Federal State Budgetary Educational Institution of Higher Education "North Ossetian State Medical Academy" of the Ministry of Health of the Russian Federation

HEMORRHAGIC DIATHESIS

(a methodological manual for students of the V-VI courses of the Faculty of Medicine, residents and graduate students)

Vladikavkaz 2022

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Content

Introduction

The hemostasis system is one of the integral systems of the body. Any

changes in organs and tissues are reflected in its functioning.

The important place of hemostasis disorders in the general human pathology is determined not only by the high frequency, variety and potentially very high danger of hemorrhagic diseases and syndromes, but also by the fact that these processes are an essential link in the pathogenesis of an extremely large number of other diseases. This demonstrates the general medical significance of the problems of hemostasis pathology, and therefore the ability to navigate these problems is necessary for doctors of all

clinical specialties.

On the globe, about 5 million people suffer from primary hemorrhagic manifestations. Given that secondary hemorrhages, such as DIC in the pre-agonal state, are not always fixed, one can imagine the prevalence of hemorrhagic diathesis.

HEMOSTASIS SYSTEM

The hemostatic system is a biological system that, on the one hand, prevents and stops bleeding by maintaining the integrity of the vascular wall and rapid local thrombosis, and on the other hand, maintaining the liquid state of the blood and its volume in the circulating bed against the background of a constant exchange of plasma and tissue fluid. The functioning of the hemostasis system is a complex self-regulating physiological mechanism, with the possible influence of the central nervous system, the endocrine system, which is mainly determined by the interaction of the following components:

- vascular wall;
- platelet link;
- plasma proteolytic systems - coagulation, anticoagulation (fibrinolytic), kallikrein-kinin and complement systems.

Until now, the “cascade” model of the blood coagulation process has been used to understand the mechanisms of hemostasis. It was proposed in 1964 by two independent groups of scientists (E. W. Davie, O. D. Ratnoff, R. G. Macfarlane), where the blood coagulation process is divided into primary, or vascular-platelet, hemostasis and secondary, or coagulation, hemostasis, with the release in the latter "external", "internal" pathways of thrombin activation and "common pathway". It is still relevant for understanding the basics of the functioning of the hemostasis system and considering the processes taking place in vitro.

I. Vascular and platelet hemostasis

Vascular-platelet (or primary) hemostasis ensures that bleeding stops in vessels with a diameter not exceeding 100 microns. Accordingly, it involves two components:

1. Vascular: if the vessels are damaged, their spasm occurs - the fastest primary reaction of the hemostasis system, as a result of which there is a temporary emptying of capillaries and venules and bleeding from them does not occur in the first 20-30 seconds. The spasm is caused by adrenaline and noradrenaline released from the adrenal glands in response to pain during injury. Serotonin, adrenaline, thromboxane, which are released from platelets at the site of vessel injury, and factors produced by the endothelium (endothelin-1 and angiotensin-II), also have a pressor effect.

Normally, the vascular endothelium prevents thrombosis. The antithrombogenic potential of the endothelium is provided by:

- synthesis of prostacyclin, nitric oxide, urokinase, tissue plasminogen activator, protein S;
- expression of thrombomodulin on the membrane of endotheliocytes (which adsorbs thrombin, after which the latter loses procoagulant activity and acquires the ability to activate primary anticoagulants - proteins C and S);
- the presence of negatively charged glycosaminoglycans on the surface of the endothelium;
- fixation on the surface of the endothelium of the heparin-antithrombin-III complex.

After damage to the endothelium (trauma, damage under the influence of immune complexes, endo- and exotoxins, inflammatory mediators, proteolytic enzymes, atherosclerotic process, etc.), procoagulant activity begins to predominate in the endothelium.

The thrombogenic potential of the endothelium is provided by:

- synthesis of thromboxane A2, tumor necrosis factor a, VWF, interleukin-1, F-II, V, XI, endothelin-I, plasminogen activator inhibitors of the 1st and 2nd types.

2. Platelet component

Platelets are platelets produced by bone marrow megakaryocytes, which are non-nuclear fragments of their cytoplasm. The normal content of platelets in the blood is 150-450 x 109 / l. Their diameter ranges from 1 to 5 μm, and the volume is about 6-9 μm3. The average lifespan of platelets is 7-10 days.

Platelet Functions:

- Adhesive-aggregative (when the subendothelial layer is exposed, they interact with the collagen present in it, VWF and stick to the edges of the damaged endothelium, sticking together, while changing the shape from discoid to spherical and spreading to form pseudopodia).
- Angiotrophic (the endothelium constantly absorbs platelets, using them to maintain the normal structure and function of the walls of blood vessels).
- Angiospastic (support spasm of damaged vessels, ejecting vasoconstrictor substances from a-granules).
- Coagulation - participate in blood coagulation and fibrinolysis.
- Reparative - in the process of adhesion, growth factors are released that activate the repair processes at the site of damage to the vessel.
- Transport (on the surface of the glycocalys of platelets, coagulation factors I, V, VIII, X, XI, XII and XIII, transported by platelets to the site of bleeding, can be deposited.

Glycoprotein receptors on the surface of platelets, platelet receptors for thrombin, fibrinogen, prostaglandins and other substances and intracellular organelles (mainly granules containing a large amount of biologically active substances) play an important role in the processes of adhesion and aggregation of platelets. There are a-granules (contain more than 30 proteins related to hemostasis - plate factor 4, fibrinogen, VWF, thrombospondin, fibronectin, coagulation factors V, XI, protein S, etc.) and dense granules (contain biologically active substances related to to vascular tone and hemostasis - ADP, adrenaline, serotonin, thromboxane, etc.). Of the other organelles in platelets, there are lysosomes containing proteolytic enzymes, mitochondria, and peroxisomes.

Platelet (cellular, lamellar) blood coagulation factors:

- Factor 1 - platelet globulin accelerator. Its action is identical to the V plasma coagulation factor.
- Factor 2 - fibrinoplastic factor (thrombin accelerator). Accelerates the conversion of fibrinogen to fibrin.
- Factor 3 - platelet thromboplastin.
- Factor 4 - antiheparin factor. Prevents the inhibitory effect of antithrobin III (plasma cofactor of heparin) on blood thrombin.
- Factor 5 - clotting factor (platelet fibrinogen). Participates in the formation of platelet receptors for plasma fibrinogen.
- Factor 6 - thrombosthenin. A platelet contractile protein (acthyosin complex) that provides thrombus retraction.
- Factor 7 - antifibrinolytic factor.
- Factor 8 - fibrinolysis activator.
- Factor 9 - fibrin-stabilizing factor. It is similar in action to XIII plasma coagulation factor.
- Factor 10 - serotonin.
- Factor 11 - ADP.

The mechanism of thrombus formation in primary hemostasis

platelet adhesion. When the vascular wall is damaged, platelets are rapidly activated due to ADP and other biologically active substances secreted by damaged erythrocytes and vascular endothelial cells. Adhesive proteins of the subendothelium (collagen, fibronectin, thrombospondin, VWF) bind to glycoprotein receptors (integrins) of platelets and promote their attachment (adhesion) to the vascular wall. It is believed that GP Ib/IX glycoprotein receptors mediate interaction with collagen with the participation of VWF, after which GP IIb/IIIa receptors are activated, mediating platelet adhesion and aggregation.

platelet aggregation. Platelet aggregation is carried out with the help of fibrinogen, a protein contained in plasma and platelets and forming connecting bridges between them, which leads to the appearance of a platelet plug. The aggregation process accelerates the release of ADP, adrenaline, arachidonic acid, prostaglandins, calcium, and serotonin from destroyed platelets. As a result, a primary,

so-called white thrombus is formed. But it is not yet dense and can pass blood plasma, break up into separate fragments. Irreversible platelet aggregation is the next step in the transformation of a white thrombus. The main stimulator of thrombus strengthening is thrombin, which managed to form in trace amounts 5-10 s after injury during coagulation hemostasis reactions occurring in parallel (the start of these reactions is initiated by a small amount of tissue thromboplastin released from damaged tissues, which interacts with VII, IV, X and V factors with the formation of tissue prothrombinase). Thrombin leads to the formation of fibrin, in the network of which individual leukocytes and erythrocytes get stuck. This is how a platelet thrombus is formed.

