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Учреждение образования
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии
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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 системы крови. Гемолитические анемии. Эритроцитозы**

Theme: **Pathophysiology of blood. Hemolytic anemias. Erythrocytosis**

Время 3 ак. часа

1.Actuality of the theme. The qualitative features of erythrocytes of peripheral blood and bone marrow allow to determine a kind of anemia, to make submission about regenerative ability of bone marrow and to inspect efficiency of treatment. For example, erythrocytes with the distinctive morphological characteristics are peculiar for iron-deficiency anemia (hypochromic erythrocytes), B₁₂ (folic)-deficiency anemia (megaloblastes and megalocytes), sickle-cell anemia (sickle-shape erythrocytes), thalassemia (target like erythrocytes), Minkovskiy-Shoffar's anemia (microspherocytes). The increase of amount reticulocytes in peripheral blood testifies for good compensator possibility of bone marrow. The availability in blood of anisocytes, poikilocytes and other degenerative forms show the heavy disorder of erythropoiesis.

Learning goals of the lesson: to study etiology, pathogenesis and the main manifestations of hemolytic anemia.

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 classification, etiology and pathogenesis of hemolytic anemia.
2. To study basic violations and compensatory-adaptive processes in the body in anemia and polycythemia.

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

1. Scheme of erythropoiesis (histology, cytology, embryology disciplines).
2. Quantitative parameters of red blood. Methods of determination of erythrocytes count, hemoglobin content (normal physiology discipline).

Control questions of the lesson:

1. Hereditary hemolytic anemia: types, causes, mechanisms of development, clinical and hematological manifestations.
2. Acquired hemolytic anemia: types, causes, mechanisms of development, clinical and hematological manifestations.
3. Autoimmune hemolytic anemia: types, causes, mechanisms of development, clinical and hematological manifestations.
4. Erythrocytosis: definition, types, causes, mechanisms of development, clinical and hematological manifestations.
5. Violations and compensatory-adaptive processes in the body with anemia and erythrocytosis.
6. Principles of anemia therapy.

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

Additional material:

HEMOLYTIC ANEMIAS

Hemolytic anemias is a group anemia caused by hereditary or acquired, a common feature of which is the shortening of the RBCs life. There are a persistent (chronic HA) or massive (acute HA) erythrocyte destruction predominance of their formation. The disease is manifested by syndromes of enhanced hemolysis and compensatory gain of erythropoiesis.

Hemolytic anemias have the following features:

- premature destruction of red cells and a shortened red cell life;
- accumulation of hemoglobin degradation products;
- compensatory increase in erythropoiesis and elevated erythropoietin levels.

Classification of hemolytic anemias:

I. Hereditary hemolytic anemia

1. Membranopathias (hereditary spherocytosis)
2. Enzymopathias (G-6-PD deficiency)
3. Hemoglobinopathias:
 - Qualitative— abnormality of primary structure (sickle cell anemia)
 - Quantative — impairment of synthesis or absence of one of the globin chains in case of intact primary structure (thalassemia)

II. Acquired hemolytic anemia

1. *Immune hemolytic anemias*

- Iso (allo) immune (transfusion of incompatible blood, hemolytic disease of newborn)
- Heteroimmune (virus, bacterial infections, chemical, drug-induced)
- Autoimmune hemolytic anemia

2. *Nonimmune hemolytic anemias*

- Toxico-hemolytic
 - mushroom and snake venoms
 - plumbum, arsenicum, phenylhydrazine
 - endotoxins (burns, uremia, cord. liver)
- Infectious (bacterial, parasitic (malaria))
- Mechanical:
 - sudden spasm of blood vessels
 - prosthetic heart valves, vascular
 - hypersplenism

In hemolytic anemia hemolysis of RBCs may occur extravascular (intracellularly as well as the physiological hemolysis), or directly into the blood vessels (intravascular).

Hemolysis is defined as shortened red cell survival, may result from any number of intrinsic or extrinsic abnormalities.

Etiology of hemolysis:

All reasons may be distinguished into two groups: intrinsic and extrinsic abnormalities. Intrinsic abnormalities of red cell defects include membrane defects, abnormal hemoglobins, and enzyme defects. Extrinsic abnormalities include microangiopathy, mechanical heart valve, anti-RBC antibody, toxins, and extreme heat.

