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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 системы крови. Патофизиология эритроцитов.
Дизэритропоэтические анемии**

Theme: **Pathophysiology of blood. Pathophysiology of erythrocytes. Dyserythropoietic anemias**

Время 3 ак. часа

1.Actuality of the theme. Anemia appear on the base of various diseases, intoxications, bloodloss. Therefore clinicists of various specialities often find them in the practical activity. The quantitative changes erythrocytes and hemoglobin are one of the most important parameters, on the basis of which diagnostics of anemia is carried out. On changes of these parameters also judge about the efficiency of treatment. Using the quantitative characteristics of erythrocytes and hemoglobin, it is possible to define one more clinically important parameter - colour index. Basing on a colour index one can judge about the saturation of erythrocytes by hemoglobin. The value of a colour index (norm, decrease, increase) has diagnostic mean.

Learning goals of the lesson: to study changes in physico-chemical properties of blood; to study etiology and pathogenesis of anemias.

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 main causes and mechanisms of changes in ESR, protein composition.
2. To know causes, mechanisms of development and clinical manifestations of dyserythropoietic anemias.
3. To be able to make a conclusion on qualitative and quantitative changes in blood according to hemogram.

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. Causes and mechanisms of changes in physicochemical properties of blood in various diseases.
2. Pathological forms of RBCs, pathological inclusions in RBCs.
3. Iron deficiency anemia: etiology, pathogenesis, clinical manifestations. Exchange and role of iron in the body.
4. Megaloblastic anemia: etiology, pathogenesis, clinical manifestations.
5. Anemia of chronic diseases.
6. Anemia in leukemia and other tumor lesions of bone marrow.
7. Aplastic anemia. Etiology, pathogenesis, main clinical manifestations.

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:

Erythrocytes (RBC): occupy about 40-45% of the total blood volume or 30 ml/kg body weight.

ERYTHROPOIESIS

There are megaloblast- and erythroblast types of hemopoiesis. First morphologically recognizable cell of erythron is erythroblast.

Further stages of erythroid maturation in **erythroblastic erythropoiesis** are following: erythrocytoblast → pronormocyte → basophilic normocyte → polychromatophilic normocyte → orthochromatophilic normocyte → reticulocyte → erythrocyte.

The cell becomes smaller, nucleus is shrunk and in orthochromatophilic erythroblasts, it is expelled from the cell. A change in cytoplasm stainability (basophilia-acidophilia) as polysomes are reduced, hemoglobin is synthesised. Reticulocyte still contains some organelles (polysomes and mitochondria). From single erythroblasts as a result of mitosis appear 16 to 32 reticulocytes. The cycle time of erythroblasts to reticulocyte ranges from 3-4 to 5-7 days. At first reticulocyte matures within the BM (approximately 2-3 days) and then the more mature reticulocytes pass in peripheral blood. Mature red blood cells normally in adults have a lifespan 100-120 days, in full-term newborns – 60-70 days and preterm – 35-50 days.

Megaloblastic erythropoiesis: promegaloblast → basophilic megaloblast → polychromatophilic megaloblast → orthochromatophilic megaloblast → megalocyte

RBCs production is stimulated by erythropoietin on erythroid progenitors in the bone marrow. Erythropoietin is a secreted glycoprotein produced by renal peritubular cells in response to hypoxia.

Hemoglobin — an oxygen-binding molecule produced only by erythroid cells, is composed of four globin chains (two alpha and two non-alpha, either beta or gamma) each of which binds one heme molecule. The three hemoglobin variants normally seen in healthy adults are hemoglobins A ($\alpha_2\beta_2$), A2 ($\alpha_2\delta_2$), and F ($\alpha_2\gamma_2$).

Heme, the oxygen-carrying prosthetic group of hemoglobin, is a Fe^{2+} -containing tetrapyrrole that functions in electron exchange. Heme synthesis is taken place in both cytoplasm and mitochondria. The 1st step is conversion of glycine and succinyl coenzyme A to delta aminolevulinic acid by the enzyme aminolevulinic acid (ALA) synthase, with pyridoxine (vitamin B6) as a cofactor. The last (and rate-limiting) step is the addition of Fe^{2+} to protoporphyrin IX by the mitochondrial enzyme ferrochelatase to form heme.

CHANGES OF ERYTHROCYTES

Changes of erythrocytes are:

- anisocytosis – change in the size of RBCs;
- poikilocytosis – change in the form of RBCs (see table 3);
- presence of pathological inclusions (see table 4);
- change in the staining of RBCs (contents of Hb).

Anisocytosis

Measuring the size of RBC can be obtained by Price-Jones curve of RBC size distribution in the peripheral blood (figure3).

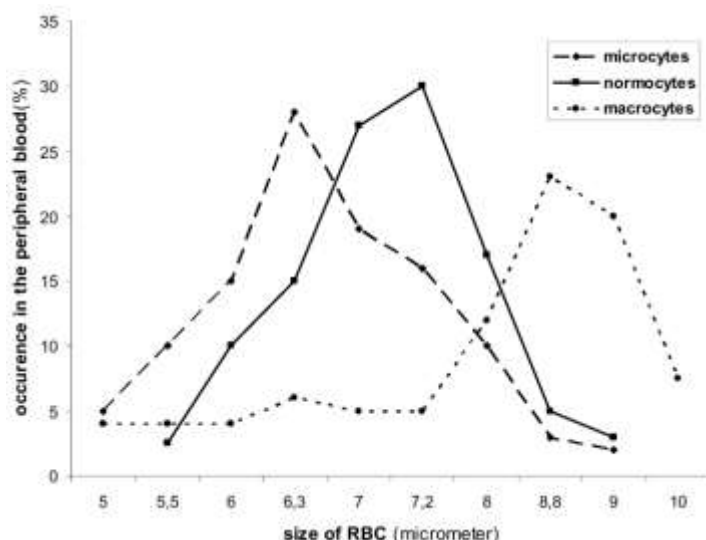


Figure 3. Price-Jones curve

Variability in size of RBC may be observed also in healthy humans (physiological anisocytosis). In healthy people, up to 5-7 % of all RBC may have smaller or bigger diameter than the mean value.

Normocytes – are RBCs with reference values of size, shape and content of hemoglobin and diameter of RBC 7,2 – 8,3 mcm.

Microcyte – diameter of RBC < 7,2 mcm.

Macrocyte – diameter of RBC from 8.3 to 12 mcm.

Megalocyte – diameter of RBC 12–15 mcm.