Retraction of platelet thrombus. From the destroyed platelets, plate factor (PF-6) is released - thrombostenin, reminiscent of actinomyosin. It is able to contract and thereby reduce the size and compact the clot.

Normally, stopping bleeding from small vessels takes 2-4 minutes. Stimulated platelets further interact with a number of F (II, V, VII, VIII, XI, XII), which further contributes to the formation of a fibrin clot. In addition, complexes are formed on the surface of platelets: prothrombinase (consisting of Xa, Va factors, calcium and platelet phospholipids) and a complex consisting of IXa, VIIIa, X factors.

II. Plasma (coagulation) secondary hemostasis (Figure 1).

It is activated after damage mainly to macrovessels, which differ from microcirculation vessels not only in anatomical structure, but also in high blood flow velocity, as well as high blood pressure. But even here, the very first, quick and effective reaction to damage is a spasm of the affected veins or arteries, which leads to a limitation or complete stop of bleeding. This explains the fact that postoperative bleeding in hemophilia, even moderate and severe, can be delayed (several hours, and sometimes days after the intervention, when the vessels dilate, and the formation of a hemostatically complete red blood (fibrin) thrombus is delayed)

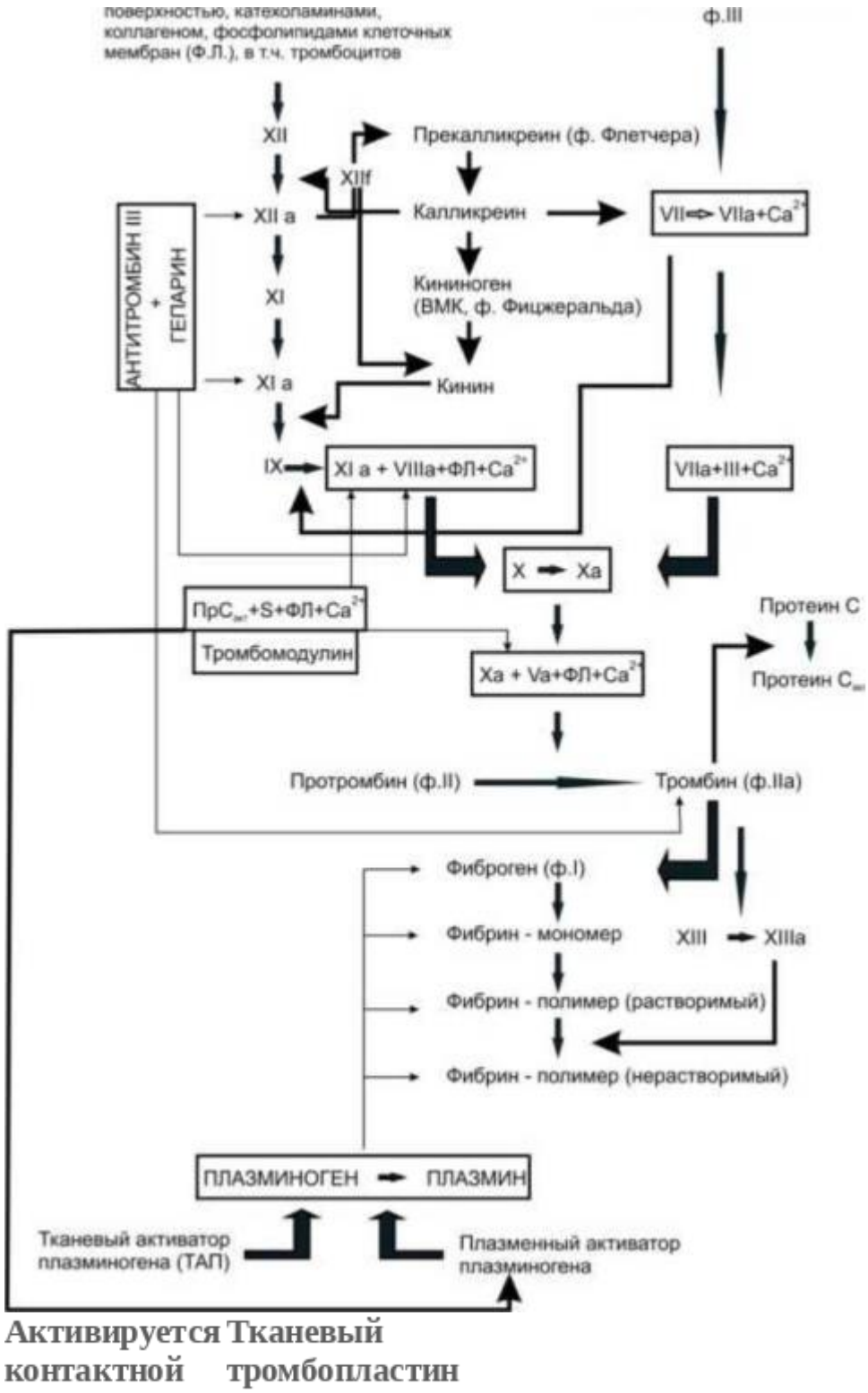

Figure 1 - Plasma (coagulation) hemostasis

The main resource is blood F, most of which are proteins. F also includes calcium ions (IVF), non-enzymatic cofactors, membrane phospholipids (FIII). All factors circulate freely in plasma (Table 1), except for tissue factors (IIIF is supplied by platelets). Plasma factors are designated by Roman numerals (numbered in the order of their discovery). Normally, protein coagulation factors are in the plasma in an inactive state. If the factor is activated, then the letter “a” is added to its designation.

Table 1 - Plasma coagulation factors

№	Name	Characteristic	Content in blood plasma / sufficient minimum for hemostasis	Vitamin K addiction
I	fibrinogen	Protein, precursor fibrin. Under the influence of thrombin, it turns into fibrin - the main component of a blood clot	2-4 г/л/ 0,8 г/л	-
II	Prothrombin	a1 globulin is produced in the liver	80 мкг 40 %	+
III	tissue thromboplastin	Phospholipoproteins. Contained in various tissues and released into the blood when they are damaged. In the presence of calcium ions, it activates factor VII and is involved in the conversion of prothrombin to thrombin	—	-
IV	Ионы Са++	ionized calcium is a biologically active form of calcium	0.09-0.1 g / l (2.3-2.75 mmol / l) the clotting process remains normal even with a decrease in calcium to the level of the onset of a convulsive syndrome	
V	Proaccelerin	в-globulin. Turns into active factor accelerin under the influence of thrombin and factor Xa	0,01 г/л 10-15 %	-
VII	Proconvertin	a2-globulin. It is the precursor of the convertin. Participates in the external pathway of activation of blood coagulation. The active form of factor VII is a serine protease	0,005 г/л 5-10 %	+
VIII	Antihemophilic globulin A	B2-globulin. This factor consists of two parts: low molecular weight and high molecular weight. The composition of the high molecular weight part includes VWF, which is a carrier protein for the low molecular weight part and promotes platelet adhesion	0,01-0,02 г/л 10-15 %	

		and aggregation		
IX	Antihemophilic globulin B (Christmas factor)	β-globulin is formed in the liver, participates in the formation of thrombin	0,003 г/л 20-30 %	+
X	Stewart factor-Prauer (a globulin)	Xa combines the extrinsic and intrinsic pathways for activating blood coagulation.	0,01 г/л./ 10-20 %	+
XI	Antihemophilic globulin C (Rosenthal factor)	necessary for the implementation of the internal pathway of activation of blood coagulation	0,005 г/л 15-20 %	-
XII	Hageman factor (contact factor)	Is the initiator internal (intravascular) pathway for activation of blood coagulation and other processes	0.03 g/l. Bleeding does not occur even with very deep factor deficiency (less than 1%)	
XIII	fibrin stabilizing factor	Participates in the formation of a stable fibrin blood clot	0,01-0,02 г/л 2-5 %	
	Прекалликреин (фактор Флетчера)	It turns into kallikrein, which activates factor XII and converts kininogen into kinins, and also participates in the functioning of the fibrinolytic system	0,05 г/л/ (менее 1 %)	
	High molecular weight kininogen (Fitzgerald factor)	Participates in the activation of factor XI	0,06 г/л/ (менее 1 %)	
	VWF	The factor VIII component is produced in the endothelium, in the bloodstream, connecting with the coagulation part forms a full-fledged factor VIII		

Note: Factor VI - accelerin, is the active form of factor V, therefore it is excluded from use.

