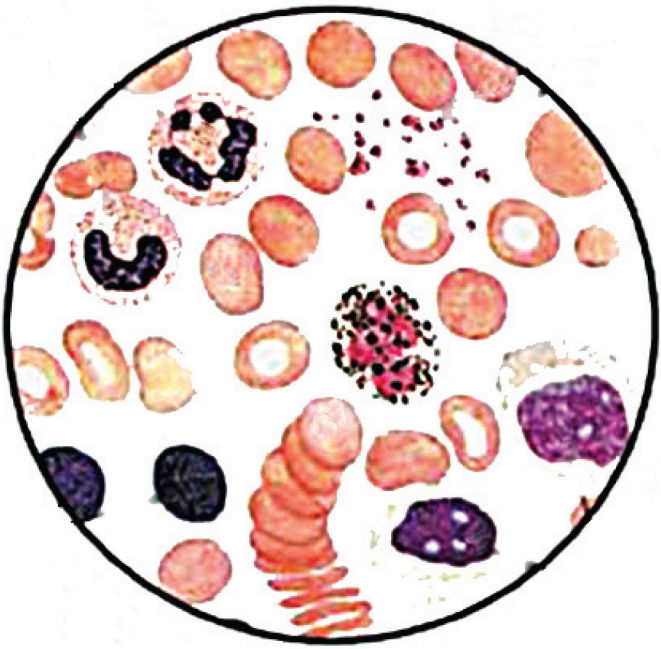
SYNDROMES AND DISEASES OF THE BLOOD SYSTEM



МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

SYNDROMES AND DISEASES OF THE BLOOD SYSTEM

Textbook

СИНДРОМИ ТА ЗАХВОРЮВАННЯ СИСТЕМИ КРОВІ

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Blood system covers a wide spectrum of medicine. The blood diseases involve specific organ and system. Other diseases affecting any system can however secondarily influence on hematholo-gical harameters making study hematology as integral part of the assessment of every medical dis-cipline. It is requires for all doctors to be aware the basic principle of examination, diagnostics and management of blood disorders.

The material containing in this textbook reviews the diseases with syndromes of anemia, lym-phadenopathy, leukocytosis, agranulocytosis, pancythopenia, bleeding signs. The definition, causes, clinical features of iron deficiency anemia, megaloblastic anemia, aplastic anemia, hemolytic ane-mias, leukemias, polycythemia vera, diseases with hemorrhagic syndrom are presented.

The textbook is dedicated to medical students, interns, family doctors and all medical specialists.

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Система крові охоплює широкий спектр медицини. До захворювань крові залучаються специфічні органи та системи. Багато хвороб, що вражають інші органи, здатні впливати на гематологічні параметри, тому гематологія розглядається як інтегральна складова кожної медичної дисципліни і вимагає від усіх лікарів бути обізнаними з базовими принципами до-слідження, діагностики та ведення гематологічної патології.

Матеріал навчального посібника містить розгляд захворювань з синдромом анемії, лімфа-денопатії, лейкоцитозом, агранулоцитозом, панцитопенією, геморагічними ознаками. Пода-но визначення, причини, клінічні прояви залізодефіцитної анемії, мегалобластної анемії, ап-ластичної анемії, гемолітичної анемії, лейкозів, поліцітемії, захворювань з геморагічним синдромом.

Навчальний посібник призначено медичним студентам, інтернам, сімейним лікарям та усім медичним фахівцям.

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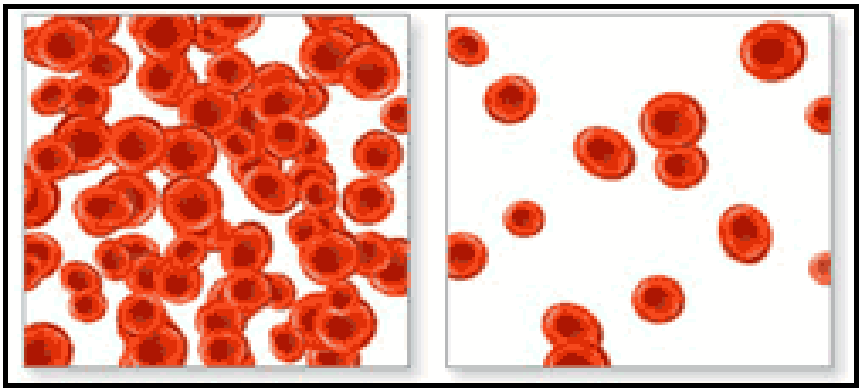
Contents

Chapter 1. Syndromes and diseases with anemia

1.1. Definition, causes and clinical features of anemia syndrome.

Anemia is a clinical syndrome characterized by reduction in the number of erythrocytes and/or hemoglobin concentration in a blood unit volume (Gr *an* not, *haemia* blood, i.e. deficiency of blood) (*Picture 1.1*).



Picture 1.1. Normal (left) and decreased (right) quantity of erythrocytes per unit of volume of the blood

Etiology.

The etiology of anemia is various and includes several factors: genetic, environmental, influence of chronic diseases, infections, iatrogenic factors, hemorrhage.

Pathogenesis.

Pathogenesis depends on the forms of anemia.

Clinical features.

Clinical features of anemia reflect the diminished oxygen-carrying capacity of the blood, reduced supplying oxygen to the organs and tissue such as heart, brain, muscles.

The general symptoms and signs are common to all anemias: fatigue, malaise, lassitude, weakness, loss of strength, reduced capacity for exercise, shortness of breath, especially during exercise – dyspnea, difficulties in breathing when lying down, palpitation, pain in the heart, anorexia, nausea, flatulence, constipation and diarrhea. Neurological disorders occur: digginess, headache, faintness, inability to concentrate. Menstrual irregularity and even amenorrhea, defects of urination may be observed in women with childbearing age.

On objective examination pallor of the skin, mucous membranes of mouth and nail beds with slight cyanosis may be observed. Cyanosis in patients with anemia appears due to the total amount of reduced hemoglobin; methemoglobin or sulfhemoglobin are present. Jaundice may be observed in the conjunctivae, mucous membranes and skin in anemic patients with hemolytic components.

Objective examination of the respiratory system reveals increased depth and rate of respiration in patients with severe anemia. Cardiovascular disorders due to the anemia are tachycardia, sometimes cardiac enlargement, functional cardiac murmurs, diminished heart sounds, low volume of pulse, hypotension. Gastrointestinal dysfunctions of anemic patients are characterized by smooth and red mouth, enlarged spleen or/and liver in some cases.

Except for these symptoms and signs there are a lot of specific clinical features relevant to every kind of anemia.

Additional methods of examination.

Additional methods of examination include: erythrocyte count, determination of hemoglobin, red cell absolute values, erythrocyte morphology, bone marrow examination, bilirubin measurement, estimation of iron metabolism, evaluation of hemoglobin structure and biosintesis, immunogematological tests for detection of hemolytic anemia.

Normal blood parameter (Oxford Handbook of General Practice, 4 edition, 2014):

- Haemoglobin concentration (Hb):
  Female: 120–150 g/l; Male: 130–170 g/l.
- Erythrocytes count (RBC – red blood cells):
  Female: 3,8–4,8 x 10^{12}/L; Male: 4,5–5,5 x 10^{12}/L.
- Reticulocyte 0,5–2,5 %.
- Hematocrit (Hct): Female: 36–46 %; Male: 40–50 %.
- Platelet count (Plt – platelet) 150–450 x 10^{9}/L.
- Leukocytes count (WBC – white blood cells) 4–11 x 10^{9}/L.

The International Committee for Standardization in Hematology has recommended that the following units be used (SI units): main cell volume as “fl” (femtoliters), mean cell hemoglobin as “pg” (picograms) and mean cell hemoglobin concentration as “g/dl” (deciliters), width of the distribution curve of erythrocyte by volume as “%” (*Table 1.1*).

Table 1.1

Red cell absolute values

MCV – average volume of erythrocyte	fl	80–95
MCH – the average content of Hb in erythrocyte	pg	27,0–31,02
MCHC – average concentration of Hb in erythrocyte	g/dL	32,0–36,0
RDW – width of the distribution curve of erythrocyte by volume	%	11,5–14,5

There are age-dependent changes of red blood cell parameters (*Table 1.2*).

Table 1.2

Age-dependent changes of red blood cell parameters.

Parameters	Age	Indices
Hematocrit	< 3 days	45–75 %
	3 days – 1 months	35–55 %
	1 months – 4 months	28–50 %
	4 months – 1 year	32–50 %
	1 year – 16 years	35–55 %
	> 16 years male female	 40–52 % 35–47 %
Hemoglobin	0–7 days	14–25 g/dl
	8 days – 1 month	12.5–20.5 g/dl
	1 months – 2 months	9–16.6 g/dl
	2 months – 1 year	9.6–13.1 g/dl
	1 year – 16 years	12–15 g/dl
	> 16 years male female	 13.5–18 g/dl 12–16 g/dl
Erytrocytes	< 1 month	3.8–6.5x10 ^{12}/L
	1 – 2 months	2.7–4.9x10 ^{12}/L
	2 – 6 months	3.1–4.5x10 ^{12}/L
	6 months 1 year	3.5–5.0x10 ^{12}/L
	1 year – 16 years	4.0–5.5x10 ^{12}/L
	> 16 years male > 16 years female	 4.4–5.8x10 ^{12}/L 3.8–5.2x10 ^{12}/L
Mean Corpuscular Hemoglobine (MCH)	< 1 month 1 month – 16 years	30–40 pg 25–35 pg
	> 16 years	27–33 pg
Mean Corpuscular Volume (MCV)	< 2 months	90–120 fl
	2 months – 6 months	75–110 fl
	6 months – 6 years	70–100 fl
	6 years – 16 years	75–95 fl
	> 16 years	78–98 fl
Width of the distribution curve of erythrocyte by volume (RDW)	< 7 days > 7 days	6–25 % 15–17 %

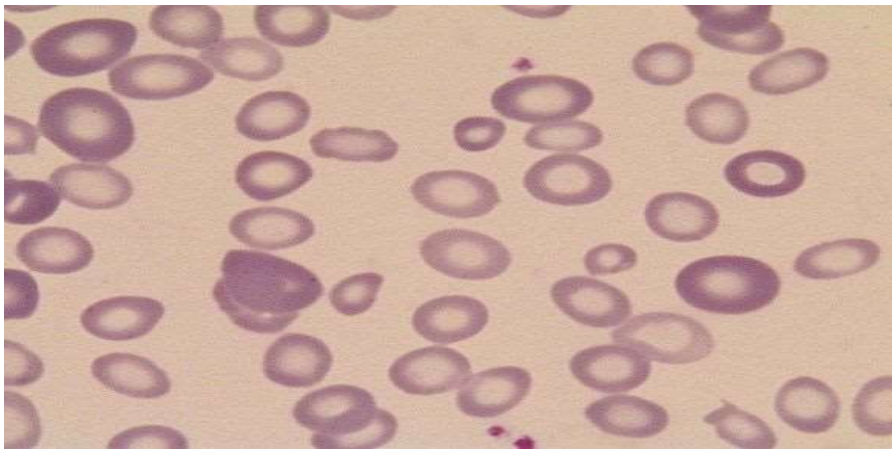
There are two main classifications of anemia:

1. The etiological classification based on the cause of the anemia.

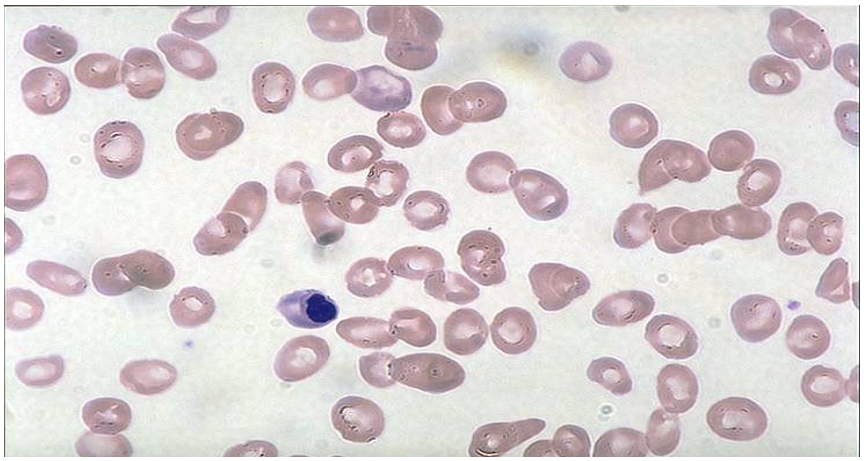
2. The morphological classification based on the characteristic of the red cell as determined by blood examination.

Classifications of anemia according to the contents of a haemoglobin in erythrocytes:

- Normochromic (MCHC 32–36 g/dL).
- Hypochromic ((MCHC) < 32 g/dL) (*Picture 1.2*).
- Hyperchromic (MCHC > 36 g/dL) (*Picture 1.3*).



Picture 1.2. Erytrocytes at hypochromic anemia (at iron-deficiency)



Picture 1.3. Erytrocytes at hyperchromic anemia (at B_{12}-deficiency anemia)

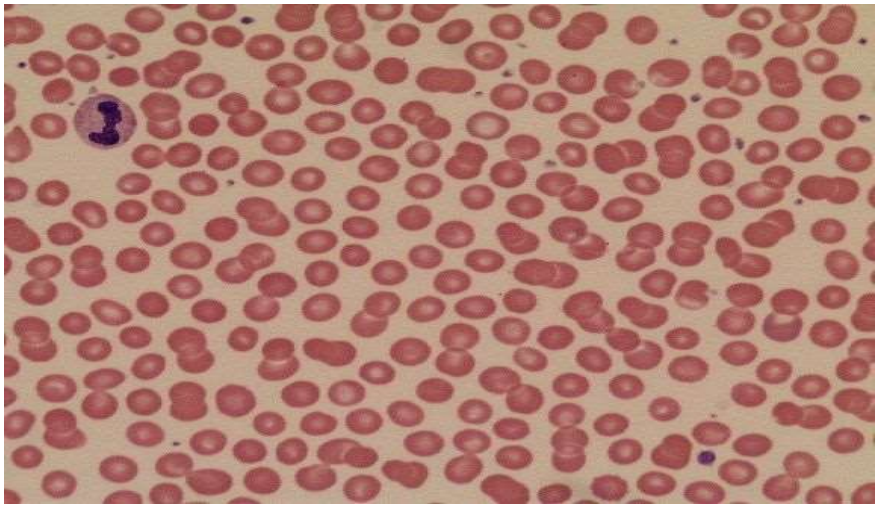
Size of erythrocytes. Normal erythrocyte are nearly uniform in size with diameter of 7.2 to 7.9 nm. An increasing and decreasing in the size of a red blood cell is known as **anisocytosis.**

Classification of anemia on according to the diameter of erythrocyte:

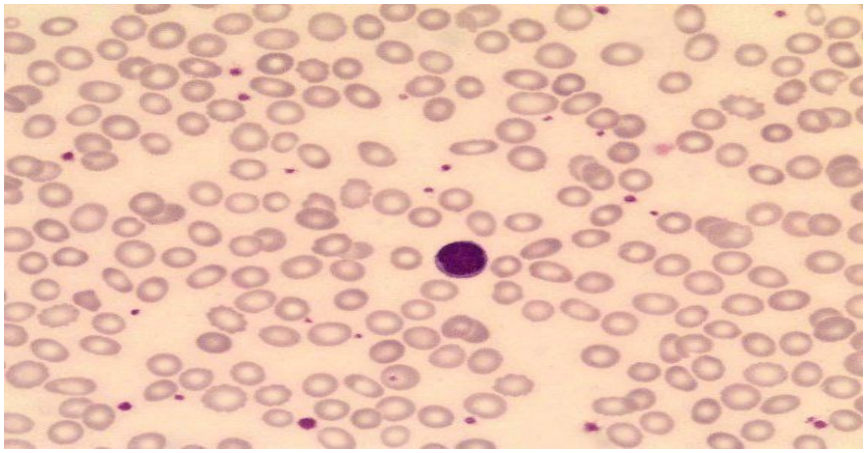
Normocytic (MCV – 80–95 fl) (*Picture 1.4*).

Microcytic (MCV < 80 fl) – iron-deficiency, hemolytic anaemia (*Picture 1.5*).

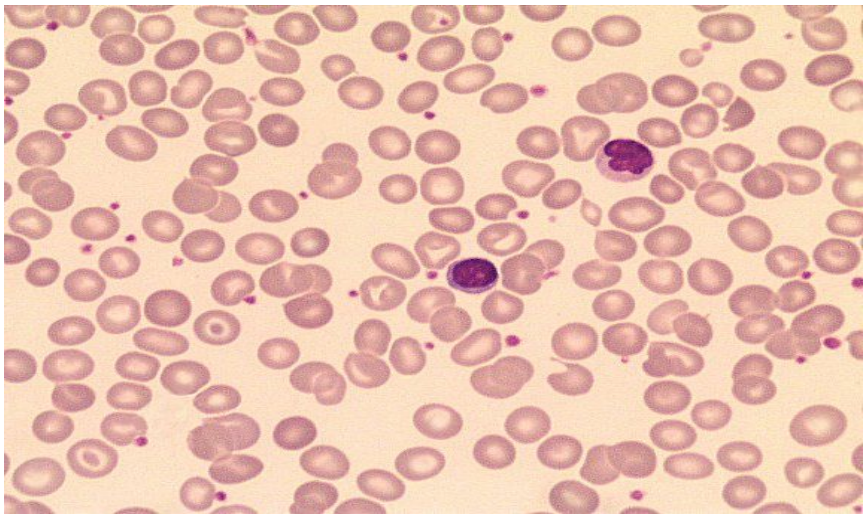
Macrocytic (MCV>95 fl) – B_{12} deficiency (*Picture 1.6*).



Picture 1.4. Normocytic anemia



Picture 1.5. Microcytic anemia



Picture 1.6. Macrocytic anemia

Shape of normal erythrocytes is a biconcave disc, which is thickest at its edges. The presence of many abnormal shapes on a blood smear is known as **poikilocytosis**. Qualitative changes of erythrocytes are depicted in *Table 1.3*.

Table 1.3

Description and significance of various forms of red blood cells

Type of cell	Description	Physiologic significance	Clinical disorders
Macro-cyte	Larger than normal (> 7.9 nm in diameter). Well filled with hemo-globin	Young red blood cells (RBC) DNA Synthesis-impaired, megalo-blastic maturation	1. Accelerated Erythropoiesis. 2. B_{12} or folate deficiency
Thin macro-cyte	Diameter increased but MCV normal; often hypochromic (see target cells)	Membrane cholesterol and lecithin increased	Liver disease, postsplenectomy
Micro-cyte	Smaller than normal (< 7.2 nm)	Differs according to whether or not: a) well filled with hemoglobin; b) normal in shape	See below
Hypo-chromic cell	Exaggeration of central pallor (> central 1/3); usu-ally also microcytic	Failure of hemoglobin due to: a) lack of iron; b) defective globin synthesis; c) defective porphyrin synthesis	Iron deficiency anemia, anemia of chronic disease Thalassaemia Sideroblastic anemias
Target cell	Hypochromic, with central pigment; thin cell; surface/ volume ratio in-creased	1. Spleneclomy decreases rate and extent of loss of lipids from reticulocytes. 2. Accumulation of both cholesterol and phospholipid on RBC. 3. Congenital	As for hypochromic cells. Also 1. Postsplenectomy. 2. In liver disease, especially obstructive jaundice
Sphero-cyte	Spherical, not hypochromic; usu-ally also microcytic; surface/volume ra-tio decreased, no central pallor	1. RBC membranes abnormality. 2. RBC's lose fragment after impact with fibrin strands, walls of diseased vessels and artificial surfaces in circulation	1. Hereditary spherocytosis. 2. Acquied irnminohemolytic anemia

Elliptocyte	Elliptical in shape, not hypochromic	1. Hereditary abnormality. 2. Acquired alteration	1. Hereditary elliptocytosis. 2. In various anemias especially megaloblastic
Sickle cell	Sickle shaped, form assumed under hypoxia (deprivation of oxygen)	Molecular aggregation of HbS	HbS trail of disease. Also seen in some other hemoglobinopathies
Schistocyte	Helmet or triangular shaped, fragmented or greatly distorted RBC; smaller than normal	RBC's lose fragments after impact with fibrin stands, walls of diseased vessels and artificial surfaces in circulation	1. Microangiopathic hemolytic anemia. 2. Hemolytic anemia due to physical agents. 3. Also in uremia, malignant hypertension
Stomatocyte	Uniconcave, as contrasted with normal biconcave RBC; slit-like instead of circular area of central pallor in RBC	1. Hereditary, primary defects in membrane structure or function resulting in abnomalities of cation permeability, content and flux. 2. Acquired alteration in cation content and flux	1. Hereditary stomatocytosis. 2. Smaller number seen in alcoholic cirrhosis, acute alcoholism, obstructive liver disease, malignancies

Inclusions in erythrocytes. The normal red blood cell filled mainly with hemoglobin. In pathological states blood films will show red blood cells with colored spots or rings inside their cytoplasms.

Howell-Jolly bodies. These are small, well-defined, round, densely staining basophilic inclusion bodies about 1 μm in diameter, which usually occur singly but sometimes in multiples. They appear after splenectomy and are also seen in cases of severe anemia from a variety of causes. They contain DNA and may be chromosomal remnants or nuclear fragments.

Cabot rings. These are blue-staining, threadlike inclusions in the red cells in severe anemia. They may appear as rings, or twisted and convoluted in a variety of shapes. They may occupy the entire periphery of the cell but frequently are much smaller. They are not often seen. It has been postulated that they are remnants of the mitotic spindle, but others have found that they contain histone and iron.

Heinz bodies can be seen with special supravital stains such as methylviolet. Heinz bodies are granules of precipitated hemoglobin.

Reticulocytes. Normal values:

The relative number of reticulocytes – 0,5–1,2 %.

The absolute number of reticulocytes – 30–70x10^9/L.

In cord blood of newborns number of reticulocytes – 20–60 %.

Classification of anemia according to ability to regeneration.

- Normoregenerative – reticulocytes 0,2–1,2 %.
- Hyporegenerative – reticulocytes < 0,2 %.
- Hyperregenerative – reticulocytes > 0,2 %.

Diagnostics of anemia

Methods of examination include:

- erythrocyte count;
- determination of haemoglobin;
- red cell absolute values;
- erythrocyte morphology;
- bone marrow examination;
- bilirubin measurement;
- assessment of iron metabolism;
- evaluation of hemoglobin structure and biosintesis;
- immunogematological tests for detection of hemolytic anemia.

Classification of anemia due to the cause

I. Blood loss:

– acute post-hemorrhagic anemia;

– chronic post-hemorrhagic anemia.

II. Impaired red cells formation:

Disturbances of bone marrow function due to deficiency of substances essential for erythropoiesis:

– iron deficiency anemia;

– megalobastic anemias due to deficiency of vitamin B_{12} or folic acid;

– aplastic anemia.

III. Increased red cells destruction (hemolytic anemia):

– hemolytic anemia due to the corpuscular defect (intracorpuscular or intrinsic abnormality);

– hemolytic anemia due to an abnormal hemolytic mechanism (extracorpuscular or extrinsic abnormality). These are acquired and resulting from either an immune or non-immune mechanisms.

1.2. Iron deficiency anemia.

Iron deficiency anemia (IDA) defined as clinical and hematological disorders caused directly of low iron body stores and iron deficiency in organism: blood, bone marrow resulted to the disturbances of hem and iron containing enzymes production.

Metabolism of iron

• The total body iron in a 70-kg man is about 4 g. The body absorbs 1–2 mg daily to maintain equilibrium, the internal requirement for iron is greater (20–25 mg).

• An erythrocyte has a lifespan of 120 days so that 0.8 % of red blood cells are destroyed and replaced each day.

• A man with 5 L of blood has 2.5 g of iron incorporated into the haemoglobin, with a daily turnover of 20 mg for hemoglobin synthesis and degradation and another 5 mg for other requirements.

• Most of this iron passes through the plasma for reutilization. Iron in excess of these requirements is deposited in body stores as ferritin or hemosiderin.

Distribution of iron in body

The total content of iron in the body – about 4.2 g. From it 75–80 % belongs to the haemoglobin, 20–25 % reserve, 5–10 % part of the myoglobin, 1 % is part of the enzyme for the tissue respiration.

Serum Transferrin (Beta-globulin). Main function is transport of absorbed iron in the depot (liver, spleen) into the medullary erythroid predecessors and into the reticulocytes. Basic place of synthesis is liver. An increase in the content of transferrin with lowering in the level of iron of serum is characteristic for the iron-deficiency state. A decrease in the level of transferrin can be with the damage of the liver (different genesis) and with the loss of protein (for example, in nephrotic syndrome). The level of transferrin is increased in the last term of pregnancy.

Ferritin Water-soluble complex of iron hydroxide with the protein apoferritin. It is located in cells of the liver, spleen, bone marrow, in the reticulocytes. Ferritin is the basic protein in human which deposits iron and concentration of ferritin in the serum reflects the reserve of iron in the organism.

Digestion and absorption of iron in body.

Heme Iron.

Heme iron is released from the globin part of hemoglobin and myoglobin by proteases from the stomach and small intestine. The proportion of heme iron absorbed depends mainly on iron status, usually 15–35 % in persons who are iron-deficient. Iron absorption can occur throughout the small intestine, but is most efficient in the duodenum.

Non-heme Iron.

Non-heme iron is also usually bound to protein or other food components and must be enzymatically liberated by gastric secretions such as protease and hydrochloric acid. Most nonheme iron is present as ferric (Fe+3) iron in the stomach. Ferrous (Fe+2) iron is absorbed much better than ferric iron because there are specific receptors on the enterocyte for ferrous iron (a membrane protein known as integrin).

Digestion

The amount of iron required from the diet to replace losses averages about 10 % of body iron content a year in men and 15 % in women of childbearing age.

Dietary iron content is closely related to total caloric intake (approximately 6 mg of elemental iron per 1000 calories).

Absorption.

Iron absorption takes place largely in the proximal small intestine and is a carefully regulated process. For absorption, iron must be taken up by the luminal cell. That process is facilitated by the acidic contents of the stomach, which maintains the iron in solution.

Causes of IDA.

Increased demand for iron and/or hematopoiesis: rapid growth in infancy or adolescence, pregnancy, erythropoietin therapy.

Decreased iron intake or absorption: inadequate diet, malabsorption from disease (sprue, Crohn's disease), malabsorption from surgery (post-gastrectomy), acute or chronic inflammation.

Blood loss:

- uterine (menorrhagia, metrorrhagia);
- chronic gastrointestinal blood loss:

– esophageal varices;
– hiatus hernia;
– peptic ulcer;
– chronic aspirin ingestion;
– carcinoma of stomach, colon, caecum, rectum;
– ulcerative colitis;
– hemorrhoids;
– diverticulosis;

- urine kidney and bladder:

– glomerulonephritis;
– carcinoma of kidney and urine bladder.

Increased requirements:

– prematurity (diminished iron stores);
– growth (infants and young children);
– females in reproductive age group: menstruation, pregnancy, lactation.

Impaired absorption:

– achlorhydria (especially in middle aged females);
– atrophic gastritis;
– gastrectomy;
– gastroenterostomy;
– tropical sprue or coeliac disease.

Inadequate intake:

– improper feeding in infants and young children;
– poverty;
– dietary fads;
– anorexia (nervosa, due to the pregnancy or malignancies).

Genital diseases in female: fibromyoma polyposis, endometriosis menorrhagia; in male – cancer of prostata.

Alimentary deficiency of iron.

Parasites invasion hookworm infestation (anemia with eosinophilia).

Pathogenesis of IDA.

The amounts of iron in organism are distributed between active iron pools (hemoglobin and tissue enzymes) and iron stores (ferritin and hemociderin). Iron deficiency develops when iron loss more than iron intake with food or when increased natural iron requirements or impaired iron absorption and appears negative iron balance between iron intake and iron stores that causes decreased iron supply to the bone marrow and iron deficiency erythropoiesis. Iron deficiency anemia occurs when the dietary intake or absorption of iron is insufficient and hemoglobin, which contains iron, cannot be formed. The pathogenesis of clinical features may be explained by decreased amount of iron resulted by insufficient tissue supply with oxygen. Reduction in oxygen carrying capacity leads to tissue hypoxia symptoms referable to systems with high oxygen requirements, such as skeletal musculature, cardiovascular system and central nervous system are particularly prominent.

Clinical features of IDA.

Anemic syndrome – is combination of laboratory signs of an anemia and its clinical manifestations caused by a hypoxia and a hypoxemia. Specific action of iron deficiency on the activity of hem content enzymes leads to the trophic disturbance of tissue.

Anemic syndrome:

Complains: general – fatigue, weakness, dizziness, tiredness, faintness, easy fatigability, dyspnea, headache, giddiness, spots before the eyes, flickering in front of eyes, noise in ears, loss of strength, reduced capacity for exercise. Muscular pain (deficit of myoglobin), muscular hypotonia.

Imperative urge to urination, disorders of sphincters.

In women with childbearing age may be observed menstrual irregularity and even amenorrhea. Loss of libido in the male appears.

Mild fever 37,2–38,2 °C is observed.

From the cardiovascular system: palpitation, heart pain, dyspnoe, palpitation, tachycardia, systolic murmur above an apex heart, in case of presence coronary artery disease occurs worsening of its symptoms.

From respiratory system: shortness of breath, especially during exercise may be dyspnea, difficulties in breathing when lying down.

Alteration in the nervous system: lack of concentration, impairment of memory, slowing of reflexes, decrease attentiveness, delay of intellectual development, drowsiness, numbness, coldness, tingling of hands and feets, syncopal and orthostatic condition, slowing of conditioned reflexes, decrease attentiveness, worsening of memory, delay of intellectual development.

Physical examination.

A compare to healthy sclera (*Picture 1.7*), pale mucous membranes of the mouth, conjunctivae, sclera (*Picture 1.8*) and nail beds with slight cyanosis may be observed.

Picture 1.7. Healthy sclera

Picture 1.8. Pallor sclera at iron deficiency anemia

Cyanosis in patients with anemia appears due to the total amount of reduced hemoglobin: methemoglobin or sulfhemoglobin.

Cardiomyopathy appears due to the anemia: the displacement of the left relative cardiac border outside, tachycardia, diminished first sound, functional systolic murmurs over sound points with maximal intensity over pulmonary artery, systolic bruits over carotis arteries. ECG changes occur: ST segment depression and flattening or inversion of T wave.

Sideropenic syndrome occurs due to deficiency of iron. Sideropenic syndrome was first described by Basenstrom in 1930.

The patient complains on the generalized muscular weakness, disorders of muscular sphincters.

Unusual predilections for some smells – acetone, petrol; decreased appetite; the distortion of taste as desire is a chalk, tooth paste, ashes, paint , soil, raw meat, ice (pagophagia)**,** decreased appetite (especially in children). These features prevously named as “pica chlorotica”.