Table 3. Pathological forms of RBCs

RBC Type	Description	Underlying Change	Disease States
Acanthocyte (spur cell)	Irregularly speculated cells with projections of varying length and dense center	Altered cell membrane lipids	Abetalipoproteinemia, cirrhosis, hepatic necrosis, pyruvate kinase deficiency, uremia, infantile pyknocytosis
Bite cell (degmacyte)	Smooth semicircle taken from one edge	Heinz body "pitting" by spleen	G6PD deficiency, drug-induced oxidant hemolysis
Echinocyte (burr cell or crenated cell)	Cells with short, evenly spaced spicules and preserved central pallor	May be associated with altered membrane lipids	Usually artifactual; seen in uremia, bleeding ulcers, gastric carcinoma, artifact
Ovalocyte (elliptocyte)	Elliptical-shaped cell	Abnormal cytoskeletal proteins	Hereditary elliptocytosis, megaloblastic anemia, myelofibrosis, refractory normoblastic anemia, thalassemia
Helmet cells	These are sharp-angled, helmet-looking distorted, fragmented cells	Mechanical destruction micro-vasculature by fibrin strands mechanical damage or prosthetic heart valve	DIC, microangiopathic hemolytic anemia, thrombotic thrombocytopenic purpura (TTP), prosthetic heart valves, severe valvular stenosis, malignant hypertension
Knizocytes (triconcave Er).	RBCs have a "handle."	Mechanical destruction	Occur mainly in hemolytic anemias
Schistocyte	Distorted, fragmented cell, two or three	Mechanical destruction micro-	Microangiopathic hemolytic anemia, DIC, TTP, prosthetic heart valves,

RBC Type	Description	Underlying Change	Disease States
	pointed ends	vasculature by fibrin strands mechanical damage or prosthetic heart valve	severe burns, HUS, giant hemangioma, metastatic carcinoma, malignant hypertension, eclampsia (toxemia of pregnancy), vasculitis, macroangiopathic hemolytic anemia
Sickle Cell (drepanocyte)	Bipolar, speculated forms, sickle-shaped, pointed at both ends	Molecular aggregation of hemoglobin S	Sickle cell disorders excludes S trait
Spherocyte	Spherical cell with dense hemoglobin and absent central pallor; usually decreased in diameter	Decreased membrane redundancy	Hereditary spherocytosis, artifact, autoimmune hemolytic anemia, acute alcoholism, hemoglobin c disease, following severe burn injury, hemolytic transfusion reactions, severe hypophosphatemia, acute oxidant injury: hexose monophosphate shunt defect
Stomatocyte	Mouth or cuplike deformity	Membrane defect with abnormal cation permeability	Hereditary stomatocytosis, immunohemolytic anemia
Target cell (codocyte)	Target-like appearance hypochromic with central hemoglobin	Increased redundancy of cell membrane	Liver disease, postsplenectomy, thalassemia, hemoglobin C disease, iron deficiency
Teardrop cell (dacrocyte)	Distorted, drop-shaped cell	Mechanical distortion of red cell	Myelofibrosis, myelophthisic anemia extramedullary hemopoiesis, severe hemolytic anemia, erythroleukemia
Xerocytes	shrink flat RBC	defects in membrane permeability, dehydrate, becoming rigid	tumors, inherited disorders

Table 4. Pathological inclusions in erythrocytes

RBC inclusions	Description	Underlying Change	Disease States
Basophilic stippling	Punctate basophilic inclusions, dispersed blue granulations	Precipitated ribosomes, mitochondria	Lead intoxication, thalassemia, arsenic poisoning, thalassemia, sideroblastic anemia, hemolytic anemia, severe anemia, unstable hemoglobin, pyrimidine 5'-nucleotidase deficiency
Pappenheimer bodies (siderocytes)	Small, dense basophilic granules	Iron-containing granules, mitochondrial remnant or siderosome, iron granules, may encircle the nucleus	Sideroblastic anemia, sideroachrestic anemias, postsplenectomy severe hemolytic anemias, lead poisoning, and pernicious anemia
Howell-Jolly bodies	small (1 mm) dense, perfectly round basophilic	Nuclear fragment containing aberrant	Postsplenectomy, hemolytic anemia, megaloblastic anemia

		chromosomes	
Cabot rings	Ring or figure- eight strand stained purple	Spindle remnant	Lead toxicity, pernicious anemia, hemolytic anemia
Heinz bodies	Round blue precipitates of hemoglobin in RBC detected by supravital staining	Aggregates of denatured hemoglobin	Postsplenectomy, megaloblastic anemia, oxidative hemolytic anemia (G6PD Deficiency)

Change in the staining of RBC (contents of Hb):

Hyperchromic – the RBCs are intensively colored.

Hypochromic – with pale staining. The cells, which have normal diameters, are conspicuous for their paucity of hemoglobin, which may form only a thin peripheral rim (anulocytes).

Polychromatophilia is an ability to perceive the acidic and basic dyes, RBCs painted in color from blue to grayish pink. They arise as a result of insufficient accumulation of hemoglobin in RBCs with the remnants of basophilic substance.

RBCs indices

1. Mean corpuscular volume (MCV)

MCV measures only average cell volume. The value is expressed in volume units (femtoliters, fl). The normal range is 80-97 fl. The formula for the calculation is:

$$MCV = \frac{Ht}{RBCs}$$

Where: Ht – hematocrit rate in %, RBC – the number of red blood cells in millions of 1 mm³ of blood.

Normocytic refers to blood with a normal MCV. The RBCs are microcytic when the MCV is low than 80 fl. Microcytosis is to look for iron deficiency or thalassemia, anemia of chronic disease, vitamin C and copper deficiencies.

RBCs are macrocytic when the MCV is high. MCV 100 – 110 fl has a clinical association with alcohol, liver disease (with and without Alcoholism), drug therapy (HIV, oncology and epilepsy), reticulocytosis due to hemolytic anemia; MCV > 110 fl — megaloblastic anemia due to B₁₂ or folate deficiency, myelodysplastic syndrome.

2. Mean corpuscular hemoglobin (MCH)

The MCH represents the mean mass of hemoglobin in the RBC and is expressed in the mass unit, pictograms (pg). The formula for the calculation is:

$$MCH = \frac{Hb}{RBC}$$

Where: Hb –count of hemoglobin in blood (g/l), RBC – the number of erythrocytes in 1 liter of blood.

The normal range is 27-31 pg. Elevated MCH is associated with macrocytic anemia. Diminished MCH is associated with microcytic anemia. Hyperlipidemia may give a false elevation of the MCH

3. Mean corpuscular hemoglobin concentration (MCHC)

This is the mean concentration of hemoglobin in the red cell. The formula is:

$$MCHC = \frac{Hb}{Ht}$$

Where: Ht – hematocrit rate in %, Hb –count of hemoglobin in blood (g/l).

Cells with normal, high, and low MCHC are referred to as normochromic, hyperchromic, and hypochromic, respectively. These terms will be important in anemia classification.

4. Red cell distribution width (RDW)

Indicator of heterogeneity of RBCs by volume is characterizing the degree of anisocytosis. At the same time RDW index characterizes fluctuations of cell volume within populations and is not related to the absolute value of the RBCs volume. Therefore, the presence of RBCs in the blood with a modified but quite uniform size (eg microcytes), RDW values may be within normal limits. Units: % – the percentage erythrocyte volume deviations from the average value in the population (% variation). In norm – 11,5-14,5%.