Blood clotting factors are divided into 3 groups:

1. Group of fibrinogen - I, V, VIII, XIII. Their level is labile, they are actively consumed in the process of blood coagulation, increase during pregnancy, when taking oral contraceptives, and inflammatory processes.

2. Prothrombin group - II, VII, IX, X. These factors are vitamin K-dependent, i.e. their content

depends on the intake of vitamin K in the body. The activity of these factors is inhibited when taking oral anticoagulants.

3. Contact group (XI, XII, Fletcher and Fitzgerald factor) - activated during contact with the negatively charged surface of the subendothelium or collagen. Participate in the internal pathway of activation of blood coagulation.

The process of plasma-coagulation hemostasis includes 5 phases, successively replacing each other:

• formation of prothrombinase — duration 5-7 minutes;

• formation of thrombin - 2-5 s;

• formation of fibrin - 2-5s;

• fibrin polymerization and clot organization;

• fibrinolysis.

1. phase - the formation of prothrombinase. Prothrombinase can be formed along the external and internal pathways that run in parallel. The efficiency of education is higher if both mechanisms are functioning normally. Starting with the formation of active factor X, both pathways have the same development. Due to the inferiority of this phase of blood coagulation, hereditary coagulopathy occurs, such as hemophilia A, B, C and others.

Internal (plasma) way of activation of blood coagulation. All of its components are in the circulating blood. It begins with the activation of factor XII after contact with the negatively charged surface of the subendothelium when the vessel is damaged. Activation of factor XII is also promoted by high molecular weight kininogen and kallikrein formed from prekallikrein. Active factor X11a converts FIX to active 1Xa, which then activates FVIII. Subsequently, active factors VIIIa, IXa, Ca++ ions and platelet membrane phospholipids form a complex - a genase that activates FX.

External (tissue) pathway of activation of blood coagulation. When cell membranes are damaged, including endothelial damage, a large amount of tissue factor (tissue thromboplastin, FIII), which has a high affinity for plasma coagulation factor VII, enters the bloodstream. Under the influence of tissue factor, inactive FVII is converted into active FVIIa. Next, a tissue factor complex + VIIA + Ca++ ions is formed, which activates FX.

The extrinsic and intrinsic pathways result in the same amount of active FXa. Further, a prothrombinase complex is formed (FXa + FVa + Ca++ ions, + platelet phospholipid).

2. phase - thrombin formation, or the general pathway for the formation of thrombin. Under the influence of the prothrombinase complex, prothrombin is converted to thrombin.

3rd and 4th phase - fibrin formation and clot organization. Under the influence of thrombin, fibrinogen is hydrolyzed to fibrinopeptides A and B. In addition, under the influence of thrombin, inactive

FXIII (fibrin-stabilizing) is converted into active XIIIa, which, in the presence of Ca++ ions, transforms the soluble fibrin polymer into a stable fibrin clot.

5th phase - fibrinolysis. Some time after the formation of a thrombus, the fibinolysis system is activated, which leads to the lysis of the fibrin clot and the restoration of vascular patency, wound healing.

FIBRINOLYSIS SYSTEM

Despite the fact that the circulation has all the factors necessary for the formation of a blood clot, under natural conditions, the blood remains liquid. This is due to the presence in the bloodstream of anticoagulants called natural anticoagulants and the fibrinolytic link of the hemostasis system.

Natural anticoagulants are divided into primary and secondary. Primary anticoagulants are always present in the circulation, secondary ones are formed as a result of proteolytic cleavage of blood coagulation factors during the formation and dissolution of a fibrin clot (they inhibit the final stage of coagulation according to the feedback principle).

The main component of the fibrinolytic system is the enzyme plasmin (fibrinolysin), which, by hydrolysis, cleaves soluble peptides from fibrin, thereby contributing to the direct dissolution of the thrombus. Plasmin also cleaves some blood coagulation factors (fibrinogen, factors V, VII, IX, XI, XII). At the same time, soluble fibrin peptides arising during thrombolysis inhibit the action of thrombin. Thus, plasmin not only dissolves the formed thrombus, but also prevents further blood clotting.

Plasmin is present in the blood as inactive plasminogen. Plasminogen activation is provided by many mechanisms, including some blood coagulation factors. There is an internal and external mechanism for the activation of fibrinolysis.

The internal mechanism of fibrinolysis activation is provided mainly by activated Hageman factor (XIIa) and its fragment (XIIF) in complex with kallikrein and high molecular weight kininogen.

The external mechanism of activation of fibrinolysis occurs through tissue plasminogen activators, which are contained in the vascular endothelium, erythrocytes, platelets, leukocytes, bile, saliva. One of the tissue activators is urokinase (present in blood plasma and urine, synthesized in the juxtaglomerular apparatus of the kidneys).

Plasmin inhibitors inhibit the process of fibrinolysis, which include fast-acting α2-antiplasmin, α1-antitrypsin, α2-macroglobulin, antithrombin III, C1 esterase inhibitor, etc. There are also inhibitors of plasminogen activators of types 1, 2 and 3. Synthetic e-AKK is a powerful inhibitor of fibrinolysis.

The most important physiological primary anticoagulants are antithrombin III-heparin and protein C-protein S complexes.

Antithrombin III inhibits almost all enzymatic plasma coagulation factors (Pa, Xa, XPa, X1a, 1Xa), as well as kallikrein and, to a lesser extent, plasmin. Inactivation occurs as a competitive reversible inhibition. This interaction occurs slowly, but is accelerated by 1000 times in the presence of heparin, the main cofactor of antithrombin III. The therapeutic effect of the introduction of heparin is extremely low with a lack of antithrombin III.

Protein C and its cofactor protein S are synthesized in the liver and are vitamin K-dependent anticoagulants. The activation of the protein C-protein S complex occurs under the action of the thrombin-thrombomodulin complex fixed on the surface of the endothelium of the vascular wall. As mentioned earlier, thrombin, after binding to membrane thrombomodulin, loses its procoagulant activity, but acquires the ability to activate protein C. The main function of the protein C-protein S complex is the inhibition of coagulation factors Va and VIIIa due to proteolysis of their heavy chains. In addition, this complex inhibits the process of fibrinolysis.

The "cascade" model of blood coagulation, which explains the stages of the blood coagulation process in vitro, does not explain the arrest of bleeding in vivo. First of all, it does not answer the question why the possibility of the formation of prothrombinase (thrombin activator) in one pathway does not compensate for the breakdown in another. Recently, convincing evidence has been obtained that in the human body both pathways are closely related to each other and to platelets.

Based on this knowledge, a cell-based model of coagulation has been developed to describe the

processes of hemocoagulation in vivo and to explain the limitations that must be taken into account when interpreting the results of laboratory coagulation tests. This theory was proposed by N. Hoffman in 2001. According to this model, activation, localization, and concentration of coagulation proteins are provided by anionic membrane phospholipids, receptors, and cell binding sites (platelets, endothelial cells, leukocytes). The coagulation process under physiological conditions is localized by the area of the vessel defect. Its nonproliferation is facilitated by the anticoagulant system and normally functioning endotheliocytes. The cellular model of coagulation does not negate the interaction reactions and the properties of the factors of the coagulation, anticoagulation and fibrinolytic systems presented in the cascade model of coagulation. It recognizes the existence of external and internal coagulation pathways, but significantly modifies them.