Iron deficiency in tissue:

– koylonyhia (concave form also known as spoon nails) (*Picture 1.9);*

– the skin is dry with creak (chirp rattle), on the legs and hands is leukoplakia;

–fragility and brittleness of nails;

–dystrophic changes in the skin and its derivates, skin dryness;

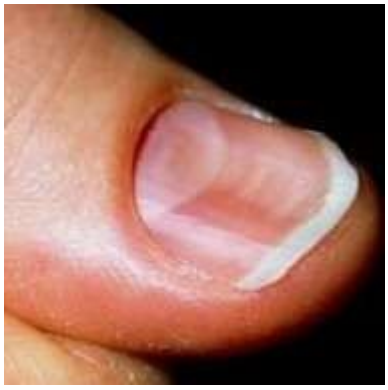
–shedding and falling of hair;

–the atrophy of the mucous membranes of nose muscular weakness,

–burning and atrophy of the tongue papillae, sore tongue, glossitis,

–angular stomatitis, gingivitis;

–muscular hypotrophy, muscular hypotonia.



Picture 1.9.
Spoon nails

Abnormality of swallowing solid food with sensation of a foreign body in throat named as sideropenic dysphagia resulted on dryness of the mucous membrane of the esophagus, the atrophy of the post-cricoid esophageal leading to esophagitis are observed. This clinical picture is known as Plummer-Vinson syndrom.

Clinical blood analysis:

- red blood cells count is decreased;
- hemoglobin concentration is decreased;
- mean cell volume (MCV) < 76 fl;
- mean cell hemoglobin (MCH) < 27 pg;
- mean cell hemoglobin concentration (MCHC) < 30 g/dL;
- color index < 0.8;

morphology of the erythrocytes:

- anisocytosis (different sizes): microcytic red cells;
- poikilocytosis (different forms): pencil shaped cells and target cells;
- hypochromia, ring or pessary cells;
- few polychromatophils;
- reticulocyte count is variable;
- red blood cells osmotic fragility is slightly decreased;
- erythrocyte sedimentation rate is increased moderately.

Bone marrow:

- micronormoblaslic erythroid hyperplasia;
- predominantly intermediate normoblasts;
- cytoplasm is decreased and shows differential staining;
- bone marrow iron is reduced or absent.

Biochemical blood analysis:

- total serum iron 50–150 μg/dL;
- total iron-binding capacity 300–360 μg/dL;
- transferrin 204–360 mg/dL;
- ferritin 30 to 300 ng/m.

In patients with IDA:

- serum iron level is reduced;
- total iron binding capacity is increased;
- unsaturated iron binding capacity is increased;
- ferritin level of serum is decreased;
- transferrin level of serum is increased;
- percentage saturation reduced.

Classification of anemia according to the level of deacreased hemoglobin(Hb).

Erythrocytes is less informative index of anemia than the level of HB therefore, in the general practice the basic criterion of severity is precisely Hb:

• light degree of anemia – Hb 110–90 g/l;

• mild degree of anemia – Hb 90–70 g/l;

• severe anemia – Hb below 70 g/l.

Classification of anemia according to the level of deacreased Hb in %:

• light degree of anemia – decreased Hb on 5–19,9 % from initial;

• mild degree of anemia – decreased Hb on 20–39,9 %;

• severe anemia – decreased Hb more than on 40 %.

The stages of IDA:

Stage 1 (pre-latent): exhaustion of tissue reserve of iron; index of the blood within the standard; there are no clinical manifestations. Reduction in iron stores without reduced serum iron levels, Hb (N), MCV (N), iron absorption (↑), transferin saturation (N), Hb serum ferritin (↓), marrow iron (↓), lower than expected blood ferritin levels. Ferritin is the storage form of iron and low ferritin levels are the first sign that the body's iron stores are compromised.

Stage 2 (latent stage): deficiency of iron in the tissue and the decrease of its reservoir transport; index of the blood within the standard; clinical picture is caused by the sideropenic syndrome. Iron stores are exhausted, transport iron is decreased, this is often accompanied by a reduction in size of red blood cells even though blood hemoglobin levels remain normal. Hb (N), MCV (N), serum ferritin (↓), transferrin saturation (N or small decreased).

Stage 3 (final stage): Hemoglobin drops in this stage and may formally be defined as iron deficiency anemia. At this stage red blood cells are fewer in number, smaller and contain less hemoglobin.

Plan of patient investigation.

Blood count.

Blood film (microcytic, hypochromic red cells with poikilocytosis, anisocytosis).

Serum iron, serum ferritin, serum total iron binding capacity.

Examinatiom of feces to search the occult bleeding.

Consultation:

– gynecology – for female, proctology – for male;

– gastroenterology with esophagogastroscopy, colonoscopy.

Criterias of IDA:

– Presence of anemic and sideropenic syndromes.

– Specific laboratory changes.

Clinical management of patients with IDA.

I. In most cases, treatment is carried out in an outpatient setting.

II. Indications for hospitalization:

– severe acute anemia;

– in order to determine the etiological factor;

– suspected oncological causes.

Treatment of IDA.

Basis for medical treatment are oral iron-containag medications (Fe-Sulfat, Fe-Fumarat, Fe-Chlorid).

Therapy lasts until normalization of hemoglobin levels and then continues for 2 months and more in order to fill the iron stores.

Indications for parenteral iron therapy:

– gastrectomy;
– enterectomy;
– malabsorption syndrome for any diseases;
– ulcerative colitis;
– acute and massive blood loss;
– severe forms of anemia.

Intravenous therapy with iron-containag medications.

Intravenous iron therapy may be associated with severe allergic reactions. Therefore, the first injection should be carried out in the presence of a doctor (introduced 1 ml of drug diluted to 20 ml of isotonic solution, slowly). A certain dose of the drug is administered, usually every other day.

Iron overload.

Parenteral iron overload usually is the result of repeated red cell transfusions in patients with chronic anemia, but occasionally it is unintentionally produced by repeated injections of iron dextran or other parenteral iron medications. Symptoms of iron overload include: fatigue, weakness, joint pain, abdominal pain, shortness of breath, low back pain.

1.3. Megaloblastic anemia.

The megaloblastic anemias are a group of disorders characterized by abnormalities in the DNA synthesis of the blast cells due to the deficiency of vitamin B_{12} and/or folic acid and the presence of distinctive morphologic appearances of the developing red cells in the bone marrow.

Vitamin B_{12} deficiency anemia.

Prevalence of vitamin B_{12} deficiency anemia is enlarged with the years and makes up at young persons about 0,1 %, at elderly up to 1 %. Women are sick more often.

Pathogenesis of vitamin B_{12} deficiency anemia.

The daily need of a healthy person in the B_{12} is 3–7 μg. Methylcolabamin is an essential cofactor in the conversion folic acid to its active form. When this reaction is impaired folate metabolism is deranged and occurs defects in DNA synthesis with megaloblastic maturation patterns in patients who are deficient to colabamin.

The lack of vitamin B_{12} lead to the biochemical disorder such as conversion of homocysteine to methionine which takes part in production of phospholipids required for myelin formation. This biochemical abnormality may contribute to the neurological complication of cobalamine deficiency.

The jaundice may be explained by the excess breakdown of hemoglobin from immature erythroid bone marrow which easily damaged than normal erythrocytes and hence have a shortened life span.

Etiology of vitamin B_{12}-deficiency anemia.

1. Reduced intake: nutritional deficiency.

2. Strict veganism.

3. Impaired absorption:

– gastric cause: total or partial gastrectomy;

– intestinal cause: chronic tropical sprue, intestinal stagnant loop syndrome (e.g. jejunal diverticulosis, blind loop, strictures), scleroderma, Crohn's disease and ileal resection, congenital selective malabsorption with proteinuria, Zollinger Ellison syndrome, severe pancreatitis, coeliac disease;

– hemodialysis;

– transport protein defects: hereditary lack of transcobalamin II, abnormal transcobalamin II, abnormal B_{12} binding protein.

4. Competition for cobalamin:

– bacterial colonization of the small intenstine;

– fish tapeworm infection;

– bacteria “blind loop” syndrome.

Dietary sourses of folic acid:

• fresh fruits and vegetables:

• meat:

• cow and human milk:

• cereales and bread (fortified).

Daily folate requirements in adult are ~100 μg (3 μg/kg).

Folate requirements are increased by 200–300 μg to ~ 400 μg daily in a normal pregnancy, partly because of transfer of the vitamin to the fetus.

Etiology of folic acid deficiency anemia.

Impaired metabolism:

– inhibitors of dihydrofolate reductase;

– purine antagonists;

– pyrimidine antagonists;

– alcohol.

Reduced intake:

– poor diet;

– alcohol;

– liver disease;

– intenstinal malabsorption (celiac disease, inflammatory bowel disease).

Increased requirements:

– pregnancy;

– childhood and adolescence;

– neoplastic disease, chronic hemolytic disease.

Antifolate Drugs.

A large number of epileptics, who are receiving long-term therapy with phenytoin or primidone, develop low serum and red cell folate levels.

Alcohol may also be a folate antagonist, as patients who are drinking spirits may develop megaloblastic anemia that will respond to normal quantities of dietary folate or to physiologic doses of folic acid only if alcohol is withdrawn. Inadequate folate intake is the major factor in the development of deficiency in spirit-drinking alcoholics. Beer is relatively folate-rich in some countries, depending on the technique used for brewing.

The drugs that inhibit folate include methotrexate, pyrimethamine, and trimethoprim. Methotrexate has the most powerful action against the human enzyme, whereas trimethoprim is most active against the bacterial enzyme and is only likely to cause megaloblastic anemia when used in conjunction with sulphamethoxazole in patients with preexisting folate or cobalamin deficiency. The activity of pyrimethamine is intermediate.

Pernicious anemia (Addison-Biermer anemia).

Pernicious anemia were decribed by Thomas Addison (1849), Anton Biermer (1872), Samuel Fenwick (1870), William B. Castle (1929).

Pernicious anemia may be defined as a severe lack of instrinct factor due to gastric atrophy. It is a common disease in north Europeans but occurs in all countries and ethnic groups.

The ratio of incidence in men and women in Caucasians is ~1:1.6 and the peak age of onset is 60 years, with only 10 % of patients being <40 years of age. However, in some ethnic groups, notably black individuals and Latin Americans, the age of onset of pernicious anemia is generally lower.

Clinical manifestation of vitamin B_{12}-deficiency anemia:

1. Anemic syndrome.
2. Gastrointestinal manifestations: jaundice; anorexia; diarrhea.
3. Neurological syndrome.

Clinical manifestation of folic acid deficiency anemia:

1. Anemic syndrome
2. Gastrointestinal manifestations: jaundice; anorexia; diarrhea;
3. Neurological syndrome – absent.

Clinical features vitamin B_{12}-deficiency anemia.

Anemic syndrome includes such complaints: fatigue, tiredness, palpitation, dyspnea, giddiness.

The skin is pallor with lemon yellow tint, slightly icteric skin and sclerae, swallowing face, slight pedal edema.

Physical examination of the cardiovascular system reveals tachycardia, systolic murmur at the apex and pulmonary artery, systolic bruits over carotid arteries, ischemic changes on ECG, heart failure.

The symptoms and signs of gastrointestinal affection: anorexia, bladde and bowel dysfunction, diarrhea, Hunter's glossitis (sore, smooth red tongue, with

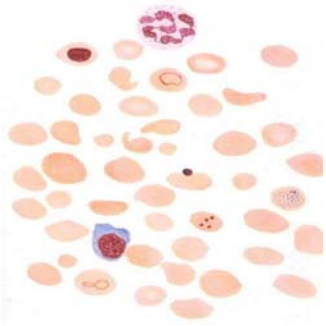
ulcer over the edge) (*Picture 10*)**,** atrophic gastritis, enlarged liver and sometimes spleen.

Picture 10.
Hunter's glossitis

Neurologic manifestations are peripheral neuropathy and combined degeneration of the spinal cord where the posterior and lateral columns undergo demyelization. The symptoms and signs are next: numbness, tingling, paresthesia in the extremities, difficulty in walking, ataxia, position and vibration senses are diminished, clumbness. There may be sphincter disturbance. Reflexes may be diminished or increased. The Romberg and Babinski signs may be positive. Affections of the mental state reflect irritability, diminished memory, even severy dementia or psychosis. In young females there may be infertility.

Clinical blood analysis.

Vitamin B_{12}-deficiency anemia *(Picture 1.11*).



Picture 1.11. Peripheral blood picture at vitamin B_{12}-deficiency anemia:

– hemoglobin concentration decreased moderately;
– red blood cell count decreased pronouncly;
– mean cell volume ranging from 100 to 140 fl;
– color index > 1,2;
– anisocytosis – macrocytosis;
– poikilocytosis – ovalocytosis;
– hyperchromia, ring or pessary cells;
– moderate leucopenia;
– mild, usually asymptomatic thrombocytopenia;
– red blood cells may show: Howel-Jolly bodies, Cabot rings;
– hypersegmentes neutrophils;
– macropolycytes (large neutrophils).

Notice that the large ovalocytes typical of megaloblastic anemia.

Macrocytic cells usually are seen in patients with B_{12} or folic acid deficiency, but can be seen in other conditions such as myeloid metaplasia, liver disease, hypothyroidism, and after treatment with some antimetabolites.

Bone marrow aspiration. In order to exam bone marrow it is necessary to aspirate ones using sternal puncture. Following local anaesthesia, the physician introduces a needle that penetrates into the sternum and aspirates 5–10 cc of bone marrow blood through a syringe. Samples collected are sent to the laboratory for analysis.

Bone marrow aspiration and *biopsy* may provide using the sample collection received after trepanobiopsy. These marrow collections are carried out on under local anaesthesia and with an execution time not exceeding 15–20

minutes. The patient is positioned prone on an examination table; the sample collection is performed with specific needles. A common site for a bone marrow aspiration and biopsy is the iliac crest of the pelvic bone, which is located in the lower back by the hip from the posterior higher iliac spine (the most protruding part of the hip bone near the sacral bone). A bone marrow biopsy can usually be done in doctor's office, without a need to stay in the hospital. Before the procedure, the skin in that area is usually numbed with medication. Other types of anesthesia (medication to block awareness of pain) may also be used.

Bone marrow at vitamin B_{12}-deficiency anemia:

- hyperplasia of erythroid elements;
- megaloblasts – gigantic cells with large nucleus oval shape and basophilic cytoplasm;
- gigantic metamyolocytes; megakaryocytes;
- bone marrow aspirate is hypercellular with a decreased myeloid/erythroid ratio;
- megaloblastic red blood cells precursors are abnormally large and have nuclei that appear less mature than would be expected from the development of the cytoplasm (nuclear-cytoplasmic asynchrony);
- nuclear chromatin is more dispersed than expected, and it condenses in a peculiar fenestrated pattern;
- abnormal mitoses may be seen.

Biochemical blood analysis at vitamin B_{12}-deficiency anemia:

- increased level of unconjugated bilirubin;
- increased level faeces stercobilin;
- increased level of lactatdehydrogenasa.

Special tests for diagnosing viamin. B_{12} deficiency:

- low serum vitamin B_{12} assay (the normal range is 300 to 900 pg/ml);
- increased urinary excretion of methylmalonic acid;
- low radioactive vitamin B_{12} absorption test (Schilling's test);
- reticulocyte response to vitamin B_{12} administration.

Treatment of cobalamin deficiency anemia.

It is usually necessary to treat patients who have developed cobalamin deficiency with lifelong regular cobalamin injections.

Cobalamin therapy: The indications for starting cobalamin therapy are a well-documented megaloblastic anemia or other hematologic abnormalities or neuropathy due to the viamin. B_{12} deficiency.

Cobalamin should be given routinely to all patients who have had a total gastrectomy or ileal resection. Patients who have undergone gastric reduction for control of obesity or who are receiving long-term treatment with proton pump inhibitors should be screened and, if necessary, given cobalamin replacement.

Replenishment of body stores should be complete with six 1000-μg IM injections. of hydroxocobalamin given at 3 to 7-day intervals. More frequent doses are usually used in patients with cobalamin neuropathy, but there is no evi-

dence that these produce a better response. For maintenance therapy, 1000 μg hydroxocobalamin IM once every 3 months is satisfactory.

Treatment of folate deficiency.

5–15 mg folic acid daily are satisfactory, as sufficient folate is absorbed from these extremely large doses even in patients with severe malabsorption. The length of time therapy must be continued depends on the underlying disease. It is customary to continue therapy for about 4 months, when all folate-deficient red blood cells have been eliminated and replaced by new folate-replete populations.

Folic acid, 400 μg daily, should be given as a supplement before and throughout pregnancy.

Criterias of effective treatment of megaloblastic anemia:

– subjective improvement during the first days of treatment;

– reticulocytosis maximally expressed (to 20 %) on 5–7th day of treatment;

– increase in hemoglobin and number of erythrocytes, beginning from the 2nd week of treatment;

– normalization of the blood index, number of leukocytes and thrombocytes in 3–4 weeks of treatment.

1.4. Definition, causes and clinical features of hemolytic anemia syndrome.

Hemolytic anemias are the geterogenous group of anemias which characterized by shortened life span of erythrocytes (less than 120 days) in the circulation resulting from their accelerated intracorpuscular (in cells of cytophagous system) or extracorpuscular (in a vascular system) destruction (hemolysis).

Types of hemolytic anemia:

I. By origin:

1) acquired (secondary);

2) hereditary or congenital (primary).

II. On the mechanisms of hemolysis:

1) anemia with intravascular hemolysis;

2) anemia with intracellular hemolysis.

Intravascular hemolysis.

Some hemolytic factors may damage the red blood cells in blood vessels:

a) physical factors (mechanical trauma, ionizing radiation, ultrasound, temperature);

b) chemical agents (haemolytic poison);

c) biological factors (infections, toxins, enzymes);

d) immune factors (antibodies).

Intravascular hemolysis is accompanied by the release of hemoglobin from the cells in the blood plasma, where it is partly connected with the protein haptoglobin:

1) haptoglobin-hemoglobin complex is absorbed by spleen macrophages and causes the formation macrophageal erythropoietin, which is affecting the red bone marrow and stimulates erythropoiesis;

2) in macrophages the protein portion of hemoglobin is splited to amino acids, and bilirubin is formed from heme, which binds to proteins and enters the blood (indirect bilirubin). As a result developed hemolytic jaundice;

3) a small portion of the hemoglobin does not bind to haptoglobin and filtered by the kidneys. Consequently, hemoglobin appears in the urine – hemoglobinuria, kidney filter becomes clogged and signs of acute renal failure developed.

Intracellular hemolysis develops as a result of the absorption and digestion of erythrocytes by macrophages of spleen.

Causes of intracellular hemolysis:

a) appearance of defective red blood cells, accompanied by their long delay in the endothelial clefts venous sinuses of spleen («splenic filter»), defective red blood cells are absorbed by macrophages;

b) hypersplenism – an increase of phagocytic activity of macrophages of spleen.

Intracellular hemolysis is accompanied by the following changes in the body:

1) formation of erythropoietin by macrophages, resulting in increased erythropoiesis in the bone marrow and there is a large number of young forms of erythrocytes in the peripheral blood;

2) formation of a large amount of bilirubin, which causes the development of jaundice, the proliferation of macrophages, which leads to an increase in the spleen (splenomegaly).

Etiology of hemolytic anemia.

The causes of hemolytic anemias may be hereditary or acquired.

The causes of hereditary hemolytic anemia are grouped into three categories:

1) defect of the cell membrane (membranopathy);

2) defects of erythrocyte metabolism (enzymopathy);

3) abnormal hemoglobin (hemoglobinopathy).

Classification of hereditary hemolytic anemias.

Defects of the cell membrane:

– hereditary spherocytic anemia;

– hereditary elliptocytic anemia.

Defects of erythrocytic metabolism: glucose-6-phosphate dehydrogenase (G-6-PD) deficiency anemia.

Abnormal hemoglobins:

– sickle cell anemia;

– thalassemia.

Acquired hemolytic anemia.

Immunological destruction of red blood cells:

– transfusion with incompatible blood;
– hemolytic disease of the newborn;
– autoimmune hemolytic anemia (AIHA) (warm-active AIHA and cold-active AIHA).

Hemolytic anemia induced by chemical agents – lead, acids etc.

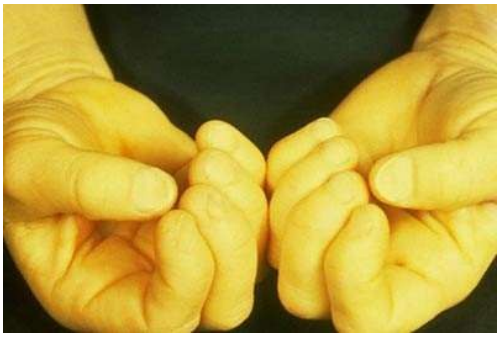
Hemolytic anemia caused by microorganism:
– anemia of malaria;
– anemia of clostridia.

Physical destruction of red blood cells:
– march hemoglobinuria;
– traumatic cardiac hemolytic anemia (in patients with prosthetic valves).

Paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome).

Clinical signs of hemolysis:
– jaundice of a sclera (*Picture 1.12*) and of a skin (*Picture 1.13*);
– jaundice of mucosa; splenomegaly, hepatomegaly due to hemosiderosis with intracellular hemolysis.

Picture 1.12.
Jaundice of a sclera and skin



Picture 1.13.
Jaundice of a skin

Clinical blood analysis:
– hemoglobin concentration decreased;
– red blood cells count decreased;
– anemic syndrome with a normochromic anemia;
– reticulocytes increased;
– macrocytosis;
– polychromasia;
– polymorphonuclear.
– life span of red blood cell shortened.

Bone marrow: compensatory erythroid hyperplasia.

Table 1.4

General features of hemolytic disorders

General examination	Jaundice, pallor
Other physical findings	Spleen may be enlarged; bossing of skull in severe congenital cases
Hemoglobin	From normal to severely reduced
MCV, MCH	Usually increased
Reticulocytes	Increased
Bilirubin	Increased (mostly unconjugated)
LDH	Increased, normal with intravascular hemolysis
Haptoglobin	Reduced to absent

Note: MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; LDH lactate dehydrogenase.

Biochemical blood analysis:

– increased plasma unconjugated bilirubin;
– increased urinary urobilinogen;
– increased fecal urobilinogen;
– increased plasma lactate dehydrogenasa.

Findings of intravascular hemolysis:

– reduced or absence of haptoglobin in the blood;
– presence of free hemoglobin in the blood;
– presence of free hemoglobin in the urine;
– presence of methemalbumemia.

Special test for determining red blood cell life span using the 51Cr.

1.5. Hereditary spherocytic anemia (the disease Minkowski–Chauffard).

This is an inherited disorder that is transmitted as an autosomal dominant trait. The patient may have a de novo mutation, that has taken place in a germ cell of one of his parents or early after zygote formation and the patient may have a recessive form of disease.

Severe cases may present in infancy with severe anemia, whereas mild cases may present in young adults or even later in life. In women hereditary spherocytic anemia is sometimes first diagnosed when anemia is investigated during pregnancy.

Pathogenesis of hereditary spherocytic anemia.

People suffering from spherocytic anemia have abnormal mutant gene for the protein spectrin, their lack weakens the structure of the red blood cell membrane. Spherocytes are rigid cells and hence they cannot pass through slit like openings of splenic cords and sinuses and may remain there for over 10 hours,

hypoxia is created which compromises red cell metabolism consequently leading to loss of red cell membrane, this causes further sphering and rigidity.

Clinical features of hereditary spherocytic anemia.

The disease can present at any age, but most patients present in the first decade of life. Anemia is mild, because the reduced life span of the red blood cells is compensated by an increased erhytrocyte production in bone marrow. Symptoms can vary to severy anemia. Episodic jaundice may be noted. The severity of the disorder tends to hemolytic crisis at times often precipitated by infections or due to no obvious cause. Splenomegaly is the characteristic of hereditary spherocytic anemia. Abdominal pain due to the hemolytic crises or splenic infarction is observed. Gallstones with calcium bilirubinate are common which may result in biliary obstruction and the pain.

If the increased hemolysis occurs in early childhood, there was a specific shape of the head, cranial deformation (tower, square), saddle-shaped nose, broken structure and position of teeth, polydactilia. Symptoms of disease are jaundice, a common anemia, nose bleeds, biliary colic due to the formation of pigment stones.

On clinical examination is observed the yellowness of skin and mucous membranes with an olive tinge. Also revealed splenomegaly, hepatomegaly.

Clinical blood analysis:

– hemoglobin concentration decreased;

– red blood cells count decreased;

– platelets decreased;

– reticulocytes increased sharp (from 5 to 20 %);

– red blood cells and platelets count return to normal after hemolytic crisis within 7–10 days;

– MCV normal or reduced;

– MCH normal;

– MCHC often increased (34–40 %).

In peripheral blood smear: reticulocytosis and microcytosis, spherocytes, microspherocytes (microcytes without central pallor), polychromatophils.

Bone marrow – normoblastemia.

Biochemical blood analysis: increased plasma unconjugated bilirubin.

Special tests:

– Coomb's test is negative;

– osmotic fragility of erhytrocytes is raised;

– red cell life span reduced with excessive counting over spleen.

What is the «osmotic fragility» test? The osmotic fragility test is done to confirm the diagnosis of hereditary spherocytosis. A patient`s red blood cells are placed in different concentrations of saline solution for 24 hours. When red blood cells are placed in saline solution, they absorb water until the cell membrane bursts. Spherocytes do not tolerate weak saline solutions, causing them to burst sooner than normal cells.

In most cases the diagnosis of hereditary spherocytic anemia is confirmed on the basis of red cell morphology and a test for osmotic fragility, a modified version of which is called the «pink test».

In some cases a definitive diagnosis can be obtained only by molecular studies demonstrating a mutation in one of the genes underlying disease. This is carried out only in laboratories with special expertise in this area.

Main principles of treatment of hereditary spherocytic anemia.

There is currently no treatment aimed at the cause of spherocytic anemia, no way has yet been found to correct the basic defect in the membrane cytoskeleton structure. However, it has been apparent for a long time that the spleen plays a special role through a dual mechanism. On one hand, the spleen itself is a major site of destruction; on the other hand, transit through the splenic circulation makes the defective red cells more spherocytic and therefore accelerates their demise, even though lysis may take place elsewhere. For these reasons, splenectomy has long been regarded as a prime, almost obligatory therapeutic measure in such pathology. However, it also increases the risk of certain infections, and therefore current guidelines (not evidence-based) are as follows – avoid splenectomy in mild cases, delay splenectomy until at least 4 years of age, after the risk of severe sepsis has peaked. Thereare proposition for surgical removal of the spleen (splenectomy) in children five years of age or older. This does not cure the patient of spherocytosis; rather it allows red blood cells to live longer. Without a spleen, a person has an increased risk for some serious infections. Several special immunizations (pneumococcal and meningococcal) are also required to help prevent some infections.

Young children (up to five years of age) should take folic acid supplements. Blood transfusions may help with severe anemia.

1.6. Glucose-6-phosphate dehydrogenase deficiency anemia.

Deficiency of glucose-6-phosphate dehydrogenase (G-6-PD) is an inherited disorder with sex linked transmittion with intermediate dominance because gene for G-6-PD is located on the X-chromosome. In males the presence of a G-6-PD deficient gene will result in the absence of any normal G-6-PD and as result in an accelerated hemolysis of the red blood cells. Heterozygous deficiency female with one normal and one abnormal gene has red blood cells that are either normal or lack the active G-6-PD enzyme. Overt signs of anemia are rare in heterozygous deficient females.

Epidemiology of glucose-6-phosphate dehydrogenase deficiency anemia.

G-6-PD deficiency is widely distributed in tropical and subtropical parts of the world (Africa, Southern Europe, the Middle East, Southeast Asia, and Oceania) and wherever people from those areas have migrated; a conservative estimate is that at least 400 million people have a G6PD-deficiency gene. It is found mainly in populations that border the Mediterranean Sea such as Sicilians, Sardinians, Greeks, Turks, Lebanese, Sephardic Jews and Arabs.

Etiology of glucose-6-phosphate dehydrogenase deficiency

There are agents who may lead to hemolytic anemia in G-6-PD deficiency. Acute hemolytic anemia can develop as a result of three types of triggers: (1) fava beans, (2) infections and (3) drugs. There is phenomenon of favism. Ingestion of the fava bean or even inhalation of fava pollen may result in a severe hemolytic crisis. Some drugs may carry risk for hemolysis (*Table 1.5*).

Pathogenesis of glucose-6-phosphate dehydrogenase deficiency.

G-6-PD is a housekeeping enzyme critical in the redox metabolism of all aerobic cells. In red cells, its role is even more critical because it is the only source of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which, directly and via reduced glutathione, defends these cells against oxidative stress. In normal individuals the level of oxidant activity and hence the level of sulfhemoglobin is carefully controlled by the compound known as reduced glutathione which neutralizes the activity of the oxidant drugs or oxidant products of infections with the aid of NADPH. The NADPH needed for reaction is provided by the hexose monophosphate shunt via the enzyme G-6-PD. Persons with lack G-6-PD have an abnormal form this enzyme will unable to generate sufficient amount of NADPH. As a consequence there will be a steady increase in the amount of oxidant in the red blood cells, resulting in the formation of sulfhemoglobin, which will precipitate out as Heinz bodes. In situation in which the body is suddenly exposed to large amount of oxidants people with abnormal or deficient G-6-PD be unable to eliminate these toxic compounds, resulting in a rapid outbreak of hemolytic anemia.

Clinical manifestations of glucose-6-phosphate dehydrogenase deficiency anemia.

The vast majority of people with G-6-PD deficiency remain clinically asymptomatic throughout their lifetime. However, all of them have an increased risk of developing neonatal jaundice and a risk of developing acute hemolytic anemia when challenged by a number of oxidative agents. Neonatal jaundice related to G-6-PD deficiency is very rarely present at birth: the peak incidence of clinical onset is between day 2 and day 3, and in most cases the anemia is not severe. However, neonatal jaundice can be very severe in some G-6-PD-deficient babies, especially in association with prematurity, infection, and/or environmental factors (such as naphthalene-camphor balls used in babies' bedding and clothing).

In these cases, if inadequately managed, neonatal jaundice associated with G-6-PD deficiency can produce icterus and permanent neurologic damage. *Clinical features.*

Acute onset associated with acute illness or infection, by taking of an offending drug or chemical, or the ingestion of fava beans. Acute hemolytic episode is observed with pallor, jaundice, abdominal pain and dark urine. Despite continuous drug intake, the hemolytic process ends spontaneously after approximately one week.

Table 1.5

Drugs that carry risk of hemolysis in persons with G-6-PD deficiency

Drugs	Definite risk	Possible risk	Doubtful risk
Antimalarials	Primaquine	Chloroquine	Quinine
	Dapsone chlorproguanil		
Sulphonamides/ sulphones	Sulphametoxazole	Sulfasalazine	Sulfisoxazole
		Sulfadimidine	Sulfadiazine
Antibacterial/ antibiotics	Cotrimoxazole	Ciprofloxacin	Chloramphenicol
	Nalidixic acid	Norfloxacin	Aminosalicylic acid
	Nitrofurantoin		
	Niridazole		
Antipyretic analgesics	Acetanilide	Acetylsalicylic acid High dose (>3 g/d)	Acetylsalicylic acid <3 g/d
	Phenazopyridine (Pyridium)		Acetaminophen

Additional methods of examination.

Clinical blood analysis:

– hemoglobin concentration decreased during the acute phase (3–4 gm % fall);
– polychromasia;
– reticulocytosis;
– basophilic stippling;
– fragmented red blood cells;
– Heinz bodies.

