies to smooth muscles (actin) SMA (smooth muscle antibodies)

Antigen S-actin observed in smooth and skeletal muscle is also present in cell membrane and cytoskeleton of hepatic cells. So, revealance of SMA testifies about hepatic cell injury.

Type II

➤ 15% of all autoimmune hepatitis

➤ 14 year old children, predominantly girls

➤ systemic manifestations are often observed

➤ antibodies — LKM (liver/kidney microsomes)

It is associated with diabetes mellitus type I, thyroiditis, vitiligo (antigen is cytochrome P-450-D₆)

Type III

➤ Antibody to soluble liver antigen — SLA (soluble liver antigen)

➤ ANA, SMA, LKM-1 are absent.

Cirrhosis

Cirrhosis is an irreversible distortion of normal liver architecture characterized by hepatic injury, fibrosis, and nodular regeneration. The clinical presentations of cirrhosis are a consequence of both progressive hepatocellular dysfunction and portal hypertension.

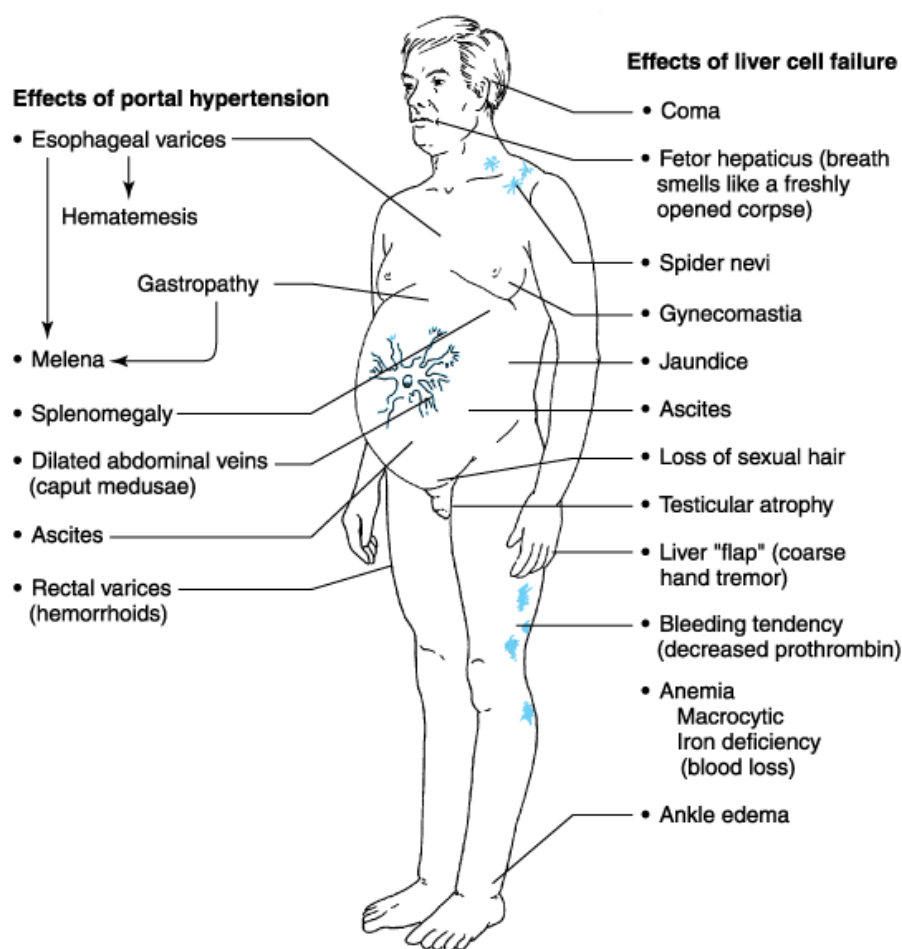
Etiology:

- Alcoholic liver disease (most common)
- Postnecrotic cirrhosis (HBV, HCV)
- Autoimmune disease (primary biliary cirrhosis)
- Metabolic disease:
- ✓ Hemochromatosis, Wilson's disease
- ✓ α₁-Antitrypsin deficiency, galactosemia

Pathogenesis of cirrhosis

- etiological factor → immune response → hepatocellular death → massive necrosis of the parenchyma
- scar formation
- vessels of portal tract approaching to the central vein → blood from the portal vein passes into the central vein, passing the sinusoid
- blood bypass the sinusoids → ischemic necrosis of undamaged cells
- necrosis activated substance that stimulating liver regeneration → regeneration nodes → compression of blood vessels
- decay product stimulate inflammatory response → intensive formation of fibrosis

- formed vascular anastomoses → blood, bypassing the parenchyma of the lobules, enters in hepatic vein system → ischemia, necrosis



Clinical effects of liver cirrhosis

Portal hypertension

Portal hypertension syndrome is caused by impaired blood flow in the portal vein.

Distinguish 3 types of portal hypertension:

- **prehepatic** occurs due to compression or thrombosis of the hepatic veins, right heart failure, pericarditis, and is characterized by obstruction of the venous outflow from the liver.

- **hepatic** at cirrhosis, tumors, echinococcosis and other liver lesions.

- **posthepatic** associated with thrombosis or compression of the portal vein (scars, compression ascites tumor) or with anomalies of development.

The main link in the

pathogenesis of portal hypertension is blood stasis in the portal vein.