Intracellular (extravascular) hemolysis

Extravascular hemolysis is a results from phagocytosis of intact (but abnormal) RBCs by macrophages in the spleen, liver, and bone marrow. Reduced deformability makes passage through the splenic sinusoids difficult, leading to red cell sequestration and phagocytosis. In the RES (bone marrow, spleen, or liver), proteases convert globin into amino acids, heme protoporphyrin is oxidized by heme oxidase to biliverdin, reduced by biliverdin reductase to indirect bilirubin. Indirect bilirubin is conjugated to form bilirubin diglucuronide (direct bilirubin) by the liver and normally excreted in the bile. In the small bowel, gut bacteria reduce bilirubin to urobilinogen. A small amount of urobilinogen is absorbed by the small bowel and excreted in the urine. Heme iron is transferred to plasma apotransferrin for transport to tissues, most prominently to the bone marrow.

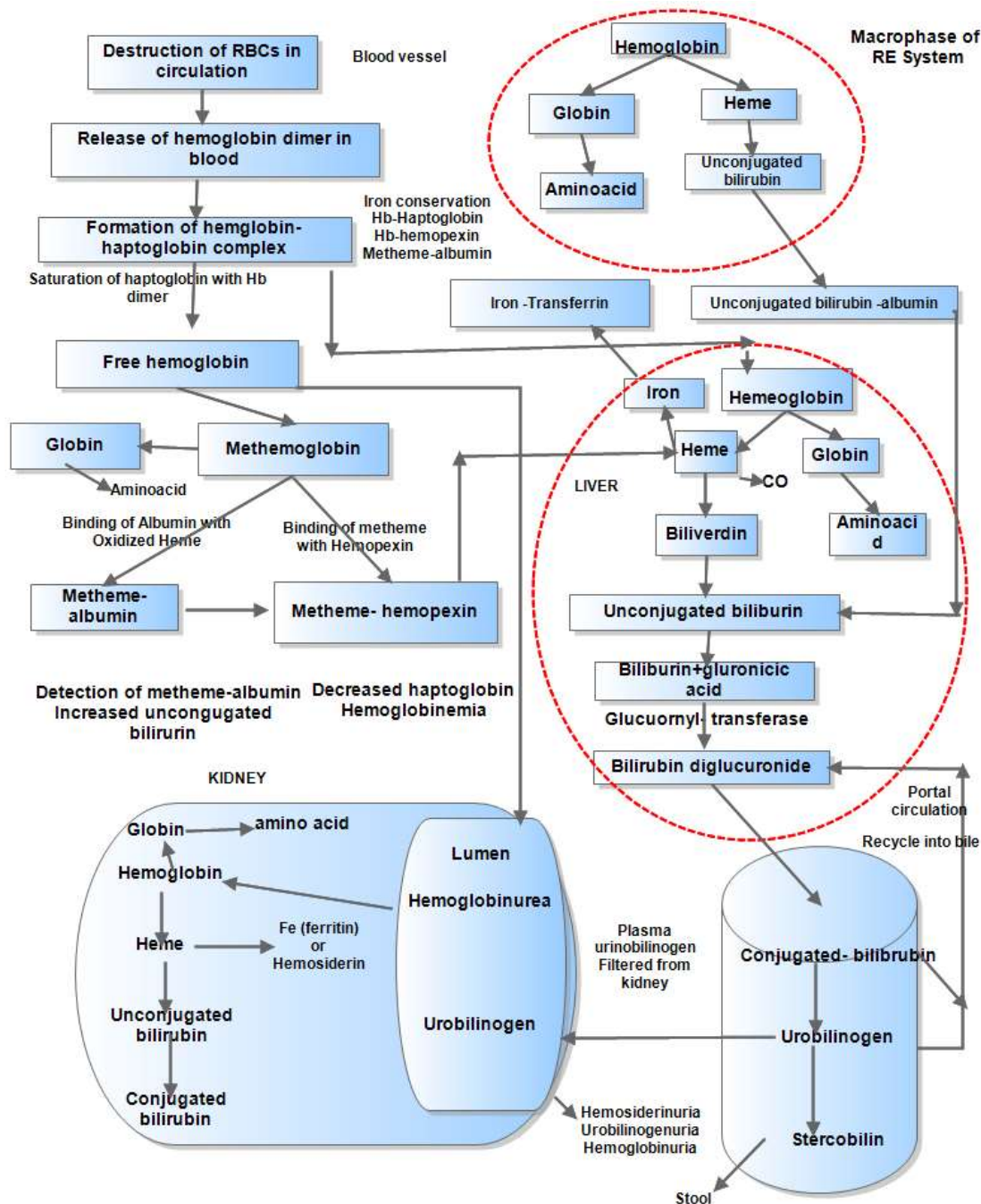


Figure 5 Scheme of hemolysis

Intravascular hemolysis

Intravascular hemolysis is caused by destruction of circulating RBCs by extreme heat, toxins, infectious agents, intracellular parasites (e.g., falciparum malaria), complement, mechanical damage by artificial vessels, heart valve, and changes the RBCs resistance, membrane permeability and integrity. As a result the red cell destabilizes to osmotic gradient, leading to rapid influx of sodium and water, cell swelling, and physical disintegration. The large amounts of free hemoglobin released from lysed red cells are promptly bound by haptoglobin, producing a complex that is rapidly cleared by mononuclear phagocytes for degradation to peptides (from globin), iron, and bilirubin (from heme). Hemoglobin binding capacity of haptoglobin is 100 mg% (100 mg of hemoglobin per 100 ml of blood). As serum haptoglobin is depleted, free hemoglobin oxidizes to methemoglobin (brown color). The renal proximal tubular cells reabsorb and catabolize much of the filtered hemoglobin and methemoglobin, but some passes out in the urine (imparting a red-brown color). Iron released from hemoglobin can accumulate within tubular cells, giving rise to renal hemosiderosis.

Table 10. Distinctive features of intravascular hemolysis and intracellular

Signs of hemolysis	Types of hemolysis	
	Intravascular	Intracellular
Localization of hemolysis	vessels	RES
Localization of hemosiderosis	tubules of the kidneys	spleen, liver, bone marrow
Yellowness of the skin and mucous membranes	moderate	severe
Enlarged liver and spleen	slight	significant
Leading laboratory signs	normochromic anemia, reticulocytosis, hypersideremia, erythroid hyperplasia in the bone marrow	