Red blood cells normally distributed in diameter in a so-called Price-Jones curve (see figure 3).

PHYSICO-CHEMICAL PROPERTIES OF BLOOD

Blood viscosity

The viscosity of blood is determined in relation to the viscosity of water, and depends on blood cell (mainly RBC) and plasma proteins. If we take the viscosity of water per 1, the average relative viscosity of blood in a healthy adult is 4,5 (3,5-5,4) and plasma viscosity – 2,2 (1,9-2,6). In this case, the viscosity of the venous blood is higher than the arterial, which is associated with the arrival of the red blood cells of carbon dioxide causes an increase in cell size.

Reasons for the increase in blood viscosity:

- age (blood viscosity increases with age);
- excessive protein diet;
- dehydration;
- polycythemia;
- emptying of depot (spleen, liver, lungs, bone marrow, etc.);
- violation of deformability and aggregation of erythrocytes;
- activation of coagulation factors.

Osmotic blood pressure

The osmotic blood pressure – is the force with which the solvent (for blood is water) passes through a semipermeable membrane from a less concentrated to a more concentrated solution. The osmotic pressure of the blood is important in the regulation of the water distribution between tissues and blood vessels, cells and interstitial fluid. The functions of the body's cells can be carried out only if it's relative stability, which is provided by neurohumoral mechanisms – antidiuretic and antinatriuretic systems.

The osmotic pressure of blood may affect the products of digestion of proteins, fats and carbohydrates are absorbed into the blood and lymph systems, as well as low molecular weight products of cell metabolism.

Erythrocytes osmotic resistance

Resistance (resistance) of red blood cells – the ability to withstand a variety of their destructive effects: osmotic, mechanical, chemical, physical, and etc.

1. *Isotonic Solutions*

Isotonic solution is the solutions having the same effective osmolality (tonicity) as body fluids (0,9% sodium chloride solution, 5% glucose solution). The osmotic is in equilibrium between inside and outside the cell across the cell membrane.

2. *Hypertonic Solutions*

Hypertonic solutions – is the solutions having greater effective osmolality than the body fluids like 2% sodium chloride solution. When RBCs are placed in hypertonic solution, water moves out of the cells (exosmosis) resulting in shrinkage of the cells (crenation).

3. *Hypotonic Solutions*

Hypotonic solutions – is the solutions having less effective osmolality than the body fluids. For example is 0.3% sodium chloride solution. When the RBCs are taken in hypotonic solution, water moves into the cells (endosmosis) resulting in swelling and rupture (hemolysis) of the cells.

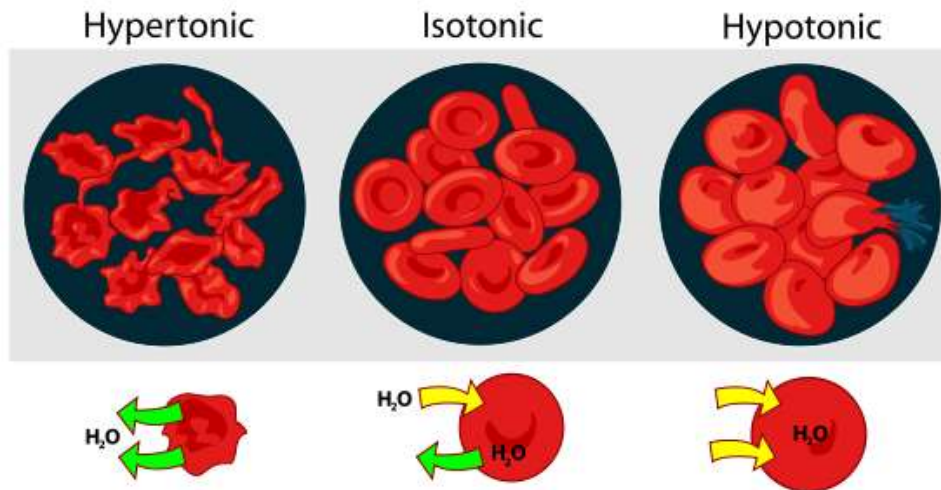


Figure 4 – Effect of hypertonic and hypotonic solutions on red blood cells

Decrease in osmotic resistance of erythrocytes (increase the minimum and maximum indicators of resistance) is observed at:

- autoimmune hemolytic anemia caused by thermal antibodies;
- hemolytic disease of the newborn;
- hereditary microspherocytosis and stomatocytosis;
- B₁₂ deficiency anemia;
- toxicosis;
- bronchopneumonia, violations of the functions liver and spleen;
- hemoblastosis.

Increase in osmotic resistance of erythrocytes observed in:

- obstructive jaundice;
- polycythemia;
- iron deficiency anemia;
- thalassemia;
- sickle cell anemia;
- after massive blood loss.

Total protein

In human plasma contains about 100 different proteins. By electrophoretic mobility can be roughly divided into five fractions: albumin, α_1 -, α_2 -, β - and γ -globulins. Separation into albumin and globulin is initially based on the difference in solubility: albumins are soluble in pure water, and globulins - only in the presence of salts. Main mass of the plasma protein synthesized in the liver. Liver cells (hepatocytes) are involved in the synthesis of albumin, fibrinogen, α - and β -globulins and components of coagulation system. Most of the β - and γ -globulins synthesized in cells of the immune system (lymphocytes).

Plasma proteins play important physiological roles in the body:

- maintain viscosity, the fluidity of blood;
- determine the volume of blood in the bloodstream;
- keep the blood cells in suspension;
- carry multiple transport of exogenous and endogenous substances (hormones, minerals, lipids, pigments, and other. Biologically important compounds);
- regulate the constancy of blood pH;
- are coagulation factors;
- involved in immune responses (immunoglobulins, opsonins, acute phase proteins).

Changes in the concentration of total protein may be physiological, relative and absolute.

Physiological hypoproteinemia may occur in young children, women during pregnancy (especially in the third trimester), lactation, prolonged bedrest.

The relative changes in protein content observed in the increase (decrease) in circulating blood volume. Hydremia (load water, "water" poisoning) results in a relative hypoproteinemia, and dehydration (dehydration) – relative to hyperproteinemia.

Absolute hypoproteinemia is observed at:

- insufficient intake of proteins in the body as a result of starvation, malnutrition, narrowing (stricture) of the esophagus, disorders of integrity and function of gastrointestinal tract and other conditions involving deterioration of digestion and absorption of proteins;
- violation of protein synthesis in the body due to violation of the protein synthetic function of the liver (cirrhosis, hepatitis, tumor metastasis to the liver etc.);
- increased body protein loss due to acute and chronic bleeding, severe burns, chronic renal disease with nephrotic syndrome;
- strengthening catabolism (decomposition) of the protein due to prolonged hyperthermia, thermal burns, hyperthyroidism, prolonged physical activity, cancer;
- redistribution of protein (protein output from the vascular bed and the formation of exudates and transudate).