Screening tests.

Tests demonstrate the presence/absence of G-6-PD by testing the ability of cells to generate NADPH from NADP, a reaction direct by dependent upon G-6-PD availability:

– brilliantcresyl blue reduction test;
– methemoglobin reduction test;
– Heinz body test;
– fluorescence spot test;
– acrobat-cyanid test;
– assays of G-6-PD activity.

Laboratory diagnostics.

In clinical practice a diagnostic test is usually needed when the patient has had a hemolytic attack: this implies that the oldest, most G-6-PD-deficient red cells have been selectively destroyed, and young red cells, having higher G-6-PD activity, are being released into the circulation. Under these conditions, only a quantitative test can give a definitive result. In males this test will identify normal hemizygotes and G-6-PD-deficient hemizygotes; among females some heterozygotes will be missed, but those who are at most risk of hemolysis will be identified.

Prevention and treatment of glucose-6- phosphate dehydrogenase deficiency anemia.

Favism is entirely preventable by not eating fava beans. Prevention of drug-induced hemolysis is possible in most cases by choosing alternative drugs. When acute hemolytic anemia develops and once its cause is recognized, no specific treatment is needed in most cases. However, if the anemia is severe, it may be a medical emergency, especially in children, requiring immediate action, including blood transfusion. If acute renal failure develops, hemodialysis may be necessary, but if there is no previous kidney disease, full recovery is the rule.

1.7. Sickle cell anemia (hemoglobin S disease).

Sickle cell anemia is chronic hemolytic anemia, which is characterized by sickling phenomenon of red blood cells that assume an abnormal, rigid, sickle shape causing by inheritance of pathological gene, determined the synthesis of abnormal hemoglobin S (HbS) and results in a risk of various complications. Sickle cell anemia is an autosomal recessive disorder characterized by the replacement of glutamate (polar) by valine (nonpolar) at the sixth position in the Beta subunit of hemoglobin due to the a point mutation in the Beta-globin chain. Life expectancy of hemoglobin is shortened to 42 days in males and 48 days in females.

Etiology sickle cell anemia is inherited as an autosomal codominant trait. In patient may be genetic defect: one normal and one abnormal gene – heterozygous, both abnormal genes – homozygous. People who are heterozygous for HbS normally produce more than 50 % of their hemoglobin in the form of HbA. HbSS disease or sickle cell anemia (the most common form) – homozygote for the S globin with usually a severe or moderately severe phenotype and with the shortest survival. HbS/b-0 thalassemia – double heterozygote for HbS and b-0 thalassemia; clinically indistinguishable from sickle cell anemia. HbS/b+ thalassemia – mild-to-moderate severity with variability in different ethnicities. HbSC disease – double heterozygote for HbS and HbC characterized by moderate clinical severity. HbS/hereditary persistence of fetal Hb (S/HPHP) – very mild or asymptomatic phenotype. HbS/HbE syndrome – very rare with a phenotype usually similar to HbS/b+thalassemia. Rare combinations

of HbS with other abnormal hemoglobins such as HbD Los-Angeles, G-Philadelphia, HbO Arab, and others.

Pathogenesis of sickle cell anemia.

Normal red blood cells are smooth and round. They move easily through blood vessels to carry oxygen to all parts of the body. There are different hypotheses regarding the molecular events of relationships between structure of HbS and formation of sickled cells. A serious condition in which red blood cells can become sickle-shaped. As the red blood cells sickle, they lose their flexibility and become rigid and in this form they don't move easily through blood. They are stiff and sticky and tend to form clumps and get stuck in blood vessels may obstruct the capillary flow. The clumps of sickle cell block blood flow in the blood vessels that lead to local the tissue, the limbs and organs hypoxia. Blocked blood vessel can cause pain, serious infection and organ damage

Pathophysiology of sickle cell anemia.

Sickling occurs when erythrocytes are exposed to oxygen less than 40mmHg for 2 to 4 minutes. Under deoxy conditions, HbS undergoes marked decreased in solubility, increased viscosity, and polymer formation at concentrations exceeding 30 g/dL. It forms a gel-like substance containing Hb crystals called tactoid.

Deoxygenated Hb S polymers are formed and membranes are damaged so red blood cells accumulate calcium, lose potassium and water and become rigid strand and irreversibly sickled. Normal red blood cells live for 90–120 days but sickle cells live for only 10–20 days.

Clinical features of sickle cell anemia.

Signs and symptoms related to anemia resulted from sickle cells break apart easily and die in a short time, the body can't get enough oxygen, causing fatigue, shortness of breath, dizziness, headache, chest pain, pale skin or nail beds. Episodes of pain occur in a form of crisis. Pain develops when sickle-shaped red blood cells block blood flow through tiny blood vessels to chest, abdomen, joints and in bones. Painful swelling of hands and feet due to blocking blood flow to the hands and feet by sickle-shaped red blood cells. Frequent infections because sickle cells can damage an organ that fights infection (spleen), leaving the patient more vulnerable to infections. People with sickle cell anemia have an increased risk of infection, and fever can be the first sign of an infection.

In infants and children observed delayed growth. Red blood cells and blood plasma carry oxygen and nutrients to the tissues. Sickle cells slow growth in infants and children and delay puberty in teenagers. They remain small and sickly. Adult patients are asthenics, body weight decreased. Tiny blood vessels that supply the eyes may become plugged with sickle cell, bleeding in the retina, vision problems. Frequently observed infarctions of lung, spleen, kidney and other organs, thrombosis of the mesentery, hepato-and splenomegaly, pigment gallstones.

Swelling of the extremities, caused by thrombosis, trophic ulcers on the extremities, asepsis necrosis of the caputs of femoral and shoulder bones with strong pain and a local soft tissue swelling occur in these patients. May be observed symptoms and signs of stroke: one-sided paralysis or weakness in the face, arms or legs; confusion; trouble walking or talking; sudden unexplained numbness or a headache.

Acute chest syndrome is a clinical syndrome characterized by chest pain, fever due to chest infection, pulmonary thrombosis, lung consolidation.

Heart: cardiomegaly and heart failure due to increased cardiac output.

Mediastinum: posterior mediastinal mass lesion due to extramedullary hemopoesis.

Abdomen: hepatomegaly due to extramedullary hemopiesis, hepatic siderosis due to repeated transfusion and iron overload.

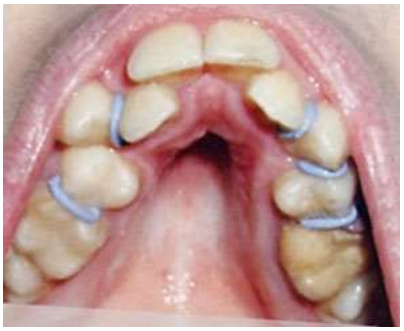
Kidney: renal papillary necrosis, renal infarcts.

Spleen: Splenic sequestration crisis

Osteoarthropatic syndrome: pain in the bones, joints, skeletal manifestations, frontal and parietal bossing and prominent maxilla, prominent malar bones and protuberant teeth due to marrow hyperplasia expanding the bone (*Picture 1.14, 1.15*).

The extremities may appear proportionately longer than normal because there is often flattening of the vertebrae. Radiographically is observed osteoporosis, in later stages osteosclerosis with thickening of the cortical layer, aseptic necrosis, osteomyelitis.

Picture 1.14.
bossing of the skull



Picture 1.15.
Prominent protuberant teeth

Course of sickle cell anemia.

The sickle cell disease has heavy course. The onset of disease usually begins at age less 2 years, because from birth to 6-months child is protected by HbF, which later replaced with HbS. By 5 months of age in a child with HbS genes appear first hemolytic crises, painful swelling of the feet, hands, legs and joints. Crises often occur against a background of infection manifested by chills, fever, hemoglobinuria, progressive anemia. Later appears yellowness of the mucous membranes and skin, increased serum bilirubin, urine urobilin and stercobilin in feces.

Clinical features vary according to the inheritance type. In cases of homozygous sickle cell disease, the clinical syndrome includes specific phenotype: phenomenon of vessels obstruction and hemolytic anemia.

Complications.

There are vaso-occlusive crisis, splenic sequestration crisis, aplastic crisis, hemolytic crisis. The most common clinical manifestation of sickle cell anemia is vaso-occlusive crisis. Vaso-occlusive crisis occurs when the microcirculation is obstructed by sickled red blood cells, causing ischemic injury to the organ supplied and resultant pain. Pain crises caused by bone marrow infarction or ischemia affecting abdomen, joints and soft tissues.

Causes of vaso-occlusive crisis.

The sickling process that prompts a crisis may be precipitated by multiple factors. A specific cause is often not identified. Vaso-occlusive crises are often precipitated by the following: cold weather (due to vasospasm), hypoxia (flying in unpressurized aircraft), infection, dehydration (especially from exertion or during warm weather), acidosis, alcohol intoxication, pregnancy. Vaso-occlusive crises lead to stroke due to brain infracts, acute chest syndrome due to pulmonary thrombosis, infection, fat embolism. Acute abdominal pain in patient is a result of splenic infarct.

Splenic sequestration crisis.

Acute painful enlargement of the spleen, associated with drop in red blood cells and platelet counts due to sudden pooling of large amount of blood in to the spleen.

Aplastic crisis.

Aplastic crisis occurs due to acute reticulocytopenia triggered by padvovirus B19.

Hemolytic crisis

Hemolytic crisis is due to acute accelerated drop in hemoglobin level. Hemolytic crisis occurs in patients with co-existent glucose 6-phosphate dehydrogenase.

Prevention of hemolytic crisis.

It is nessesary identify what can trigger the crisis such as stress, avoid extremes of heat and cold weather, don't travel airplane that is not cabin pressurized, maintain healthy lifestyle habits, eating healthy, avoid dehydration, exercise regularly, get enough sleep and rest, avoid alcohol and don't smoke, regular medical checkups and treatment are important.

Symptom control and management of sickle-cell anemia.

In order to treat the complications strategies include the following seven goals:

- management of vaso-occlusive crisis;
- management of chronic pain syndromes;
- management of chronic hemolytic anemia;
- prevention and treatment of infections;

• management of the complications and the various organ damage syndromes associated with the disease;

• prevention of stroke;

• detection and treatment of pulmonary hypertension.

Treatment of sickle-cell anemia.

1. 1 mg of folic acid daily for life.

2. The first approved drug for the causative treatment of sickle-cell anemia, hydroxyurea, was shown to decrease the number and severity of attacks and shown to possibly increase survival time. This is achieved, in part, by reactivating fetal haemoglobin production in place of the haemoglobin S that causes sickle-cell anemia. Hydroxyurea had previously been used as a chemotherapy agent, and there is some concern that long-term use may be harmful, but this risk has been shown to be either absent or very small and it is likely that the benefits outweigh the risks.

3. Bone marrow transplants have proven to be effective in children.

1.8. Thalassemias.

The term thalassemia comes from the Greek words «thalas», meaning sea, and «emia», which stands for blood.

28 % of the red blood cells mass are composed by hemoglobin. The hemoglobin molecule is roughly spherical with a maximum molecular diameter of about 6.4 μm. It is a tetramer, consisting of two pairs of polypeptide chains. To each of the four chains is attached a highly coloured prosthetic group – heme, a complex of iron and protoporphyrin. Protein portion of the molecule is called globin.

An adult mature red cell has:

• hemoglobin A1 (α2 & β2 chains) – 97 %;

• hemoglobin A2 (α2 & δ2 chains) – 2,5 %;

• hemoglobin F (α2 & γ2 chains) – < 1 %.

Epidemiology of thalassemias.

The thalassemia trait occurs with high frequency in certain population. Thalassemia is most prevalent in populations that border the Mediterranean sea in the Far East, in certain African population as well as in American black.

Pathogenesis of thalassemias.

Normal adult hemoglobin contains two α- and β-chains. In the thalassemias production of one of these globin chains is deficient. Consequently, less than the normal amount of adult hemoglobin is produced and occur anemia. Thalassemia may be divided into two major groups according to the globin chain that is deficient into α- thalassemia and β-thalassemia.

α-Thalassemia

Deficiency is in the synthesis of α-globin. The β-globins are not affected and are produced at their normal rate. Four different patterns of α-thalassemia can occur: one-gene deletion – silent carrier; two-gene deletion – α-thalassemia

trait; three-gene deletion – HbH disease; four-gene deletion – failure of HbA and HbF synthesis.

Clinical features.

If one gene is deleted there is no clinical effect. The α-thalassemia trait is also asymptomatic as hemoglobin levels usually reach 10 to 12 g/dl as defined as mild hypochromic anemia. People with this disorder will have from 5 to 40 % of HbH in their blood, which tends to precipitate with formation of Heinz bodies. Such red blood cells are then catched by the mononuclear phagocytic cells of the spleen and shortened life span of these red blood cells.

The clinical features include skeletal changes in these patients due to the hyperactivity of bone marrow, leg ulcers, icterus and splenomegalia. Anemia frequently worsens during pregnancy and infectious disease. In case of four α-globin genes deletion followed complete failure of HbA and HbF synthesis.

Total absence α-globin leads to death either in utero or very soon after birth due to hypoxia. This phenomenon is known as hydrops fetalis.

Additional methods of examination.

Clinical blood analysis:

– hemoglobin concentration decreased corresponds to type thalassemia;

– the total red blood cell count may be fairly normal due to a moderate increase in reticulocytes;

– microcytic hypochromic cells;

– target cells.

Special tests:

Electrophoresis of the blood hemoglobin allows to detect the presence of HbH.

β-Thalassemia

β-Thalassemia is characterized by a deficiency in β-globin chain synthesis.

Etiology and pathogenesis

Etiology and pathogenesis β-thalassemia are caused by mutations affecting the functional capacity of mRNA and normal transcription of β-globin genes. There are the some forms of β-thalassemia:

– β-thalassemia major;

– homozygous with complete suppression of HbA;

– β-thalassemia inter media;

– β-thalassemia with incomplete suppression HbA (10–20 %);

– β-thalassemia minor, heterozygous (Hb – 90–95 %).

Clinical feature.

β-thalassemia major appears in first year of life with insidious onset and development of severe chronic anemia. In the absence of transfusion therapy, hemoglobin falls to 3 to 5 gm %. Skeletal changes in hands and feet, the metacarpals and phalanges, which become rectangular and frankly convex shaped.

Stature is shortened, head is large and abdomen protrudes. In the long bones widening of medullary portions predisposing to pathologic fractures. Compression factures of vertebrae may occur. The facial manifestations of

β-thalassemia are specific: thickening of the cranial bone produces frontal bossing. Prominence of the check bones lend to obscure base of the nose and expose the upper teeth. Growth and mental retardation in early childhood occurs due to anemia.

In patients are observed myocardial hemosiderosis with arrhythmias and leading effect heart failure, which cause death in transfused patients with thalassemia.

Hepatomegaly is due to myeloid metaplasia but later results from iron deposits suggested microscopically hemochromatosis. Splenomegaly is common feature of β-thalassemia.

Additional methods of examination

Clinical blood analysis:

– erythrocytes count decreased;
– platelet count normal but decreased;
– leucocytosis;
– reticulocytosis (10 %);
– hemoglobin level below normal;
– MCV, MCH, MCHC are diminished;
– marked microcytosis with hypochromia;
– numerous Heinz bodies;
– target cells;
– normoblasts;.
– granular inclusions are in cytoplasm.

Bone marrow:

– erythroid hyperplasia;
– normoblasts present.

Special test:

– osmotic fragility of erythrocytes is decreased;
– serum bilirubin elevated due to hemolysis.

β-Thalassemia minor

The individual has at least one normal functioning β-globin gene, which produces sufficient quantities of HbA. Heterozygous state prevents severe symptoms of anemia. Seldom may the disease manifestate with icterus, splenomegaly, by ulcers or radiographic changes of long bones. Sometimes pathology is detected occasionally during routine examination.

Clinical blood analysis:

– erythrocytes count decreased;
– hemoglobin level slightly below normal or normal;
– MCV and MCH are reduced;
– MCHC is normal;
– microcytic hypochromic cells;
– target cells;
– stippled erythrocytes present.

Bone marrow is normal except for mild erythroid hyperplasia.

Biochemical blood analysis:

– serum bilirubin may be slightly elevated.

Special tests:

– osmotic fragility of erythrocytes is decreased;

– erythrocytes life slightly shortened.

1.9. Paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome).

Paroxysmal nocturnal hemoglobinuria, sometimes referred to as Marchiafava-Micheli syndrome, is a rare, acquired, potentially life-threatening disease of the blood characterized by complement-induced intravascular haemolysis due to destruction of red blood cells in the blood stream which lead to hemolytic anemia, formation of blood clot (thrombosis), red or dark urine (due to the appearance of hemoglobin in the urine) and decreased function of bone marrow (pancytopenia).

Paroxysmal nocturnal hemoglobinuria a unique clinical and hematological syndrome with the triad:

– thrombosis of large vessels, such as cerebral, abdominal, hepatic and subdermal veins;

– anemia resulted to acquired intravascular haemolysis due to abnormal susceptibility of red blood cells membrane to haemolytic activity of complement;

– pancytopenia – deficiency in haematopoiesis.

Pathogenesis of paroxysmal nocturnal hemoglobinuria (PNH).

PNH can present on its own (primary) or as a result of other bone marrow disorder such as aplastic anaemia (secondary). PNH is caused by a defect in glycolipid protein structures on the surface of red blood cell. The most common defective enzyme in PNH is phosphatidylinositol glycan A (PIGA), one of the enzymes needed to make glycosyl phosphatidylinositol (GPI) which anchors proteins on the cell surface. This signalling protein on the cell surface helps the cell to communicate with its surrounding environment. The gene for PIGA is located on the X chromosome. A mutation in the PIGA gene can lead to an absence of GPI anchors on the cell membrane, when this occur in an hematopoietic stem cell in bone marrow, all of the cells it produces will have this defect. Several of these proteins that anchor to GPI on cell membrane are used to protect the cell from destruction by the complement system, an absence of these anchors will lead to easy destruction of red blood cells by the complement system.

Also intravascular hemolysis leads to an increasing in free hemoglobin in plasma, these free hemoglobin starts binding to haptoglobin, after a while the haptoglobin becomes saturated and cannot accept anymore hemoglobin so hemoglobins binds irreversibly to nitric oxide which is needed for the relaxation of smooth muscle. An absence of protectin CD59 on platelet membranes can induced platelet aggregation which is highly thrombogenic particularly in the venous system. Bone marrow failure can be due to damage by complement system.

Clinical features:

- paroxysmal nocturnal hemoglobinuria with partial clearing during the day;
- abdominal pain (mesenteric ischemia, abdominal vein thrombosis);
- Budd-Chiari syndrome (hepatic vein thrombosis);
- raised painful red nodules (dermal vein thrombosis);
- severe headache (cerebral vein thrombosis);
- esophageal spasm;
- erectile dysfunction;
- pulmonary embolism (due to deep vein thrombosis);
- signs of anemia (pallor, dyspnea, palpitations);
- haemorrhagic rashes;
- mucosal bleeding;
- fever;
- splenomegaly;
- hepatomegaly and ascites;
- papilledema;
- skin nodules;
- diminished bowel sounds.

Hemoglobinuria observed mostly at night, in connection with the development in this period of acidosis. Typical symptoms: a selection of dark urine (hemoglobinuria, gemosiderinuria) after sleep and bouts of abdominal pain (thrombosis and embolism of small mesenteric vessels), moderate splenomegaly and chronic hemolysis.

The disease is undulating; the periods of hemolytic crises are changing the clinical well-being. Patients live after identifying of disease an average of 10 years.

Classic PNH may be accompanied with setting of another specified bone marrow disorder (PNH/aplastic anemia or PNH/refactory anemia-myelodysplastic syndrome); subclinical PNH in the setting of another specified bone marrow disorders.

Additional examination.

Clinical blood analysis: red blood cell count – hemoglobin decreased, increased reticulocytes count (immature red cells released by the bone marrow to replace the destroyed cells); leukopenia and thrombocytopenia.

Biochemical analysis: increased bilirubin (a breakdown product of hemoglobin), decreased haptoglobin, increased lactate dehydrogenase.

Urine alnaysis – hemosiderin, haemoglobin.

Computer tomography: presence of hemosiderin sediment accumulating around kidney.

Specific test:

– flow cytometry: trying to detect a glycoprotein CD59 and CD55 (DAF) in regulation of complement action. Absence or reduced expression of both CD59 AND CD55 is diagnostic of PNH;

– complement lysis sensitivity test;
– sugar water or sucrose lysis test;
– the acid test hema (hemolysis in acidified serum at pH 6.8);
– immunotyping;
– fluorecin-labeled proaerolysin test.

Treatment of paroxysmal nocturnal hemoglobinuria.

PNH is a chronic condition. In patients with only a small clone and few problems, monitoring of the flow cytometry every six months gives information on the severity and risk of potential complications. Given the high risk of thrombosis in PNH, preventative treatment with warfarin decreases the risk of thrombosis. Episodes of thrombosis are treated as they would in other patients, but, given that PNH is a persisting underlying cause, it is likely that treatment with warfarin or similar drugs needs to be continued long-term after an episode of thrombosis.

Treatment of acute attacks of paroxysmal nocturnal hemoglobinuria.

There is disagreement as to whether steroids (such as prednisolone) can decrease the severity of hemolytic crises. Transfusion therapy may be needed; in addition to correcting significant anemia, this suppresses the production of PNH cells by the bone marrow and indirectly the severity of the hemolysis. Iron deficiency develops with time may have to be treated if present. Iron therapy can result in more hemolysis as more PNH cells are produced.

A new monoclonal antibody, eculizumab, protects blood cells against immune destruction by inhibiting the complement system. It has been shown to reduce the need for blood transfusion in patients with significant hemolysis.

1.10. March hemoglobinuria.

In healthy people (athletes, soldiers) after a long walk or run for several hours, there is a black urine (hemoglobinuria) and sometimes pain in the legs, vomiting. Anemia and pathological changes in erythrocytes cannot find. Cause hemolysis considered unusual arrangement of vessels feet and proximity of the capillary surface network to the skin.

1.11. Hemolytic-uremic syndrome.

Hemolytic-uremic syndrome (HUS) is a disease characterized by hemolytic anemia, acute renal failure and a low platelet count (thrombocytopenia). It observed predominantly but not exclusively affects children.

Etiology of hemolytic-uremic syndrome.

A. Infections:
– Neuraminidase secreting microorganisms (Str. pneumoniae, etc.);
– HIV;
B. Noninfectious:
– idiopathic HUS;
– hereditary HUS;

– drug: cyclosporin A, mitomycin C, bleomycin, cytosine arabinozid, cyclophosphamide, carboplatin, doxorubicin, oral contraceptives, etc.;

– HUS associated with pregnancy;

– HUS associated with transplantion organ;

– HUS associated with systemic lupus erythematosus;

– HUS associated with tumors;

– HUS associated with scleroderma;

– HUS associated with malignant hypertension.

Clinical features.

Most cases are preceded by an episode of diarrhea caused by E. coli O157:H7, which is acquired as a foodborne illness. The duration of prodromal period of HUS 2–14 (average 6) days and is characterized by diarrhea mixed with blood. The beginning of HUS: the deterioration of general condition of the child and pale skin, in some patients occur icteric skin. Fever is present in 5–20 % of patients. Noted decreased urine output, appearance edema of eyelid, legs and azotemia. In 50–70 % of children develop anuria. There is a persistent hypertension. In severe HUS appeared extrarenal lesions. It is a medical emergency and lead to 5–10 % mortality.

The symptoms of affection of central nervous system are convulsions, coma, blindness, paralysis. The symptoms of heart affection are ischemia with the development of failure, arrhythmia. The symptoms of lung affection are hemorrhage, edema. The symptoms of affection of the digestive tract: esophagitis, enterocolitis, necrosis, perforation, intussusception, hepatitis, pancreatitis.

Laboratory examination.

Anemia – rapid decline in hemoglobin to 60–80 g/l, sometimes to the critical numbers (30–40 g/l), reticulocytosis, anisocytosis.

In addition, there is leukocytosis.

Thrombocytopenia is mild, sometimes short-lived or recurrent, can cause petechiae (in 15–18 % of patients), but usually occurs without bleeding.

Hemolytic-uremic syndrome prognosis.

With aggressive treatment > 90 % patients survive acute phase.

About 9 % patients may develop end stage renal disease. About one-third of patients with hemolytic-uremic syndrome have abnormal kidney function many years later, and a few require long-term dialysis.

Another 8 % of patients with hemolytic uremic syndrome have other life-long complications, such as high blood pressure, seizures, blindness, paralysis, and the effects of having part of their colon removed.

The overall mortality rate from HUS is 5–15 %. Children and the elderly have a worse prognosis.

Unfavorable prognostic signs are:

– the early appearance of anuria and its duration longer than 2 weeks;

– progressive central nervous system complication;

– leukocytosis over $20x10^9$/L;

– less than 6 months of age and older than 4 years.

Test-control

1. In normal individual, the average red cell life span is:

A. 10 days.
B. 30 days.
C. 120 days.
D. 6 months.
E. 1 year.

2. Iron deficiency anemia is known as:

A. Sideropenic anemia.
B. Polycythemia.
C. Erythrocytosis.
D. Hemolytic anemia.
E. Aplastic anemia.

3. Lesions of the gastrointestinal tract in patients with iron deficence anemia are characterized by:

A. Development of hypertrophic gastritis.
B. Development of ulcus pepticus.
C. Development of atrophic gastritis.
D. Development of Crohn's disease.
E. Development of ulcerative colitis.

4. Sideropenic dysphagia is the result of:

A. Dryness of the mucous membrane of the esophagus.
B. Narrowing of the esophagus associated with anemia.
C. Metaplasia of the esophageal epithelium.
D. Spasm of the circular muscle of the esophagus.
E. Thyroid enlargement associated with anemia.

5. Heart disease in patients with iron deficiency anemia develops by type:

A. Aseptic myocarditis.
B. Rheumatic pericarditis.
C. Libman-Sachs endocarditis.
D. Dismetabolic cardiomyopathy.
E. Idiopathic hypertrophic cardiomyopathy.

6. The sign of advanced tissue iron deficiency is:

A. Cheilosis.
B. Sinusitis.
C. Orchitis.
D. Hepatitis.
E. Arthritis.

7. Note the incorrect sentence. Sideropenic syndrome include all, exept:

A. Bridou.

B. Imperative urge to urination.
C. Disorders of sphincters.
D. Fragility of nails.
E. Jaundice.

8. What is anisocytosis?
A. Different intensity of staining of erythrocytes.
B. Different sizes of red blood cells.
C. Different shape of red blood cells.
D. Different degree of maturity of red blood cells.
E. Different elasticity of red blood cells.

9. What is poikilocytosis?
A. Different intensity of staining of erythrocytes.
B. Different sizes of red blood cells.
C. Different shape of red blood cells.
D. Different degree of maturity of red blood cells.
E. Different elasticity of red blood cells.

10. In the asymptomatic patient with established iron deficiency anemia treatment is usually adequate:
A. With oral iron.
B. Intravenous iron.
C. Red ells transfusion.
D. Intramuscular injection.
E. Subcutaneous injection.

11. Efficiency of treatment iron deficiency anemia is estimated on the following parameters:
A. Reticulocyte crisis at 7–10 days of starting treatment.
B. Increase in hemoglobin of at least 10 g/L within a week.
C. Increase in systolic blood pressure of at least 20 mm Hg.
D. The appearance of red blood cells in urine.
E. Increase in the number of red blood cells by 10 % within a week.

12. Addison Biermer's disease is:
A. Autoimmune disease caused by the presence of antibodies against intrinsic factor or cells overlying the bottom of the stomach.
B. Systemic connective tissue disease characterized by achlorhydria and atrophic gastritis and the development of anemia.
C. Variant of systemic vasculitis, mainly affecting elastic vessel and the development of anemia.
D. Polyvalent drug allergy characterized by depression of bone marrow.
E. Variant of hypertrophic gastritis, characterized by hyperproduction of gastrin and hydrochloric acid and the development of anemia.

13. The main cause of megaloblastic anemia is usually deficiency of:
A. Transferrin.
B. Calcium.
C. Potassium.
D. Ascorbic acid.
E. Vitamin B_{12}.

14. Hunter glossitis is a manifestation of deficiency:
A. Iron.
B. Ascorbic acid.
C. Vitamin B_{12}.
D. Vitamin B_6.
E. Vitamin B_1.

15. Laboratory features of hemolytic disorders are:
A. Increasing the number of leukocytes.
B. Increasing the number of reticulocytes.
C. Increasing the number of platelets.
D. Increasing the number of granulocytes.
E. Increasing the number of lymphocytes.

16. Extracorpuscular cause of hemolytic anemia is:
A. Familial hemolytic uremic syndrome.
B. Paroxysmal nocturnal hemoglobinuria.
C. Hemoglobinopathies.
D. Membrane-cytoskeletal defects.
E. Enzymopathies.

17. General features of hemolytic disorder are:
A. Low level of lactate dehydrogenase.
B. High level of pyruvate kinase.
C. Low level of glucose 6-phosphate dehydrogenase.
D. High level of aldolase.
E. High level of lactate dehydrogenase.

18. Hemolytic anemia due to abnormalities of the membrane cytoskeleton is:
A. March hemoglobinuria.
B. Paroxysmal nocturnal hemoglobinuria.
C. Minkowksy – Chauffard disease.
D. Paroxysmal cold hemoglobinuria.
E. Cold agglutinin hemolytic anemias.

19. Marchiafava-Micheli disease is:
A. Congenital hemolytic anemia with predominantly intravascular hemolysis.
B. Acquired hemolytic anemia caused by defective red blood cell membranes.
C. Microspherocytic hereditary anemia.

D. Idiopathic immune hemolytic anemia.
E. Paroxysmal cold hemoglobinuria.

20. Hereditary spherocytosis is a type of:
A. Aplastic anemia.
B. Anemia due to blood loss.
C. Hemolytic anemia.
D. B_{12} deficiency anemia.
E. Iron deficiency anemia.

21. In patients with sickle cell anemia is observed all of the following except:
A. Splenic infarction.
B. Hemorrhages in the retina.
C. Trophic ulcers on the extremities.
D. Hepatocellular failure.
E. Kyphosis of the thoracic spine.

22. Osteoporosis is observed at:
A. Anemia Minkowski–Shoffara.
B. Sickle cell anemia.
C. Disease Marchiafava–Michele.
D. March hemoglobinuria.
E. Posthemorrhagic anemia.

23. Cause of pain in the abdomen in paroxysmal nocturnal gemoglobinouria is:
A. Thrombosis of small mesenteric vessels.
B. Enterospasm.
C. Reactive inflammation of the nerve solar plexus.
D. Stretched capsule of the liver.
E. stretched capsule of the spleen.

24. The cause of biliary colic with disease Minkowski–Chauffard is:
A. Noncalculous cholangitis.
B. Reactive hepatitis.
C. Formation of stones in the bile duct.
D. Spasm of the sphincter Oddi.
E. Formation of stones in the pancreatic ducts.

25. Most favorable outcome for the patient's life is observed at:
A. Marchiafava–Micheli disease.
B. March hemoglobinuria.
C. Microspherocytic hereditary anemia.
D. Idiopathic immune hemolytic anemia.
E. Paroxysmal cold hemoglobinuria.