	Hemoglobinemia; hemoglobinuria; hemosiderinuria; indirect hyperbilirubinemia; absence or reduced of free serum haptoglobin	elevated stercobilinogen in feces and urine urobilinogen indirect hyperbilirubinemia increased excretion of bilirubin by bile

Hemolysis can occur continuously (chronic course) or occasionally in the form of crises resulting from a sharp increase of erythrocytes degradation via the action of provocative agent. Depending on the pathogenesis and clinical course there are several types of crises: hemolytic, aregenerative, sequestration and painful.

Hemolytic (hyperregenerative) crisis is a classic manifestation of acute hemolytic anemia in action of provocative factor (infection, cold, drugs, chemicals, hypoxia and others.). Clinical and laboratory is characterized by anemia, hyperreticulocytosis, hyperbilirubinemia and jaundice.

Aregenerative (aplastic) crisis is a consequence of defect compensatory-adaptive capabilities of hematopoiesis and violations of production of erythroid cells in BM. Most often occurs when an infection caused by parvovirus B₁₉. Appears anemic syndrome, may be accompanied by hepatomegaly, splenomegaly. Number of reticulocytes in peripheral blood strongly reduced.

Sequestration crisis is rare. It is based on intravascular hemolysis. Primary place of RBC destruction are the spleen vessels, rarer – liver. Along the symptoms of hemolysis (jaundice, anemia syndrome) appear sudden pain in the spleen and liver, abdominal pain, nausea, splenomegaly, hepatomegaly, hypovolemic shock (due to discharge a large amount of blood in the spleen).

Vasoocclusive (painful) crisis is common in qualitative hemoglobinopathies. Aggravating factors are dehydration, infections, hypothermia. By clinical hemolysis is attached pain resulting from vascular occlusion (eg, by sickle cells). The most characteristic pain is musculoskeletal (myalgia, arthralgia) and abdominal localization.

HEREDITARY MEMBRANOPATHIAS

Hereditary spherocytosis (anemia Minkovsky-Shoffar's)

Hereditary spherocytosis is a hereditary membranopathy with intracellular hemolysis. This disorder is caused by intrinsic defects in the red cell membrane skeleton that made red cells spheroid, less deformable, and vulnerable to splenic sequestration and destruction. In about 75% of cases is an autosomal dominant inheritance pattern.

Pathogenesis

Membrane protein defects are mutation in ankyrin (the most common) and mutation in band 2, spectrin (α and β) or band 3 account. Due to membrane defect and dysfunctional Na⁺/K⁺-ATPase pump the results it is an increasing permeability of RBC to sodium and spherocytes formation. In spleen spherocytes lose part of erythrocytes membrane and turn into microspherocytes. Life time of spherocytes decreases until 8-12 days.