Absolute hyperproteinemia (relatively rare) is observed at:

- acute and chronic infectious diseases (due to globulin);
- autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, rheumatism, etc.);
- oncological diseases with pathological overproduction of proteins – paraproteinemia (multiple myeloma (plasmacytoma), Waldenstrom's macroglobulinemia).

Erythrocyte Sedimentation Rate (ESR)

Erythrocyte sedimentation rate (ESR) – separation rate stabilized with anticoagulants blood into two layers: upper –transparent plasma and lower –sedimented erythrocytes. The main influence on the ESR exercises aggregation of RBCs, force of which depends on surface charge of them and plasma concentrations of asymmetric molecules (proteins). Aggregation leads to the formation of agglomeration and adhesion of erythrocytes ("coin columns"), moves to the lower layers on standing blood.

The ESR depending on:

1. Changing the ratio of different fractions of blood proteins: decrease in concentration of albumin or/and increase in levels of coarse protein (α -globulins, γ -globulins, fibrinogen) elevated ESR;
2. Increase in volume, number and diameter of RBC slows down the ESR, their decrease in elevate ESR;
3. Cholesterol adsorbed on red blood cells accelerates ESR; lecithin, bile acids and pigments, slow down the ESR
4. The pH of the blood: alkalosis elevates ESR, acidosis — slows down the ESR.
5. The viscosity of the blood. Dilution anemia leads to elevating ESR, an increase in blood viscosity (dehydration) – ESR slow down.

Table 5. Main reasons of ESR changes

Disease	ESR	Reasons
Acute inflammation	↑	Fibrinogen ↑, albumen ↓
Liver cirrhosis	↑	Ig ↑, albumen ↓↓
Nephrotic syndrome	↑	albumen ↓↓, RBC ↓
Leucemia	↑	Fibrinogen ↑, albumen ↓, RBC ↓
Monoclonal gammopathy	↑	Ig ↑↑
Anemias	↑	RBC ↓
Primary and secondary polyerythremias	↓	RBC↑
Cryoglobulinemia	↓	Monoclonal Ig ↑

Great influence on the ESR provides certain medications and therapeutic interventions. Thus, the acceleration of erythrocyte sedimentation is observed in specific and nonspecific irritant therapy, vaccine

therapy, blood transfusions, long reception of soda, vitamin A, contraceptives, etc. The slowdown of ESR is observed in the reception of salicylic, mercury and calcium preparations, diuretics, hypnotics and anti-malarial drugs.

ANEMIA

Anemia – clinical –hematological syndrome characterized by deficiency of hemoglobin or/ and erythrocytes content in units of blood.

Table 1 Classification of anemia

According to cause:	primary secondary
According to the rate of development:	acute chronic
According to mechanism:	post-hemorrhagic hemolytic dyserythropoietic
According to hemopoietic type:	erythroblastic megaloblastic
According to regenerative ability of bone marrow:	regenerative >1.5% of reticulocytes hyperregenerative >15% of reticulocytes hyporegenerative 0,2-1% of reticulocytes aregenerative (aplastic) < 0,2% of reticulocytes
According to color index:	Normochromic: CI=0,8–1,05; MCH 25,4-34,6 pg Hyperchromic: CI > 1,05; MCH >34,6pg hypochromic: CI <0,8; MCH <25,4pg
According to Er size:	normocytic — 7,2–8,3 mcm (MCV=80-100fl) microcytic — < 7,2 mcm (MCV<80fl) macrocytic — > 8,3–12 mcm (MCV>100fl) megalocytic — 12–15 mcm (MCV=110-120fl)
According to severity:	mild — Hb 110-90 g/l; Er >3,0·10 ¹² /l medium — Hb – 90–70g/l; Er – 3,0 – 2,0·10 ¹² /l severe – Hb <70g/l; Er< 2,0·10 ¹² /l

DYSERYTHROPOIETIC ANEMIAS

Dyserythropoietic anemias:

- **Disorders of erythropoiesis:**
 - ✓ Deficiency anemias (B₁₂-, Fe-, folic acid)
 - ✓ Achrestic anemias (due to inability to absorb by bone marrow hematopoietic agents (B₁₂ achrestic, sideroachrestic))
- **Aplastic anemia** (due to damage of bone marrow by different factors (ionizing radiation, toxic drugs))
- **Metaplastic anemia** (during leukemia, metastasis of tumors in bone marrow)

Iron deficiency anemia

Iron deficiency is the most common cause of anemia world-wide. Iron balance is regulated by several conditions including the following:

- amount of iron ingested;
- amount of iron absorbed;
- RBCs formation using recycled and new iron;
- iron stores;
- iron loss through blood loss or other sources.

Total body iron store is about 4 g. Normal diet provides approximately 15 mg of iron in day, of which 5-10% is absorbed in duodenum and upper jejunum. About 15-30% of total iron is stored for later

use, mainly in the reticuloendothelial system and liver parenchymal cells in the form of ferritin. Iron is important for Hb formation and also myoglobin, cytochromes, cytochrome oxidase, peroxidase, catalase.

Heme, the oxygen-carrying prosthetic group of hemoglobin, is a Fe^{2+} -containing tetrapyrrole that functions in electron exchange. Heme synthesis is taken place in both cytoplasm and mitochondria. The first step is conversion of glycine and succinyl coenzyme A to delta aminolevulinic acid by the enzyme aminolevulinic acid (ALA) synthase, with pyridoxine (vitamin B₆) as a cofactor. The last (and rate-limiting) step is the addition of Fe^{2+} to protoporphyrin IX by the mitochondrial enzyme ferrochelatase to form heme.

Etiology of the iron deficiency anemia

The iron deficiency anemia may occur as a result of an iron-deficient diet, inadequate intestinal iron absorption, chronic blood loss (menorrhagia or gastrointestinal) or intravascular hemolysis with hemoglobin loss in urine (hemoglobinuria).