Chapter 2. Syndromes and diseases with lymphadenopathy

2.1. Definition, causes and clinical features of lemphodenopathy.

A lymph node is a small, round or bean-shaped cluster of cells covered by a capsule of connective tissue. The cells are a combination of lymphocytes which produce protein particles that capture invaders, such as viruses and macrophages, which break down the captured material. Lymphocytes and macrophages filter lymphatic fluid as it travels through body and protect organism by destroying invaders. Lymph nodes are located in groups, and each group drains a specific area of body. Regional lymph nodes include: occipital, auricular, posterior cervical, anterior cervical, submandibular, supraclavicular, subclavicular, axillary, cubital, inguinal, popliteal.

Definition of the term "lymphadenopathy": lymphadenopathy is a term meaning "disease of the lymph nodes"; refers to nodes that are abnormal in either size, consistency or number, however almost synonymously used with "enlarged lymph nodes".

There are various classifications of lymphadenopathy, but a simple and clinically useful system is to classify lymphadenopathy in such way:

– "generalized" if lymph nodes are enlarged in two or more noncontiguous areas;

– "localized" if only one area is involved.

The main causes of the swollen/enlarged lymph nodes:

• inflammation local or generalized;

• infections: bacterial (S.aureus, S.pneumoniae, T.pallidum,) strep throat, measles, ear infections, plague, infected (abscessed) tooth, skin or wound infections, F.tularensis – tularemia, Brucellae F – brucellosis, mycobacterial, Chlamydia;

cat scratch fever is a bacterial infection from a cat scratch or bite;

infections: mononucleosis, tuberculosis;

protozoa: toxoplasmosis a parasitic infection resulting from contact with the feces of an infected cat or eating undercooked meat, leishmaniosis, filariasis;

viral infections; herpes, influenza, adenoviruses;

infections transmitted by sexually way: gonorrhea, syphilis, human immunodeficiency virus (HIV), AIDS;

• immune system disorders: lupus is a chronic inflammatory disease that can target the joints, skin, kidneys, blood cells, heart and lungs; rheumatoid arthritis is a chronic inflammatory disease that targets the tissue that lines the joints (synovia); sarcoidosis;

• diseases of the blood: non-Hodgkin and Hodgkin lymphoma are cancer that originates in lymphatic system; leukemia is cancer of body's blood-forming tissue, including bone marrow and lymphatic system;

• cancers that have spread (metastasized) to lymph nodes;

• medications that may cause lymphadenopathy: allopurinol, atenolol, captopril, carbamazepine, cephalosporins, hydralazine, penicillin, quinidine.

Clinical examination:

✓ anamnesis morbi, (beginning, symptoms, fever, acute or chronic infections, duration of lymphadenopathy);

✓ anamnesis vitae: contact with animals, taking some drugs;

✓ occupational anamnesis: fishermen (erysipeloid), hunter (tularemia);

✓ epidemiological anamnesis: travel.

Table 2.1

Risk factors of enlarged lymph nodes

Risk factor	Disease
Undercooked meat	Toxoplasmosis
Cat	Cat-scratch disease, toxoplasmosis
High-risk sexual behavior	HIV, syphilis, herpes simplex virus, cytomegalovirus, hepatitis C infection
Intravenous drug use	HIV, syphilis, herpes simplex virus
Tick bite	Lyme disease, tularemia
Tuberculosis	Tuberculous adenitis
Blood transfusion	Cytomegalovirus, HIV

Principles of Internal Medicine 17th ed., 2008.

Objective examination: palpation of lymph nodes.

• Lymph nodes may reveal using superficial palpation of the symmetrical region following the certain consequence: location, size, consistency, pain, mobility, color of the skin over the lymph nodes.

• Palpation is used to assess the enlargement of the lymph nodes and their properties.

• "The body has approximately 600 lymph nodes, but only those in the submandibular, axillary or inguinal regions may normally be palpable in healthy people" (Harrison's Principles of Internal Medicine 17th ed., 2008)

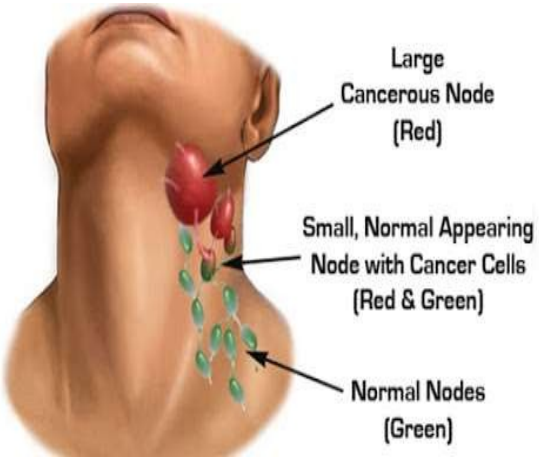
Diagnostic meaning of enlarged lymph nodes:

• occipital: lymph nodes: local infections, measles erhytema, lymphoblastic and lymphocytic leukemia;

• cubital lymph nodes: local infections, lymphoma, sarcoidosis, tularemia, syphilis;

• submandibular lymph nodes: infections of head, neck, sinuses, ears, eyes, scalp, pharynx;

• cervical lymph nodes: chronic tonsillitis, tuberculosis, infectious mononucleosis, Hodgkin and nonHodgkin lymphoma, lymphoblastic and lymphocytic leukemia, metastatic tumor (*Picture 2.1*).

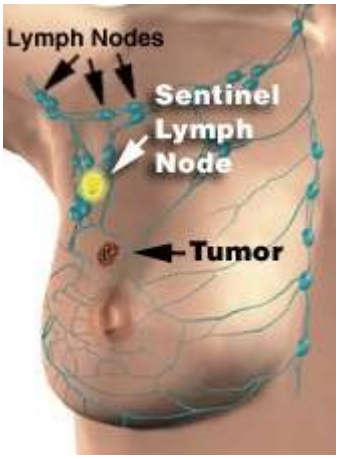


Picture 2.1. Cervical lymph nodes: normal and metastatic tumor

Right supraclavicular lymph nodes: lung, retroperitoneal or gastrointestinal cancer; left supraclavicular lymph nodes: lymphoma, thoracic or retroperitoneal cancer, bacterial or fungal infection;

Virchow's node (Virchow's gland): metastatic tumor in supraclavicular lymph nodes, commonly in left supraclavicular lymph nodes in patients with stomach cancer (*Picture 2.2*).

Picture 2.2.
Virchow's node



Picture 2.3.
Breast cancer (metastatic process)

Axillary lymph nodes: purulent process at the hand, cat-scratch disease, lymphoma, silicone implants, brucellosis, melanoma, breast cancer (metastatic process) (*Picture 2.3*).

Inguinal lymph nodes: infections of the leg or foot, purulent process of the leg or foot, pelvic malignancy, cancer of the abdomen cavity, bubonic plague, herpes simplex virus, granuloma inguinale, lymphogranuloma venereum (sexually transmitted diseases: gonococcal infection, syphilis, chancroid, AIDS), lymphoma.

Characteristic of enlargement lymph nodes (different pathology).

• Cervical lymphadenitis occurs in tuberculosis, which characterized by enlargement of lymph nodes with purulent foci with subsequent formation of fistulae and immobile cicatrices.

• The diseases of the blood are characterized by systemic symmetrical enlargement of the peripheral nodes and mediastinal, mesenterial ones. The nodes firm and tender, their surface is rough, with formation of conglomerates.

• Lymphatic metastatic spread is as a rules local enlargement of lymph nodes, which are hard, rough, palpation is painless.

Differential diagnosis of lymphadenopathy.

• In most patients, lymphadenopathy has a readily diagnosable infectious cause.

• A diagnosis of less obvious causes can often be made after considering the patient's age, the duration of the lymphadenopathy and whether localizing signs or symptoms, constitutional signs or epidemiologic clues are present.

• When the cause of the lymphadenopathy remains unexplained, a three- to four-week observation period is appropriate when the clinical setting indicates a high probability of benign disease. (Harrison's Principles of Internal Medicine 17th ed., 2008).

Cause of lymphadenopathy may be lymphoid neoplasms.

2016 WHO classification of mature lymphoid neoplasms (S. H. Swerdlow, E. Campo, S. Pileri et al. The updated WHO classification of hematological malignancies. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood, 2016, volume 127, number 20, p. 2375-2390).

Mature B-cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia.
Splenic B-cell lymphoma/leukemia, unclassifiable
    Splenic diffuse red pulp small B-cell lymphoma
    Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
    Waldenstöm macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM
Large B-cell lymphoma with IRF4 rearrangement
Primary cutaneous follicle center lymphoma
Diffuse large B-cell lymphoma
    Germinal center B-cell type
    Activated B-cell type
T-cell/histiocyte-rich large B-cell lymphoma

Hodgkin lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma

Lymphoid neoplasm is a disease of the whole blood system characterized by:

1) hyperplasia with pronounced prevalence of proliferation of lymphoid cells;

2) metaplasia of these pathological cells instead of normal cells to hemopoietic organs;

3) developments of pathological foci of hemopoiesis in various organs.

2.2. Non-Hodgkin lymphoma.

Risk factors of non-Hodgkin lymphoma:

- family history (hereditary ptedisposition);
- occupational exposures;
- Helicobacter pylori (HP): the presence of HP infection in the stomach may be associated with gastric lymphoma;
- Epstein-Barr virus is associated with Burkitt's lymphoma;
- human immunodeficiency virus;
- chronic infection hepatitis C virus.

Clinical examination includes: anamnesis morbi, anamnesis vitae, epidemiology anamnesis, palpation of the lymph nodes.

Symptoms and signs of non-Hodgkin lymphoma.

Some people with Non-Hodgkin lymphoma have what are known as *B symptoms* (Large B-cell lymphoma):

- chills;
- weight loss;
- fatigue (feeling very tired);
- feeling full after only a small amount of food;
- easy bruising or bleeding;
- chest pain or pressure;
- shortness of breath or cough;
- swollen abdomen;
- enlarged lymph nodes close to the surface of the body such as on the sides of the neck, in the groin or underarm areas, or above the collar bone, may be seen or felt as lumps under the skin. These are usually not painful.

Signs from lymphoma in the skin.

Lymphomas of the skin may be seen or felt. They often appear as itchy, red or purple lumps or bumps under the skin.

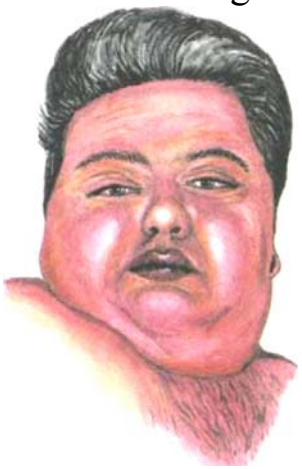
Signs from lymphoma in the chest.

When lymphoma starts in the thymus or lymph nodes in the chest, it may press on the nearby trachea (windpipe), which can cause coughing, trouble breathing, or a feeling of chest pain or pressure.

Signs from lymphoma in the mediastinum.

The superior vena cava is the large vein that carries blood from the head and arms back to the heart. It passes near the thymus and lymph nodes inside the chest. Lymphomas in this area may push on the superior vena cava, which can cause the blood to back up in the veins. This can lead to swelling and sometimes a bluish- red color in the head, arms and upper chest (*Picture 2.4*). It can

also cause trouble breathing and a change in consciousness if it affects the brain. This is called superior vena cava syndrome. It can be life-threatening and must be treated right away.



Picture 2.4. Diffuse swelling of the neck and face with obstruction of the superior vena cava

Signs from lymphoma in the abdomen.

Lymphomas that start or grow in the abdomen (belly) can cause swelling or pain in the abdomen. This could be from lymph nodes or organs such as the spleen or liver enlarging, but it can also be caused by the build-up of large amounts of fluid

An enlarged spleen might press on the stomach, which can cause a loss of appetite and feeling full after only a small meal. Lymphomas in the stomach or intestines can cause abdominal pain, nausea or vomiting. Enlargment of the spleen, hepatomegaly.

Symptoms from lymphoma affecting the brain.

Lymphomas of the brain, called primary brain lymphomas, can cause headache, trouble thinking, weakness in parts of the body, personality changes. Other types of lymphoma can spread to the area around the brain and spinal cord. This can cause problems such as double vision, facial numbness and trouble speaking.

Additional examination: ultrasound examination, chest X-ray radiographs, ultrasound examination, computerized tomography, magnetic resonance imaging, bone marrow examination, lymph node biopsy.

Ultrasound examination allows for both superficial lymph nodes to be properly defined and measured, and abdominal lymph nodes and the spleen to be assessed. Although it has some limits, it has the advantage of not exposing patients to radiations or to side effects as well as being very economical.

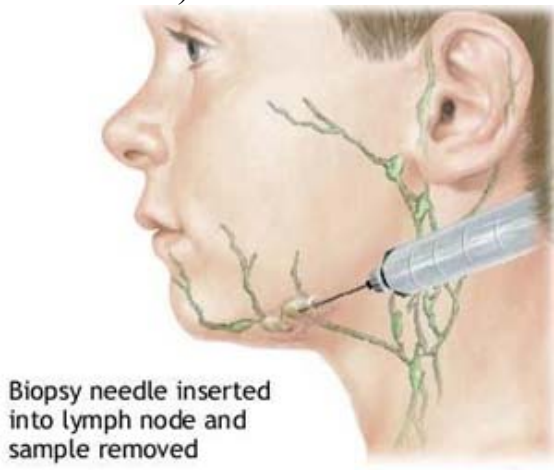
Computerized tomography is a radiological examination that allows for internal organs (chest, abdomen and pelvis) to be assessed more precisely compared to regular X-rays. In general it is carried out with a contrast medium injected into the patient's arm vein. It's a fast, easily accessible, repeatable and comparable examination.

Magnetic resonance imaging in clinical practice has specific indications, for example when it is essential to explore the central nervous system or a bone. It does not expose patients to ionizing radiation and can therefore be used with children or pregnant women.

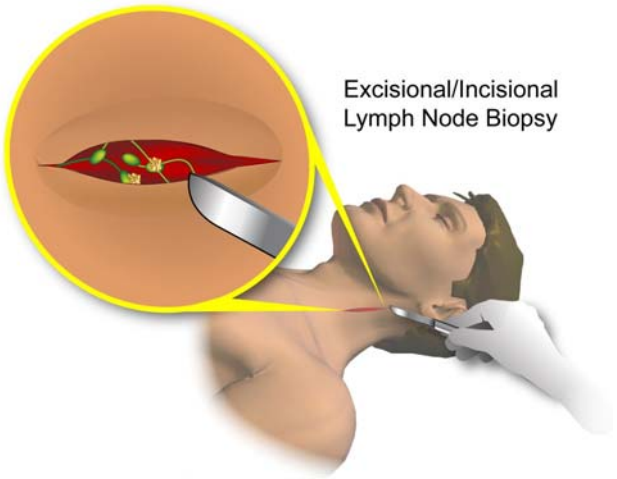
Puncture of hemopoetic organs: sternal puncture, trepanobiopsy. Bone marrow examination allows evaluating whether a lymphomatous infiltration of bone marrow is present.

Lymph node biopsy. Lymph node biopsy consists in the partial or full removal of a lymph node in order to analyse the tissue under the microscope and determine the presence and type of lymphoma cells, if any. It is a simple intervention that is mostly carried out by the surgeon under local anaesthesia and usually does not require hospitalisation.

There are two types of lymph node biopsy: puncture of enlarged lymph node using needle (*Picture 2.5*) and excisional/incisional lymph node biopsy (*Picture 2.6*).



Picture 2.5. Lymph node biopsy using needle



Picture 2.6. Excisional/incisional lymph node biopsy

The diagnosis can be establishment only by tissue biopsy, usually of lymph node. Should the biopsy show the presence of a lymphoma, further examinations will then be required in order to obtain information on the extension of lymphoma in the body (staging procedures).

Treatment of lymphoma includes: chemotherapy, radiotherapy, monoclonal antibodies, new target drugs.

2.3. Hodgkin's lymphoma.

Hodgkin's lymphoma was first described by Thomas Hodgkin in 1832 report while he occupied as museum curator at Guy's Hospital, London. Hodgkin studied seven patients with painless lymph node enlargement. Hodgkin's report on these seven patients, entitled "On some morbid appearances of the absorbent glands and spleen", was presented to the Medical and Chirurgical Society in London in January 1832 and was subsequently published in the society's journal of Medical-Chirurgical Society.

Risk factors of Hodgkin lymphoma:

- Epstein-Barr virus;
- Chlamidia psittaci, infection associated with orbital outbuildings;
- human deficience virus;
- chronic infection with hepatitis virus C;

• impaired immune system due to exposure of toxic agents chemicals and pollutants;

• human immune deficience virus HIV/AIDS;

• drugs that suppresses immune system; such as those given after organ transplantation (heart, lung, etc.);

• autoimmune diseases and radiation.

Pathogenesis: as with all neoplasms, the DNA mutations underlying the neoplastic-lymphomatous transformation due to exogennic and endogenic factors.

Clinical examination includes: anamnesis morbi, anamnesis vitae, epidemiology anamnesis, palpation of the lymph nodes.

Symptoms and signs of Hodgkin's lymphoma:

• unexplained fever;

• swollen abdomen;

• abnormal sweating, especially at night;

• tiredness;

• loss of appetite;

• itch skin (pruritus);

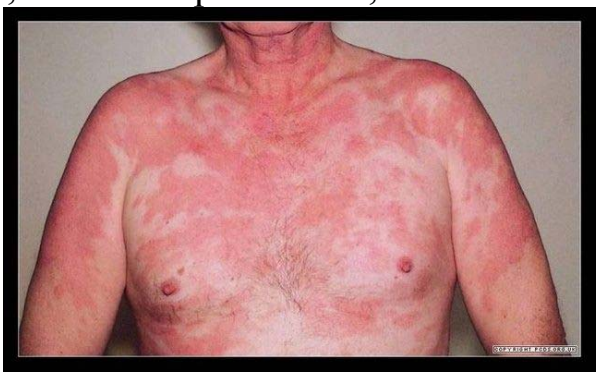
• bruising or bleeding easily;

• pronounced weight loss.

Cyclical fever: patients may present with a cyclical high-grade fever known as the Pel-Ebstein fever or more simply "P-E fever.

The most common symptom of Hodgkin's lymphoma is enlargement of one or more superficial lymph nodes in the neck, armpit and groin. Enlarged lymph nodes are often painless. More lymph node regions may be swollen at the same time. The enlarged nodes may also feel rubbery and swollen when examined. The nodes of the neck (cervical) and shoulders (supraclavicular)) are most frequently involved (80–90 % of the time, on average).

Red-colored patches on the skin, easy bleeding and petechia due to low platelet count as a result of bone marrow infiltration, increased trapping in the spleen, decreased production, increased removal. (*Picture 2.7*).



Picture 2.7.
Red-colored patches on the skin at Hodgkin's lymphoma

Splenomegaly: enlargement of the spleen occurs in about 30 % of people with Hodgkin's lymphoma. The enlargement, however, is seldom massive. Hepatomegaly: enlargement of the liver, due to liver involvement, is present in

about 5 % of cases. Hepatosplenomegaly: the enlargement of both the liver and spleen caused by the same disease.

Clinical blood analysis:

• normochromic and normocytic anemia;
• normal white cell count;
• sometimes neutrophil leucocytosis;
• lymphocytopenia indicates on bad prognosis;
• in the terminal stage are leucocytopenia and thrombocytopenia.

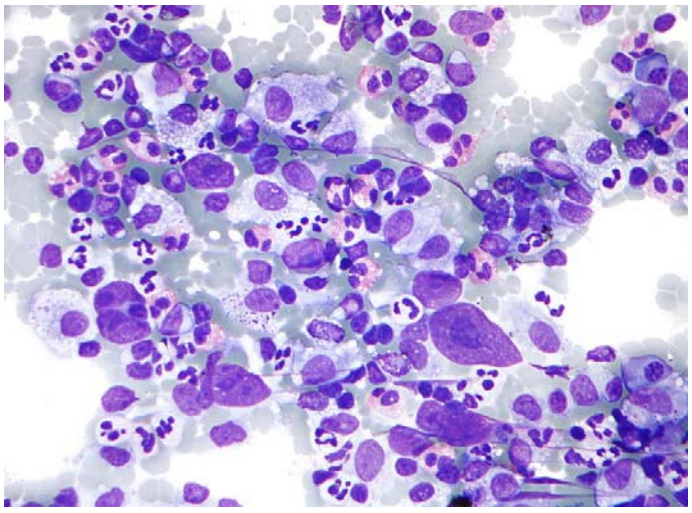
Instrumental examination:

• chest X-ray radiographs;
• computed tomography;
• positron emission tomography;
• magnetic resonance imaging scans of the chest, abdomen and pelvis.

Puncture of hemopoetic organs: sternal puncture, trepanobiopsy. Bone marrow involvment is uncommon in the onset of disease but may be found later.

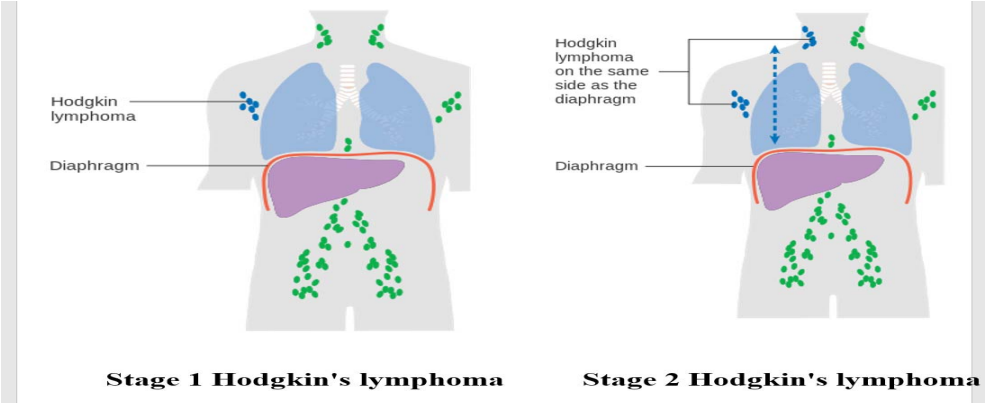
Puncture of enlarged lymph node, excisional/incisional lymph node biopsy.

The diagnosis can be establishment only by tissue biopsy, usually of lymph node. The most important histological criteria of Hodgkin's lymphoma is presence of Reed-Sternberg cells in lymph node. (*Picture 2.8*).

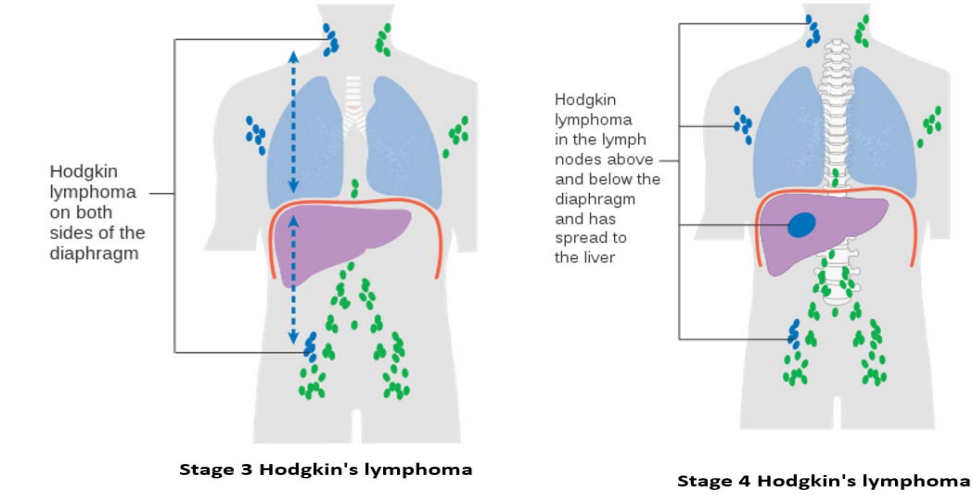


Picture 2.8. Micrograph of Hodgkin's lymphoma shows a mixture of cells common in lymph node: eosinophils, Reed-Sternberg cells, plasma cells, histocytes

Classification of Hodgkin's lymphoma. There are 4 stages of Hodgkin's lymphoma (*Picture 2.9, 2.10*).



Picture 2.9. 1–2 Stages of Hodgkin lymphoma



Picture 2.10. 3–4 Stages of Hodgkin lymphoma

There are some difference between Hodgkin's and non-Hodgkin's lymphomas (*Table 2.2*).

Table 2.2

Differential diagnosis (main criterias) of Hodgkin's and non-Hodgkin's lymphomas

Criterias	Hodgkin's lymphoma	non-Hodgkin's lymphoma
Age	Young adults	In 40–70 years
B symptoms	40 %	20 %
Spread	Contiguous	Multiple remote nodal groups invoved
Stage at presentation	>80 % early stage I and II	>80 % late stage III and IV
Nodal groups	Cervical, thoracic, para-aortic	Mesenteric, para-aortic thoracic, cervical

Treatment of Hodgkin's lymphoma similar to non-Hodgkin's lymphoma and includes: chemotherapy, radiotherapy, monoclonal antibodies, new target drugs.

Chemotherapy is often administered through venous infusion; however there exist a number of drugs which are administered orally and, in some forms of lymphoma, also intrathecally (in the cefalo-rachidian fluid through lumbar puncture).

Radiotherapy is an important therapy option in the treatment of lymphoma. Depending on the type of lymphoma and on the different presentations of the illness, this can be used as single treatment or combined with other systemic treatments (chemotherapy, chemo-immunotherapy).

Monoclonal antibodies are antibodies produced in the laboratory that selectively bind to molecules on the cell surface of the lymphocyte subtypes giving rise to lymphoma, such as the CD20 antigen which is expressed by most B-cell lymphomas or the CD30 antigen expressed by Hodgkin's lymphoma and by a number of T-lymphomas.

New targeted drugs tend to constitute a new precision "therapy", will be indicated for very specific subtypes of lymphoma and will find indication alone or in combination with more traditional therapy in specific situations.

2.4. Acute lymphoblastic leukemia.

The term leukemia comes from the Greek words for "white" (leukos) and "blood" (haima). Acute lymphoblastic leukemia characterized by proliferation of poorly differentiated lymphoid blast cells with reduction of normal hematopoietic cells. Acute lymphoblastic leukemia is a malignant disease characterized by the accumulation of lymphoblasts. The most important sign of acute lymphoblastic leukemia is infiltration by malignant lymphoblasts almost any body organs and tissue first of all lymph nodes.

This is the most common type of leukemia in children, teens, young adults and those up to 39 years of age. About 54 % of new cases occur in those under the age of 20.

Etiology of acute lymphoblastic leukemia:

• genetic predisposition: Klinefelter's syndrome, Fanconi's anemia, Bloom's syndrome, neurofibromatos, Schwachman-Diamond syndrome;

• radiation: the incidence of acute lymphoblastic leukemia was increased almost 20-fold in survivors of the atomic bomb explosions in Japan, with a peak incidence occurring 6 to 7 years after the radiation exposure;

• chemicals: the risk for the development of acute lymphoblastic leukemia may also be increased after exposure to chemical agents, such as benzene or other agents capable of producing bone marrow aplasia, including chemotherapeutic drugs;

• environmental factors with mutagenic properties can be causal for onset of acute lymphoblastic leukemia;

• virus theory: at the present time more than 20 viruses have been isolated that can cause leukemia in animals.

Two kind of hemoblastosis resulted by virus:

a) endemic African type of Burkitt's lymphoma, the Epstein-Barr virus, a DNA virus of the herpes family has been implicated as a potential causative agent;

b) endemic infection with human T-cell leukemia virus I in Japan and the Caribbean has been shown to be an etiologic agent for adult T-cell leukemia/lymphoma.

Pathogenesis of acute lymphoblastic leukemia.

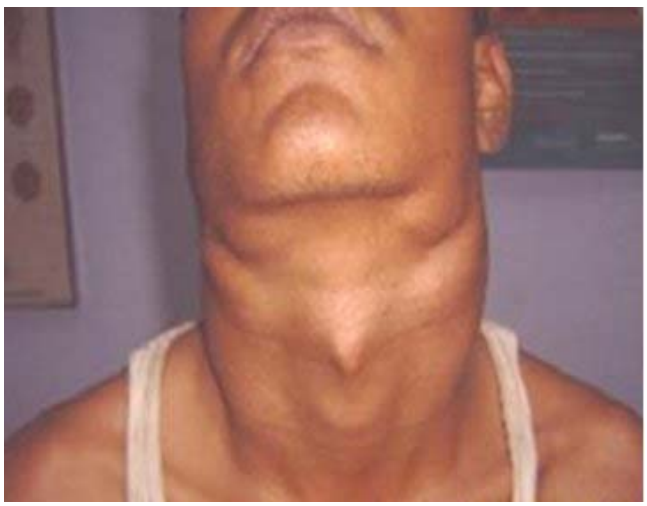
Acute lymphoblastic leukemia starts with a somatic mutation in the bone marrow single stem cell, damage of DNA that leads to uncontrolled cellular growth producing clones with excessively proliferation especially lymphoblast cell lines which can't develop and function normally and spread throughout the body. Immunological markers indicate that most of these lymphoblasts belong to the non B-cell group and B-cell group of lymphocytes.

Clinical features of acute lymphoblastic leukemia.

Symptoms and signs:

• lymphadenopathy 57 %;
• splenomegaly 56 %;
• hepatomegaly 47 %;
• infections/fever 36 %;
• hemorrhages 33 %;
• mediastinal mass 14 %;
• central nervous system involvement 7 %;
• pleura, lung involvement 2.9 %.

Lymphadenopathy is a common feature, as a rule at the lymphoblastic form of leukemia. Approximately 75 % of acute lymphoblastic leukemia cases exhibit lymph node enlargement (*Picture 2.11*).



Picture 2.11. Lymphadenopathy at acute lymphoblastic leukemia

Infiltration of the bones and the joints may cause localized lesions and pain.

Tender bones, painful sternum (sternalgia) are explained by organ infiltrationwith extramedullary hematopoiesis.

Infiltration of the skin may result in local lesions.

The lung is common site of infiltration by cancerous lymphoblasts which may result in pulmonary lesions.

The infiltration of gastrointestinal tract is also common in acute lymphoblastic leukemia cause damage the mucosa and local ulceration with hemorrhage.

Fundal examination may reveal papilloedema and sometimes hemorrhage.

Special type of acute lymphoblastic leukemia known as meningeal leukemia due to the infiltration with leukemic lymphoblasts the membranes surrounding the brain may observe. Neurological syndrome include headache, nausea, vomiting, blurring of vision and diplopia.

Testicular infiltration by malignant lymphoblasts is observed in male patients with acute lymphoblastic leukemia.

Clinical blood analysis: there are age-dependent characteristic of count lymphocytes : 0–3 days – 15–45 %; 3 days – 6 months – 30–70 %; 6 months – 6 years – 30–60 %; 6 years – 16 years – 25–50 %; > 16 Jahre years 25–40 %.

Clinical blood analysis at acute lymphoblastic leukemia:

– white blood cells count may vary from low level (less than $10x10^9$/l) to high level (more than $5x10^{11}$/l);

– red blood cell count decreased;

– thrombocytopenia;

– lymphoblast cells.