Portal hypertension is accompanied by compensatory shunting of blood through the portocaval anastomosis (lower third of the esophagus and cardiac part of the stomach, the anterior abdominal wall at the navel - "Medusa head" system hemorrhoidal veins), followed by varicose vessels. This makes the walls of blood vessels vulnerable to mechanical damage, which may be the outcome of gastrointestinal bleeding, often with fatal outcome. As a result of portal hypertension develop splenomegaly (enlargement of the spleen), hypersplenism (increased spleen functions), resulting in pancytopenia (thrombocytopenia, anemia, leukopenia) and ascites (accumulation of fluid in the abdominal cavity).

In the mechanism of ascites development the following contributing factors play the role:

- increased pressure in the portal vein;
- decrease in blood oncotic pressure (violation of the protein synthesis);
- violation of lymph circulation;
- secondary aldosteronism (due to decreased metabolism in the liver), which is accompanied by hypernatremia, hypokalemia, hypervolemia.

Wilson's disease

Autosome recessive type of inheritance (1:30,000), pathologic gene is localized on chromosome 13. Gene codes type P-ase-protein. Type P-ase-protein transfers Cu through the membrane and participate in Cu transference from hepatocyte lysosomes into the bile. In-cell Cu accumulation results from the lack of type P-ase-protein. High level of in-cell Cu is hepatotoxic.

It is a disease of young and old people. It does not clinically manifested up to 5 years old. It is manifested by 15 years in 50 per cent of patients. It is rarely diagnosed in 40–50 year-old men. There is a characteristic greenish brown ring in the cornea (the Kayser-Fischer ring).

The liver is always involved in pathological process — cirrhosis, plus eyes, kidneys, joints are injured. Erythrocyte hemolysis and degeneration of basal ganglions (including lentiform nuclei) are observed.

There is a decrease in caeruloplasmin level in blood serum (caeruloplasmin normally forms a non-toxic complex with copper). Clinical manifestations include: ophthalmologic manifestations, blue demilunes on

the nails, neurologic impairments (mental retardation and symptoms resembling parkinsonism, nephrolithiasis, joints pathology, hemolytic anemia.

α 1-Antitrypsin (AAT) deficiency

Alpha 1-antitrypsin deficiency is an inherited metabolic disorder in which mutations in the coding sequence of the serine protease inhibitor, alpha 1-antitrypsin, prevent its export from the hepatocyte. Autosomal recessive disorder, alleles are inherited codominantly (each allele expresses itself). The major function of AAT is to protect the tissues against the enzyme neutrophil elastase.

Pathogenesis

decreased AAT levels in serum + production of a mutant protein that cannot be secreted into blood→ accumulation of AAT in hepatocytes causes liver damage.

Affecting the lung and liver. The typical pulmonary manifestation is chronic obstructive pulmonary disease and emphysema. Severe chronic obstructive pulmonary disease may occur in young adulthood, and terminal respiratory insufficiency causes premature death in many patients. In the liver, alpha-1 antitrypsin deficiency may manifest as benign neonatal hepatitis syndrome; a small percentage of adults develop liver fibrosis, with progression to cirrhosis and hepatocellular carcinoma.

Questions for self-control of knowledge:

1. What are main liver functions?
2. What experimental models of liver.
3. What are bile pigments found in normal blood, urine and feces?
4. What is etiology and pathogenesis of main pathophysiological syndromes that develop in liver disease?
5. In what types of jaundice may occur urobilinuria?
6. In what types of jaundice may appear unconjugated bilirubin in urine?
7. What is mechanism of physiological functions impairment in different types of jaundice?
8. Specify consequences of acute stoppage of bile secretion.
9. What antibodies are defined in autoimmune hepatitis?
10. What is mechanism of liver failure with changes in systemic blood circulation?
11. What are pathogenetic mechanisms of manifestation in liver cirrhosis?

Tasks for self-managed student work:

1. Autoimmune hepatitis, etiology and pathogenesis.
2. Violation of systemic circulation in hepatic insufficiency.

Literature

Basis literature:

1. Литвицкий, П. Ф. Патофизиология = Pathophysiology: лекции, тесты, задачи : учеб. Пособие / П. Ф. Литвицкий, С. В. Пирожков, Е. Б. Тезиков. – М. : ГЭОТАР-Медиа, 2016.– 432 с.

Additional literature:

2. Kumar, V. Robbins and Cotran Pathologic basis of disease, 7th Edition / V.Kumar, A.K. Abbas, N. Fausto. — Philadelphia: Elsevier Inc., 2005. — 1629 p. Режим доступа: <http://www.rkmyat.in/up1/34/1629.pdf>. – Дата доступа: 30.08.2016.
3. Кидун, К. А. Тестовые задания по патологической физиологии = Test tasks on pathological physiology : в 3-х ч. Ч. 3, Частная патофизиология : учеб.-метод. пособие для студ. 3 курса фак. по подг. спец. для зарубеж. стран, обуч. на англ. яз. по спец. «Лечебное дело», мед. вузов / А. К. Кидун. – Гомель : ГомГМУ, 2015. – 113 с.
4. Научная электронная библиотека eLIBRARY.RU [Электронный ресурс] / Научная электронная библиотека. – М., 2005. – Режим доступа: <http://www.elibrary.ru>. – Дата доступа: 26.08.2017.

Compiler:

senior lector

K.A. Kidun