Table 7. Causes and mechanisms of development of iron deficiency

Groups of etiological factors	Characteristics	Mechanisms
Special periods of life	Premature and newborn children Children first years of life	Lack of initial level of iron
	Intensive growth (puberty) pregnancy lactation	Increased iron consumption
Pathological conditions	Chronic blood loss: frequent therapeutic phlebotomy, blood donation; Cardiovascular disease (hypertension, hemorrhagic telangiectasia, etc.); Gastrointestinal pathology (esophageal varices, diaphragmatic hernia, gastric and duodenal ulcers, ulcerative colitis, diverticulosis, etc.); Urogenital system (alcohol nephropathy, renal tuberculosis, nephrolithiasis, polyps and cancer of bladder, profuse menorrhagia, endometriosis, uterine fibroids, etc.); Respiratory system (lung cancer, tuberculosis, bronchiectasis, etc.); Blood diseases (leukemia, aplastic anemia, etc.); Pathology of the hemostatic system (autoimmune thrombocytopenia, hemophilia, DIC, etc.)	Increased iron lose
Pathological conditions and diseases	Pathology of the gastrointestinal tract: resection of the stomach and intestines, gastric hyposecretion, chronic enteritis, dysbacterioses, helminthic invasion, etc.	Impaired iron absorption
	Hereditary atransferrinemia Acquired hypotransferrinemia (violation of the liver protein synthesis)	Impaired iron transport
	Alcoholism	Combination of factors: insufficient intake of iron, impaired iron absorption and transport, iron loss
Impaired iron absorption	Irrational nutrition: starvation, vegetarian diet, artificial feeding of infants	Insufficient intake of iron
	Excessive exercise	Increased consumption of iron

Pathogenesis

Hemoglobin — an oxygen-binding molecule produced only by erythroid cells, is composed of four globin chains (two alpha and two non-alpha, either beta or gamma) each of which binds one heme molecule. Four iron molecules are needed in each hemoglobin unit. The main role for iron is as the ion in the center of the body's oxygen-carrying molecule, heme. Iron, held stably in the ferrous form by the other atoms in heme, reversibly binds oxygen.

When there is iron deficiency, the final step in heme synthesis is interrupted. In this step, ferrous iron is inserted into protoporphyrin IX by the enzyme ferrochelatase. When heme synthesis is interrupted, there is inadequate heme production. A result of heme deficiency is elevation of heme-regulated translational inhibitor activity, which inhibits a key transcription initiation factor for heme synthesis. Thus, there are less heme and fewer globin chains available in each red cell precursor. This decrease in the hemoglobin concentration of the blood directly causes anemia.

Clinical manifestations

There are 2 main syndromes during iron deficiency anemia: general symptoms of anemia and sideropenic syndrome.

General symptoms of anemia:

- weakness;
- dizziness;
- impaired memory and attention;
- pale skin with a greenish tinge.

Sideropenic syndrome:

- trophic disorders of the skin, mucous;
- cheilitis (inflammation around the lips);
- atrophic glossitis;
- koilonychia (spooning of the nail beds), angular stomatitis;
- pica (abnormal craving for unusual substances such as dirt, ice, or clay);
- sideropenic dysphagia (Plummer-Vinson syndrome);
- iron deficiency in infants may result in developmental delays and behavioral disturbances.

Stages of iron deficiency anemia

Stage 1: iron stores depleted; test for absence of stainable bone marrow iron, decreased serum ferritin level, increased TIBC;

Stage 2: iron-deficient erythropoiesis; test for slight microcytosis, slight decreased hemoglobin, decreased transferrin saturation;

Stage 3: iron deficiency anemia; test for decreased serum iron, decreased serum ferritin, increased TIBC, decreased transferrin saturation.

Laboratory tests

Peripheral blood smear:

- Hb and Ht are decreased usually to moderate levels, the MCV and MCHC are decreased;
- hypochromia, poikilocytosis; microcytosis and normocytic cells with decreased central area of pallor;
- decrease in color index below 0.8;
- reticulocytes in normal or slightly increased, with the progression of IDA their number decreases;
- often developing neutropenia (by reducing the content of iron-containing enzymes in leukocytes);
- ESR is normal or slightly increased;
- platelet count may be slightly elevated (on the background of bleeding).

Biochemical analysis of blood

- serum iron in severe IDA drops to 5,4-1,8 mmol/l at norm 12,5-30,4 mmol/l men, women 10-15% lower;
- increased concentration of transferrin;

- decrease of transferrin saturation with iron less than 20% (in norm 30-50%), it means a decrease of iron transport to the bone marrow;
- decrease of serum ferritin less than 12 mkg/l (in norm 12-200 mkg/l);
- increased concentration of TIBC;
- decreased synthesis of some iron-contacting enzymes in erythrocytes (catalase, glutathionperoxidase) results in erythrocytes increased sensitivity to hemolyzing effect of oxidizers (the lifetime of RBCs gets reduced to 20-30 days);
- increase in the content of soluble receptors to transferrin in serum;
- increase in free protoporphyrin IX in erythrocytes.

Bone marrow examination:

- normoblastic hyperplasia with impaired hemoglobinisation (predominance of basophilic and polychromic normoblasts while reducing oxyphilic);
- decrease in the index of normoblast maturation;
- decreased a count of sideroblasts until their complete absence;
- myeloid and megakaryocyte germs are not changed.

Anemia of chronic disease

Anemia of chronic disease is a mild to moderate anemia associated with chronic inflammation or infection (meningitis, pneumonia, tuberculosis, osteomyelitis, syphilis, fungal infections etc.), systemic connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, etc.) and tumors (multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's disease, lung cancer, breast cancer etc.). This form of anemia is due to a combination of mildly decreased red cell survival and inadequate erythropoiesis.

Pathogenesis:

1. inflammatory cytokine-mediated activation of splenic and hepatic macrophages and increased binding of antibody and complement to red cells leads to an increased rate of hemolysis;
2. inflammatory cytokines interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF α) inhibit erythropoietin synthesis;
3. inflammatory cytokine IL-6 induces hepatic synthesis of hepcidin (the iron-regulating hormone). Hepcidin binding to the cell membrane iron transporter protein ferroportin leads to ferroportin degradation, blocking the release of iron by macrophages and intestinal cells and preventing the transfer of iron to red cell precursors in the marrow;
4. in patients with malignant tumors, along with the cytokine-mediated inhibition of erythropoiesis, is also associated with metastatic lesions of the bone marrow and myelofibrosis.

The anemia may be hypochromic, microcytic. Serum iron is decreased, TIBC is decreased (blood levels of the negative acute-phase reactant transferrin drop in response to inflammation). Serum ferritin is increased.

Examination of the marrow in anemia of chronic disease reveals numerous iron-laden macrophages and markedly decreased sideroblasts (nucleated red cells with particles of stainable iron).

Anemias associated with internal diseases

Anemias associated with internal diseases include anemias of endocrine, liver and kidney diseases.

Anemias in endocrine diseases: anemia in diseases of the thyroid and parathyroid glands, adrenal glands, gonads, hypopituitarism etc.

The most common pathogenic is depression of erythropoiesis due to deficiency or hypersecretion of several hormones. For example, thyroxine, cortisol, testosterone in very high concentrations cause inhibition of proliferative activity of erythroid precursors.

Anemias in liver diseases occur when the diffuse lesions (cirrhosis, chronic hepatitis, hemochromatosis, etc.). Distinguish the following mechanisms of anemia:

- suppression of hematopoiesis in the bone marrow (due to the direct toxic effects on the hematopoietic progenitor cells of alcohol (in alcoholic liver disease) and endogenous toxins (in violation of

neutralizing and clearance liver function); disorders of iron metabolism and deposition of vitamin B₁₂ and folic acid in the damaged liver);

- shortening the lifetime of erythrocyte (as a result of direct damaging action of exogenous (alcohol) and endogenous (endotoxemia) toxic products; hypersplenism; disorders of intracellular metabolism of erythrocytes (e.g., NADP⁺ deficient in the cells) and their ability to deform (due to pathological changes in the cell membrane);
- varical bleeding from the gastrointestinal tract (in liver cirrhosis), nasal, hemorrhoidal and other sites (in insufficient synthesis of coagulation factors due to violations of protein metabolism).