Clinical manifestations:

- intracellular hemolysis lead to splenomegaly;
- jaundice due to increased unconjugated bilirubin;
- due to increased concentration of conjugated bilirubin in bile increased incidence of calcium bilirubinate gallstones.

There are three variants of the clinical course: mild, medium and heavy. Manifested in mild compensated hemolytic anemia; patients do not need blood transfusions. Hereditary spherocytosis

moderate severity is the most common manifestation of the disease and is characterized by moderate anemia, splenomegaly and the need for transfusion only during hemolytic crisis. Severe form is rare (3% of patients) and shows a heavy anemia (require regular substitution hemotherapy), severe splenomegaly and development of aplastic crises. The children with severe form is revealed specific skeletal deformities (stigmas of dysmaturity): a square tower skull; poor dentition; high (gothic) upper palate; syndrome of short little finger. A typical complication is cholelithiasis. A relatively rare complication is shin trophic ulcers.

Peripheral blood smear:

- normochromic normocytic hyperregenerative anemia varying severity: HB out of crisis is 100-110 g/l, during hemolytic crisis up to 40-50 g/l; in 50% of cases MCHC increased to 38-39%;
- microspherocytosis, anisocytosis, poikilocytosis, target cells; reticulocytosis out of crisis 3-10%, immediately after the crisis – more than 10%;
- WBC out of crisis is normal, during hemolytic crisis – leukocytosis with neutrophilia;
- ESR during the crisis increased.

Bone marrow examination

Bone marrow at spherocytosis hyper- or normocellular predominate red cell line (leuko-erythroblastic ratio is 1:2-1:3). Type of hematopoiesis is normoblastic. After the crisis increases the amount of basophilic erythroblasts and normoblasts ("blue" bone marrow). In frequent hemolytic crisis appear megaloblasts (due to the rapid consumption of folic acid). At aregenerative crisis changes in bone marrow are the same as in aplastic anemia.

Biochemical analysis of blood: hyperbilirubinemia, increased LDH activity and the concentration of iron, at least – serum ferritin.

Hereditary elliptocytosis

Hereditary elliptocytosis is usually seen as an autosomal dominant disorder affecting primarily people of African descent.

Pathogenesis

It results from defects in the membrane proteins spectrin, protein 4.1 or glycophorin C.

Clinical manifestations

Hereditary elliptocytosis does not usually lead to symptomatic disease. Majority of patients have no anemia or a mild hemolytic anemia and splenomegaly.

Peripheral blood smear:

- elliptocytes virtually 100% of RBCs in peripheral blood;
- decreased RBC osmotic resistance.

HEREDITARY ENZYMOPATHIES

Hereditary enzymopathies arise due to defect of erythrocytes enzymatic systems:

1. abnormalities of the pentose phosphate shunt: deficiency of glucose-6-phosphate dehydrogenase (the most widespread); deficiency of 6-phosphogluconate dehydrogenase; defect of glutathione synthesis;
2. deficiency of enzymes of glycolysis: deficiency of pyruvate kinase (the most widespread), hexokinase, glucose phosphate isomerase, phosphofructokinase, aldolase, triose phosphate isomerase, phosphoglycerate kinase;
3. deficiency of enzymes of glutathion cycle: glutathione synthetase, glutathione reductase, glutathione peroxidase;

G-6-PD deficiency (glucose-6-phosphate dehydrogenase deficiency)

X-linked recessive disorder.

Pathogenesis

It is a decreasing synthesis of NADPH and glutathione in the pentose phosphate pathway which defends red cell proteins (particularly hemoglobin) against oxidative damage. Proper RBCs function requires only 20% of the enzyme. Glutathione normally neutralizes hydrogen peroxide, an oxidant product in RBC metabolism. Peroxide oxidizes Hb, which precipitates in the form of Heinz bodies. Heinz bodies are removed in the spleen, leaving erythrocytes with a missing section of cytoplasm (formatted "bite cells"). The altered erythrocytes undergo both intravascular and extravascular destruction.

Clinical manifestations:

Most patients have no clinical or laboratory evidence of ongoing hemolysis until an event — infection, drug reaction (primaquine, chloroquine, dapsone, sulfonamides) or ingestion of fava beans or inspiration of it pollen (mainly in Mediterranean variant). After an oxidant stress, sudden onset with back pain and hemoglobinuria up to 2-3 days

Clinical forms of G-6-PD deficiency:

- acute intravascular hemolysis;
- favism;
- hemolytic disease of newborn, not associated with the blood group and rhesus;
- hereditary chronic hemolytic anemia (non-spherocytic);
- latent (asymptomatic) form.