The modern model of secondary hemostasis includes three phases:

• initiation, or start signal (the complex "tissue factor (TF)/TFA" is formed on the surface of the subendothelium at the site of injury, which is accompanied by the production of thrombin);

• strengthening of the process (under the influence of thrombin, a number of coagulation factors are activated);

• expansion of the process (thenase (VIIIa/HCa) and prothrombinase (Va/Xa/calcium/platelet factor III) complexes are formed, which provokes the so-called thrombin explosion and the formation of a stable fibrin clot).

I. Initiation: in the first phase (initiation), FU11 is activated on the surface of cells containing TF (under physiological conditions, TF contain fibroblasts, vascular smooth muscle cells; in inflammation, endothelial cells and monocytes become TF-bearing; in a number of pathological conditions, including AFLS - neutrophils). When the vascular wall is damaged, cells carrying TF begin to contact with plasma. At the same time, subendothelial structures (collagen) are exposed, which leads to the accumulation of platelets in this area (adhesion). TF binds to FVII to form a TF/FVIIa complex. This complex activates FX and FIX locally on the surface of TF-bearing cells. Factor IXa migrates and binds to the surface of platelets, while factor Xa remains on the surface of TF-bearing cells. According to the cellular model, factor IXa does not play a significant role in the first phase of coagulation. Factor Xa activates FV. As a result, the FXa/FVa complex formed on the surface of TF-bearing cells cleaves prothrombin with the formation of a small amount of thrombin, a key factor in the subsequent increase in the activation of the coagulation system.

II. Amplification: Amplification phase reactions (amplifications) occur on the platelet surface. Spatial separation of coagulation processes (the initiation phase is on the surface of TF-bearing cells, the amplification phase is on the surface of platelets) is one of the mechanisms for limiting their severity in the absence of the need for clotting. A small amount of thrombin formed during the initiation phase activates platelets, factors V, VIII and CT. Thrombin promotes the release of FVIII from the complex with VWF, resulting in the formation of FVIIIa. Activated FXI (FXIa) acquires the ability to bind to the surface of platelets. Activated by a small amount of thrombin formed in the initiation phase, factors in the next phase (spread phase) ensure the formation of a huge amount of thrombin on the platelet matrix, which is capable of converting fibrinogen into fibrin. Thus, thrombin released from the initiation phase acts as a powerful coagulation enhancer.

III. Spread: During the spread phase, tenase (FVIIIa/FIXa) and prothrombinase (FVa/FXa) complexes are formed on the surface of activated platelets. FVIII is activated during the amplification phase and is fixed on platelets. FIXa is transferred to the surface of platelets from the site of activation (the surface of TF-bearing cells) during the initiation phase; its additional amount is formed on platelets under the action of FXIa formed in the amplification phase. The tenase complex on the platelet surface activates FX bound to its cofactor FVa (coming from the amplification phase). The resulting prothrombinase complex provides an avalanche-like increase in the level of thrombin. Thrombin converts fibrinogen to fibrin and also activates FXIII, which ensures the stabilization of fibrin strands and the formation of many covalent cross-links between them.

DIAGNOSTICS OF DISORDERS OF THE HEMOSTASIS SYSTEM

Based on the analysis of the anamnesis, clinical data and data from laboratory research methods.

In the anamnesis of patients, the presence of previous bleeding and their duration, the timing of occurrence, frequency throughout life, and the circumstances of occurrence are specified. It is found out

whether the bleeding is local or generalized, delayed or occurs immediately after the injury, the genealogical history is specified, the obstetric and gynecological history in female patients, the presence of concomitant diseases that can lead to changes in the hemostasis system, whether the patient is taking drugs with antiplatelet and anticoagulant effect.

To assess clinical data, it is convenient to distinguish 5 main types of bleeding, first identified by Z. S. Barkagan in 1988:

1. The hematoma type is characterized by the appearance even after very small bruises of hemorrhages in the tissues, in the cavity of the joints, the abdominal cavity, the formation of retroperitoneal hematomas. There may be prolonged and profuse bleeding after surgery, which usually occurs delayed. Spontaneous nasal, renal and gastrointestinal bleeding is possible. Hematoma type of bleeding is typical for the two most common types of hereditary coagulopathy - hemophilia A and B.

2. Microcirculatory (petechial-bruising, petechial-spotted) type of bleeding (purpura) is characterized by the slight appearance of petechiae (petechial hemorrhages) and practically painless, most often small bruises on the skin of the limbs and trunk, as well as a tendency to menorrhagia, nosebleeds and hematuria, increased bleeding after medical manipulations with damage to small vessels (tooth extraction, operations in otolaryngology). It is characterized by superficial, capillary bleeding. There are practically no hematomas, hemarthrosis and other lesions of the musculoskeletal system, as well as delayed postoperative bleeding. This type of hemorrhagic syndrome is characteristic of thrombocytopenia and thrombocytopathies.

3. Mixed (bruising-hematoma) type. In this type, microcirculatory hemorrhages predominate, but hematoma hemorrhages, abundant spontaneous and postoperative bleeding, large blood loss during childbirth, and menorrhagia are periodically superimposed on them. Hemarthroses are extremely rare. A mixed type of bleeding is observed in severe form of von Willebrand disease (VW), deficiency of factors II, V, VII, X and XIII, DIC.

4. Vasculitis-purple type of bleeding is characterized by symmetrical inflammatory-hemorrhagic rashes on the skin of the extremities and lower body. At the same time, the inflammatory basis of these hemorrhages is clearly detected, often the elements of the rash have an erythematous rim or bluish-brown pigmentation around them. This type of bleeding is observed in systemic vasculitis (a classic example is Shenlein-Genoch disease), infectious-immune, allergic vasculitis.

5. Angiomatous type (microangiomatous type) of bleeding is usually associated with genetically determined or secondary (symptomatic) telangiectasia, in which small angiomas are detected in the form of vascular nodules, loops or "spiders" in various areas of the skin or mucous membranes. A classic example of a disease that occurs with this type of bleeding is hereditary hemorrhagic telangiectasia (Rendu-Osler disease).

Laboratory diagnosis of disorders of the hemostasis system.

A hemostasiogram is a set of clinical and laboratory tests characterizing primary (vascular-platelet) and secondary (hemocoagulation) hemostasis. Laboratory diagnosis of disorders of the hemostasis system is one of the most difficult and expensive in laboratory practice. Performing all existing tests for each patient is impossible and impractical. The choice of a set of tests is carried out on the basis of clinical and anamnestic data. Moreover, screening tests are initially carried out, and then clarifying (this rule is neglected to save time in the case of urgent pathology - for example, with DIC).

Screening tests include:

• counting the number of platelets, bleeding time, testing for capillary resistance in assessing vascular-platelet hemostasis;

• indicative coagulogram tests, reflecting the state of whole links of the hemostasis system in the assessment of plasma hemostasis.

The diagnostic significance of screening tests is determined by the fact that their normal results make it possible to exclude the presence of significant deviations in the content of the system components, while abnormal results make it possible to specify the direction of the defect search.

Clarifying tests include: tests for platelet aggregation, determination of the activity of various coagulation factors, VWF, determination of lupus anticoagulant, activity of the fibrinolytic system (physiological anticoagulants - antithrombin III, protein C and S, determination of anti-Xa activity of

heparin), etc.

Methods for studying primary hemostasis:

- Tests for resistance, fragility of capillaries - cuff, can, pinch, tourniquet, etc.
- Determination of the duration of bleeding - according to Duke, Ivy.
- Counting the number of platelets.
- Thrombocytometry - mean platelet volume (MPV).
— Study of adhesiveness and aggregation function of platelets.
— Study of spontaneous platelet aggregation in the bloodstream.
- Retraction of the blood clot.
— Determination of life span of platelets in circulation.
— Determination of antiplatelet antibodies.