Examination of bone marrow:

– lymphoblast cells;

– normal erytrhropoietic, granulopoietic elements;
megakaryocytic elements reduced.

Special test:

– immunological identification of certain surface markers of the neoplastic lymphocytes;

– imaging tests: imaging tests such as an X-ray, a computerized tomography scan, ultrasound scan may help determine whether cancer has spread to the brain and spinal cord or other parts of the body.

Spinal fluid test: a lumbar puncture test, also called a spinal tap, may be used to collect a sample of spinal fluid, that surrounds the brain and spinal cord. The sample is tested to see whether cancer cells have spread to the spinal fluid.

Acute lymphoblastic leukemia. Classification. French-American-British Group (FAB):

• L1: presence of small blast cells with immunological markers of non B-cell group of lymphocytes. This type of acute lymphoblastic leukemia observed in 85 % children and 5–10 % adults is characterized by slowly progressive course with most favorable prognosis.

• L2: morphological features of lymphocytes are large and small cells with immunological markers of non B-lymphocytes, T-cells and natural killer cells. This form is common for adults.

• L3: Burkitt's type of acute lymphoblastic leukemia. The cells are large and homogenous, belongs to the B-cell group. In children, adolescence acute lymphoblastic leukemia is very rare.

Treatment of the patients with acute lymphoblastic leukemia:

• chemotherapy is typically used as an induction therapy for children and adults; chemotherapy drugs can also be used in the consolidation and maintenance phases;

• radiatiotherapy uses high-powered beams, such as X-rays or protons;

• targeted therapy uses drug treatments alone or in combination with chemotherapy for induction therapy, consolidation therapy or maintenance therapy;

• bone marrow transplant from a compatible donor (allogeneic transplant) may be used as consolidation therapy or for treating relapse if it occurs.

The mortality in acute lymphoblastic leukemia arises mainly from neutropenia, thrombocytopenia and anemia because of bone marrow failure.

2.5. Chronic lymphocytic leukemia.

Chronic lymphocytic leukaemia is a type of leukaemia that affects developing B-lymphocytes also known as B-cells specialized white blood cells. Under normal conditions they produce immunoglobulins also called antibodies that help protect human bodies against infection and disease. In people with chronic lymphocytic leukaemia lymphocytes undergo a malignant cancerous change and become leukaemic cells. Chronic lymphocytic leukemia is now regarded as a tumor of the immunocompetent lymphatic tissue.

Chronic lymphocytic leukaemia is the most common type of leukemia in the Western world (4 per 100 000). Chronic lymphocytic leukemia is a disease of middle-aged and elderly persons. There is peak occurrence between 50 and 60 years of age. The median age of presentation is 65 years.

Etiology chronic lymphocytic leukaemia: some environmental factors such ionizing radiation, mutagenic chemicals have been implicated at the onset of disease.

Pathogenesis of chronic lymphocytic leukemia.

Similar to other types of leukaemia, chronic lymphocytic leukemia is thought to arise from an acquired mutation of cell – precursors of lymphopoiesis resulted in abnormal growth with formation of lymphoid hyperplasia. The original mutation is preserved when the affected stem cell divides and produces a 'clone'; that is a group of identical cells all with the same defect. This disease is characterized by the presence of increased number of small, normal-looking lymphocytes in the blood, bone marrow and lymphoid tissue. Over 90 % of all cases are caused by B-cells, the remaining are T-cells. Lymphocytes morphologically mature, but functionally inadequate. Immunological failure occurs

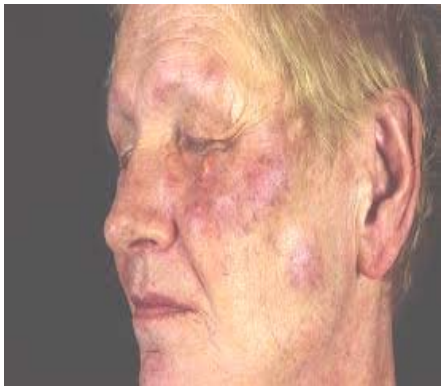
from reduced humoral and cellular immune processes. Generalized hyperplasia of lymphoid organs causes the main signs of disease. Lymphoid infiltration of the organs and tissue (lung, brain, spleen, liver, skin) leads to clinical features.

Clinical features of chronic lymphoblastic leukemia.

This disease has slowly onset with non-specific symptoms and signs: fatigue or a general decrease in energy, bone pain, bleeding from the gums, decreased appetite, unintentional loss of weight, fever, frequent infections, frequent or severe nosebleeds, pale skin, shortness of breath.

The first specific clinical finding at the beginning of the disease is symmetrical, discrete, non-tender peripheral lymphadenopathy in the neck, underarm, groin which observes at about 80 % patients. Palpation is used to assess the enlargement of the lymph nodes and their properties. The lymph nodes are elastic, they do not fuse with the skin or with one another; they are painless in most cases. The lymph nodes never ulcerate or suppurate.

In some patients may observe the appereance on skin the specific signs – lymphoma and non-specific signs such as herpetic lesions, weals. Widespread erythroderma occurs in some cases with skin itching (*Picture 2.12*). Skin leukemic lymphoderma on the face made it like «lion face».



Picture 2.12. Chronic lymphocytic leukemia – skin involvement

The progression of the disease is characterized by high temperature, intoxication, dispnoe. In thrombocytopenic patients appear bruising or purpura. There may be an increased incidence of bacterial, viral or fungal infections due to a lack of functional white blood cells.

At terminal stages observe bleeding complications, heart and renal failure.

Compression syndrome:

- dyspnea and attacks of asphyxia are observed related to the enlargement of mediastinal lymph nodes and compression of trachea and bronchi;
- diffuse swelling of the neck and face may occur with obstruction of the superior vena cava.

Affection of the gastrointestinal tract by lymphoid infiltration: dyspepsia, diarrhea. The liver and the spleen are enlarged and consolidated. Infraction of the spleen can occur; its palpation then becomes tender.

Abdominal fullness, belching discomfort, abdominal pain may arise from intestinal obstruction by lymph nodes.

Pronounced enlarged lymph nodes may obstruct the gallbladder.

Enlarged mesenterial lymph nodes cause compression of inferior vena cava.

Pronounced enlarged lymph nodes may obstruct the urinary tract.

Clinical blood analysis.

Although chronic lymphocytic leukemia is characterized by leukocytosis, the proportion of neutrophils is always reduced to some degree, from as low as 1 % to as high as 40 %. The absolute neutrophil count may be normal, extremely low, or extremely high, depending on total leukocyte count and percentage of neutrophils; red blood cell count decreased; platelet count decreased; when preparing a smear specific Botkin-Gymprecht shadows are formed.

Between 70 and 90 % of white cells on blood film appear as mature lymphocytes. However, it is believed that functionally they are not mature as they are arrested at an intermediate level of differentiation. Lymphocytes in chronic lymphocytic leukemia are usually small, with the nucleus filling almost the entire cell, and the nuclear chromatin is dense , clumped and without any discernible.

Bone marrow. The count of bone marrow aspirate smear may reveal lymphocytes accounting for as little as 30 % of all nucleated cells or as much as 99 %. Lymphocytes comprise 25–95 % of all the cells in early stage; in the latter, the marrow is totally replaced by monotonously similar-appearing lymphocytes. In terminal stage total lymphoid metaplasia; enlargement of mediastinal lymph nodes can be detected by standard X-ray examination or by tomography.

Immunophenotyping or flow cytometry test is commonly used to confirm a suspected diagnosis of chronic lymphocytic leukemia and to distinguish it from other similar diseases. This technology uses the special markers, called antigens, found on the surface of cells.

Cytogenetic tests. Leukaemic cells have developed mutations in their genetic make-up which can be detected using cytogenetic testing. The two main types of tests are chromosome analysis, which examines chromosomes under a microscope, and FISH (fluorescent in situ hybridisation) which ‘paints’ the genes of interest with fluorescent dye.

Treatment of chronic lymphocytic leukemia:

- chemotherapy;
- glucocorticosteroids;
- radiation therapy (splenic irradiation, irradiation of large lymphoid masses localized in one region, nonresponsive to chemotherapy);
- bone marrow transplant from a compatible donor (allogeneic transplant) may be used as consolidation therapy or for treating relapse if it occurs;
- splenectomy is an effective treatment for chronic lymphocytic leukemia in specific clinical situations: extensive splenomegaly unresponsive to chemotherapy and with significant anemia or thrombocytopenia attributed to hypersplenism.

Prognosis of chronic lymphocytic leukemia.

Just as the initial extent of disease is variable in chronic lymphocytic leukemia, the prognosis and clinical course also are extremely variable. Some patients have a rapid downhill course and die within 2 to 3 years after diagnosis,

whereas others have a very benign and live for 10 or 20 years without major problems from chronic lymphocytic leukemia.

Traditionally the Rai and Binet staging systems have been used to estimate prognosis in chronic lymphocytic leukemia (*Table 2.3*). Using these systems patients are assigned to one of three major subgroups (good, intermediate or poor prognosis) depending on the number of lymphoid areas affected by the disease (lymph nodes, spleen or liver), and the red cell and platelet counts in the blood. Stage A refers to early disease, where in many cases people are asymptomatic and require no treatment. Stage B and C refer to more advanced disease which usually requires treatment.

Table 2.3

The Rai and Binet staging systems of chronic lymphocytic leukemia

Stage	Findings
Binet stage A / Rai stage 0	< 3 lymphoid areas involved. Increased lymphocyte count
Binet stage B / Rai stage I and II	> 3 lymphoid areas involved. Increased lymphocyte count
Binet stage C/ Rai stage III and IV	Increased lymphocyte count Low red cell count (anaemia) +/- low platelet count (thrombocytopenia)

Factors associated with a poor prognosis of chronic lymphocytic leukemia:

- clinical factors: lymphadenopathy, splenomegaly, hepatomegaly;
- hematological factors: anemia, thrombocytopenia, large and atypical lymphocytes in blood, diffuse bone marrow lymphocytic infiltration;
- laboratory abnormalities: increased serum lactatedehydrogenase level, hypoalbuminemia, increased serum calcium level;
- immune factors: hypogammaglobulinemia, increased serum-soluble CD25 receptors, increased serum-soluble CD23 receptors;
- phenotype: CD38, aberrant surface phenotypes;
- molecular and genetic factors: genetic aberrations, β_2-microglobulin;
- other factors: poor response to therapy.

Test-control

1. Most frequent symptoms in patients with acute lymphocytic leukmia are:

A. Splenomegaly and lymphadenopathy.
B. Fever and hemorrhages.
C. Involvement pleura and pericardium.
D. Central neurous system involvement.
E. Kidney involvement.

2. Most frequently observed abnormal finding on physical examination in patients with chronic lymphocytic leukemia is:

A. Enlargement of spleen.
B. Enlargement of liver.
C. Enlargement of lymph nodes.
D. Infiltration meninges by limphocytic cells.
E. Infiltration skin by limphocytic cells.

3. Location of Virchow's node is:

A. Left supraclavicular lymph nodes.
B. Occipital lymph nodes.
C. Cervical lymph nodes.
D. Submandibular lymph node.
E. Right supraclavicular lymph nodes.

4. Reed-Sternberg cells are characteristic of:

A. Lymphoblastic leukemia.
B. Lymphocytic leukemia.
C. Metastatic tumor.
D. Myeloid leukemia.
E. Hodgkin's lymphoma.

5. Diagnostic meaning of Virchow's node:

A. Lymphoblastic leukemia.
B. Lymphocytic leukemia.
C. Metastatic tumor.
D. Myeloid leukemia.
E. Mononucleosis.

6. Botkin-Gymprecht shadows are characteristic of:

A. Lymphoblastic leukemia.
B. Lymphocytic leukemia.
C. Metastatic tumor.
D. Myeloid leukemia.
E. Mononucleosis

7. Pel-Ebstein fever ("P-E fever“) is characteristic of:

A. Lymphoblastic leukemia.
B. Lymphocytic leukemia.
C. Metastatic tumor.
D. Hodgkin’s lymphoma.
E. Myeloid leukemia.

8. Which examination is most informative for diagnosis of Hodgkin’s lymphoma:

A. Clinical blood analysis.
B. Clinical features.
C. Sternal puncture.
D. Trepanobiopsy.
E. Puncture of enlarged lymph node.

9. In patient with infectious mononucleosis present all, exept:

A. Acute tonsillitis.
B. Splenomegaly.
C. Blast cells in blood.
D. Enlardgement of lymph nodes.
E. Mononuclear cells in blood.

Chapter 3.
Syndromes and diseases with leukocytosis and leukocytopenia

3.1. Causes and clinical significance the change of peripheral blood cells.

White blood cells (leukocytes): normal ranges for male 4.0–8.8x10^9/l, for female 4.0–8.8x10^9/l.

There are age-dependent changes of indices of white blood cells (*Table 3.1*).

Table 3.1

Age-dependent changes of white blood cells

Parameters	Age	Indices
Neutrophils	0–3 days	30–75 %
	3 days – 6 months	20–65 %
	6 months – 6 years	25–60 %
	6 years – 16 years	40–70 %
	> 16 years	50–75 %
Monocytes	0–1 months	0–20 %
	1 months – 16 years	0–15 %
	> 16 years	0– 2 %
Eosinophils	< 16 years > 16 years	0–5 % 0–4 %
Basophils		0–1 %

Increasing of leukocytes number is classified as leukocytosis, decreasing – as leukocytopenia.

Leukocytosis may be to physiological condition and to the pathological condition (*Table 3.2*)

Table 3.2

Physiological and pathological causes of leukocytosis

Physiological condition	Pathological condition
new born	acute myeloblastic leukemia or chronic myelocytic leukemia
digestive process (after taking food, rich of protein)	infections, inflammatory process, purulent process
physical exercise	myocardial infarction
pregnancy	malignant tumor

Leukocytopenia may be to physiological condition and to the pathological condition (*Table 3.3*).

Table 3.3

Physiological and pathological causes of leukocytopenia

Physiological condition	Pathological condition
deep sleep	some bacterial infections, virus infections
starvation	autoimmune diseases
	hypo-aplastic condition (administration X-ray, chemical substances, radiation)
	agranulocytosis (after administration some medications)

Increasing of neutrophils number is classified as neutrophilia, decreasing – as neutropenia.

Neutrophilia. Diagnostic meaning.

• Infections:

– pyrogenic bacterial: staphylococcal, streptococcal, pneumococcal, meningococcal, gonococcal;

– non pyrogenic: acute rheumatic fever, diphtheria, scarlet fever, acute poliomyelitis, cholera, herpes zoster, mycobactcrial, fungal, spirochaetal, parasitic.

• Metabolic disorders (liver failure, uremia, diabetes, acidosis, gout, eclampsia);

• Neoplasms with myeloproliferative disorders.

Other malignancies: carcinoma (metastatic or otherwise), sarcomas.

Conditions causing cell necrosis or destruction (acute hemolysis, infarctions, drug intoxication nephrotoxins, hepatotoxins).

Trauma and hemorrhage.

Collagen disease (polyarteritis nodosa, acute phase of rheumatoid arthritis, dermatomyositis).

The leukocyte formula: leucocytes formula is counted in stained smear. It is percentage ratio of separate white blood cell types. The changes of different forms of leukocytes have clinical significance. It is necessary to account the degree of lobation in the neutrophil nuclei. After the assessment of nuclear shift in the leukocyte formula the following types of neutrophilic leukocytosis are distinguished:

• increased number of mature segmented neutrophils with leukocytosis. It is characneristic of inflammation;

• hyporegenerative shift to the left – an increased number of band forms of neutrophils. It is characneristic of a slight course of bacterial infections and inflammation;

• regenerative nuclear shift to the left which indicates the reactive activation of granulocytopoiesis. On the background of neutrophilia and increased

number of metamyelocytes and sometimes myelocytes occur. It is characteristic of the purulent process.

Leukemoid reactions are present with high leukocytosis and occurrence of immature leukocytes in the blood, which are similar to those in leukemias, but are temporary and convertible. They occur in infections, inflammatory diseases, intoxication, parasitic infections, infections mononucleosis/collagenosis and etc.

Neutropenia. Diagnostic meaning.

Distributive neutropenia is observed in shock, inflammatory process, resulted to bacterial diseases (typhoid fever etc.), virus diseases. This neutropenia is temporary and is usually replaced by leukocytosis.

Neutropenia may be result of intensive destruction of neutrophils under influence of toxins, ionizing radiation, the poisoning substances.

Neutropenia owing to intensive destruction of neutrophils under influence of antibodies leukoagglutinins, which are formed in blood uncompatable transfusions and the result of diseases accompanied by increased number of the circulated immune complexes (autoimmune diseases, leukemia, tumor).

Neutropenia owing to inhibited leukopoesis under influence of ionizing radiation, toxic substances, some drugs, in replacement of the bone marrow by leukemic or tumor tissue.

Neutropenia is the hematological feature of myelodysplastic syndromes – a group of clonal bone marrow neoplasms characterized by ineffective hematopoiesis, manifested by morphologic dysplasia in hematopoietic cells and by peripheral cytopenia.

Agranulocytosis is a condition in which the severy neutropenia – absolute neutrophil count is less than 100 neutrophils per microlitre of the blood. Agranulocytosis can be broadly classified into two distinct categories – inherited and acquired. The hereditary disease is due to genetic mutations in the gene coding for neutrophils elastase or ELA2. Acquired diseases may be due to various medications, chemicals, autoimmune conditions and infections. The following are the medications commonly involved with agranulocytosis: cancer chemotherapies, analgesic and anti-inflammatory, anti-depressants, anticonvulsants, anti-malarials, antibiotics, miscellaneous. Infections that can cause agranulocytosis include: bacterial, viral, rickettsial, parasitic. Autoimmune conditions such as lupus, rheumatoid arthritis, and bone marrow diseases like myelodysplastic and leukemias are also associated with agranulocytosis.

The main complication of agranulocytosis is infection. The duration and severity of agranulocytosis directly correlate with the incidence of infection. When the absolute neutrophil count remains lower than 100 cells per microlitre of blood for longer than 3–4 weeks, the incidence of infection approaches 100 %. Sepsis is another major complication of agranulocytosis.

A number of adverse prognostic factors are associated in the patient with agranulocytosis. These include: age > 65 years, absolute neutrophil count at the

time of diagnosis <100/micro L, development of severe intercurrent infection (e.g., septicemia, septic shock), pre-existing comorbidities (e.g., renal, cardiac, respiratory, and systemic inflammatory diseases).

Eosinophils. Normal range: 0–5 %. Increasing of eosinophils number is classified as eosinophilia, decreasing of eosinophils number is classified as eosinopenia.

Eosinophilia. Diagnostic meaning.

Allergic slates (asthma, fever, exfoliative dermatitis, erythema multiforme, urticaria, food sensitivity, angioneurotic edema, serum sickness, drug allergy).

Parasitic disease (intestinal forms, tissue forms).

Skin disorders (pemphigus, dermatitis herpetiformis, psoriasis, scabies, prurigo).

Drug administration (liver extracts, penicillin, streptomycin, chlorpromazine).

Neoplasms (myeloproliferative (eosinophilic leukemia, chronic myeloid leukemia, polycythemia), others (Hodgkin's disease, multiple myeloma, metastatic and necrotic, occult tumor).

Miscellaneous (familial eosinophilia, eosinophilic syndrome, eosinophilic granulomatosis, scarlet fever, polyartritis nodosa, tropical eosinophilia, pernicious anemia, postsplenectomy, idiopathic neutropenia.

Eosinopenia. Diagnostic meaning.

Drug/hormone therapy: adrenocortical steroids, adrenaline, ephedrine.

Response to stress: acute infections, traumatic shock, surgical operations, severe exercise, burns, acute emotional stress, exposure to cold. Endocrine diseases: Cushing's disease, acromegaly. Miscellaneous: aplastic anemia.

Basophils. Normal range: 0–1 %. Increasing of basophils number is classified as basophilia.

Basophilia. Diagnostic meaning.

Chronic myeloid leukemia.

Myelosclerosis.

Polycythemia vera.

Hypersensitivity states.

Myxoedema.

Iron deficiency anemia (some cases).

Long standing hemolytic anemias.

Monocytes. Normal range: 2–9 %. Increasing of monocytes number is classified as monocytosis.

Monocytosis. Diagnostic meaning.

• Infections:

– bacterial: brucellosis, sub-acute bacterial endocarditis, tuberculosis, typhoid fever, recovery stage of an acute infection;

– rickettsial: rocky mountain spotted fever, typhus;

– protozoan: malaria, kala-azar, trypanosomiasis, oriental sore;

– viral: infections mononucleosis.

• Neoplasms: monocytic leukemia, carcinomatosis, Hodgkin's and other lymphomas, myeloproliferative disorders, multiple myeloma.

• Collagen diseases; rheumatoid arthritis.

• Miscellaneous: chronic ulcerative colitis, regional enteritis, sarcoidosis, lipid storage diseases, hemolytic anemia, hypochromic anemia, recovery from agranulocylosis.

3.2. Definition and classification of myeloproliferative syndrome.

The term "myeloproliferative disorder" was first used to described polycythemia vera and related disorders in 1951. In 2008, the World Health Organization reclassified "myeloproliferative disorder" to "myeloproliferative neoplasms" to reflect the consensus that these diseases are blood cancers (neoplasms). This group of disorders is characterized by the overproduction (proliferation) of one or more of the three main blood cell lines – red or white blood cells or platelets. Red blood cells carry oxygen to the body. White blood cells fight infection. Platelets are involved in clotting of the blood in response to injury. The development of a proliferative abnormality can proceed in one direction (for example: myeloid metaplasia – acute myeloblastic leukemia or chronic myelocytic leukemia) or in several direction simultaneously for example – polycythemia vera. Because myeloproliferative neoplasms are characterized by uncontrolled cell growth, they may also be classified as blood cancers. Myeloproliferative syndrome is characteristic of hemoblastosis.

Hemoblastosis is a disease of the whole blood system characterized by:

1) progressive cell hyperplasia in the hemopoietic organs with pronounced prevalence of proliferation of certain cells;

2) metaplasia of these pathological cells instead of normal cells to hemopoietic organs;

3) development of pathological foci of hemopoiesis in various organs.

WHO classification of myeloid neoplasms and acute leukemia in a short form is presented below.

2016 WHO classification of myeloid neoplasms and acute leukemia (Arber D.A., Orazi A., Hasserjian R. et al. The updated WHO classification of hematological malignancies. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia BLOOD, 2016 volume 127, number 20 p. 2391-2405).

Acute myeloid leukemia

Acute myeloid leukemia and related neoplasms

Acute myelomonocytic leukemia

Acute monoblastic/monocytic leukemia

Acute megakaryoblastic leukemia

Acute basophilic leukemia

Acute myeloid leukemia with recurrent genetic abnormalities

Myeloproliferative neoplasms

Myeloid proliferations related to Down syndrome
Chronic myeloid leukemia BCR-ABL11
Chronic neutrophilic leukemia
Chronic myelomonocytic
Polycythemia vera

3.3. Acute myeloblastic leukemia.

Leukemia is a broad term covering a spectrum of diseases and defined a type cancer of the blood or bone marrow characterized by an abnormal increase of white blood cells. Acute myeloblastic leukemia is characterized by profuse proliferation of the blast element of blood with their subsequent disturbed differentiation, with development of foci pathological hemopoiesis in various organs.

Acute myeloblastic leukemia is age dependent occurs in all age groups less in children but commonly in adults. Acute myeloblastic leukemia is predominantly a disease of adults with two peaks, one at 15 to 20 years of age and another peak after 50 years of age. Acute myeloid leukaemia incidence, rising markedly in patients aged ≥60 years. Ageing of the European population may therefore contributes to the reported increase in acute myeloblastic leukemia incidence in Europe from 3.48 in 1976 to 5.06 patients per 100 000 people in 2013. Across all age groups, the incidence of acute myeloblastic leukemia is higher in males than in females. The median age at diagnosis is 70 years.

Etiology of acute myeloblastic leukemia.

1. Environmental exposures: chemical concerogenous substances (benzpyrence, benzol), ionizing radiation.

2. Therapy-related leukemia – alkylating agent-induced damage (cisplatin, cyclophosphamide, chlorambucil, other agents (hydroxyurea, chloroquine, chloramphenicol, azathioprine).

3. Hematologic disorders predisposing to development of leukemia: polycythemia vera, essential thrombocythemia, paroxysmal nocturnal hemoglobinuria.

4. Inherited predisposition to leukemia (Down syndrome, Fanconi's anemia, Wiskott-Aldrich syndrome, Bloom's syndrome). Acute leukemia develops due to the congenital or acquired damage to the chromosome structures of low differentiated cells of the hemopoietic organs.

5. Viruses theory connects the appearance of acute myeloblastic leukemia with DNA or RNA damage, but only animal experimental studies support this point of view.

Pathogenesis of acute myeloblastic leukemia.

Due to primary mutation in one of the hemopoietic cells occurs its subsequent multiplication and formation of a clone of blast cells. These cells fail to differentiate properly and proliferate without maturing to the normal nonproliferating stages. Acute myeloblastic leukemia is characterized by the rapid increase of immature blood cells. The accumulation of this immature, continually dividing cells results to the replacement of the normal hematopoietic precursor

cells by these neoplastic cells. This crowding makes the bone marrow unable to produce healthy blood cells and will cause complete bone marrow failure. Expansion and infiltration of tissue and organs with abnormal white blood cells lead to the main clinical features.

Clinical featurs of acute myeloblastic leukemia.

The onset of the disease is in most cases acute or subacute. In some cases the onset disease is gradually with non specific general symptoms: weakness, fatigue, subfebrile temperature, weight loss.

There are some syndromes of acute myeloblastic leukemia:

- intoxication;
- anemia;
- ulcerative necrotic;
- infections;
- bleeding;
- splenomegaly and hepatomegaly;
- neurological syndrome.

Syndrome of intoxication are as follows: high temperature (remittent or hectic), profuse sweating, chills, pronounced weakness, fatigue and malaise, reduced exercise tolerance, general loss of strength, anorexia. Diffuse bone pain (long bones, ribs, and sternum) is the initial clinical manifestation in 25 % of patients. The bone pain, which can be severe, is caused by the expansion of the intramedullary space or direct involvement of the periosteum by the leukemic cells. Joints are swelling, localized to large joints. Tenderness of the sternum may be quite pronounced.

Syndrome of anemia is explained by depressed erythropoiesis; increased bleeding; accelerated destruction of red blood cells. The degree of anemia depends on the speed of the development of acute myeloblastic leukemia as well as on iron and folic acid stores. There are general symptoms of anemia: fatigue, dizziness and dyspnea. The mucous membranes and nail beds are pallor. Anemia results in the onset of cardiovascular symptoms.

Ulcerous complication: necrotic syndrome is characterized by pain in the throat, swallowing becomes painful. Ulcerous of the oral mucosa occurs commonly in acute myeloblastic leukemia. There may be infiltration of the gums with swelling and bleeding. Ulcerous and necrotic tonsillitis, gingivitis and stomatitis are quite characteristic of this disease.

Despite the markedly increased production of white blood cells, their function is inadequate. This fact is explained such complications as secondary infections due to the pathogenetic agents: gram negative bacteria, staphylococci and streptococci, viral – herpes simplex and zoster, fungal – Candida, protozoal – pneumocystitis carinii. Pericarditis and pleuritis are possible. The infections of skin, mouth, throat, respiratory and urinary tract including septicemia are common usually.

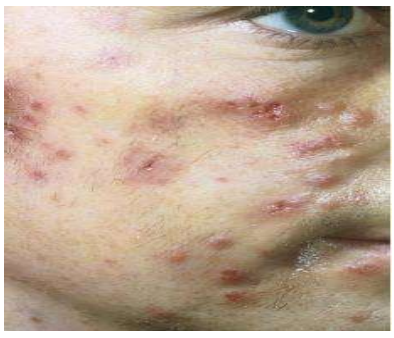
Bleeding syndrome due to thrombocytopenia which produces hemostatic defects, which result in petechiae and ecchymosis, traces of subcutaneous and intracutaneuos hemorrhages can be seen. The lesions vary in size from small pointed hemorrhages (petechiae) to large black and blue spots (ecchymoses) which appear spontaneously or at points of injections and may appear suddenly after minor physical activity or standing for prolonged periods. Spontaneous bruises, purpura, bleeding gums and bleeding after dental procedures or minor trauma are common due to thrombocytopenia. Occasionally initial manifestation there may be major internal hemorrhage.

Splenomegaly occurs in up to 50 % of patients with acute myeloblastic leukemia, but the enlargement usually is modest, with the spleen rarely extending more than 5 cm below the left costal margin. A very large spleen suggests that the leukemia has evolved from an underlying myeloproliferative disorder.

Neurological disorders. Blast infiltration of meningeal membranes lead to neurological disorders with clinical features of meningitis.

Other organs in patients with acute myeloblastic leukemia.

Skin involvement occurs in about 10 % of patients and usually manifests as violaceous, raised, nontender plaques or nodules, rash, which on biopsy are found to be infiltrated with myeloblasts (*Picture 3.1*). Sweet's syndrome, acute neutrophilic dermatosis, is a cutaneous paraneoplastic syndrome that is associated with acute myeloblastic leukemia and other hematologic disorders. It is characterized by red plaques and nodules, usually on the extremities, and may precede the diagnosis of acute myeloblastic leukemia by several months. Sweet's syndrome is more common in the monocytic leukemia.



Picture 3.1. A rash at acute myeloblastictic leukemia

Lymphadenopathy is rare in acute myeloblastic leukemia in contrast with acute lymphoblastic leukemia. Sometimes enlarged cervical and supraclavicular lymph nodes are detected in the superficial areas by palpation.

Ophthalmic problems. All portions of the eye may be involved, including the optic nerve, choroid and retina. Leukemia can involve the optic disc and optic nerve, resulting in the sudden onset of blurred vision, which can rapidly progress to total blindness.

Respiratory system. Pneumonia is the most common problem. Gram-positive and gram-negative bacteria are the major pathogens. In patients who are neutropenic, there is an increased risk for pulmonary infection with fungi or other opportunistic organisms. Pulmonary leukostasis is a serious potential problem for patients who present with a blast count greater than $500x10^9$/l. In this setting, formation of leukocyte thrombi and plugging of pulmonary microvascular channels lead to vascular rupture and infiltration of the lung paren-

chyma. The leukemia associated with acute respiratory failure also may be due to pulmonary hemorrhage or to direct damage of the pulmonary endothelium from the lysed leukemic blasts.

Cardiac abnormalities usually are a result of derangements in metabolic, electrolyte and pulmonary functions. Leukemic infiltration of the heart or great vessels is rare, but there are reports of leukemic involvement of the conduction system, pericardium and myocardium, as well as involvement of the arterial endothelial wall with monoblasts and subsequent formation and rupture of an aortic aneurysm. Chemotherapy-related toxicities produce a majority of the cardiovascular problems in patients with acute myeloblastic leukemia Patients in whom progressive cardiorespiratory failure develops and who require intubation and respiratory support continue to have grave prognoses.