Peripheral blood smear:

- normochromic, normocytic hyperregenerative anemia;
- aniso- and poikilocytosis (bite cells), basophilic stippling, Heinz-Ehrlich bodies in erythrocytes,
- leukocytosis with left shift.

Bone marrow examination: hypercellular, reactive hyperplasia of erythroid line in which the proportion of erythroid cells can reach up to 50-70% of the total number of myelokaryocytes. Type of hematopoiesis is normoblastic. The phenomenon erythrophagocytosis is detected.

Biochemical analysis of blood

- at hemolysis increases the content of unconjugated bilirubin in the serum, but its level rarely reaches very high rates.
- a sharp increase in the concentration of free hemoglobin in the blood and decreased levels of haptoglobin.

Urinalysis: hemosiderin and free hemoglobin are detected in urine.

Pyruvate kinase (PK) deficiency

Autosomal recessive pattern.

Pathogenesis

It is a rare enzyme disorder of the Embden-Meyerhof pathways. RBCs lacking this enzyme are unable to generate ATP from adenosine diphosphate for membrane function. Chronic lack of ATP causes membrane damage. Result is dehydration of the RBC (echinocytes).

Clinical manifestations

Hemolytic anemia with jaundice is begun at birth. Hemolysis was localized intracellularly occurs evenly in different organs containing reticuloendothelial cells. In patients are detected pallor, jaundice and splenomegaly. With age, developed gallstone disease, secondary iron overloads and changes of bones (due to frequent blood transfusions). Aplastic crises triggered by parvovirus B₁₉ infection.

Peripheral blood smear:

- normochromic, normocytic hyperregenerative anemia;
- aniso- and poikilocytosis (echinocytes).

Bone marrow examination: normoblastic erythroid hyperplasia. Erythrophagocytosis

HEREDITARY HEMOGLOBINOPATHIAS

Hemoglobinopathias

1. Qualitative — abnormality of primary structure of Hb (sickle cell anemia)
2. Quantative — impairment of synthesis or absence of one of the globin chains in case of intact primary structure (thalassemia)

Sickle cell anemia

Sickle cell anemia is autosomal codominant, inherited in simple mendelian fashion.

Pathogenesis

It results from point mutation: replacement of glutation acid (HbβA) by valine (HbβS) in the 6th amino acid of the β chain. Homozygous inheritance results in sickle cell disease, with most of the hemoglobin being HgβS. Heterozygous inheritance results in sickle cell trait, in which HgβS and Hgβ A are present. Red blood cells possessing HgβS as the majority hemoglobin are insoluble or rigid in areas of low oxygen concentration, such as the spleen, liver, kidneys, joints and extremities. Hgβ S is structural

instability and forms liquid tactoids or polymers of hemoglobin that appear as long, thin bundles of fibers under electron microscopy (sickle cells). Formation of sickle cells is also induced by hypoxia, acidosis, dehydration, fever, and exposure to cold. Sickle cells adhere to vascular endothelium and plug small arterioles, capillaries (leads to infarction) and veins (predisposes to thrombosis). Fragility of sickled RBCs destroys it by mechanical trauma of circulation and causes hemolysis.

Sickle cells may be able to revert to the discoid shape or wheat shape (reversible sickle cell) in to the oxygenated environment of the lung

Clinical manifestations

Most symptoms occur only in patients who are homozygous.

Main manifestations are:

- chronic hemolytic anemia;
- recurrent painful attacks;
- bacterial infections;
- deterioration of tissue and organ function;
- shortened life expectancy.

Anemia is usually severe but varies highly among patients; mild jaundice and pallor are common. Painful crisis (due to ischemia and infarction) causes severe bone pain usually in low back, also in the tibias and arms, and in joints (result from hemarthrosis or femoral head necrosis). Severe abdominal pain often intractable may develop with or without vomiting must be differentiated from pain due to surgical causes.