Methods for studying secondary hemostasis:

- Blood clotting time.
- APTT.
- PT (Quick prothrombin time - Quick test).
— MNO.
- TV plasma or blood.
— Quantification of scarce factors.

Indicators characterizing platelet-vascular hemostasis

1. Platelet count:

norm 150-400 x 109 / l.

2. The duration of bleeding according to Duke (Duke) is the time from the moment a standard skin wound is applied to the moment the bleeding stops. According to this technique, the tip of the finger or earlobe is pierced with a scarifier to a depth of 3 mm. Spontaneously flowing blood is blotted with paper every 30 s. The normal duration of bleeding is 2-4 minutes.

Ivy bleeding time. According to this technique, an incision is made on the forearm with a length of 9 mm and a depth of 1 mm using a special template against the background of venous plethora, which is provided by applying a cuff with a maintained pressure of 40 mm Hg. Art. The normal duration of bleeding is 2-5 minutes. Prolongation of bleeding time to 10 minutes or more indicates serious violations of hemostasis.

3. Retraction of the blood clot. The essence of the method is to determine the amount of serum formed 1 hour after the formation of a blood clot - the norm is 48-60%. A decrease is observed with thrombocytopenia, some thrombocytopathies, an increase with thickening of the blood.

4. Tests for resistance (fragility) of capillaries. There are a number of tests that allow to detect increased bleeding after a mechanical effect of a slight damaging force on intradermal capillaries. The most common of these are the pinch, tourniquet, or cuff tests. The pinch test is performed by squeezing the skin fold with moderate force fingers. This is done either under the collarbone or below the angle of the shoulder blade. Normally, after a pinch and over the next 24 hours, hemorrhagic spots do not occur, the appearance of petechiae after a given period of time indicates a violation of capillary resistance. A tourniquet test (cuff test) is performed as follows. A circle with a diameter of 5 cm is drawn on the inner side of the forearm below the elbow. Art. and hold in this position for 5 minutes. After that, the number of petechiae in the outlined circle is counted. Normally, their number should not exceed 10.

5. If, when counting platelets in the blood, their content turned out to be normal with symptoms of increased bleeding, the patient should be tested to determine the functions of platelets - the ability to adhere and aggregate. For the study, physiological inducers of platelet aggregation are used: thrombin, adrenaline, ADP, collagen or special inducers, such as ristomycin with graphic registration of the aggregation process on an aggregometer. The main parameters of the aggregogram are the degree of aggregation (in percent) and the aggregation time (in minutes). An increase in platelet aggregation activity is characteristic of pre-thrombotic conditions, thrombosis, atherosclerosis, vasculitis, possibly during pregnancy. A decrease in platelet aggregation activity is observed in primary and symptomatic thrombocytopathies, during treatment with antiplatelet agents.

Normal platelet aggregation according to Weiss with the addition of ADP is 77.7% at an ADP

concentration of 10 μm/ml; at an ADP concentration of 5 μm/ml - 66.1%; at an ADP concentration of 2 μm/ml - 47.7%.

Assessment of plasma hemostasis.

A coagulogram is a set of clinical and laboratory tests characterizing only hemocoagulation hemostasis.

Phase I - prothrombinase formation.

In the hemostasiogram, this phase is characterized by the following indicators:

1. The Lee-White blood clotting time is the time for the formation of a venous blood clot at a temperature of 37 ° C (the norm is 7-10 minutes).

• hypercoagulability can be noted in case of increased thrombus formation, for example, in the early stages of DIC.

• hypocoagulation - with hemophilia, heparin therapy.

2. APTT - koalin-kephalin time. Reference values of APTT: 28.6-33.6 s. APTT - is the time during which, after adding the active substance (calcium chloride and a special kaolin-kephalin mixture) to the citrate plasma, a blood clot forms. Kaolin stimulates coagulation factor XII, being a contact clotting activator, and cephalin contains phospholipids that stimulate X F. The term "partial thromboplastin" means that the reagent contains only phospholipids, it does not contain tissue factor.

APTT is one of the most sensitive indicators of blood coagulation, which evaluates the "internal" (intravascular) pathway of blood coagulation, i.e. without the participation of tissue thromboplastin.

Increased APTT:

• indicates a decrease in blood coagulation, deficiency of VIII, IX, XI, XII coagulation factors with normal PT results, deficiency of factors II, V and X with simultaneous prolongation of APTT and PT, DIC (hypocoagulation phase), VWF deficiency, the presence of lupus anticoagulant , conducting heparin therapy.

Shortening of APTT:

• activation of the internal coagulation mechanism in thrombosis, thromboembolism. This may be due to factor V resistance to activated protein C, increased levels of factor VIII, or activated F;

• with DIC (hypercoagulation phase);

• possible with a normal pregnancy.

I. phase of blood coagulation - thrombin formation.

In the coagulogram, this phase is characterized by the following indicators:

1. PV (thromboplastin): norm 11-17 s.

This is the time during which prothrombin is converted to thrombin. It detects a disturbance in the extrinsic pathway of blood clotting. The test determines the activity of prothrombin complex factors (II, VII, X, V). In addition to characterizing phase II of blood coagulation, PV allows you to control the effectiveness of oral indirect anticoagulants, such as warfarin, which binds vitamin K, therefore, due to a decrease in the formation of prothrombin, PV will increase.

Shortening PV:

• observed with DIC (in the phase of hypercoagulability), during pregnancy, when taking oral contraceptives, treatment with prothrombin complex factor concentrates in inhibitory forms of hemophilia.

PV extension:

• occurs with a deficiency or anomaly of prothrombin complex factors (VII, X, Y, II), in cases of taking indirect anticoagulants (warfarin), with diseases of the liver and biliary system, DIC (consumption of coagulation factors in the transitional phase and the hypocoagulation phase).

2. Prothrombin index.

Currently, this indicator is considered obsolete and the INR is used instead.

INR = patient prothrombin time / control prothrombin time raised to the power equal to MIC (International Sensitiviti Index (ISI), which is indicated in the instructions for tissue thromboplastin. In this way, standardization of measurements occurs. The doctor and patient can be sure that when measuring INR in various laboratories with different batches of reagents, they will receive comparable results: the INR norm is 0.7-1.3.

In the prevention of systemic thromboembolism, including after surgery, atrial fibrillation,

cerebrovascular accident, the INR is considered the norm - 2.0-3.0, and after valve replacement - the INR norm is 2.5-3.5. It is used to control the dose of warfarin and other indirect anticoagulants, diagnose liver diseases, coagulopathy.

II. phase of blood coagulation - fibrin formation.

In the coagulogram, this phase is characterized by the following indicators:

1. Plasma fibrinogen concentration: normal 2-4 g/l;

Fibrinogen is an acute phase protein.

Boost:

• observed in inflammatory processes, systemic diseases of the connective tissue, trauma, thrombosis, atherosclerosis, malignant neoplasms, stage I DIC;

Reduction:

• with liver diseases, DIC, administration of streptokinase and other thrombolytic agents.

2. TV is the time of formation of a fibrin clot from the moment of adding thrombin, i.e., this is the time for the transition of fibrinogen to fibrin.

Normal indicators - 18-24 s. It is influenced by plasma fibrinogen concentration and the presence of fibrin degradation products.

Shortening TV:

• observed in hyperfibrinogenemia (fibrinogen 6.0 g/l and above), DIC (in the phase of hypercoagulability).

TV extension:

• occurs with heparin therapy with conventional heparin, hypofibrinogenemia (fibrinogen below 1.0 g/l), with DIC (in the stage of hypocoagulation), with thrombolytic therapy, the effect on the polymerization of paraprotein fibrin monomer in multiple myeloma, and other factors.