Anemias in kidney disease can be detected in patients with acute glomerulonephritis, interstitial nephritis and chronic renal failure. The pathogenesis of anemia is determined by decreased production of erythropoietin, depression of hematopoiesis in bone marrow (as a result of violations of the proliferative activity of erythroid cells, inhibition of heme synthesis) and shortened lifetime of red blood cell (40-50 days) under the action of toxic products of nitrogen metabolism.

Megaloblastic anemias

The megaloblastic anemias are a group of disorders caused by defects in DNA synthesis. Anemia develops as a result of the production of enlarged erythroid precursors that are destroyed within the marrow (ineffective erythropoiesis) as a result of their inability to undergo normal DNA replication and cell division. Folate and vitamin B₁₂ are both essential for DNA replication and are therefore required for normal hematopoiesis.

Vitamin B₁₂ deficiency anemia

B₁₂ (cobalamin) is a cofactor involved in DNA synthesis.

Etiology of vitamin B₁₂ deficiency anemia

In the diet, cobalamin is found only in animal products. Dietary deficiency, which occurs only in strict vegetarians, is rarely.

Pernicious anemia (Addison-Birmer's disease) is the most common cause of vitamin B₁₂ deficiency. The fundamental defect in pernicious anemia is severe gastric atrophy, with loss of all gastric secretions including intrinsic factor, the presence of which is necessary for absorption of vitamin B₁₂. About 90% of patients with pernicious anemia have antiparietal cell IgG antibodies in the serum, while 60% have serum anti-intrinsic factor antibodies. These antibodies are not specific for pernicious anemia.

Table 8. Causes of Vitamin B₁₂ deficiency anemia

Causes	Mechanisms	Clinical conditions
Inadequate intake	Dietary deficiency (rare)	Strict vegetarian, breastfed infants of deficient mothers
Defective absorption	Decreased intrinsic factor	Pernicious anemia (the most common cause), juvenile pernicious anemia, gastrectomy
	Inadequate pancreatic proteases	Pancreatic insufficiency, Zollinger-Ellison syndrome
	Compete with the host for cobalamin	Parasitic or bacterial overgrowth, fish tapeworm
	Mucosal defects	Sprue, surgical resection, amyloidosis
	Drug-induced effect	Colchicine, paraaminosalicylate, neomycin, colestyramine
	Decreased transcobalamin -II	Congenital deficiency
Increased requirements	Increased utilization or loss	Hemolysis, pregnancy, lactation, infancy, intensive growth, hemodialysis
Disorders of metabolism	Inhibition of synthesis of enzymes	Hereditary enzyme defects, nitrous oxide inhalation (inactivates coenzyme forms of vitamin B ₁₂)

Pathogenesis

Vitamin B₁₂ is freed from binding proteins in food through the action of pepsin in the stomach and binds to salivary proteins called cobalophilins. In the duodenum by the action of pancreatic proteases bound vitamin B₁₂ is released. It then binds to intrinsic factor. This complex is transported to the ileum. Ileal enterocytes express intrinsic factor receptors on their surfaces, where it is endocytosed and associated with a major carrier protein (transcobalamin II). Transcobalamin II delivers vitamin B₁₂ to the organs (liver, bone marrow, gastrointestinal tract). In addition to this major pathway, there is also a poorly understood alternative uptake mechanism that not on an intact terminal ileum. 1% of a large oral dose can be absorbed by independent on intrinsic factor way.

Cobalamin accepts a methyl group from methyltetrahydrofolate, which leads to the formation of methylcobalamin and reduced tetrahydrofolate. Cobalamin deficiency depletes stores of reduced tetrahydrofolate and impairs DNA synthesis because of lowered purine production. Tetrahydrofolate is required as the single-carbon donor in purine synthesis.

In DNA synthesis, cobalamin, along with folic acid, is crucial as a cofactor in the synthesis of deoxythymidine from deoxyuridine. Methylcobalamin need for formation of thymidinemonophosphate from uridine monophosphate it lead to disorders in DNA synthesis, production of myelin, neurotransmitters / protein, fatty acid, phospholipid and DNA methylation. Thus deficiency of methylcobalamin lead to development of megaloblastic anemia, disorders of regeneration. Methylcobalamin serves as an essential cofactor in the conversion of homocysteine to methionine by methionine synthase.

Deoxyadenosylcobalamin involved in metabolism of fatty acid and conversion of methylmalonic acid to succinic acid. Accumulation of methylmalonic acid during pernicious anemia facilitates development of dystrophy of dorsolateral columns of the spinal cord, lead to development of funicular myelosis and dysfunction of central nervous system.

Clinical Manifestations

Pernicious anemia is manifested by a triad of symptoms:

- 1) impairment of hemopoiesis;
- 2) atrophic changes of the mucus of the gastric intestinal tract;
- 3) dysfunction of the nervous system.

Anemia is the most commonly encountered abnormality. Typical symptoms are fatigue, dyspnea, dizziness, due to a decreased oxygen-carrying capacity of the blood. High-output congestive heart failure is relatively common, with tachycardia and signs of left ventricular failure.

Gastric intestinal symptoms are less prevalent and include malabsorption diarrhea (more common), and glossitis (most common).

Dysfunction of central nervous system is characterized by appearance of mental disorders (delusions, hallucinations), wobbly gait, paresthesia, pain, numbness of limbs, paraparesis, occurrence of pathological reflexes, development of funicular myelosis. Funicular myelosis manifests by impaired perception of deep touch, pressure and vibration, disappear of touch sense, decrease or disappear of deep muscle-tendon reflexes, annoying and persistent paresthesias, ataxia of dorsal cord type.

In the serum may be founded low vitamin B₁₂, and elevated levels of homocysteine and methylmalonic acid.

Peripheral blood smear

In peripheral blood is founded hyporegenerative, hyperchromic megaloblastic anemia, leukopenia with neutropenia and hypersegmented granulocytes, relative lymphocytosis, thrombocytopenia. In smear are revealed megaloblasts, megalocytes, macrocytosis, anisocytosis, poikilocytosis, erythrocytes with Jolly's bodies, Kabo's rings and azurophilic granularity, giant hypersegmented neutrophils.

Bone marrow examination

The bone marrow is hypercellular with megaloblastic anemia, dominated by red cell lines (leuko/erythroblastic ratio of 1: 2 – 1: 3). Type of erythropoiesis with mild to moderate disease severity mixed - normo-megaloblastic (found erythroblasts and normoblasts along with promegalo- and megaloblast). In severe is a megaloblastic erythropoiesis (all the cells of red line are pro-megaloblast and megaloblast), often with signs of degeneration. There is a marked macrocytosis of neutrophils, especially metamyelocytes and polymorphonuclear neutrophils. The number of megakaryocytes is usually not changed, but in severe cases can be reduced.