Peripheral blood smear:

- normal profile of peripheral blood in HbAS –HbA 55% to 60%, HbS 40% to 45%; in HbSS – HbS 90% to 95%, HbF 5% to 10%, no HbA; there are sickle cells and target cells.
- normochromic, normocytic hyperregenerative (reticulocytosis > 5%), anemia, hemoglobin concentration 60-80 g/l;
- aniso- and poikilocytosis (sickle cells, target cells, ovalocytes, schistocyte), polychromatophilia of erythrocytes, basophilic stippling of RBCs, single normoblasts,
- sickle cell screen: sodium metabisulfite reduces O₂ tension, which induces sickling.
- leukocytosis up to $12-20 \times 10^{12}/l$, neutrophilia, shift to the left;
- thrombocytosis;
- ESR reduced.

Bone marrow examination: hypercellular, reactive hyperplasia of erythroid line

Biochemical analysis of blood: hyperbilirubinemia, elevated LDH, increased serum iron and ferritin, hemosiderosis is rare.

Thalassemia

Thalassemia is among the most common inherited disorders of Hb production.

Pathogenesis

By the genetic mechanism thalassemia divided into homozygous and heterozygous. At homozygous form there is a mutation of all thalassemia genes, which lead to a complete blockade of synthesis of the corresponding globin chain. At heterozygous forms along with the gene of thalassemia a healthy pair of this gene, resulting in the synthesis of globin chain is partially blocked. Homozygous thalassemia determines a more severe course of the disease.

Full or partial violation of the synthesis of one of the globin chains leads to violations of erythrocyte hemoglobinization, hemolysis and ineffective erythropoiesis. It results from unbalanced Hb synthesis of at least one globin polypeptide chain (α , β , δ , γ) distinguish α -, β -, δ -, and γ -thalassemia.

Full clinical picture of severe hemolytic anemia occurs when homozygous inheritance violations of β -chains synthesis – Cooley's disease. It manifests physical and mental immaturity, pale-icteric skin with signs of hemosiderosis (gives for skin a greenish-brown color), the deformation of the skull bones (tower skull, maxilla enlargement, malocclusion, on X-ray - expansion of the medullary canal of long bones, transverse striations of the skull flat bones - the needle periostosis), leg ulcers, severe hepato- and splenomegaly.

Peripheral blood smear:

- hypochromic microcytic hyperregenerative anemia, the severity of which depends on the form of thalassemia;
- anisocytosis (microcytes), poikilocytosis (target cells);
- hypochromia of RBCs, polychromatophilia, basophilic stippling;
- increase in siderocytes;
- number of WBCs and platelets - within norm.

Bone marrow examination: hypercellular, reactive hyperplasia of erythroid line, sideroblasts content increased.

Biochemical analysis of blood: hyperbilirubinemia, elevated LDH, increased serum iron and ferritin.

ISOIMMUNE HEMOLYTIC ANEMIAS

Hemolytic disease of newborn (HDN)

Acquired HA, resulting antigenic differences of RBCs mother and child, mothers develop antibodies against fetal Ag. The transplacental passage of maternal IgG antibodies through the placenta (e.g., anti-D antibodies, anti-AB antibodies in O mothers) resulting in an extravascular hemolytic anemia in the fetus.

Pathogenesis

The first pregnancy Rh-negative mother with Rh-positive fetus usually proceeds normally. During childbirth occurs maternal immunization by antigens of the fetus RBCs with development of anti-erythrocytic antibodies (anti-Rh(D)-IgG). During her second pregnancy with Rh-positive fetus, antibodies fixed on fetal erythrocytes and cause the death of RNCs by intracellular hemolysis with the development of fetal erythroblastosis.

Types of HDN:

1. Intrauterine fetal death with maceration
2. Edematous
3. Anemic
4. Congenital icteric
5. Postnatal icteric

Manifestations

The main symptoms of HDN are jaundice, hepato-splenomegaly and, in severe cases - edema, ascites (due to lack of blood flow). The most dangerous symptom of anemia is "kernicterus" with signs of the nervous system damage due to the toxic effect of indirect bilirubin, which include nystagmus, twitching, high-pitched cry. There are cases of stillbirth.

Transimmune hemolytic anemia

Hemolytic anemia occurs at penetration into the body of newborn erythrocytic antibodies from mother suffering from autoimmune hemolytic anemia.

HETEROIMMUNE HEMOLYTIC ANEMIAS

Heteroimmune hemolytic anemias develop due to formation of antibodies against haptens. These haptens may be drugs (penicillin, sulfonamides and etc.) or viruses.

About 15% of acquired immune hemolytic anemias are related to drug administration. Some drugs lead to development of autoimmune hemolytic anemia, other as a haptens lead to formation of drug-dependent antibodies that react with RBCs only in the presence of this drug resulting in hemolysis by complement activation.