Gastrointestinal abnormalities. Dysphagia is common and usually is a result of oral or pharyngeal infections, mucosal involvement with leukemia or chemotherapy-induced mucositis – oral candidiasis, esophageal candidasis. The anal and perirectal areas are important potential sources for infection in neutropenic patients. Patients initially may complain only on pain at defecation and diffuse anal tenderness, without signs of infection. Perirectal abscesses usually are due to gramnegative bacteria and in the setting of granulocytopenia can rapidly progress to perirectal cellulitis and septicemia. Typhlitis is a fulminant necrotizing colitis related to granulocytopenia and cytotoxic therapy. It occurs in up to 10 % of patients with acute myeloblastic leukemia who are undergoing intensive therapy. The clinical presentation frequently mimics that of acute appendicitis. The pathogenesis of neutropenic colitis is multifactorial and related to the chemotherapy administered and local mucosal damage.

Additional methods of examination.

Clinical blood analysis:

- leukocytosis 30–300x10^9/l;
- white blood cells count may be normal or even decreased;
- red blood cells count decreased;
- hemoglobin concentration decreased;
- severe thrombocytopenia;
- blood film examination show variable numbers of blast cells – 95 %.

In patients with acute myeloblastic leukemia present the myeloblast and mature white blood cells. This hematological phenomen is called on “hiatus leukemicus”. In blood smear are there absence of eoisinophyl and basophil.

The blood smear usually is sufficient to make the presumptive diagnosis of acute myeloblastic leukemia but in the 10 % of patients who may present with only a modest thrombocytopenia and a normal white blood cells count without circulating blasts, a bone marrow examination is required to make the diagnosis.

The bone marrow aspiration and biopsy should be performed at a time when the necessary therapy studies can be obtained. Even in the severely neu-

tropenic and thrombocytopenic patient, bone marrow biopsy and aspiration can be safely performed. Local bleeding or infection at the site of the procedure is very rare. The posterior iliac crest is the preferred site, unless the patient has received previous radiation therapy to the pelvis or has evidence of an active infection at the site. The sternum is an alternate site for performing bone marrow aspiration.

Bone marrow is hypercellular with a marked proliferation of blast cells which typically amount to over 75 % of the marrow cell total. A small amount of bone marrow is removed during a bone marrow aspiration. The procedure is uncomfortable, but can be tolerated by both children and adults. The marrow can be studied to determine the cause of anemia, the presence of leukemia or other malignancy, or the presence of some "storage diseases" in which abnormal metabolic products are stored in certain bone marrow cells.

Additional special methods examinations include cytogenetic and molecular investigations to identify urgently the forms of acute myeloblastic leukemia, assess risk stratification and treatment strategies.

Molecular testing: recommended testing the leukemia cells for specific genes, proteins, and other factors unique to the acute myeloblastic leukemia.

Imaging tests required for detection if the leukemia is affecting other parts of the body. A common using an ultrasound high-frequency sound waves to create a picture of the inside of the body, measure the size of the spleen in people with acute myeloblastic leukemia. Computed tomography scan is sometimes used to look at and takes pictures of the inside of the body. A computer combines these images into a detailed, 3-dimensional image that shows any abnormalities. Sometimes, a special dye called a contrast medium is given before the scan to provide better detail on the image. This dye can be injected into a patient’s vein or given as a liquid to swallow.

Treatment of acute myeloblastic leukemia.

• Immediate treatment is required in acute leukemia due to the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body.

• The traditional goal of the treatment of acute myeloblastic leukemia is to produce and maintain a complete remission. Criteria for complete remission are a platelet count higher than $100x10^9$/L, a neutrophil count higher than $1x10^9$/L, and a bone marrow specimen that has less than 5 % blasts. Patients who have been in continuous complete remission for 3 years can, for operational purposes, be considered potentially cured.

3.4. Chronic myelocytic leukemia.

Chronic myelocytic leukemia is defined as the myeloproliferative disorders. It is as a neopastic disease of bone marrow stem cell precursor of myelopoiesis, which is common for granulocytes, erythrocytes and megakariocytes with excessive production of granulocytes in the bone marrow and other hema-

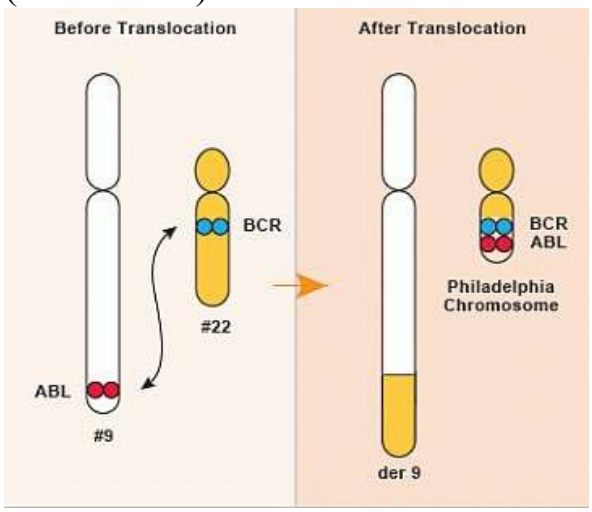
topoietic organs. Chronic leukemia is distinguished by the excessive build up of relatively mature, but still abnormal, white blood cells which are produced at a much higher rate than normal cells, resulting in many abnormal white blood cells in the blood. Chronic leukemia mostly occurs in older people, but can theoretically occur in any age group.

Etiology of chronic myelocytic leukemia.

The specific factors haven't been established. The causative agents of chronic myelocytic leukemia are suspected such as ionizing radiation, exposure some chemical carcinogens, which damage bone marrow.

Pathogenesis of chronic myelocytic leukemia.

Due to the excess radiation or mutagenic chemicals occur mutation in the bone marrow stem cell, damage of DNA, and transformation it in neoplastic cell with chromosomal disorders. The history started in 1960, when an abnormal, shortened chromosome 22, termed the Philadelphia chromosome (Ph chromosome**)**, was described in the leukemic cells of a patient affected by chronic myelocytic leukemia by two scientists from USA Nowell and Hungerford. Only 13 years later, using the special investigation allowed to clarify that Ph chromosome is the result of a translocation of part of chromosome 22 to chromosome 9 (*Picture 3.2*).



Picture 3.2. Philadelphia chromosome

This chromosomal abnormality translocation or rearrangement of chromosomes 9 and 22 leads to the formation new hybrid onkogene BCR/ABL which processes an increased enzyme activity and produces clones of changed bone marrow stem cells with abnormal chromosome. Clones of bone marrow stem cells develop an ability to proliferate excessively, especially the granulocytic cell lines, resulting in a tremendous increase the leukocytes in the peripheral blood stream. Some of these cells preserve the ability to differentiate in mature cells. Bone marrow may be further damaged by infiltration of abnormal cells with replacement of normal hematopoietic process because interferes with normal production of hemapoietic cell lines. Continuous proliferation of mutative cells promotes their expansion in the organs and tissue in a form of metastasizing tumor cells. Thus the expression of the hybrid BCR/ABL protein is presumed to be an early pathogenic event and its elevated tyrosine kinase activity to be a central event in Philadelphia chromosome positive patients.

Clinical feature of chronic myelocytic leukemia.

According to hematological disorders is appeared some clinical syndromes: anemic due to the decreased red blood cell production; greater tendency

to bleeding due to decreased platelet production and infections due to the increased nonfunctional white blood cell production and decreased normal ones.

The initial symptoms and signs are not specific such as general malaise, fatigue, weight loss, low-grade fever. These disorders are observed accidentally as a rule. Many patients will complain on pain of the bones especially the sternum and ribs, which are the major sites of blood cell production. Myeloid infiltration in the lung can be caused some additional symptoms, such as coughing. Features of anemia may include dyspnea and tachycardia, lethargy. Chronic myelocytic leukemia is associated with increased susceptibility to infections such as pneumonia, pleuritis, pyelonephritis.

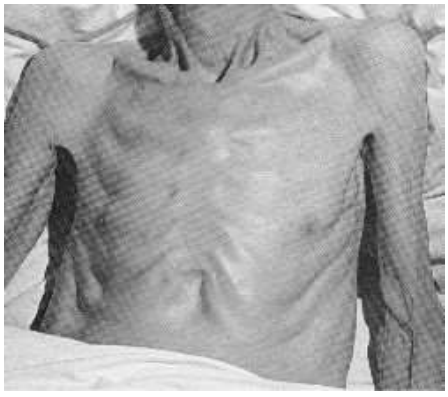
Objectivel examination reveals pallid skin with yellowish or grayish tint due to the anemia. The specific sign of disease is skin leukemic infiltration and local lesions. Infiltration of the bones and the joints may cause localized lesions.

In patients occurs considerable nonsymmetrical enlargement of abdomen predominantly in the left hypochondrium, due to the marked enlarged spleen. In about 10 % patients the enlargement is massive, extending to over 15 cm below the costal margin. The spleen is usually firm, smooth and painless. The presence of splenomegaly may be explained by excessive work to eliminate senescent and abnormal white blood cells. Enlarged liver is fairly common also. Less common neurological presentations include dizziness, visual disturbances, convulsions, paralysis resulting from the affection of the brain and spinal cord. In patients is common bleeding syndrome with bruising, epistaxis, menorrhagia or hemorrhage from other sites.

There are three clinical stages of disease:

- stage I – initial;
- stage II – accelerated phase;
- stage III – dystrophy and blast crisis.

The disease develops gradually. In the accelerated phase weakness becomes considerable, present night sweating profuse, elevation of temperature periodically to 37.5–39 °C, pain in the left hypochondrium, abdominal fullness and discomfort. In stage III may observe cachexia (*Picture 3.3*), secondary prolonged infections, progressive anemia, bleeding. Finally, this chronic condition may transform to blast crises similar to an acute form of leukemia with the production of large number of immature myeloblasts in the bone marrow and the bloodstream. This new blastic phase is fatal.



Picture 3.3. Chronic myelocytic leukemia. Cachexia

Additional methods of examination of chronic myelocytic leukemia

Clinical blood analysis:

- number of white blood cells between $50x10^9$/l and $300x10^9$/l;
- number of red blood cells decreased;
- number of platelet decreased;
- complete spectrum of myeloid cells is seen: blast cells, myelocytes, metamyelocytes, band cell, nature polymorphonuclear neutrophils (hiatus leucemicus);
- myeloblasts are usually less than 10 %;
- increased count of eosinophils and basophils.

Bone marrow.

Hypercellular with granulopoietic predominance.

Phyladelphia chromosome in bone marrow cells is detected during cytogenetic analysis.

Cytogenetics is a type of genetic testing that is used to analyze a cell's chromosomes. It looks at the number, size, shape and arrangement of the chromosomes. Occasionally, this test can be done on the peripheral or circulating blood when the chronic myelocytic leukemia is first diagnosed, but immature blood cells that are actively dividing need to be used. Because of this, a bone marrow sample is usually the best way to get a sample for testing. Cytogenetic testing for chronic myelocytic leukemia is used to monitor how effective treatment is working. Another aim of this method is to assess the number of reducing cells with the Philadelphia chromosome.

Fluorescence in situ hybridization (FISH) is a test used to detect the BCR-ABL gene and to monitor the disease during treatment. This test does not require dividing cells and can be done using a blood sample or bone marrow cells. This test is a more sensitive way to find chronic myelocytic leukemia than the standard cytogenetic tests that identify the Philadelphia chromosome.

Polymerase chain reaction (PCR) is a DNA test that can find the BCR-ABL fusion gene and other molecular abnormalities. PCR tests may also be used to monitor how effective treatment is working. This test is quite sensitive and, depending on the technique used, can find 1 abnormal cell mixed in with approximately 1 million healthy cells. This test can be done using a blood sample or bone marrow cells.

For most people with chronic myelocytic leukemia, the Philadelphia (Ph+) chromosome and the BCR-ABL fusion gene can be found through testing, which confirms the diagnosis. For a small number of patients, increased blood cell counts may suggest chronic myelocytic leukemia, but the Philadelphia chromosome cannot be found on the usual tests even though the BCR-ABL fusion gene is there. Treatment for these patients is the same and works as well as it does for patients with a detectable Philadelphia chromosome. After treatment begins, cy-

togenetic and/or molecular testing is repeated on another bone marrow sample to find out if there are fewer cells with the Philadelphia chromosome.

3.5. Polycythemia vera.

Polycythemia vera defined as a myeloproliferative disorder characterized by a clonal stem cell disorder with neoplastic hyperproduction of blood cells in the bone marrow as a rule erythrocytic, granulocytic and megakaryocytic cell lines. Polycythemia vera is a rare, chronic disease which was first reported in the medical literature in 1892.

Epidemiology of polycythemia vera.

Polycythemia vera occurs in population 2–3/100000. It occurs most often in elderly individuals, median age at presentation 55–60 years, but can affect individuals of any age. It is extremely rare in individuals under 20 age and rare in childhood. Male/female ratio: 0.8:1.2.

Etiology of polycythemia vera.

Polycythemia vera is caused by a malignant change in the genetic material (DNA) within a single cell of the bone marrow (clonal disorder). The underlying reason why this malignant change occurs is unknown.

Pathogenesis of polycythemia vera.

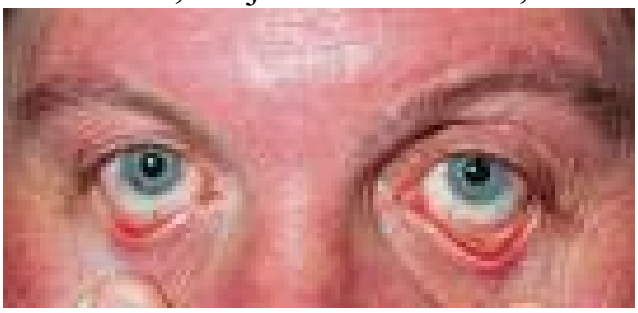
90 percent of individuals with polycythemia vera have a variation in the JAK2 gene. Genes provide instructions for creating proteins that play a critical role in many functions of the body. When a mutation of a gene occurs, the protein product may be faulty, inefficient, absent, or overproduced with cell lines. Since red blood cells are overproduced in the marrow, this leads to abnormally high numbers of circulating red blood cells (red blood mass) within the blood. Consequently, the blood thickens and increases in volume, a condition called hyperviscosity. Thickened blood may not flow through smaller blood vessels properly. Pathogenic appearance of hypervolemia, stagnation of the blood flow resulted in affection many organ systems of the body and onset of clinical features. Increased blood thickness and decreased blood flow, as well as abnormalities in platelets, raise risk of blood clots, a condition in which a blood clot forms in the main blood vessel. Blood clots can cause a thrombosis (arterial or venous) in a form of stroke, myocardial infarction, a blockage in an artery in lungs, vein deep thrombosis, thrombosis in the hepatic-portal system (Budd-Chiari syndrome). Phlebitis is the specific signs of this disease due to the increased viscosity of the blood, a large number of platelets and microcirculation disorders. According to increased blood volume and peripheral resistance the hypertension and further left ventricular hypertrophy occur. The increased number of blood cells caused by polycythemia vera makes spleen work harder than normal, which causes it to enlarge.

Clinical features of polycythemia vera.

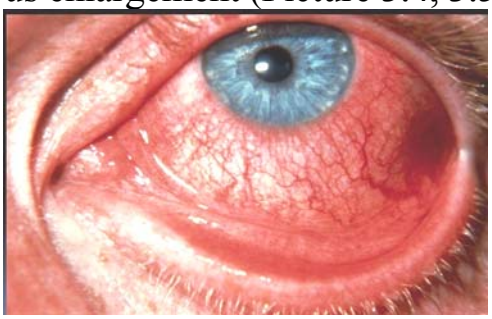
Many individuals with polycythemia vera slowly developted a variety of general, nonspecific symptoms that are common to many disorders such as

headaches, fatigue, weakness, mental acuity, dizziness, excessive sweating especially at night, weight loss, insomnia, pain in the heart, bones, difficulty breathing when lying down, dyspnea, blurry or double vision, ringing in the ears (tinnitus), toggling of the finger. The specific symptom is itching skin, after contact with water, in severe cases may be worse after taking a shower or a warm bath with appearance of pruritus.

Symptoms common to erythrocytosis: erythromelalgia is a condition characterized by burning painful sensation or swelling of the affected areas, and abnormal redness or purplish appearance with cyanosis of the skin especially on the face, (facial plethora), the hands and feet. The skin may feel warm to the touch. Very important in diagnosis is plethoric appearance – redness cyanosis of the skin and mucosa, conjuctival suffusion, retinal venous enlargement (Picture 3.4, 3.5).



Picture 3.4. The face of patient with polycythemia vera



Picture 3.5. Retinal venous enlargement

Redness cyanosis are explained by is plethoric appearance, high concentration of hemoglobin and increased number of red blood cells, disturbances of arterial oxygen saturation, presence of methemoglobin.

Physical examination.

On examination of the eye grounds, the vessels may be engorged, tortuous, and irregular in diameter; the veins may be dark purple (fundus policythaemicus).

Splenomegaly – is present in 75 % of patients at the time of diagnosis as a result of myeloid metaplasia and excessive work for elimination of abnormal red blood cells.

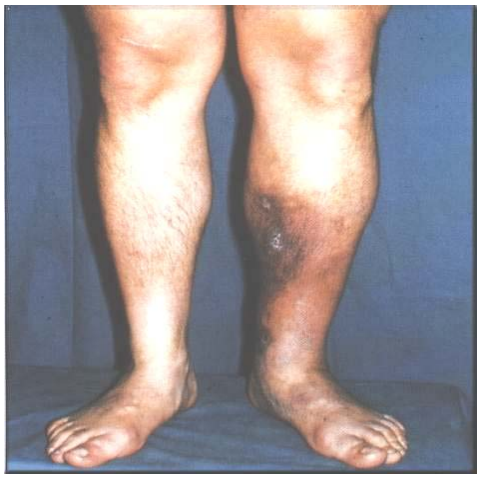
Hepatomegaly is present in approximately 30 % of patients at the time of diagnosis.

Hepatosplenomegaly is present. Some individuals with polycythemia vera have symptoms of Budd-Chiari syndrome include pain in the upper right part of the abdomen, an abnormally enlarged liver (hepatomegaly), yellowing of the skin and the the eyes (jaundice), and/or accumulation of fluid in the space (peritoneal cavity) between the two layers of the membrane that line the stomach (ascites).

Too many red blood cells can lead to a number of other complications, including open sores on the inside lining of stomach, upper small intestine or esophagus (peptic ulcers) and inflammation in joints (gout).

Arterial hypertension occurs as secondary form.

During the disease progression appears complication in a form of thrombosis of arterial and venous vessels. Thrombosis may occur at any site (*Picture 3.6*).



Picture 3.6. Thrombosis of vessels in left extremitas

Many platelets have functional defects that lead in some patients with polycythemia vera to hemorrhage. The most common form is bleeding into the gastrointestinal tract.

In rare cases, polycythemia vera can lead to other blood diseases, including a progressive disorder in which bone marrow is replaced with scar tissue, a condition in which stem cells don't mature or function properly, or cancer of the blood and bone marrow (acute leukemia).

Additional methods of examination.

Clinical blood analysis:

- increase in hemoglobin above 17.5 g/dl in males; above l5,5 g/dl in females;
- increase in red cells count above 6x1012/l in males; above 5.5x1012/l females;
- increase in hematocrit above 55 % in males; above 47 % in females;
- leucocytosis;
- thrombocytosis;
- neutrophile leukocytosis;
- moderate basophilia.

Pay attention! During providing blood analysis it may be in some cases in patient the erythrocytosis that requires differential diagnostics. According to classification is distinquished absolute primary erythrocytosis (polycythemia vera) and secondary erythrocytosis.

The causes of secondary erythrocytosis: some people living in high altitudes may develop secondary secondary erythrocytosis in response to poor oxygenation of tissue; conditions that deprive the body of oxygen such as certain lung or heart diseases; certain tumors that may secrete erythropoietin (a hormone that stimulates red blood cell production); some kidney disorders can result in the excessive production of erythropoietin and, in turn, overproduction of red blood cells.

Erythrocytosis secondary to decreased tissue oxygenation:

- chronic lung diseases;
- cyanotic congenital heart diseases;
- high-altitude erythrocytosis (Monge disease);
- hypoventilation syndromes (Sleep apnoe);
- hemoglobin-oxygen dissociation abnormalities;
- hemoglobinopathies associated with high oxygen affinity;

• carboxyhemoglobin in „smoker's polycythemia".

Secondary erythrocytosis (abnormal increase of serum erythropoietin level):

• erythropoietin-producting tumors: hepatoma, uterine leiomyoma, cerebellar hemangioblastoma, ovarian carcinoma, pheochromocytoma;

• renal diseases: renal cell carcinoma, renal cysts and hydronephrosis, renal transplantation;

• androgen abuse: adrenal cortical hypersecretion, exogenous androgens.

Gematological difference between primary and secondary erythrocytosis: secondary erythrocytosis is cheracterized with isolated increasing only red blood cells; primary erythrocytosis (polycythemia vera) is accompanied increasing of red blood cells, leukocytes and platelet.

Bone marrow in polycythemia vera is hypercellular with large numbers of erythrocytic, granulocytic precursor cells, later due to scar tissue replaces the marrow and the disorder resembles idiopathic myelofibrosis. When this occurs, the marrow can no longer produce blood cells resulting in low levels functioning red blood cells (anemia), platelets (thrombocytopenia) and white blood cells (leukopenia). In rare cases, polycythemia vera may eventually progress into a form of leukemia known as acute myeloid leukemia.

Serum erythropoietin level. This test measures how much of the hormone erythropoietin is in patient's blood. People who have polycythemia vera have very low amounts of it.

Specific gene testing. The discovery of novel molecular findings in JAK2 gene mutations provide proof of clonality, diagnostic importance and influence prognosis.

Diagnostic criteria of polycythemia vera (Polycythemia Vera Study Group).

Major criteria:

Elevated red blood cells mass.

Oxygen saturation >92 %.

Splenomegaly.

Minor criteria:

Platelet count > 400,000.

White blood cells > 12,000.

Serum vitamin B_{12} >900 pg/mL or serum unbound B_{12} binding capacity >2,200 pg/mL.

All 3 major criteria or the first 2 major and any 2 minor criteria.

2008 WHO Diagnostic criteria for primary polycythemia vera.

Major criteria:

Hgb > 18.5g/dl (♂) or 16.5g/dl or

Hgb or Hct > 99 % or

Hgb > 17g/dl (♂) or 15 g/dl (♀) and a documented increase of 2 g/dl or

RBC mass > 25% of mean normal

Presence of a JAK2 V617F or similar mutation.

Minor criteria

Bone marrow trilineage expansion.

Subnormal erythropoietin level.

Endogenous erytyhroid colony growth.

Two major or first major and two minor criteria.

Treatment people with polycythemia vera. Treatment focuses on reducing risk of complications and may also ease symptoms of disease.

Blood withdrawals. The most common treatment for polychythemia vera is having frequent blood withdrawals, using a needle in a vein (phlebotomy). Patients under the age of 50 with no history of thrombosis and without severe thrombocytosis (greater than 1000 G/L) phlebotomy alone initially 450–500 ml phlebotomy every other day until the hematocrit is less than 46 %. Older patients or these with underlying cardiovascular diseases should undergo smaller phlebotomies 200–300 mL twice weekly or 100–150 ml every day until Ht<46 % subsequently, Ht should be mainted between 42–46 % fluid replacement.

Drugs that reduce the number of red blood cell. If phlebotomy alone doesn't help enough, doctor suggests medications that can reduce the number of red blood cells in patient's bloodstream: myelosuppressive agents, hydroxyurea and others.

Antiplatelets agents in order keeps platelets from sticking together. That makes patient less likely to get blood clots, which in turn makes heart attacks or strokes less likely. Most people with polycythemia vera take aspirin initially 150–300 mg/d, maintence therapy 75–100 mg.

Treatment to reduce itching. Medication, such as antihistamines agent.

3.6. Definion, causes and clinical features of pancytopenia.

Pancytopenia is defined as a reduction in all blood cell lines – few red blood cells, white blood cells and platelets in peripheral blood.

Cause of pancytopenia:

• exposure to chemicals in the environment, such as, arsenic, benzene or ionizing radiation;

• drugs side effects: chemotherapeutic agents, chloramphenicol, nonsteroidal antiinflammatory drugs, certain antiepileptic drugs and various other drugs;

• infections: parvovirus B_{19}, hepatitis, HIV, cytomegalovirus, Epstein-Barr virus;

• immune disorders may play a role in the development of aplastic anemia, for example autoimmune disease, such as systemic lupus erythematosus;

• vitamin deficiencies (vitamin B_{12} and folate deficiencies) should always be considered in patients with pancytopenia;

• neoplasms: leukemia, myelodysplastic syndrjme, multiple myeloma, Hodgkin's or non-Hodgkin's lymphoma, paroxysmal nocturnal hemoglobinuria, metastatic malignancies;

• hypersplenism.

Clinical features of pancytopenia may explain on decreasing red blood cells that can result in increased fatigue, shortness of breath, fast heart rate, head pain,

dizziness, pale skin. Due to decreasing number of platelets and their abnormal function appears hemorragic syndrome: easy bruising, purple spots on skin, called petechiae, tiny larger purple spots on skin, called purpura, bleeding gums and nosebleeds, mucosal bleeding, hemarthrosis, and spontaneous internal bleeding. Neutropenia predisposes patients to bacterial infections with high fever. The risk for infection increases substantially after the neutrophil count falls below 500 cells/μL. During physical examination doctor should carefully examine the spleen and lymph node in order to exclude hemablastosis and other malignancy.

Complications from pancytopenia occur due to a lack of red blood cells, white blood cells and platelets. These problems can include: pronounced anemia, excess bleeding if platelets are affected, increased risk for infections if white blood cells are affected. Severe pancytopenia can be life-threatening.

Clinical blood analysis. Reduction in all blood cell lines: hemoglobin <13.5 g/dL in men and a hemoglobin <12.0 g/dL in women; the platelet count approaches 50,000 cells/μL, an absolute neutrophil count of <1500 cells/μL.

Bone marrow biopsy is essential to determine the etiology of pancytopenia.

Vitamin B_{12} and folate levels are required to exclude Vitamin B_{12} deficiency anemia and folic deficiency anemia.

Viral serologies. Assessment for viral exposures often by quantitative polymerase chain reaction testing for parvovirus B_{19}, HIV.

Treatments for pancytopenia include: drugs to stimulate blood cell production in bone marrow; blood transfusions to increase number of red blood cells, white blood cells and platelets; antibiotics to treat an infection; bone marrow transplantation, which replaces damaged bone marrow with healthy stem cells that rebuild bone marrow. Pancytopenia is specific hematological characteristic of aplastic anemia.

3.7. Aplastic anemia.

Aplastic anemia is a bone marrow failure syndrome characterized by peripheral pancytopenia and marrow aplasia because it involves a disorder of stem cells and therefore affects all cell lines. Aplastic anemia is a condition where bone marrow does not produce sufficient number of new cells to replenish blood cells and patients have lower counts of all three blood cell types: red blood cells, white blood cells and platelets, which termed pancytopenia.

Epidemiology of aplastic anemia.

The incidence of acquired aplastic anemia in Europe is 2 cases per million persons annually. In Thailand and China, rates of 5 to 7 per million have been established. In general, men and women are affected with equal frequency, but there is a biphasic age distribution, with the major peak in the teens and twenties and a second rise in the elderly.

Etiology of aplastic anemia.

Aplastic anemia is associated with exposure ionizing radiation from radioactive materials or radiation-producing devices, certain drugs and toxins, the ac-

tion of viruses (Epstein-Barr, hepatitis B and C, parvovirus). In some cases, the etiology cannot be determine and is considered to be idiopathic, but one known cause is an autoimmune disorder in which blood cells attack the bone marrow.

Pathogenesis of aplastic anemia.

Defect of hematopoietic stem cells cause the aplasia of hemopoiesis, delay the maturation and differentiation of the bone marrow elements to mature cells: erythrocytes, granulocytes and thrombocytes that transforms in clinical syndroms of anemia, infections and bleeding.

Clinical manifestations of aplastic anemia.

Clinical symptoms and signs of aplastic anemia depend on severity of hematological defect and characterized by anemic syndrome, hemorrhagic syndrome and syndrome of infections complications. The tissue hypoxia due to erythrocytopenia leads to such complains: fatigue, malaise, weakness, loss of strength, shortness of breath, dyspnea, palpitations, pain in the heart, digginess, headache. On objective examination – pallor of the skin, mucous membranes of mouth and nail beds may be observed. Leukocytopenia (low white blood cells count) leading to increased risk of secondary immunodeficiency, infection, ulcer-necrotic processes and sepsis complication. Thrombocytopenia (low platelets count), leading to increased risk of hemorrhage, bruising and petechiae, ecchymoses, bleedings (nasal, uterine, gastrointestinal).

Clinical blood analysis:

- hemoglobin concentration decreased pronounsly;
- red blood cell count decreased pronounsly;
- severe leukocypenia;
- severe thrombocytopenia.

Bone marrow: aplasia of erythroid, metamyolocytes; megakaryocytes elements.

Treatment of aplastic anemia:

Removal of potential etiologenic factors.

Blood transfusions can help keep blood cell counts at acceptable levels. Transfusions require careful matching of donated blood with the recipient's blood.

Blood transfusions help relieve the symptoms of aplastic anemia, but they are not a permanent treatment.

Pharmacologic therapy. Decisions regarding therapy are dependent on the severity of the aplastic anemia as well as the age of the patient. Pharmacologic therapy is the preferred treatment for patients who are greater than 40 years of age, or in younger patients without a sibling-matched donor for allogeneic stem cell transplantation. Antithymocyte globulin is usually the first-line pharmacologic treatment for patients with severe aplastic anemia. Immunosuppressive agents are used in conjunction with antithymocyte globulin and increase the likelihood of remission;

Bone marrow transplantation. A blood and marrow stem cell transplant replaces damaged stem cells with healthy ones from another person (a donor). Blood and marrow stem cell transplants often cure aplastic anemia in 80% of patients who can

have this type of treatment. The transplant works best in children and young adults with severe aplastic anemia who are in good health and who have matched donors. For those younger than 40 years without a matched-related donor, immunosuppressive therapy is the current first-line treatment option. Older people may be less able to handle the treatments needed to prepare the body for the transplant. They are also more likely to have complications after the transplanation.

3.8. Fanconi's anemia.

Fanconi's anemia was first described in 1927 by the Swiss pediatrician Guido Fanconi. He provided information on three boys from the same family who were found to have pancytopenia and a number of physical abnormalities.

Epidemioigy of Fanconi's anemia. Pathology is considered rare. Its frequency is 1: 350,000. Boys suffer from it more often. It is most common among the peoples of South Africa and Ashkenazi Jews.

Etiology of Fanconi's anemia.

Fanconi's anemia is most often inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Very rarely, this condition is inherited in an X-linked recessive pattern. The gene associated with X-linked recessive Fanconi's anemia is located on the X chromosome. The inheritance of the disease is autosomal recessive and manifests itself in homozygotes. Anemia can be detected in early childhood, but more often after 5 years.

Pathogenesis of Fanconi's anemia.

Mutations in at least 15 genes can cause Fanconi's anemia. Proteins produced from these genes are involved in a cell process known as the "Fanconi's anemia pathway" which is turned on when the process of making new copies of DNA, called DNA replication, is blocked due to DNA damage. The "Fanconi's anemia pathway" send certain proteins to the area of damage, which trigger DNA repair so DNA replication can continue.

Symptoms and signs of Fanconi's anemia.