III. the phase of blood coagulation is the polymerization of fibrin.

This phase is characterized by retraction of the blood clot. Blood clot retraction - this indicator reflects the ratio of blood serum volume to volume to blood taken for examination (3-5 ml) after the formation of a blood clot in it. The normal range of values is 48-64%.

IV. phase - spontaneous fibrinolysis.

Assessing this process, it is considered that if from 10 to 20% of the blood cells come out of the clot in the process of its spontaneous lysis, then fibrinolysis proceeds normally.

Methods for the study of fibrinolysis.

The most common methods in clinical practice for assessing the state of the fibrinolytic system are based on:

1. study of the time and degree of lysis (dissolution) of blood clots or plasma euglobulin fraction (general evaluation samples);

2. determining the concentration of plasminogen, its activators and inhibitors;

3. detection of soluble fibrin-monomer complexes (SFMK) and fibrinogen/fibrin degradation products (PDF). Since the definition of D-dimers is already available in almost any laboratory and is widely used in clinical practice, let us dwell on it in more detail.

D-dimers are specific fibrin degradation products that are part of a thrombus. They are formed during the lysis of a blood clot under the influence of plasmin. The concentration of D-dimers in serum is proportional to the activity of fibrinolysis and the amount of fibrin lysed. This test allows you to judge the intensity of the processes of formation and destruction of fibrin clots. Determination of D-dimers is carried out by enzyme immunoassay using monoclonal antibodies. Normal serum PDP concentration is 250-500 ng/ml.

Increasing the level of D-dimers:

• occurs with venous thrombosis, atherothrombosis, pulmonary embolism, DIC (included in the examination protocol), and other conditions with increased fibrin formation.

D-dimers circulate in the blood for a long time, their half-life is more than 24 hours. An increase in the level of D-dimers can be determined within a few weeks after acute thrombosis.

Soluble fibrin-monomeric complexes. When blood coagulation is activated (DIC, thrombosis, thrombophilia), the fibrinogen pool expands, resulting in an increase in the amount of RFMK. The normal

values of RFMK according to the orthophenanthroline test are up to 4.0 mg%.

RFMK increase:

- occurs with DIC, deep vein thrombosis, pulmonary embolism, possibly during treatment with anticoagulants, physical and psychological stress, normal pregnancy, during the neonatal period.

CLASSIFICATION OF HEMORRHAGIC DIATHESIS

Hemorrhagic diathesis is a group of diseases and syndromes united by the leading clinical sign - increased bleeding caused by a defect in one or more components of the hemostasis system.

Taking into account the pathophysiological mechanisms of hemostasis: vascular platelet and coagulation, three groups of hemorrhagic diatheses are distinguished:

1. Thrombocytopenia and thrombocytopathy are diseases caused by changes in the quantity or quality of platelets. These include primarily ITP and thrombocytopathies of various types.

2. Vasopathy - processes associated with a defect in the vascular wall. This group includes various diseases according to the mechanism of occurrence: hemorrhagic vasculitis, Rendu-Osler disease, infectious toxic vascular damage (bacterial endocarditis), beriberi C, etc.

3. Coagulopathy is a very large group of diseases caused by deficiency or molecular defects in plasma coagulation factors. The most common forms from the group of hereditary coagulopathy are hemophilia A (68-78%), von Willebrand disease (9-18%) and hemophilia B (6-13%), hypoprothrombinemia, hypofibrinogenemia and other hereditary defects F.

Acquired coagulopathies can occur as a result of impaired synthesis of coagulation factors in the liver, vitamin K deficiency (diarrhea, cholestasis, liver cirrhosis, use of indirect anticoagulants), the formation of antibodies to blood coagulation factors (autoimmune hemophilia A), heparin overdose, hemoblastoses, DIC, and others

IDIOPATHIC

THROMBOCYTOPENIC PURPLE

Idiopathic thrombocytopenic purpura is a disease with isolated immune thrombocytopenia below 100.0 x 109/l, accompanied or not by hemorrhagic syndrome of varying severity.

In 2008, the International Consensus for the Diagnosis and Treatment of ITP suggested that idiopathic thrombocytopenic purpura, or Werlhof's disease, be called primary immune thrombocytopenia.

The incidence of ITP in the world is 1.6-3.9 cases per 100 thousand population per year. The prevalence has no geographic regions. Women get sick more often. Age from 20-40 years. Provoking factors of ITP can be viral infections, pregnancy, stress, surgical procedures, vaccinations, excessive hypothermia or insolation. These factors realize their effect against the background of the genetic predisposition of the organism. But a third of patients develop ITP for no apparent reason.

Pathophysiology of ITP

ITP is based on the breakdown of immunological tolerance to unchanged antigens of one's own platelets and the formation of ATA. It is still not known exactly what causes the production of autoantibodies (usually of the IgG class) directed against components of the platelet membrane. The membrane glycoprotein 2b-3a complex is most commonly affected, although other membrane glycoproteins (GPs) may be involved. In the case of an autoimmune conflict, the amount of IgG per platelet is approximately 200 times greater than the number of IgG molecules on the surface of a healthy person's platelet. Other classes of immunoglobulins - IgM, IgA - can also possess ATA properties.

Currently, other pathogenetic mechanisms of ITP are also described:

• direct cytotoxic effect of T-killers;

• imbalance of cytokines towards the predominance of pro-inflammatory cytokines (IL-2, INF-y), decrease in anti-inflammatory (IL-10);

• decrease in the number of T-cells with suppressive properties, capable of suppressing the immune response;

• complement activation, which leads to the formation of a membrane-attacking complex that damages the platelet membrane.

The main site of ATA formation and the organ in which platelet destruction occurs is the spleen. Sensitization of platelets by IgG leads to a significant reduction in their life time due to phagocytosis by splenic macrophages. As a result of the above reactions, the life span of platelets is sharply reduced from 7-

10 days to several hours.
The key modulator of platelet production is thrombopoietin. Endogenous thrombopoietin has an affinity for receptors on megakaryocytes located in the red bone marrow. The level of platelet production is directly proportional to the level of endogenous thrombopoietin.
In most cases, with ITP, the rate of platelet formation in the bone marrow increases, which is due to an increase in the synthesis of thrombopoietin and an increase in the number of megakaryocytes (hyperregenerative thrombocytopenia). But in some cases, the maturation of megakaryocytes in the bone marrow is disrupted. Antibodies that have an affinity for platelets can attach to megakaryocytes, resulting in impaired megakaryocytopoiesis. Platelet production is reduced and thrombocytopenia is hyporegenerative in nature.
Features of the pathogenesis of ITP in childhood
Typically, ITP is acute in children. Provoking factors - viral infections, vaccination. The pathogenesis is based on the production of ATA directed against the antigens of viral proteins. On the membrane of circulating platelets, adsorption of the viral antigen (which subsequently binds to the antibody) or virus-antibody immune complexes occurs. Since the antigens of the virus are necessarily eliminated, acute ITP resolves spontaneously in 80% of cases.
Patients with ITP may develop autoantibodies to other organs and tissues, most commonly affecting the thyroid gland. Approximately 40% of patients with ITP have antibodies to thyroid tissues, and a quarter of these patients suffer from symptoms of hyper- or hypothyroidism.
Clinic
1. Asymptomatic. Patients learn about ITP after routine examinations.
A safe platelet level of 50 x 109/l and above ensures normal life without spontaneous bleeding and does not reduce the patient's quality of life.
2. Spontaneous or post-traumatic cutaneous hemorrhagic syndrome - single or multiple petechiae and ecchymosis, which are located on the skin of the trunk, limbs.
3. Petechiae and ecchymosis on the mucous membranes of the oral cavity, tonsils, posterior pharyngeal wall, soft and hard palate in the form of enanthemas, submucosal hematomas.
4. Nose and gingival bleeding, meno-metrorrhagia, hematuria, bleeding from the gastrointestinal tract. Cerebral hemorrhage (up to 1%) of cases, which is the main cause of death in ITP.
There is a clear relationship between platelet count and bleeding severity (Table 2). Hemorrhagic syndrome in patients with platelet levels above 100 x 109/l requires the exclusion of their qualitative defect (thrombocytopathy). If a severe hemorrhagic syndrome develops with a platelet count of more than 30.0 x 109/l, then it is necessary to exclude additional causes of bleeding - coagulopathy, vascular pathology. It is also necessary to take into account other factors that predispose to bleeding: age, taking drugs that are not related to ITP therapy, comorbidities, and the patient's lifestyle.
Table 2 - Platelet levels and the risk of developing hemorrhagic syndrome

platelet count (x 10^9/л)	Symptoms
> 50	Missing
30-50	Increased tendency to bruise with minor injuries
10-30	Spontaneous occurrence of petechiae and hematomas
< 10	Risk of internal bleeding