Biochemical analysis of blood

- decrease of B₁₂ in serum and in RBCs;
- increases of methylmalonic acid and homocysteine in serum and urine;
- megaloblastic anemia - usually accompanied by moderate hyperbilirubinemia (due to indirect bilirubin) to 28-47 mmol/l, and an increase in LDH activity (due to the disintegration of intramedullary structures containing a large amount of this enzyme).

Folic acid deficiency

Folic acid deficiency anemia occurs much less frequently than B₁₂ deficiency. Folic acid is a water-soluble, heat-labile vitamin. Folate found in meat, liver, vegetable products (spinach, asparagus, lettuce, beans, vegetables, fruits, mushrooms), yeast, milk. More than 50% of folate is destroyed when the long cooking. To meet the needs of the organism in folate should eat fresh vegetables and fruits. Folate absorption occurs in the duodenum and proximal jejunum.

Table 9. Etiology of folate deficiency anemia

Causes	Mechanisms	Clinical conditions
Inadequate intake	Dietary deficiency	Alcoholism, starvation, diet without green vegetables, long thermal cooking of food, nurse of infants by goat milk
Increased requirements	Growth, proliferative states, or loss exceeds intake	Pregnancy, lactation, intensive growth of child, increased hematopoiesis (hemolytic anemias, multiply myeloma), malignant diseases, hemodialysis, exfoliative skin disorders, tuberculosis
Defective absorption	Gastrointestinal abnormalities	Sprue and other small bowel disorders, surgical resection, amyloidosis, congenital malabsorption
	Interference of absorption by drugs	Phenytoin, primidone, phenobarbital, oral contraceptives
Disorders of metabolism	Inhibition of folate metabolism	Inhibitors of dihydrofolate reductase: methotrexate, pentamidine, pyrimethamine; alcohol
	Inherited disorders	Congenital enzyme deficiencies (dihydrofolate reductase), others (rare)
	Disorders of depot in liver	Toxic and viral hepatitis, cirrhosis, hepatocellular cancer

Pathogenesis

Folate is required for synthesis of three of the four bases used for deoxynucleotide synthesis, the two purine bases, adenine and guanine, and the pyrimidine base thymidine. It is the role of folate in thymidine synthesis that is most critical for DNA replication. Methylene tetrahydrofolate is the form required for the conversion of deoxyuridine to thymidine and the production of this form of folate requires vitamin B₁₂. This results in defective DNA synthesis and abnormal growth and maturation of hematopoietic and other rapidly dividing cells.

Deficiency of folate may also cause several complications that affect other organ systems. It is an increased risk of neural and other developmental defects in infants born to folate deficient mothers. Raised homocysteine level has been implicated as an independent risk factor for cardiovascular disease as well as neurodegenerative disease such as Alzheimer -type dementia. As in vitamin B₁₂ deficiency, serum homocysteine levels are increased, but methylmalonate concentrations are normal. However, funicular myelosis do not occur.

Picture of peripheral blood and bone marrow corresponds to B₁₂ deficiency anemia, changes are less pronounced

Biochemical analysis of blood:

- decrease of folic acid in serum and red blood cells;
- increases of homocysteine in serum and urine; level of methylmalonic acid is normal;

- usually accompanied by moderate hyperbilirubinemia (due to indirect bilirubin) to 28-47 mmol/l, and an increase in LDH activity (due to the disintegration of intramedullary structures containing a large amount of this enzyme).

ACHRESTIC ANEMIAS

Achrestic anemias is developed due to inability to absorb by bone marrow hematopoietic agents (vitamin B₁₂, iron).

B₁₂- achrestic anemia

The development of this anemia is associated with a metabolic disorder of methylcobalamin, resulting in bone marrow hematopoietic loses the ability to utilize the substance, there is megaloblastic erythropoiesis. Changes in the digestive and nervous systems are not available. Blood picture, as in B₁₂ deficiency anemia. The vitamin B₁₂ in plasma may be normal or elevated

Sideroahrestical anemia (SAA)

Sideroahrestical (sideroblastic) anemia – is a heterogeneous group of inherited and acquired diseases resulting from violations of porphyrin synthesis or recycling. Deficiency in formation of porphyrins at SAA leads to a violation of iron using.

Classification of sideroblastic anemias:

- Congenital (X- linked, autosomal dominant, autosomal recessive pattern, sporadic (hereditary character is unclear), associated with mitochondrial cytopathy (syndrome Pearson), DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, deafness; Wolfram syndrome)
 - Acquired:
 - idiopathic: refractory anemia with ringed sideroblasts (variant of MDS);
 - associated with hematologic neoplasia (multiple myeloma, malignant non-Hodgkin's lymphoma, acute leukemia);
 - deficiency of vitamin B₆;
 - medications: azathioprine, isoniazid, melfolan;
 - toxic: alcohol, lead, cadmium, nickel poisoning).

The **pathogenesis** of SAA is defective enzymes involved in the synthesis of protoporphyrin and heme: 5-aminolevulinate synthase, CPG decarboxylase, CPG-oxygenase, ferrochelatase and others. Activity deficit of listed above enzyme promotes disturbance of protoporphyrin formation at various stages (depending on the level of metabolic block). As a result, the level of protoporphyrin in erythrocytes of BM sharply reduced. Iron cannot connect to the protoporphyrin and incorporated into the structure of hemoglobin. It is deposited in the mitochondria of erythrocytes, forming a large number of ringed sideroblasts. Thus develops ineffective erythropoiesis, intramedullary hemolysis of erythrocytes and as a consequence anemia.

Peripheral blood smear:

- hypochromic microcytic anemia: anisocytosis due to microcytes; poikilocytosis due to target cells;
- reticulocytes in normal or reduced;
- increased siderocytes;
- leukocytes and platelets are normal.

At lead intoxication:

- reticulocytes increased up to 3-8% (due to RBCs hemolysis);
- basophilic stippling in erythrocytes;
- thrombocytopenia.

Bone marrow examination: hypercellular due to severe hyperplasia of red sprout, increase in erythroblasts, basophilic normoblasts and decreased oxyphylic normoblast (decrease maturation index of erythrocytes). Increased (up to 70% in hereditary forms) content sideroblasts (ringed sideroblasts).

Biochemical analysis of blood:

- increase in serum iron (up to 62,7-98,5 mmol/l);
- reduction of TIBC;
- increase in the degree of transferrin saturation (in most patients is almost 100%);
- increase in serum ferritin.

APLASTIC ANEMIA

Aplastic anemia (AA) is broadly defined as pancytopenia (anemia, low leukocyte and platelet count) with a hypocellular bone marrow.