About 75 % of patients with Fanconi's anemia have birth defects, such as low birth weight (10 %), altered skin pigmentation and/or café spots (>50 %), short stature (50 %), absence or malformity in hands and arms, hypoplastic thumb or absence of a thumb, the presence of polydactyly (40 %), abnormal male gonads (30 %), microcephaly (25 %), eye anomalies (20 %), structural renal defects, presence of only one kidney or a horseshoe kidney (20 %), cardiac malformations (10 %), developmental delay (10%) and abnormal ears or hearing (10 %).

The specific syndrome of disease is painful crisis due to the vascular obstructions with consequence of disorders of the local microcirculation by intravascular sickling which will produce local tissue injury in a form of chronic ulcers on the skin. Bone and joint crises, pulmonary crises, abdominal crises re-

sulted in small infarcts of mesentry and abdominal viscera are characterized by severe abdominal pain of peritoneal irritation. Myocardial infection result in congestive heart failure. Formation of gallstones in the gallbladder, splenomegaly are the signs of disease. May be observed onset glomerylonephritis with high levels of hematuria. Central nervous crises, intracerebral and subarachnoid hemorrhages are occurred.

Hemolytic crises occur suddenly following by oxidant drugs and infections with common signs conjuctival, skin icterus and pallor. The combination of accelerated hemolysis and temporary arrest of erythropoiesis may result in severe life-threatening anemia.

Hematological abnormalities are the most serious symptoms in Fanconi's anemia. By the age up 40, 98 % of Fanconi's anemia patients will have developed some type of hematological abnormality. However, there are a few cases in which older patients have died without ever developing them. Symptoms appear progressively and often lead to complete bone marrow failure and many other diseases. When the build up of errors in DNA leads to uncontrolled cell growth, affected individuals can develop acute myeloid leukemia or other cancers. Fanconi's anemia is associated with an increased risk of aplastic anemia.

Screening:

- clinical blood analysis;
- DEB test (diepoxybutane analysis);
- Immune-blotting and immune-fluorescence;
- prenatal screening;
- genetic counseling – carriers of Fanconi's anemia.

Treatment:

- retrovirus mediated gene transfer;
- lentivirus mediated gene transfer.

Test-control

1. Most rare manifestation of acute myeloblastic leukemia is:

A. Anemia.
B. Thrombocytopenia.
C. Splenomegaly.
D. Lymphadenopathy.
E. Hepatitis.

2. Indicate main reason of bone pain in patients with acute myeloblastic leukemia:

A. Intoxication.
B. Thrombosis of intraosseous vessels.
C. Involvement of the periosteum by the leukemic cells.
D. Secondary osteomyelitis due to reduced immunity.
E. Osteoporosis.

3. The diagnosis of aplastic anemia is based on the:

A. Presence of Philadelphia chromosome.
B. Combination of leucocytosis with erithrocytopenia.
C. Presence of Glucose 6-phosphate dehydrogenase deficiency.
D. Combination of pancytopenia with an empty bone marrow.
E. Presence of purpura.

4. Hematological characteristic of agranulocytosis is decreasing count:

A. Eosinophils.
B. Monocytes.
C. Neutrophils.
D. Basophils.
E. Lymphocytes.

5. **Philadelphia chromosome is translocation between chromosomes;**

A. 9 and 22.
B. 2 and 22.
C. 3 and 9.
D. 22 and 9.
E. 3 and 22.

6. Which complication most common in aplastic anemia:

A. Gastritis.
B. hepatitis.
C. Sepsis.
D. Gingivitis.
E. Bronchitis.

7. Itching skin after contact with warm water is characteristics of:
A. Acute limphoblastic leukemia.
B. Aplastic anemia.
C. Policytemia vera.
D. Acute myelocblastic leukemia.
E. Chronic lymphocytic leukemia.

8. Hiatus leukemicus is hematological characteristics of:
A. Acute lymphoblastic leukemia.
B. Aplastic anemia.
C. Policytemia vera.
D. Acute myelocblastic leukemia.
E. Chronic lymphocytic leukemia.

9. Pancytopenia defined as decrasing count of:
A. White blood cells and platelets.
B. White blood cells and red blood cells.
C. Platelets and red blood cells.
D. White blood cells, platelets and red blood cells.
E. Platelets and lymphocytes.

10. Which is the most effective treatment of aplastic anemia:
A. Blood transfusions.
B. Antithymocyte globulin.
C. Antibiotics.
D. Folic acid.
E. Bone marrow transplantation.

Chapter 4. Diseases with bleeding syndrome

4.1. Definition, causes and clinical features of bleeding syndrome.

Hemostasis is the mechanism that leads to physiological cessation of bleeding from a blood vessel. The cessation of bleeding involves multiple interlinked steps – the interaction of vasoconstriction, platelet aggregation and coagulation. The basic mechanism of hemostasis includes platelet-vascular (spasm of vessels to form a platelet plug) and coagulation (blood clots) factors; can divide into four stages: constriction of the blood vessel, formation of a temporary “platelet plug", activation of the coagulation cascade, formation of “fibrin plug” or the final clot. Thus, process of hemostasis involves such components: formed blood elements, enzymatic plasma system of blood clotting and fibrinolysis, vessel walls.

Requiment for normal hemostasis:

1. Sufficient count and function of platelets;
2. Normal state of the coagulation and fibrinolysis pathway;
3. Normal vessels wall.

1. Platelets (thrombocytes*)* are non-nucleated disc-like cells created from megakaryocytes that arise from the bone marrow. They are about 2 to 3 microns in size. Some of their unique structural elements include plasma membrane, open canalicular system, spectrin and actin cytoskeleton, microtubules, mitochondria, lysosomes, granules and peroxisomes. These cells release proteins involved in clotting and platelet aggregation.

Normal range of thrombocytes is 180–320x10^9/l. Increasing thrombocytes number is classified as thrombocytosis, decreasing – as thrombocytopenia. The causes of thrombocytopenia may be primary (hereditary) or secondary (acquired) as symptoms some pathological states.

The etiology of thrombocytopenia (secondary).

Insufficient production of thrombocytes due to selective megakaryocytic depression in bone marrow resulted cytostatic or radiation therapy, poisoning by the chaemical substances, metaplasia of the bone marrow, endogenous intoxication.

Increased destruction/consumption of platelets due to the suppressive effect on bone marrow: a viral infection (mumps, chickenpox, measles, rubella, cytomegalovirus infection, parvovirus infection), scarlet-fiver, sepsis, sometimes – with infectious mononucleosis (one case per 2000 patients).

Infiltration of bone marrow may be in leukemia, lymphoma, multiple myeloma, megaloblastic anemia; carcinoma.

Symptomatic thrombocytopenia caused by malnutrition. 20 % of patients with megaloblastic anemia have moderate thrombocytopenia as a result of a deficiency of vitamin B_{12} and deficiency of folic acid. Sometimes, thrombocytopenia accompanies iron deficiency.

Thrombocytopenia may be at hypersplenism. Sequestration of platelets in the spleen leads to a decrease in their content in the peripheral blood. The spleen is deposited typically around 1/3 of all platelets. Number of deposited platelets increased with splenomegaly, liver cirrhosis with portal hypertension, sarcoidosis, Felty's syndrome. Accumulation of platelets in the spleen in these diseases potentially is reversible. Lifespan of platelets in most cases is normal. Thrombocytopenia in hypersplenism usually minor, platelet count is not below $50.0x10^9$ per liter.

Symptomatic thrombocytopenia may be at alcoholism. Thrombocytopenia usually occurs in alcoholics as a result of cirrhosis, splenomegaly, or folic acid deficiency. Drinking large amounts of alcohol for 5–10 days causes thrombocytopenia and reduced the number of megakaryocytes in bone marrow. Platelet count returned to normative values for 5–20 days after the cessation of alcohol intake.

Hypothermia can cause transient thrombocytopenia in humans and animals. Cooling the body leads to sequestration of platelets in the spleen and liver.

Dilution (massive transfusion) leads to symptomatic thrombocytopenia.

Redistribution of thrombocytes (in trauma, epylepsia, anaphylactic shock, etc.) accompanied by thrombocytopenia.

Increased expenditure of thrombocytes in local and generalized intravascular blood clotting may cause thrombocytopenia.

Thrombocytopathy is characterized by affected function of platelets due to the suppressive effect on bone marrow: a viral infection, cytostatic or radiation therapy, poisoning by the chaemical substances, metaplasia of the bone marrow, endogenous intoxication, leukemia, lymphoma, pancytopenic syndrom, aplastic anemia.

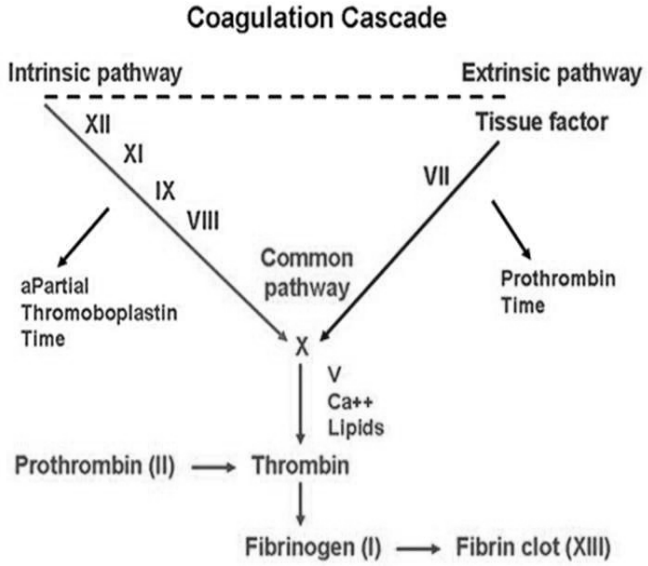
Primary thrombocytopenia has hereditary origin: idiopathic thrombocytopenic purpura (Werlhof's disease).

Primary thrombocytopathy has hereditary origin: von Willebrand disease, Glanzmann thrombasthenia.

2. Coagulopathy is characterized by bleeding syndrom in some pathological situation.

Factors of the coagulation and fibrinolysis pathway is presented on *Picture 4.1*.

The normal clotting process depends on the interplay of various proteins in the blood. Coagulopathy is a disease or condition affecting the blood's ability to coagulate (*"*Merriam-Webster.com Medical Dictionary*,* Merriam-Webster, https://www.merriam-webster.com/medical/coagulopathy. 2021). It is a condition in which the blood's ability to form clots is impaired. This condition can cause a tendency toward prolonged or excessive bleeding which may occur spontaneously or following an injury of medical and dental procedures.



Clotting Factors in Blood and Their Synonyms

Clotting Factor	Synonyms
Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight kininogen	Fitzgerald factor; HMWK (high-molecular-weight) kininogen
Platelets	

Picture 4.1. Factors of coagulation and fibrinolysis pathway

Etiology of defect in blood-clotting is multifactorial. The physiology of coagulation undergoes alteration due to various factors, including quantitative defects of the integral components of the coagulation and qualitative defects of the integral components of coagulation. Risk factors are malignancy-related hypercoagulable state, hormone replacement therapy, inflammation, infection with certain pathophysiologic process – hypothermia, acidosis, and shock which generally play important roles.

Iatrogenic coagulopathy resulted from using pharmacolodical agents with antiplatelet effect like aspirin, clopidogrel, ticagrelor and anticoagulants like warfarin, heparin, low molecular weight heparin, rivaroxaban, apixaban, dabigatran, fondaparinux amongst others for various commonly encountered clinical conditions like cardiac stenting/ percutaneous coronary intervention, atrial fibrillation, deep venous thrombosis, pulmonary embolism, and many more. The way these medications affect the functionality of the various components of clotting cascade can help patients with their clinical conditions. However, it can lead to bleeding in cases of inappropriate dosage, non-compliance, medication interactions.

Coagulopathy may be caused also by reduced levels or absence of blood-clotting protein, known as clotting factors or coagulation factors due to the hereditary origin:

• congenital affibrinogenemia (absence of fibrinogen in the blood) and dysfibrinogenemia (structural defects of fibrinogen molecules);

• haemophilia A (deficiency of anti-hemophilic globulin coagulability factor VIII), hemophilia B (coagulation factor deficiency IX) and hemophilia C (thromboplastin deficiency – factor XI).

3. The vasopathy is syndrome characterized by bleeding sings due to damage of blood vessel walls and is classified as vasculitis.

Etiology of vasculitis isn't fully understood. Vasculitis refers to a heterogenous group of disorders in which there is inflammation in blood vessel walls. Possible triggers for this immune system reaction include: infections, such as hepatitis B and hepatitis C; immune system diseases, such as rheumatoid arthritis, lupus and scleroderma? reactions to certain drugs; blood cancers.

Three possible mechanisms of vascular damage are: immune complex deposition, antineutrophil cytoplassmic antibodies (humoral response) and T-lymphocyte response.

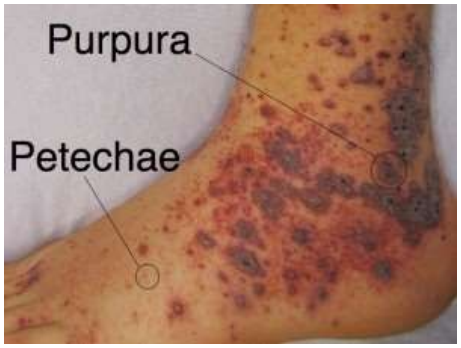
To vasculitis refer such diseases: Henoch-Schonlein purpura, Kawasaki disease,Takayasu's arteritis, Buerger's disease, granulomatosis with polyangiitis and others.

Symptoms and signs of bleeding (hemorrhagic) syndrome.

The first signs are the tendency to hemorrhages in the skin and subcutaneous tissue. They are caused by bleeding underneath the skin.

Purpura (from the Latin, purpura, meaning "purple") is the appearance of red or purple discolorations on the skin that do not blanch on applying pressure. Small red-violet spots appear on the skin of the legs in the region of the ankles and on the soles – petechiae (capillary hemorrhage). Purpura measure 0.3–1 cm, whereas petechiae measure less than 3 mm, and ecchymoses greater than 1 cm (*Picture 4.2*, *4.3*).

Subcutaneous hematomas are characteristic of most acquired coagulation disorders, including after prolonged use of anticoagulant drugs.



Picture 4.2.
Skin signs of hemorrhagic syndrome

Picture 4.3.
Subcutaneous hematomas

Hemorrhages in the skin and subcutaneous tissue depend on types of bleeding which may be capillary, hematologic or mixed. Thus, in the case of deficiency of such clotting factors as prothrombin, proaccelerin, proconvertin, Stewart-Prower factor (in von Willebrand disease, thrombocytopenia or dysfibrinogenemia), small red-violet spots appear on the skin of the legs in the region of the ankles and on the soles – petechiae (capillary hemorrhage).

If there is a deficit of antihemophilic globulin, bruises (ecchymoses) constantly appear. Subcutaneous hematomas occur in hemophilia and other acquired coagulation disorders.

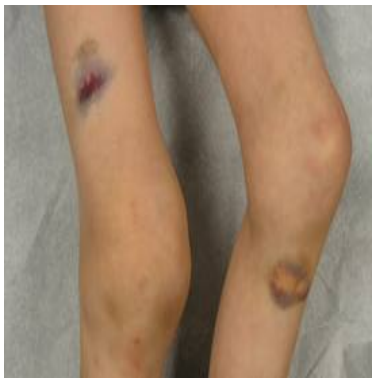
Symptoms of clotting disorders are expressed in unreasonable bleeding of any damage, including minor injuries, difficulties with stopping blood (*Picture 4.4)*.

Hemorrhagic syndrome may appear quickly emerging bruises on the body, which are sometimes accompanied by bleeding gums from the nose (*Picture 4.5*).

Picture 4.4. Unreasonable bleeding from minor injuries

Picture 4.5. Bleeding from the nose

In hemophilia, blood flows not only into the tissues of the abdominal organs and muscles, but also to the joints (hemarthrosis). This causes necrosis of bone tissue to reduce the content of calcium in it and subsequent functional complication of the musculoskeletal system (*Picture 4.6)*.



Picture 4.6. Subcutaneous hematomas and hemarthrosis in hemophilia

In addition significant loss of blood during menstruation (menorrhagia), prolonged bleeding even with minor injuries to the smallest vessels. There may be frequent reddening of the eye proteins, melena (black feces) can also be observed, which indicates bleeding localized in the digestive tract.

The causes of bleeding disorders.

The causes of bleeding disorders include the following genetic and congenital abnormalities:

- Idiopathic thrombocytopenic purpura (Werlhof's disease).
- Von Willebrand disease.
- Glanzmann's thrombasthenia.
- Hemophilia.
- Osler-Rendu disease.
- Henoch-Schonlein purpura.
- Childhood vasculitis.

4.2. Idiopathic thrombocytopenic purpura (Werlhof's disease).

Idiopathic thrombocytopenic purpura is most common form of bleeding disorders due to the quantitative abnormalities of platelets. Because a number of platelets reduce in the blood stream, their function is impaired.

Epidemiology of idiopathic thrombocytopenic purpura.

The prevalence of idiopathic thrombocytopenic purpura is an average of 60–100 cases per 1 million persons. The incidence curve has two peaks – in the age group 20 years and in the age group after 50 years. Women suffer more often than men. In children, boys and girls such disease are detected with equal frequency.

Etiology of idiopathic thrombocytopenic purpura.

Etiological factor in initiating the disease is usually not specified. Relationship exists between the occurrence of idiopathic thrombocytopenic purpura and viral infections (Epstein-Barr virus, HIV), a bacterial infection (septicemia). There is a clear relationship of idiopathic thrombocytopenic purpura to the reception of pharmacological agents. The most frequent causes in this group are oral diuretics (including such medications as derivatives of thiazide and furosemide), followed by quinidine, indomethacin, phenylbutazone, sulfa drugs. Causes of decreased platelet production due to Infiltration of bone marrow are leukemia, multiple myeloma, megaloblastic anemia.

Pathogenesis of idiopathic thrombocytopenic purpura.

The disease is caused by enhanced and accelerated destruction of platelets as a result of autoantibodies directed against their own platelets. Reason of autoaggression is unknown. Decreased platelet production result from such mechanisms: failure of megakaryocyte, defect of maturation, excessive platelet consumption and their sequestration in an enlarged spleen. Increased sequestration and destruction of platelets in the spleen is a major pathogenetic mechanism.

Clinical features of idiopathic thrombocytopenic purpura.

Idiopathic thrombocytopenic purpura more commonly affects females at an early age. The main complaints are easy bruising in skin and bleeding from mucosa with sudden onset after easy trauma and sometimes spontaneously.

Very often symptoms are the bleeding from nose, gastrointestinal tract, lung and kidney hemorrhage, in women menorrhagia.

The course of disease is chronic, with remissions and relapses.

On objective examination.

• General patient’s condition is satisfactory.

• If bleeding persists for more than some days resulted acute posthemorrhage anemia. The patient’s condition become grave and required immediately treatment.

• The main clinical signs are the presence features of skin bruising different size: petechiae, purpura and even hematoma, which located at the anterior part of trunk and extremities.

• According to the term of bruising appearance may be change of color with different tint: read, blue, green and yellow.

• Skin bruising sometimes accompanied with profuse mucosa bleeding and become insidious character because occur posthemorrhage anemia.

• Splenomegaly is observered in about 10 % of the cases.

There are differences in the course of the disease in children and adults. Idiopathic thrombocytopenic purpura is acute disease for children. Spontaneous recovery occurs within 6 months.

Idiopathic thrombocytopenic purpura is a chronic disease in adults. Spontaneous recovery is very rare. Hemorrhagic bubbles may appear in the mouth and other mucous membranes. In severe forms may occur renal bleeding, bleeding in the sclera or retina of the eye, bleeding in the ovaries (apoplexia ovarii), which simulates an ectopic pregnancy. The most dangerous complication is a brain hemorrhage and hemorrhage in subarachnoid space. This is the most common cause of patient's death.

Clinical management of patients with idiopathic thrombocytopenic purpura.

Form of the disease, which occurs without hemorrhage and with the amount of platelets above the critical number should be under observation at a hematologist. The indication for initiation of therapy is increased bleeding.

Indications for hospitalization include:

1. The presence of pronounced hemorrhagic syndrome, which requires the appointment of high and moderate doses of steroid hormones or other treatments.
2. Acute posthemorrhagic anemia.
3. Perform a splenectomy.
4. The need for other operational interventions (ovarian apoplexy, etc.).

Prognosis.

With adequate therapy prognosis of patients with idiopathic thrombocytopenic purpura is favorable. Fatality rate is about 10 %. The main cause of patient's death is bleeding in the brain.

Diagnostics.

To determine the causes of the disease and choose effective treatment, doctor should to conduct a series of studies: complete blood count possible to evaluate the number of red and white cells, especially thrombocytes; bone marrow examination, coagulogram tests, platelet specific tests.

Clinical blood examination:

• platelets count is usually $10–50\times10^9$/l;

• blood film shows reduced numbers of platelets.

Usually symptoms appear at lower number of thrombocytes $<20.0\text{x}10^9$ /l, but sometimes at a level from 30.0 to $80.0\text{x}10^9$ per liter.

Bone marrow examination usually shows increased number of megakaryocytes.

Coagulogram tests evaluate specific events in the coagulation cascade. They help in the determination of where the deficiency exists in the intrinsic,

extrinsic, or the final common pathways as well as identification of qualitative or quantitative defects of the specific clotting factors. Evaluation of the bleeding duration is possible to determine how quickly blood vessels clog after a puncture. Such blood tests are necessary:

- prothrombin time assesses the extrinsic and common coagulation cascade function;
- thrombin time evaluates the formation of fibrin in the final common pathway of coagulation;
- activated partial thromboplastin time assesses the intrinsic and the common pathways of coagulation;
- reptilase time and the various fibrinogen assays assess the fibrin formation step;
- antithrombin III is glycoprotein-anticoagulant blood, which inhibits the process of its coagulation;
- international normalized ratio.

Platelet specific tests. Analysis of platelet aggregation (This study helps evaluate the ability of platelets to attach to each other):

- bleeding time;
- the aggregation of platelets with stimulation of adenosine diphosphate (ADP);
- light transmission platelet aggregation;
- impedance platelet aggregation;
- global thrombosis test;
- thromboelastography;
- flow cytometric analysis of platelet function.

Sensitive tests can demonstrate antiplatelet IgG either alone or with complement, on the platelet surface or in the serum in most patients.

Instrumental diagnostics (fluoroscopy, ultrasound, MRI) can be used to clarify the condition of the liver, spleen, intestine or brain.

4.3. Von Willebrand disease.

Von Willebrand disease was first described in the medical literature in 1926 by Erik von Willebrand, who published report about observation of hereditary form of bleeding in some relatives the same family. The hemorrhagic signs were: bleeding from the oral mucosa, nose, gums. During research investigation Erik von Willebrand decteted glycoprotein that performs functions in primary hemostasis: it acts as a bridging molecule at sites of vascular injury for normal platelet adhesion, and under high shear conditions, it promotes platelet aggregation. He supposed that low level this glycoprotein is responsible for bleeding appearance reported disease. This glycoprotein was named von Willebrand factor and pathology named von Willebrand disease.

Epidemilogy von Willebrand disease.

The most spread disease in bleeding syndrom and prevalence in the general population 100 cases per 1 million persons. Von Willebrand disease is regis-

tered in 1 % of population. Such disease is the most common of the inherited bleeding disorders, with an estimated prevalence in the general population of 1 percent by laboratory testing. Symptomatic von Willebrand disease is less common, approximately 0.01 percent, as estimated in hemostasis clinics.

Cause of von Willebrand disease.

Disease is caused by various quantitative and qualitative defects in the synthesis of von Willebrand factor, which is a plasma protein that contains many domains and each domain has its own function: initiate the adhesion of platelets to the damaged wall of the vessel and stabilizes the circulating clotting factor VIII due to complexation with him and perfoms thrombus formation and blood coagulation. The usual cause of von Willebrand disease is an inherited abnormal gene that controls von Willebrand factor. Subdivisions of von Willebrand Disease: von Willebrand syndrome type 1, von Willebrand syndrome type 2A, von Willebrand syndrome type 2B, von Willebrand syndrome type 2M, von Willebrand syndrome type 2N, von Willebrand syndrome type 3.

Pathogenesis.

A bleeding disorder called von Willebrand disease occurs when von Willebrand factor is deficient or qualitatively abnormal. The disease is usually an autosomal dominant inherited disorder, which means that an abnormal gene from only one parent to be affected. The most severe form of the condition is autosomal recessive, which means both parents have to pass an abnormal gene to children.

Most cases of von Willebrand disease are caused by mutations of the von Willebrand factor gene. In the von Willebrand factor type 1 and most forms of type 2, the mutation is inherited as an autosomal dominant trait. In some cases, the mutation occurs randomly without cause (spontaneously) with no previous family history (i.e., new mutation). The von Willebrand factor type 3 and some cases of the von Willebrand factor type 2 are inherited as an autosomal recessive trait.

In type 1 is partial quantitative defect of von Willebrand factor, in type 2 – qualitative defects of structure and function of von Willebrand factor, in type 3 – complete absence von Willebrand factor. Every type reflects the pathophisiological mechanism which correlate with clinical manifestation and treatment such patients.

In patients with von Willebrand disease due to low levels of von Willebrand factor platelets cannot stick together properly nor attach themselves normally to the blood vessel walls when an injury has occurred resulted to thrombopathy and coagolopathy – mixed type of bleeding syndrom.

This interferes with the clotting process and can sometimes cause uncontrolled bleeding. Rarely, von Willebrand disease can develop later in life in people who didn't inherit an abnormal gene from a parent. This is known as acquired von Willebrand syndrome, and it's likely caused by an underlying medical condition.

Clinical features von Willebrand disease. The most frequent symptoms von Willebrand disease: bleeding from the oral mucosa, nosebleeds (epistaxis) that don't stop within 10 minutes, bleeding from the gums, bleeding after tooth extrac-

tions, easy bruising or lumpy bruise, easy bruising and prolonged bleeding from minor cuts, may also occur easy formation of hematomas. Some individuals may experience heavy, prolonged bleeding following trauma, or surgery manipulation. More than half of patients have hemarthrosises which like hemophilia.

Complications. Women may experience heavy and prolonged bleeding during their menstrual period (menorrhagia) or during and following childbirth. If left untreated, heavy menstrual bleeding may lead to anemia and iron deficiency. Rarely, von Willebrand disease can cause uncontrollable bleeding, which can be life-threatening and can include gastrointestinal bleeding, solid swellings of congealed blood (hematomas). Bleeding into the muscle and joints (hemarthrosis) can cause progressive joint damage and degeneration.

Laboratory testing. Individuals may undergo standard blood screening tests including a complete blood count, which may be normal or may show microcytic anemia or low platelet count, especially in individuals with von Willebrand disease type 2B.

Screening coagulation tests: activated partial thromboplastin time; prothrombin time; thrombin time.

Special tests: Von Willebrand factor (VWF) activity assays, VWF antigen immunoassay, VWF ristocetin cofactor assay, VWF Collagenn Binding Assay, ristocetin-induced platelet aggregation assay.

Treatment of von Willebrand disease

The specific treatment of von Willebrand disease varies depending on the subtype and severity of the disorder. Minor bleeds such as nosebleeds, small bruises, and minor cuts may not require therapy. In mild cases, individuals may only require treatment before undergoing surgery or a dental procedure or following trauma or injury. Individuals with von Willebrand disease should receive prompt treatment during severe bleeding episodes.

Synthetic analogue of vasopressin is desmopressin (DDAVP). DDAVP is used intravenously, subcutaneously or intranasally for relief of hemorrhages. Injection to repeat in 12–24 hours, but after 3–4 injections therapeutical effect is reduced, since the store in endothelial cells depleted. Next courses of injections sgould be provide in 7–10 days. There is a form of DDAVP for intranasal use as a spray. Apply one spray in each nostril in patients weighing less than 50 kg and two sprays – with more than 50 kg.

Antifibrinolitiks are derivatives of aminocaproic and tranexamic acid.

Replacement therapy: fresh frozen plasma, cryoprecipitate.

The U.S. Food and Drug Administration have approved the VWF/FVIII replacement therapies (concentrates of factor VIII, with a high content of VWF) for the treatment of individuals with von Willebrand disease. Replacement therapy is usually administered through intravenous infusion.

For prevention von Willebrand disease should be consider genetic counseling persons with presence such patients among relatives, in women prolonged

bleeding during their menstrual period (menorrhagia), complicated delivery accompinied with bleeding, family history of this condition.

4.4. Glanzmann's thrombasthenia.

Glanzmann's thrombasthenia is a hereditary disease characterized by qualitative inferiority of platelets in normal quantity and manifested bleeding (ecchymosis, and hematoma).

Development of the disease is associated with abnormalities of the glycoprotein IIb/IIIa, which leads to insufficient retraction of the thrombus, disruption of the morphology of platelets, reduced platelet adhesion, disruption of platelet aggregation, blood clotting time and platelet count normal.

Glanzmann's thrombasthenia: clinic, treatment.

Glanzmann's thrombasthenia has the same clinical picture as thrombocytopenic purpura.

In the treatment of Glanzmann's trhombastenia use drugs that improve the adhesively-aggregation properties of platelets: aminocaproic acid, etamzilat; trifosadenin (ATP), magnesium preparations. In addition, prescribe calcium chloride, askorutin, local hemostatic medications.

Prognosis. The disease incurable, but with age, bleeding may be reduced.

4.5. Hemophilia

Hemophilia is a hereditary disease associated with blood coagulation disorders.

Epidemiology of hemophilia. It is a rare disease, 1 in every 20000 newborn boys. Worldwide, there are about 350 000 people with hemophilia.

Etiology of hemophilia.

Hemophilia is a hereditary disease. Hemophilia is caused by a mutation or change, in one of the genes, that provides instructions for making the clotting factor proteins needed to form a blood clot. This change or mutation can prevent the clotting protein from working properly or to be missing altogether. These genes are located on the X chromosome. Males have one X and one Y chromosome (XY) and females have two X chromosomes (XX). Males inherit the X chromosome from their mothers and the Y chromosome from their fathers. Females inherit one X chromosome from each parent. Thus, males can have a disease like hemophilia if they inherit an affected X chromosome that has a mutation in either the factor VIII or factor IX gene. A female with one affected X chromosome is a carrier of hemophilia. Usually the disease affects men (sex-linked inheritance), women are the carriers of hemophilia. Women usually do not get sick, but may be mothers of ill sons or daughters carriers. Inheritance of hemophilia is sex-linked character males are damaged while females act as carrier.

A sick gene can be transmitted from generation to generation through the female line and women are not ill at the same time. The sick father passes the hemophilia to the daughter, who will not have any external signs of the disease.

And her daughter will give it to her son, whose hemophilia manifests itself in full picture.

Pathogenesis of hemophilia.

Hemophilia occurs as a result of low level or either absence of coagulation factor VIII, which primary synthesized by liver, but other organs such as the spleen. Kidney may also contribute to the plasma level. The factor VIII gene is localized on the X chromosome that is way the hemophilia a sex-linked disorder. All daughters of patient with hemophilia are obligate carriers and sisters have a 50 % chance of being a carrier. If a carrier has a son, he has a 50 %, chance of having hemophilia, and daughter has a 50 % chance of being a carrier. 33 % cases do not have family history.

There are several different types of hemophilia. The following ones are the most common: hemophilia A, hemophilia B (Christmas disease) and hemophilia C.