- DIAGNOSIS OF ITP
- Diagnostic criteria:
- • isolated thrombocytopenia less than 100.0 x 109 /l in two blood tests;
- • visual assessment of the number and morphology of platelets;
- • increased or normal amount of MCC in the myelogram;
- • normal size of the spleen;
- • N.B.! exclusion of other pathological conditions that cause thrombocytopenia;
- • ATA in high titer.

• There is no "gold standard" for diagnosing ITP. Since the diagnosis of ITP is a diagnosis of exclusion, a full comprehensive examination is necessary.

• Basic examination methods

• History of the disease: determination of factors preceding thrombocytopenia — bacterial / viral infection, vaccination, stress, medication, anticoagulant therapy, antiplatelet agents, the presence and duration of bleeding after surgical interventions, somatic diseases that occur with thrombocytopenia. Thrombocytopenia, thrombosis and diseases of the hematopoietic system in blood relatives.

• Objective examination: hyperthermia, weight loss and symptoms of intoxication, hepatomegaly and splenomegaly, lymphadenopathy, pathology of the mammary glands, heart, veins of the lower extremities, congenital anomalies, etc.

• Complete blood count: N.B.! Optical (visual) counting of platelets and reticulocytes. In ITP, there is isolated thrombocytopenia. Signs of posthemorrhagic anemia and reticulocytosis after massive blood loss.

• Biochemical blood test: to assess the condition of internal organs and diagnose somatic diseases. Patients with anemia and reticulocytosis require a direct Coombs test.

• Detailed coagulogram: (APTT, prothrombin and thrombin time, fibrinogen, antithrombin 3, fibrinolytic activity, platelet aggregation with ADP, ristomycin, adrenaline, platelet aggregation rate, factor 13 activity, RKMF, protein C activity).

• Virological study: diseases of a viral nature that occur with thrombocytopenia - viral hepatitis A, B, C, HSV, CMV, Ebstein-Barr virus, HIV.

• Ultrasound or CT of the abdominal cavity and retroperitoneal space. WG-graphy or CT scan.

• FGDS, FCS, ultrasound of OMT, prostate gland.

• Cytological examination of the bone marrow to exclude thrombocytopenia in MDS, LPD, AA, tumor metastases in the bone marrow. Indicated in patients over 60 years of age, with abnormal blood pressure, those with a poor response to first-line therapy who are sent for splenectomy. With ITP, the number of MCC is increased or normal.

• Additional research methods:

• • specific antibodies to platelet glycoproteins;

• • antiphospholipid antibodies (lupus anticoagulant and antibodies to cardiolipins);

• • antibodies to thyroid peroxidase and evaluation of thyroid function to rule out AIT;

• • antibodies to native DNA to rule out SLE;

• • pregnancy test (thrombocytopenia syndrome is registered in 10% of pregnant women);

• - PCR to detect parvovirus.

• DIFFERENTIAL DIAGNOSIS OF ITP

• To confirm the diagnosis of ITP, differential diagnosis should be carried out with the following diseases and conditions that occur with thrombocytopenia:

• I. "False" or pseudothrombocytopenia.

• II. Increased destruction of platelets:

• 3. Autoimmune:

• • ETC.

• • Secondary: post-infectious, in pregnant women, against the background of autoimmune thyroiditis, SLE, AFLS and other collagenoses, with LPZ, drug genesis - the interaction between the drug and a component of the platelet membrane makes the glycoprotein, drug or glycoprotein-drug complex immunogenic. Specific antibodies bind to these components, opsonization and removal of the platelet through the reticuloendothelial system of the spleen, or complement activation with subsequent intravascular destruction of platelets. Also, the cause of thrombocytopenia may not be the drug itself, but its metabolite. Drugs that cause thrombocytopenia - heparin, quinidine, gold preparations, digoxin, rifampicin, sulfonamides.

• 2. Alloimmune:

• • Neonatal thrombocytopenia - transplacental transmission of maternal antibodies that react with fetal platelets. The reason is the incompatibility of the fetus and mother for platelet antigens, most often for PLA1. PLAl antigen is absent on maternal platelets, but present on fetal platelets. The sensitized

mother's body produces ATA, which cross the placenta and cause the destruction of fetal platelets.

- • Post-transfusion purpura (repeated women; patients who have previously received blood transfusions or blood components).
- 3. Destruction of non-immune origin:
- • ICE;
- • cardiovascular anomalies and diseases (aneurysms, heart defects, stenting);
- • thrombotic microangiopathy (microthrombosis) is a clinical syndrome characterized by thrombocytopenia, MAGA, microvascular thrombosis of arterioles and capillaries, dysfunctions of many organs and systems. TMA includes hemolytic uremic syndrome, thrombotic thrombocytopenic purpura. TMA can develop in a number of diseases (diffuse connective tissue diseases, oncopathology, after taking drugs - thienoperidines, calcineurin inhibitors, oral contraceptives, cytostatics);
- • thrombotic thrombocytopenic purpura (TTP) - a sharp increase in platelet aggregation with the formation of platelet clots, consisting of platelets and VWF in the small vessels of most organs (more often - the kidneys, central nervous system, heart). In patients with TTP, the VWF molecule is large. The VWF macromolecule causes platelet hyperaggregation. Increased consumption of platelets leads to thrombocytopenia, vasoconstriction leads to the development of MAHA (mechanical destruction of red blood cells). Patients with TTP have a metalloproteinase enzyme deficiency. Metalloproteinase reduces the size of VWF molecules by cleaving them. Enzyme deficiency may be due to the presence of autoantibodies to the enzyme or a mutation in the ADAMTS-13 gene. A decrease in enzyme activity is observed in conditions such as DIC, sepsis, uremia, heparin-induced thrombocytopenia. TTP is more common in adults. The "five" signs of TTP are consumption thrombocytopenia, MAGA, fever, intermittent neurological symptoms, renal failure;
- • Hemolytic-uremic syndrome (HUS) is an acute disease in which MAHA, thrombocytopenia, AKI develop in the prodromal period against the background of infectious diarrhea. In 90% of cases it develops in childhood. HUS is preceded by bloody diarrhea caused by Shigella dysenteriae or enterotoxic Escherichia coli serotype O157:H7. These microorganisms form toxins that destroy the endothelial cells of the renal capillaries, which leads to the entry into the vascular bed of a significant amount of VWF multimers, followed by platelet aggregation. HUS associated with Streptococcus pneumonia occurs mainly in children under 2-5 years of age. Streptococcus pneumoniae neuraminidase attacks the N-acetyl-neurominic acid of the cell surface, making the T-antigen on the cell surface available for interaction with self T-antibodies. Normally, the T-antigen is "encrypted" - covered with sialic acids and therefore not available for T-antibodies. T-antigen (Thomsen-Friedenreich crypt antigen) is a component of the cell membranes of erythrocytes, platelets, and glomerular endothelial cells. Natural T-antibodies are present in the blood serum of every person, their level is almost constant from birth.
- III. Disruption of platelet production:
- 3. Drug-mediated thrombocytopenia.
- 4. Infectious diseases.
- 5. Toxic (alcohol has a suppressive effect on developing megakaryocytes, leads to reduced production of thrombopoietin in the liver, etc.).
- 6. Metastatic lesion of the bone marrow in neoplasms.
- 7. Diseases of the hematopoietic system (acute leukemia, AA, MDS, LPZ).
- . Hereditary thrombocytopenia:
- 1. Glanzman's thrombasthenia.
- 2. Bernard-Soulier syndrome.
- 3. Gray platelet syndrome.
- 4. Wiskott-Aldrich syndrome.
- 5. Congenital amegakaryocytopenia.
- 6. Anemia Fanconi and others.
- CLASSIFICATION OF ITP
- According to the course of the disease:
- • first diagnosed with a duration of up to 3 months from the moment of diagnosis;
- • persistent (protracted) with a duration of 3-12 months. from the moment of diagnosis;