Table 12. Drug-induced immune hemolysis

Type of serological reaction	Severity of hemolysis	Detection of drug-induced antibodies	Drugs
Drug-dependent antibody	Severe often with intravascular hemolysis and renal failure	Serum+drug+ RBCs	Quinidine, quinine
Passive agglutination	Moderate severity usually without	Serum+drug-coated	Penicillins,

	intravascular hemolysis	RBCs	cephalosporins
Autoantibody	Moderate severity usually without intravascular hemolysis	Serum+RBCs	Methyldopa, procainamide

AUTOIMMUNE HEMOLYTIC ANEMIAS

Classification of autoimmune hemolytic anemia:

- With incomplete warm agglutinins:
 - ✓ Idiopathic
 - ✓ Symptomatic
- With full cold agglutinins:
 - ✓ Idiopathic cold hemagglutinin disease
 - ✓ Symptomatic
- Paroxysmal cold hemoglobinuria (anemia Donath-Landsteiner)
 - ✓ Acute form
 - ✓ Chronic form
- Hemolysine :
 - ✓ Acid-hemolysine
 - ✓ Warm hemolysine

Types of antibodies:

1. Incomplete warm agglutinins
2. Full cold agglutinins
3. Warm hemolysins
4. 2-phase hemolysins

AIHA with warm antibodies is diagnosed in 70% of cases as idiopathic AIHA and as symptomatic (on background of different diseases – Hodgkin's disease, CLL, systemic lupus erythematosus, at certain medications, such as penicillin). It occurs in all age groups. Heat antibodies often belong to the class IgG (sometimes - to IgA), predominantly directed against antigens of the Rh system and cause hemolysis at 37°C. The leading mechanism for implementing the immune effect is the interaction of anti-erythrocytic antibodies with Fc-receptor of phagocytic cells and the subsequent development of intracellular hemolysis.

AIHA with warm antibodies can have both acute and gradual onset. Patients with acute onset have rapidly increasing weakness, shortness of breath, sometimes pain in the heart, fever, vomiting, severe pallor, intense jaundice. At the gradual beginning appears arthralgia and subfebrile temperature, slow increase in anemia, weakness, jaundice. The majority of patients have splenomegaly, hepatomegaly and related calculous cholecystitis.

AIHA with cold antibodies found in 20% of cases. Often affects the elderly people. In childhood is observed as a symptomatic form, complicating the course of acute Mycoplasma pneumonia, infectious mononucleosis and systemic connective tissue diseases. Interaction of antigens with RBCs occurs when the temperature drops below 37°C. The most active binding of cold antibodies to the erythrocytes is observed in the temperature range +4–+15°C. Cold antibodies cause predominantly intra-vascular hemolysis, with the participation of the complement system.

AIHA with cold antibodies begins gradually. Patients complain of weakness, malaise, decreased performance, cold intolerance. At low temperatures, observed acrocyanosis (blue, then paleness of fingers, toes, ears, nose); there is a sharp pain in the limbs. With a significant supercooling occurs typical Raynaud's syndrome. Hemolysis has predominantly intravascular character, so it is possible appearance of dark-colored urine due to hemoglobinuria and hemosiderinuria. The liver and spleen are usually not enlarged. The course of disease is chronic. Hemolytic crises are rare.

AIHA with biphasic Donath-Landsteiner antibodies is rare and accounts for about 2% of all AIHA. Etiologic factor often is hypothermia, viral infection, congenital syphilis. Donath-Landsteiner antibodies belong to the class IgG and directed toward the erythrocyte P-antigen. Binding of biphasic antibodies to erythrocytes occurs at temperature of 0- 15 ° C (cold phase), but hemolysis occurs only at a

temperature of +37°C when the resultant antigen-antibody complex fix complement. Hemolysis is intravascular character.

Paroxysmal cold hemoglobinuria is an example of AIHA with biphasic antibodies. The clinical picture develops within a few hours after hypothermia and is characterized by fever, chills, pain in the abdomen or in the lumbar region, nausea, vomiting and appearance of dark brown or black urine. Most of the symptoms are stopped after a few hours. Excretion of black urine (due to intravascular hemolysis) is lasts for about two days. Spleen may be palpable in the background of hemolytic crisis. There are vascular manifestations: chilliness, acrocyanosis, Raynaud's syndrome.