Hemophilia A (Classic Hemophilia) is caused by the lack of blood antihemophilic globulin, or coagulation factor VIII due to F8 recessive gene mutation in X-chromosome. The most common form of the disease is, according to statistics, 80–85 % of all cases of the disease. On the average, one baby out of 10 thousand is sick. About 70 percent of people with hemophilia A have the severe form.

Hemophilia B or Christmas disease. This type is caused by a lack or decrease of clotting factor IX. It is noted as much more rare: the risk of getting sick is six times lower than in case of variant A.

Hemophilia C (Rosenthal syndrome). There is no coagulation factor IX. It is inherited as a recessive trait. This species is unique: it is peculiar to both men and women.

Moreover, most often the Ashkenazi Jews are ill (which is generally uncharacteristic for any ills: they are usually international and equally "attentive" to all races, nationalities.). The clinical feature similar to the hemophilia A but bleeding is usually not as severe because factor IX is more stable than factor VIII.

Clinical feature of hemophilia.

Hemophilia is a hereditary disease associated with coagulation disorders, in this disease arise bleeding into joints, muscles and internal organs. If a person has bleeding problem a physician will ask about the personal medical history, as this can help to identify the cause. The main patients complaints are spontaneous increased domestic bleeding of the nasal, mouth and gums even when cleaning teeth. Bleeding into the skin, muscle and soft tissue cause a build-up of blood in the area (hematoma). Hemophilia manifests itself as the formation of large edematous hematomas from absolutely insignificant effects (for example, pressing the finger).

Bleeding into the joints is known as hemarthrosis begin spontaneously without apparent trauma. This can cause pain, swelling, tightness and enlargement in the joints; it often affects the knees, elbows, and ankles that can lead to chronic joint disease. May be bleeding as a result of trauma or surgery and re-

peated bleeding from a seemingly already healed wound. Bleeding after having shots, such as vaccinations is observed. The patient complains on the presence of blood in the urine or stool. In case such complaints a physical examination of patients will be carried out.

On objective examination.

General patient's condition is usually satisfactory.

In case of prolonged and recurrent hemorrhages and loss of large amount of blood general condition may be middle, grave or grave.

The posture of the patients is active with restriction due to the pain and walking difficulties in damaged joints and muscles caused by spontaneous bleeding.

The color of the skin and visible mucosa as a rule is pallor, with hemorrhages lesions: petechia, ecchymoses, and hematoma. Joint deformity and crippling are observed.

The course of hemophilia.

The course of disease is characterized by bleeding in the head of an infant after a difficult delivery and early onset in babies about 6 months old, when superficial bruising or a hemarthrosis may occur. Bleeding after circumcision which defined as surgery performed on male babies to remove the hood of skin, called the foreskin, covering the head of the penis. The spontaneous bleeding episodes are observed entire the patient life and they may be manifested by nasal, pulmonary gastrointestinal, genitourinary systems hemorrhage and hemorrhages in the joints. Bleeding is hard to stop.

Complications of hemophilia.

Poor blood coagulability is a rather dangerous violation, which can cause dangerous health consequences.

The joints most commonly damaged are: knees, elbows, ankles and hips. Bone destruction occurs due to repeated sub-perioctal hemorrhages. The defects undergo neoossification causing expansion and pathological fractures in the bones. The deformities of joints and bones are specific signs of hemophilic patients.

Muscle hemotomas are also characteristic of hemophilia. Secondary to hematomas appear atrophy of muscles.

Patients with severe hemophilia are disability due to frequent bleeding into joints – hemarthrosis and muscle tissue – hematoma.

Bleeding in the absence of obvious causes from the nose, eyes, especially from pulmonary, gastrointestinal, genitourinary systems, after losing a tooth, operative and postoperative state which frequent hard to stop are dangerous and lead to posthemorrhagic anemia. Death can occur if the bleeding cannot be stopped or if it occurs in a vital organ such as the brain.

Bleeding in the brain can cause seizures and paralysis. Intracranial hemorrhage is rare, but in severe and prompt case it may be fatal outcome.

Hemophilia dramatically increases the risk of dying from a brain hemorrhage and other vital organs, even with minor injuries.

Detection of hemophilia.

If hemophilia is suspected a physician should ask about the person's family a presence in relatives the similar symptoms.

Blood tests are important to diagnosing hemophilia.

Clinical blood analysis can provide information about hemorrhagge anemia. Examination of erytrocytes in urine (hematuria) and traces blood in feces (melena) due to the bleeding from gastrointestinal, genitourinary systems. Hematuria is more frequently than gastrointestinal bleeding.

Blood tests show how long it takes for blood to clot, the levels of clotting factors, and which clotting factors, if any, are missing. Blood test results can identify the type of hemophilia and its severity.

For a more accurate diagnosis, it may be necessary to define some tests: thrombin time, prothrombin index, activated partial thromboplastin, amount of fibrinogen, factor clotting VIII, factor clotting IX. In patients with hemophilia there are changes in these parameters:

- blood coagulation time is raised;
- activated partial thromboplastin time is raised;
- bleeding time and prothrombin time tests normal;
- factor VIII dolling assay (VIII C) reduced;
- factor IX clotting assay is reduced.

X-ray examination:

- broadening of femoral epicondyles;
- sclerosis, osteophyte and bony cists;
- atrophy of muscles.

The computer tomography scan: intracerebral hematoma.

Often, these tests are also accompanied by DNA testing.

Management the patients with hemophilia.

Treatment should be started as soon as possible, only in this case it will be possible to achieve good results. If this is not done, complications such as: bleeding into the brain, bleeding in the digestive tract, bleeding and pain in the joints.

Not allowed intramuscular, subcutaneous, intradermal injections. All medications were injected into a vein or taken in through the mouth.

Hemophilia is treated with replacement therapy. This involves giving or replacing the clotting factors that are too low or missing in a patient with the condition. Patients receive clotting factors by intravenously injection. Clotting factor treatments for replacement therapy can be derived from human blood, or they can be synthetically produced in a laboratory. Synthetically produced factors are called recombinant clotting factors. Indications for the introduction of antihemophilic drugs: bleeding of any severity and location, swelling and joint pain, suspicion of internal bleeding, injury to a violation of skin integrity; for any surgical

operation. Recombinant clotting factors are now considered the treatment of choice because they further reduce the risk of transmitting infections that are carried in human blood. Some patients will need regular replacement therapy in order to prevent bleeding. This is called prophylactic therapy. This is typically recommended for people with the severe forms of hemophilia A.

There is no way to cure hemophilia, but there are ways to reduce the risk of excessive bleeding and to protect joints.

In the future, gene therapies may be available.

For pregnant women who are carriers of hemophilia, doctors are able to test the fetus for the condition after 10 weeks of pregnancy so called prenatal diagnostics.

4.6. Henoch-Schonlein purpura.

Henoch-Schonlein purpura is the vascular disorders (vasophaty) characterized by inflammation and hemorrhagic signs in the small blood vessels in skin, joints, kidneys, intestines etc. Vascular disorders resulting in abnormal hemostasis are classified into two major groups: inherited and acquired. Henoch-Schonlein purpura belongs to acquired vascular disorders.

Etiology of Henoch-Schonlein purpura. Etiology is still unknown, but it was observed that this disease often begin after the ingestion of certain drugs or as a result of a group A streptococcal infection.

Pathogenesis of Henoch-Schonlein purpura.

Pathogenesis may considered as hypersentivity response to the external factors with development of allergic reaction associated with acute inflammation of the small blood vessels and disorders of microcirculation, resulting in increased vascular permeability and easy bleeding.

Clinical features of Henoch-Schonlein purpura.

The specific signs are the appearance on the skin rash (purpura) accompanied with itching. Reddish-purple small pinpoint hemorrhages that look like bruises and develop on the buttocks, legs and feet. The rash can also appear on the arms, face and trunk and may be worse in areas of pressure, such as the sock line and waistline. The mucosa doesn't affect in adults. During severe course of disease appear the additional points anywhere in the body with swelling and necrosis.

The abrupt onset with pain in the joints and elevated temperature are the features of disease. People with Henoch-Schonlein purpura often have pain around the joints, mainly in the knees and ankles which swollen, sore joints (arthritis). Joint pain sometimes precedes the classical rash by one or two weeks. These symptoms subside when the disease clears and leave no lasting damage.

Henoch-Schonlein purpura can also affect the kidneys. In most cases, this shows up as protein or blood in the urine. The hematuria may be the additional sign of disease. Usually this goes away once the illness passes, but some people develop persistent kidney disease. After two weeks the lesions disappeared without skin changing.

Many patients with Henoch-Schonlein purpura develop belly pain, nausea, vomiting and bloody stools. These symptoms sometimes occur before the rash appears and indicate on the involvement of gastro-intestinal tract.

Examination of the patients.

Clinical blood analysis: normal erythrocytes and platelets count; leucocytes count increased; regenerative nuclear shift to the left; erythrocyte sedimentation rate accelerated.

Treatment:

- injection use of vitamin K;
- preparations for improving coagulation;
- transfusion of frozen blood plasma.

4.7. Childhood vasculitis.

4.7.1. Henoch-Schonlein purpura.

In 2005 the European League Against Rheumatism (EULAR) and the Paediatric Rheumatology European Society (PReS) developed the first paediatric-specific classification of vasculitis. Classification of childhood vasculitis is based on clinic, the size of predominantly affected vessels and the histopathology of inflammatory infiltrates.

Table 4.1

EULAR/PReS classification of pediatric vasculitis

Type of vessel	Vasculitis category
Predominately large vessel	Takayasu arteritis
Predominately medium vessel	Childhood polyarteritis Nodosa. Cutaneous polyarteritis. Kawasaki disease
Predominately small vessel	**Granulomatous:** Wegener's granulomatosis* Churg-Strauss syndrome. **Non-granulomatous:** Microscopic polyangiitis. Henoch-Schonlein purpura. Isolated cutaneous leucocytoclastic vasculitis. Hypocomplementemic urticarial vasculitis
Others	Behçet disease. Vasculitis secondary to infection, malignancy, drugs. Vasculitis associated with connective tissue disease. Isolated vasculitis of the central nervous system. Cogan syndrome. Unclassified

The two most common forms of the primary vasculitis in children are Henoch-Schonlein purpura and Kawasaki disease, accounting for 49 % and 23 % of all childhood vasculitis, respectively.

Henoch-Schonlein purpura **(**also known as anaphylactoid purpura or purpura rheumatica, immunoglobulin A vasculitis**)** is an acute immunoglobulin A – mediated disorder characterized by a systemic vasculitis, which affects the small blood vessels of the skin, causing a distinctive rash called purpura, the kidneys, the joints, the gastrointestinal tract, and, rarely, the central nervous system and the lungs.

Epidemiology of Henoch-Schonlein purpura.

Henoch-Schonlein purpurais the most common form of vasculitis in children, affecting 10–20 per 100000 children every year under the age of 17 and the peak age of osen is between 4 and 6 years. Boys are affected more commonly than girls with a ratio of approximately 2 to1. Caucasians have the highest incidence and African Americans have the lowest.

Etiology of Henoch-Schonlein purpura.

The cause of the disease has not been established, but in some children its association with previous viral or bacterial infections within the past 2–4 weeks *(*β-hemolytic streptococcus, staphylococcus aureus*,* influenza, parainfluenza, Epstein-Barr virus, adenovirus, parvovirus, and mycoplasma), preventive vaccinations, administration of γ-globulin, cold exposure, drug and food allergies, helminthiasis has been recorded.

Autoimmune risk factors such as complement deficiencies and hereditary fever syndromes, such as Familial Mediterranean Fever syndrome, may predispose a child to Henoch-Schonlein purpura

Pathogenesis of Henoch-Schonlein purpura.

Henoch-Schonlein purpura is systemic disease caused by generalized aceptic inflammation of small vessels. Arterioles, capillaries with more or less deep destruction of the walls and perivascular edema with cellular infiltration of erythrocytes and neutrophils are observed. Immunoglobulin A-containing complexes deposit in small vessels and cause immune cell invasion, complement and endothelial activation. These phenomena cause microthrombovasculatis with fibrinoid necrosis, perivascular edema, hemorrhages.

Clinical features of Henoch-Schonlein purpura.

Henoch-Schonlein purpura typically has a prodrome, which includes the general symptoms, such as fever, headache, fatigue, poor appetite, diffuse pain. Subsequently, after the prodrome the following most common symptoms develop: non-blanching vascular rashes – purpura (95–100 % of cases), arthralgia/arthritis (60–84 %), especially involving the knees and ankles, abdominal pain and/or bloating (35–85 %), subcutaneous edema (20–50 %), scrotal edema (2–35 %).

Erythematous, macular, or urticarial rashes predominantly occur on the ankles and lower legs in older children and adults; on the back and buttocks in toddlers; and on the face, trunk, and upper extremities in younger children. Localized subcutaneous edema is a common feature in children less 3 years old, usually occurring in dependent and periorbital areas. In adults it usually involves the dorsum of the hands. The rash may be itchy but is rarely painful.

The main differences between children and adults appear to be the chronicity and severity of the eruption in the latter population; bullae and ulcers are more common in adults, and cutaneous exacerbations may be seen for 6 months or longer. Younger children tend to have a better outcome than older children and adults.

Less than 10 % patients will develop more severe renal involvement, haematuria/proteinuria, hypertension, requiring kidney biopsy and more intensive therapy and monitoring.

The EULAR/PReS classification criteria are shown in *Table 4.2*.

Arthritis affects 3/4 of children and the most commonly affected joints are the knees and ankles. The arthritis is usually transient, oligoarticular, self-limited, and non-destructive. Joints may be swollen, tender, and painful. Young children with lower extremity involvement will refuse to walk.

The abdominal syndrome develops approximately in 2/3 of children and is characterized by sudden cramping, very sharp pains, which are more often localized near the navel, may be accompanied by melena, nausea, repeated vomiting. Gastro-intestinal manifestations may precede the purpura by up to 2 weeks in 20 % of children. Intestinal bleeding, manifested as gross or occult blood per rectum, occurs in approximately 1/3 of children, bowel perforation and peritonitis in 2–3 % of patients. Intussusception occurs in 1 to 5 % of children and is mostly ileo-ileal in location.

Table 4.2

EULAR/PReS classification criteria for Henoch Schonlein purpura

Purpura or petechiae with lower limb predominance and at least one of the following:
• arthritis or arthralgias;
• abdominal pain;
• histopathology demonstrating IgA deposition;
• renal involvement (hematuria or proteinuria).

Renal syndrome occurs in 1/3–1/2 of children and the most common manifestation is microscopic hematuria with or without proteinuria. Renal disease rarely precedes the onset of rash. Children may present with nephritic or nephrotic syndrome, or rarely renal failure. The majority of children who develop renal disease do so within the first 6 weeks and 97 % within 6 months.

Unusual clinical manifestations of Henoch-Schonlein purpura may include edema of scrotum, eyes, or hands, pulmonary hemorrhage, seizures, stroke, and

mental status changes. The mean duration of symptoms is 3 to 4 weeks and up to one-third of children have at least 1 recurrence.

The diagnosis of the disease is based on the presence of characteristic hemorrhagic rashes of the vasculitic-purple type, arthralgias, abdominal and renal syndromes, increased capillary fragility (positive pinch and tourniquet tests).

Examination of the digestive system in abdominal syndrom can reveal bloating, tenderness on palpation of various parts of the abdomen and tension of the abdominal wall.

Henoch-Schonlein purpura should be distinguished from other causes of purpura in childhood including acute hemorrhagic edema of infancy, immune thrombocytopenic purpura, acute post-streptococcal glomerulonephritis, hemolytic-uremic syndrome, disseminated intravascular coagulation, infections and hypersensitivity vasculitis.

*Laboratory examination***.**

Laboratory finding are unspecific and include mildly elevated inflammatory parameters (erythrocyte sedimentation rate and C-reactive protein), moderate leukocytosis, neutrophilia, eosinophilia, thrombocytosis. In urinalysis are revealed hematuria with mild-to-moderate proteinuria. Normal or slightly reduced serum C3 and/or C4, the absence of high-titer autoantibodies (particularly anti-neutrophil cytoplasmic antibodies ANCA and anti-neutrophil antibodies ANA) and, in 50 % of all cases, elevated serum IgA and/or IgM. Plasma D-dimer may be substantially increased. Plasma thrombin-antithrombin (TAT) complex, prothrombin fragment (PF)-1, and PF-2 may be abnormal. Prothrombin time and activated partial thromboplastin time may be reduced. cylindruria. Antistreptolysin O (ASO) is elevated in 30 % of patients.

*Henoch-Schonlein purpura.*Treatment depends on clinical presentation and organ involvement. Non-steroidal anti-inflammatory drugs or acetaminophen/paracetamol can be considered for relief from fevers, joint and abdominal pain. Treatment with corticosteroids (usually 1–2 mg/kg/day for 1 week, followed by taper over 2–3 weeks) can be considered. In life-threatening cases or acute renal failure, plasmapheresis followed by a more potent immunosuppressive agent should be considered. Other drugs are currently under investigation.

Folow-up for children presenting with Henoch-Schonlein purpura should be for at least 6 month and should include regular urine testing for proteiuria and hematuria, and a blood pressure measurement. Patient with confirmed renal involvement need long-term follow-up, this usually manifests within 3 months from the date of onset, but can present up to 12 months later.

4.7.2. Kawasaki disease.

Kawasaki disease, also known as mucocutaneous lymph node syndrome, according to EULAR/PReS classification belongs to predominantly medium-sized vessel vasculitis, especially occurring in children aged 6 months to 5 years. Boys are affected more frequently than girls, with a ratio of 1.5 to 1.8

to 2. Kawasaki disease is the second most common childhood vasculitis, accounting for 23% of all vasculitides. Kawasaki disease is the leading cause of acquired heart disease in children.

Epidemiology of Kawasaki disease.

The annual incidence in children less than 5 years old is highest among Asian populations. The Japanese incidence is 100 per 100,000 children and 69 per 100,000 children in Taiwan. In the US the annual incidence is 20 per 100,000 children. Caucasian incidence is 9–17 per 100,000 children in the UK approximately 8 per 100,000 children.

Etiology of Kawasaki disease.

The etiology of KD is unknown, but the epidemiology and clinical manifestations suggest an infectious nature or an atypical immune response to infection in genetically susceptible children.

Pathogenesis of Kawasaki disease.

An autoimmune nature of the disease is considered. In the acute phase of Kawasaki disease monocytes/macrophages and T cells produce pro-inflammatory mediators that result in endothelial inflammation and the clinical picture. Extravascular tissues can also be involved in inflammation including the upper respiratory tract, pancreas, biliary tract, kidneys, mucous membranes and lymph nodes.

Clinical picture of Kawasaki disease.

The EULAR/PReS classification criteria for Kawasaki disease are shown in *Table 4.3*.

Table 4.3

The EULAR/PReS classification criteria for Kawasaki disease

EULAR/PReS classification criteria for Kawasaki disease:
1. Bilateral conjunctival injection.
2. Changes of the lips and oral cavity.
3. Cervical lymphadenopathy.
4. Polymorphous exanthem.
5. Changes in the peripheral extremities or perineal area.

The acute stage of Kawasaki disease is characterized by fever more than 38.5°C, which is minimally responsive to antipyretics, and can last up to 14 days; subacute stage of 2–4 weeks, and a convalescent stage can last months to years. The disease is associated with irritability, sometimes lethargy, or occasional colic-like abdominal pain. Usually within one or two days of the onset of fever, bilateral nonexudative conjunctival injections is developed.

Signs of Kawasaki disease:

- oral mucous membrane findings are seen in approximately 90 % of cases;
- polymorphous rash in 70 to 90 %;
- extremity changes in 50 to 85 %,;

• ocular changes in 75 %;

• cervical lymphadenopathy in 25 to 70 %.

There is no typical order of appearance of these findings. Some patients have only developed fever and cervical lymphadenopathy.

Coronary artery aneurysm occurs in 25 % of untreated patients, and 4 % – with treatment. Children younger than 12 months are at the highest risk for coronary aneurysms.

Atypical Kawasaki disease occurs in persons with fever lasting five or more days and with two or three of these findings.

Diagnosis of Kawasaki disease is based on criteria summarized below:

Fever of unknown origin for more than 5 days plus 4 days of the following if not explained by another condition. The diagnosis can also be made on day 4 in the presence of ≥ 4 principal clinical criteria:

bilateral conjunctivitis (80–90 %);

change to oropharyngeal mucous membranes, including injected and/or fissured lips, strawberry tongue and enanthema (80–90 %);

palmar and/or plantar erythema and/or periungual desquamation (in convalescent phase (80 %);

polymorphous exanthema, primarily truncal, not vesicular (≥90 %);

cervical lymphadenopathy (at least one lymph node more than 1.5 cm (50 %).

Delayed diagnosis and treatment result in coronary artery aneurysms in up to 25% of all affected individuals.

Kawasaki disease should be distinguished from infections (Epstein Barr virus, adenovirus, echovirus, measles); toxin-mediated illnesses (toxic shock syndrome, scarlet fever), inflammatory conditions (systemic juvenile idiopathic arthritis, polyarteritis nodosa), hypersensitivity reactions (mercury), and drug reactions (Stevens Johnson syndrome).

Laboratory examination and findings reflect systemic inflammation and include elevated C reactive protein (≥30 mg/l) and erythrocyte sedimentation rate (>40 mm/h), elevated liver enzymes (ALT ≥50 U/l), hypoproteinemia, thrombocytosis, leukocytosis, and/or anemia).

The febrile period of disease is related to elevated concentrations of proinflammatory cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α)(9).

For uncomplicated Kawasaki disease, an echocardiogram should be performed at diagnosis, at 2 weeks, and then again at 6–8 weeks to assess treatment efficacy for the prevention of aneurysm formation.

*Kawasaki disease.*Treatment with intravenous immunoglobulin reduces the incidence of aneurysms by approximately 80 %, and in combination with high dose aspirin reduces this severe complication to approximately 4 %. If there is no response to treatment, patients are given a second dose of intravenous immunoglobulin with or without corticosteroids.

Standard treatment includes salicylic acid (initially during febrile period 30–50(−80) mg/kg/day, followed by 3–5 mg/kg/day for 6–8 weeks), and intravenous immunoglobulins (usually 2 g/kg over 8–12 h). Intravenous immunoglobulin should be applied within the first 7–10 days of fever to reduce the risk for coronary aneurysms.

Kawasaki disease is a self-limited vasculitis, but 25 % of untreated patients suffer from coronary artery aneurysm, which decreases to 4 % with proper treatment. The majority of Kawasaki disease patients will be expected to survive into adulthood.

4.8. Osler–Weber–Rendu disease (hereditary hemorrhagic telangiectasia)

Hereditary hemorrhagic telangiectasia was first reported by Henry Gawen Sutton in 1864. Later in 1896 Henri Jules Louis Marie Rendu described disease with hemorrhagic symptoms similar symptoms to hemophilia. William Osler connected the disease's presence in families with an inherited disorder. In 1907 Frederick Parkes Weber reported to characteristic such disease in published article. The name "hereditary hemorrhagic telangiectasia" was coined in 1909.

Etiology of Osler–Weber–Rendu disease.

Osler–Weber–Rendu disease is a rare autosomal dominant disorder that affects blood vessels throughout the body causing vascular dysplasia and results in development of multiple abnormal blood vessel formation (telangiectasia) on different parts of the skin and mucous membranes and often in organs such as the lungs, liver, and brain with in a tendency for bleeding.

Osler–Weber–Rendu disease is caused by mutations in five different genes.

Pathogenesis.

Mutations of the *ENG* gene and abnormalities of the protein it produces (endoglin) result in hereditary hemorrhagic telangiectasia. Endoglin is found on the surface of the cells that line the inside of the blood vessels. In mice that are deficient in endogolin, the blood vessels do not mature and there is a failure in vascular smooth muscle development.

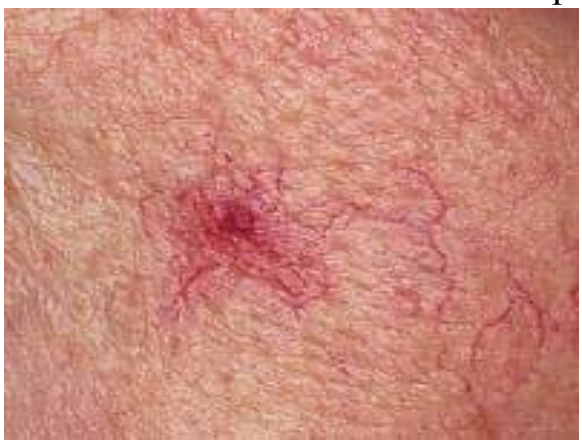
Clinical picture.

Differences in disease expression partially reflect the specific gene that is mutated. Phenotypic penetrance is age dependent. Some individuals may experience symptoms during infancy or early childhood. Sometimes the disease starts after puberty, others may show few signs or symptoms until the thirties, forties or later in life.

In many patients, the first apparent symptom of Osler–Weber–Rendu disease is nosebleeds (epistaxis). Recurrent nosebleeds occur in approximately 90 % of affected individuals. Nosebleeds occur because of the formation of small, fragile vascular malformations (telangiectases) in the mucous membranes. Telangiectasia – a red-purple spots or reddish papules with a diameter

of 1 to 3 mm, which are dilated capillaries skin, pulsation in the central part of telangiectasia is absent, when pressed, they fade away (*Picture 4.7*).

Telangiectases occur when capillaries fail to develop between arterioles and venules and most often affect the skin and the mucous membranes. The tongue, lips, face, ears, and fingers are the areas most often affected. Telangiectases may develop at any age including during infancy, but usually become apparent during adolescence and later. The disease manifests by easy bleeding blood vessels located on different parts of the skin and mucous membranes.



Picture 4.7. Telangiectasia

Telangiectases also occur in the gastrointestinal tract. Gastrointestinal bleeding (hemorrhaging) which affects about 25–30 %, usually does not present until the fourth decade of life or later. Affected individuals with gastrointestinal bleeding may note dark stools – sometimes black and tarry (melena) – but only rarely do they have red blood in their stools (hematochezia) or vomit (hematemesis). Because bleeding episodes become more severe with age, they often lead to chronically low levels of iron in the blood and eventually to a low red blood cell count – iron deficiency anemia.

Many individuals with Osler–Weber–Rendu disease develop arteriovenous malformations which are direct connections between blood vessels of larger caliber than in telangiectases, most commonly affect the lungs, brain, spinal cord, and liver.

Pulmonary arteriovenous malformations observed in about 50 % of individuals with Osler–Weber–Rendu disease and may result in fatigue, difficulty breathing (dyspnea), episodes of coughing up of blood (hemoptysis), headaches, abnormal bluish discoloration of the skin due to low levels of circulating oxygen in the blood (cyanosis) and/or abnormally increased levels of red cells in the blood (polycythemia).

Arteriovenous malformations of the brain occur in about 10 % of individuals with Osler–Weber–Rendu disease and may result in headache, dizziness (vertigo), and seizures.

Liver vascular malformations are seen in up to 75 % of individuals with such disease.

Diagnostic criteria.

An international group of experts on hereditary hemorrhagic telangiectasia established diagnostic criteria for such disease. The four criteria are: recurrent spontaneous nosebleeds; the presence of multiple telangiectases in characteristic locations; the presence of internal (visceral) telangiectases or arteriovenous

malformations; and a family history of definite hereditary hemorrhagic telangiectasia. A diagnosis is defined if at least three of the four criteria are present.

Additionl examination.

Molecular genetic testing is available to determine if a mutation is present in ENG, ACVR1, SMAD4, RASA1 or BMPR9 genes. Genetic testing will detect the mutation in nearly 90 % of people who meet clinical criteria for defined HHT.

Treatment of disease Osler-Rendu and prevention of complications

It is nessesary to stop the bleeding using a means of local and general hemostatic therapy (irrigation 5 % solution of aminocaproic acid, oil tamponade of the nose swabs).

If conservative measures are insufficient, then oral tranexamic acid or surgical ablation using laser, bipolar cautery, coblation or sclerotherapy should be considered. More effective is cryotherapy.

Sometimes – surgical treatment (excision of angiomas, plastic nasal septum, ligation and embolization of the arteries).

Patients should avoid trauma of the mucous membranes in the locations of telangiectases or arteriovenous malformations.

Test-control

1. For evaluation of coagulation hemostasis doesn't use:

A. Clotting time of venous blood.
B. Activated thromboplastin time.
C. Prothrombin test.
D. Platelet count.
E. Fibrinogen concentration.

2. Anomalies of platelet glycoprotein receptors underlie the pathogenesis:

A. Osler–Weber–Rendu.
B. Hemophilia B.
C. Glanzmann thrombasthenia.
D. Von Willebrand disease.
E. Werlhof's disease.

3. Approach to treatment in idiopathic thrombocytopenic purpura involves initiation of therapy with:

A. Glucocorticoids.
B. Immunoglobulins.
C. Paracetamol.
D. Interferon-alpha.
E. Immunosuppressants .

4. Primary thrombocytopathies is

A. Osler–Weber–Rendu disease.
B. Henoch-Schonlein purpura.
C. Glanzmann thrombasthenia.
D. Hemophilia B.
E. Werlhof's disease.

5. The main cause of death in patients with Werlhof's disease is:

A. Acute gastrointestinal bleeding.
B. Septic complications.
C. Cerebral subarachnoid hemorrhage.
D. Syndrome disseminated intravascular coagulation.
E. Infarction of spleen.

6. Characteristic of petechia. Choose the correct definition;

A. Superficial, painless, does not create the compression of the surrouning tissues.
B. Massive, deep, painful, located under the aponeurosis and fascia.
C. Insignificant in size, very painful, located mainly in the same places.

D. Surface, creating a compression of the surrounding tissues.
E. Hemorrhage occurred after intramuscular, subcutaneous injection .

7. Diagnostic criteria of idiopathic thrombocytopenic purpura are all of the following except:
A. The absence of clinical and laboratory signs of disease in blood reltives.
B. Normal or increased number of megakaryocytes in the bone marrow.
C. Absence of laboratory signs for hereditary forms of thrombocytopenia.
D. The effect of aminocapronic acid therapy.
E. The effect of corticosteroid therapy.

8. Pathogenesis of Werlhof's disease is:
A. Destruction of platelets by macrophages in the spleen.
B. Platelet destruction by phagocytes of blood.
C. Decrease in the synthesis of platelets in the bone marrow due to viral infections.
D. Destruction of platelets due to the action of autoantibodies.
E. Destruction of platelets due to activation of complement in combination with inhibition of synthesis of membrane proteins.

Test-control answers

Chapter 1
1 C, 2 A, 3 C, 4 A, 5 D, 6 A, 7 E, 8 B, 9 C, 10 A, 11 A, 12 A, 13 E, 14 C
15 B, 16 A, 17 C, 18 C, 19 B, 20 C, 21 D, 22 B, 23 A, 24 C, 25 B
Chapter 2
1 A, 2 C, 3 A, 4 E, 5 C, 6 B, 7 D, 8 E, 9 C, 10 A
Chapter 3
1 E, 2 C, 3 D, 4 C, 5 A, 6 C ,7 C, 8 D, 9 D, 10 E
Chapter 4
1 D, 2 C, 3 A, 4 C, 5 C, 6 A, 7 E, 8 E

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