Classification of aplastic anemias:

1. Congenital (Fanconi's anemia, Shwachman-Diamond syndrome)
2. Acquired:
 - a. Secondary – resulting from exposure to one of the possible causative exogenous or endogenous factors:
 - physical (radiation);
 - chemical (drug-induced, industrial toxins—benzene, other aromatic hydrocarbons, pesticides, arsenic);
 - biological (hepatitis B virus, parvovirus B₁₉, Epstein-Barr virus);
 - pregnancy.
 - b. Idiopathic.

Depending on the type of bone marrow involvement is distinguish:

- AA with the oppression of all germs of hematopoiesis (Fanconi's anemia, acquired anemias);
- AA with only red germ inhibition (Diamond-Blackfan anemia);
- Neutropenia (congenital dyskeratosis, anemia Shwachman-Diamond-Oski);
- Thrombocytopenia (congenital amegakaryocytic thrombocytopenia).

Congenital Aplastic Anemia

Congenital aplastic anemias are typically associated with dysmorphic physical features, such as growth retardation, limb hypoplasia, and cardiac or renal abnormalities.

Diamond-Blackfan anemia or constitutional pure red cell aplasia, is a results from sporadic abnormalities at chromosome 19q13. This mutation lead to defects in erythroid precursors that prevent them from responding to growth signals. In 40% anemia is associated with congenital craniofacial, neck, or thumb defects. In all these anemias, the bone marrow shows well-developed granulopoiesis and megakaryopoiesis, but erythropoiesis is (more or less) entirely lacking. The anemia is normochromic and macrocytic.

Fanconi's anemia familial bone marrow failure is characterized by an impaired ability to repair damaged DNA crosslinks. These patients often are associated with other phenotypic abnormalities, such as skin pigmentation, renal or splenic hypoplasia, hypoplastic thumbs or radii, microcephaly, and mental retardation.

Fibroblasts and lymphocytes from these patients have a high incidence of gaps, breaks, chromatid exchanges, and endoreduplication. These patients have an increased incidence of acute myelogenous leukemia.

Secondary Aplastic Anemia

1. Radiation

Acute radiation sickness with high-dose whole-body irradiation typically develops marrow aplasia (often fatal) at 3-6 weeks. Chronic exposure to low-dose radiation may result in aplastic anemia, presumably as a result of hematopoietic stem cell injury.

2. Chemical

Drugs induced AA may be due to treatment by antibiotics (chloramphenicol), nonsteroidal anti-inflammatory drugs, antiplatelet agent (ticlopidine), anticonvulsants (hydantoin compounds, valproic acid, and carbamazepine), gold salts or other drugs.

Chloramphenicol has the best-known association with aplastic anemia. Chloramphenicol metabolites produced by intestinal bacteria are predominantly responsible for marrow aplasia. Reversible agranulocytosis is observed in 2.4% of patients that have a therapy with ticlopidine (antiplatelet agent used following cerebrovascular accidents and myocardial ischemia); aplastic anemia is much less frequent. These events are characteristically observed in the first 12 weeks of therapy. Anticonvulsants are the drugs most commonly implicated in blood dyscrasias. Gold salts, used in the management of advanced rheumatoid arthritis, were associated with 1.6 aplastic anemia-related deaths per 10,000 prescriptions. The mechanism of aplasia is unclear. A variety of other drugs, including oral hypoglycemic drugs, neuroleptics (particularly phenothiazines), antithyroid agents, and diuretics, have been associated with aplastic anemia.

The association between industrial hydrocarbons such as benzene (and its metabolites particularly hydroxyquinone phenols) and pancytopenia or aplastic anemia is well established. Organochloride and organophosphate pesticides are associated with aplastic anemia based on epidemiologic data. The mechanism of aplastic anemia is unclear.

Deposition of crystalline arsenic in marrow has direct toxicity toward hematopoietic progenitors/precursors resulting in aplasia.

3. Viral infections

Variety of viral infections, including hepatitis B, parvovirus B19, and Epstein-Barr virus are associated with aplastic anemia. Some investigators have suggested that antiviral therapy should be considered early in the treatment of aplastic anemia.

4. Pregnancy

Pregnancy associated aplastic anemia is a rare association. The relation between these two conditions is still unclear.

Idiopathic Aplastic Anemia

Despite efforts to identify an etiology, approximately 50% of cases of aplastic anemia appear to be of idiopathic origin. The success immunosuppressive therapy in managing of these patients suggests that immunologic mechanisms may be involved in a majority of these cases.

The basic mechanisms of AA pathogenesis are:

- inherited (congenital) or acquired defect of pluripotent stem cells;
- stromal microenvironment change that leads to disruption of the development and maturation of hematopoietic stem cells;
- insufficient production of hematopoietic growth factors;
- cellular and / or humoral immune suppression of hematopoietic stem cells;
- progressive humoral violation of reparations of the chromosomes telomeres (due to mutations in telomerase).

Clinical manifestations

The clinical picture is due to the development of pancytopenia and consists of three main syndromes: anemic, haemorrhagic and infection. Anemic syndrome is characterized by pallor of the skin and visible mucous membranes, fatigue, weakness, tachycardia, shortness of breath. Hemorrhagic syndrome characterized by spotty-petechial type of bleeding (hemorrhagic rash on the skin, oral mucosa, nasal and gingival bleeding, etc.). Bacterial and fungal infections develop as a result of neutropenia (tonsillitis, pneumonia, sepsis).

Congenital forms of AA are accompanied by congenital malformations and abnormalities of various organs and systems (strabismus, polydactyly, and others.)

Peripheral blood smear: pancytopenia (severe anemia, Hb - 20-80 g / l; normochromia, macrocytosis, decreased reticulocyte count, leukopenia, absolute neutropenia, relative lymphocytosis, thrombocytopenia, increased ESR up to 30-50 mm/h);

Bone marrow examination: reducing the amount of hematopoietic tissue, bone marrow substitution by adipose tissue.

Biochemical analysis of blood: increase in serum iron, ferritin, decrease of TIBC and total protein.

At Fanconi anemia increased the levels of fetal hemoglobin in venous blood.

METAPLASTIC ANEMIAS

This pathology occurs when the proliferation in the bone marrow cells that are not related to erythropoiesis (acute leukemia, multiple myeloma, myelofibrosis, osteomyelosclerosis, tumor metastasis). Blood picture is determined by the underlying disease.

Questions for self-control of knowledge:

1. What are the main physico-chemical properties of blood?
2. What are dyserythropoietic anemia?
3. Give a definition achrestic anemia?
4. What is the difference between B-12 deficiency anemia and folic acid deficiency anemia?
5. Describe the state of blood in megaloblastic anemia.
6. What are the etiology, pathogenesis and manifestations of megaloblastic anemias.
7. What is characteristic of pernicious anemia (Addison-Biermer disease)?
8. What do you know about pathologic shaped red blood cells?

Tasks for self-managed student work:

1. Mechanisms of changes in osmotic and oncotic blood pressure in various diseases.
2. Achrestic anemias.

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