Peripheral blood in AIHA:

- normochromic, normocytic anemia;
- poikilocytosis of RBCs: schistocyte, single microspherocytes;
- single normoblasts;
- reticulocytosis;
- leukocytosis up to $10-15 \times 10^9/l$ with a shift of leukocyte formula to the left;
- increased ESR (30 mm/h);
- platelet count is normal or reduced.

Bone marrow

Red lineage sharply expanded. Type of hematopoiesis is normoblastic, sometimes with megaloblastic features due to folic acid deficiency, heavily consumed during hemolytic crisis.

Biochemical blood analysis: hyperbilirubinemia, increased LDH, reduced haptoglobin. The content of serum iron increased or upper limit of normal.

NON-IMMUNE HEMOLYTIC ANEMIAS

The main reasons for non-immune hemolytic anemias:

1. Infectious agents: intracellular parasites (*Plasmodium falciparum*, *Bartonella*), bacterias (meningococcus, pneumococcus, Gram-negative bacteria) cause microangiopathic hemolysis;
2. Chemical and physical factors: drugs, industrial chemicals, high body temperature (including - in burn disease);
3. The mechanical lysis of erythrocytes: DIC syndrome, vasculitis, vascular and intracardiac prostheses;
4. Acquired erythrocyte membrane damage: liver disease, paroxysmal nocturnal hemoglobinuria.

Non-immune hemolytic anemia is characterized by the combination of clinical and laboratory signs of intracellular and intravascular hemolysis. Coombs test negative. For adequate treatment is necessary to remove the causes or to stop contact with the substance, that caused hemolysis. With the development of renal failure, hemodialysis is shown.

ERYTHROCYTOSIS

Erythrocytosis – is an increase in the content of red blood cells. There are two groups of erythrocytosis: relative (increase in red blood cells and hemoglobin in a unit volume of blood without increasing their absolute number) and absolute (absolute increasing the number of red blood cells).

Relative erythrocytosis is divided into:

- **hemoconcentration** – occur with a decrease in plasma volume (hemoconcentration) due to dehydration (with uncontrollable vomiting, diarrhea, sweating, burn patients, etc.);
- **stress-erythrocytosis** – develop due to the "release" of the erythrocytes from blood-pool (as the stress response in vascular-reflex phase of compensatory reactions in acute blood loss, Gaisbock's syndrome (spurious polycythaemia smokers), hypertension, etc.).

Absolute erythrocytosis are due to an increase in erythropoietic bone marrow function, with an increased production of erythropoietin in the body are:

- **hypoxic** – develop as a result of increased production of erythropoietin by cells of kidney juxtaglomerular apparatus in response to long-term hypoxia: the decrease in partial pressure of oxygen in the air (in people who have caisson work at mountainous disease, etc.), and respiratory diseases (asthma, emphysema, interstitial pneumonia, diffuse pneumosclerosis, etc.), pathology of the cardiovascular system (heart disease, hypertrophic cardiomyopathy, hemorrhagic

telangiectasia, etc.), local ischemia of the kidneys (renal cysts, hydronephrosis, renal vascular damage, etc.);

- **tumor** – developed through the production of erythropoietin by tumor cells: in pheochromocytoma, hypernephroma, hepatocellular carcinoma, gastric carcinoma, and others

Production of erythropoietin by juxtaglomerular apparatus of the kidneys is normal – erythremia (or polycythemia vera) arising from myeloproliferation due to tumor erythroid hyperplasia in a defect of precursor cells of myelopoiesis.

The group of the absolute erythrocytosis also includes endocrine erythrocytosis arising from the ability of a number of hormones have a direct or indirect (via increased production of erythropoietin by juxtaglomerular apparatus of kidney cells), stimulating effect on erythropoiesis: with hyperthyroidism, Cushing's syndrome, hyperaldosteronism, hyperandrogenemia, and others. Hereditary (family) erythrocytosis described.

Questions for self-control of knowledge:

1. What are principles of classification and manifestations of primary and secondary polycythemia?
2. What are hereditary hemolytic anemias? What are their etiology and mechanisms of development. Describe a blood picture. What are principles of diagnosis.
3. What are causes of hemolytic disease of newborn (HDN)? Provide a general description of main forms. What are principles of therapy and prevention.
4. What is autoimmune hemolytic anemia (AIHA)? What are mechanisms of its development?

Tasks for self-managed student work:

1. Features of embryonic hematopoiesis; hemogram of newborn.
2. Polycythemia vera

Literature

Basis literature:

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