- • chronic with a duration of more than 12 months. from the time of diagnosis.
- 2. By the nature and severity of hemorrhagic syndrome (WHO classification):
- • 0th degree - no hemorrhagic syndrome;
- • 1st degree - petechiae and ecchymosis (single);
- • 2nd degree - minor blood loss (melena, hematuria, hemoptysis);
- • 3rd degree - severe blood loss (bleeding requiring blood transfusion or blood substitutes);
- • 4th degree - severe blood loss (hemorrhage in the brain and retina, bleeding, ending in death).
- severe ITP
- • cases that are characterized by symptoms of bleeding at the onset of the disease;
- • cases requiring initiation of therapy;
- • cases of recurrent bleeding with the need for additional therapeutic benefits with various drugs that increase the number of platelets;
- • the need to increase the dosage of the drugs used.
- Refractory ITP is the inability to maintain a long-term clinical effect after splenectomy (cannot be diagnosed before it). It occurs in 25% of patients with chronic ITP.
- In this case, a re-examination is mandatory to rule out other causes of thrombocytopenia and confirm the diagnosis of ITP.
- Treatment
- The main goal of ITP therapy is to achieve a safe or hemorrhagic syndrome-limiting platelet count. Age is an independent factor in the development of severe bleeding: the older the patient, the higher the risk of life-threatening bleeding. 30.0-50.0 x 109/l is a safe concentration of platelets, which ensures the existence of the patient without spontaneous bleeding and does not reduce the quality of life. The platelet count of 100.0 x 109/l fully provides hemostasis and allows for surgical interventions and delivery without the risk of bleeding.
- Therapy of patients with ITP
- • if the platelet count is at least 30.0-50.0 x 109/l and there is no hemorrhagic syndrome, specific pathogenetic therapy is not carried out. Vascular strengthening agents are used: dietion (etamsylate) 0.25-0.5 g 3-4 times a day orally or intravenously, ascor-
- tin 1-2 tablets 3 times a day;
- - with a platelet count of 30.0-50.0 x 109 / l and the presence of hemorrhagic syndrome / thrombocytopenia less than 10.0-20 x 109 / l / presence of hemorrhagic syndrome, 1st line therapy is prescribed:
- 1st line therapy:
- • GKS. The effect of corticosteroids is to inhibit the interaction between IgG-coated platelets and Fc receptors of spleen macrophages, which impairs phagocytosis. With prolonged use of corticosteroids inhibit the formation of ATA. GCS - prednisolone at a dose of 1 mg / kg of body weight orally for 2-4 weeks. After stopping the hemorrhagic syndrome and increasing the platelet count above 50.0 x 109/l, it is necessary to start a gradual decrease in the drug. With a decrease in the number of platelets and the appearance of hemorrhagic syndrome, a return to the previous dosage is mandatory. Maintenance therapy in small doses of 10-15 mg / day, then every other day for 4-8 months. is not accompanied by a pronounced side effect and stabilizes the achieved effect, without violating the quality of life and working capacity of patients. If there is no effect, it must be completely canceled by the end of the 5th week. from the start of therapy.
- • VVI) saturates Fc-receptors of splenic macrophages, which leads to a decrease in the rate of phagocytosis. Intravenous administration of high doses of polyvalent immunoglobulin provides a more rapid increase in platelet count compared to corticosteroids. The hemostatic effect occurs 1-2 days after administration.
- Indications for the appointment of IVIG:
- => massive bleeding (uterine, gastrointestinal tract, the threat of hemorrhage in the brain, organs of vision);

- => contraindications to the appointment of GCS;
- => treatment of pregnant women with ITP;
- => emergency surgery, before splenectomy.
- Therapy 2 lines:
- • Splenectomy. It is recommended to observe the patient for at least 6 months from the onset of the disease before deciding on a splenectomy.
- Indications for splenectomy:
- => resistance to GCS therapy;
- => intolerance and contraindications to the treatment of corticosteroids and IVIG;
- => massive bleeding;
- => severe uncontrolled exacerbations of ITP in pregnant women in the 1-2 trimesters of pregnancy;
- => frequent relapses (more than 3 per year), accompanied by severe bleeding.

Thrombopoietin receptor agonists (romiplostim, enplate) - activate the thrombopoietin receptor, resulting in stimulation of platelet production. Indications for treatment with romiplostim: ineffectiveness of 1st line therapy, pronounced side effects and contraindications in the treatment of corticosteroids, IVIG, impossibility of splenectomy, the need to reduce the risk of bleeding before elective and emergency surgery.

• Immunosuppressants — azathioprine (AZA), cyclosporine A, mycophenol mofetil, cyclophosphamide (CF).

• Monoclonal antibodies. In case of ineffectiveness of previous methods of treatment, as well as a categorical refusal of splenectomy, by decision of the medical council and with the consent of the patient, it is possible to prescribe rituximab (mabthera).

Symptomatic therapy aimed at stopping hemorrhagic syndrome:

=> locally to stop bleeding, a hemostatic sponge, tampons moistened with dicynone (for nosebleeds), rinsing the mouth with a solution of aminocaproic acid, etc. are used;

=> antifibrinolytic drugs - tranexamic acid, ACC inhibit the action of the plasmin activator and plasminogen, have a hemostatic effect in bleeding, in addition, they have an anti-allergic and anti-inflammatory effect by suppressing the formation of kinins and other active peptides involved in allergic and inflammatory reactions. In patients with thrombocytopathies, they are most often used in case of development of nasal, gingival bleeding, menorrhagia. They are also prescribed to prevent the development of bleeding during minor surgical interventions and dental treatment. Oral and intravenous administration is possible. The drug of choice in this group is tranexamic acid. Compared to ACC, it has 8 times greater antifibrinolytic activity. The dose of tranexamic acid is 15-25 mg/kg orally 3-4 times a day or 10 mg/kg intravenously 3-4 times a day. It can also be used as a mouth rinse in case of gingival bleeding - 10 ml of a 5% solution 4-6 times a day, if swallowed, the equivalent dose is 500 mg. Antifibrinolytics are contraindicated in hematuria due to the risk of developing acute renal failure!

Forecast

The outcomes of ITP are highly individual. In children, ITP is more likely to be acute, and recovery almost always occurs. In adult patients, there is a tendency to chronicity of the process, spontaneous recovery is not typical. But in most patients, ITP becomes stable and no therapy is required.

Lethal outcome - 3% of patients. These are patients who do not respond to therapy. The causes of deaths are intracranial hemorrhages, infections.

THROMBOCYTOPATHIES is a group of syndromes and diseases characterized by qualitative inferiority and dysfunction of platelets, while the number of platelets in the CBC is within the normal range or slightly reduced. The hemorrhagic syndrome in thrombocytopathy does not differ from that in thrombocytopenia.

Thrombocytopathies are divided into:

Primary (hereditary):

The following functional-morphological forms are distinguished:

1. Violation of platelet adhesion:

• Bernard-Soulier syndrome (deficiency or defect of the platelet GP 1b complex. GP 1b is the

main receptor for VWF, as a result of the defect, platelet adhesion to the vascular subendothelial matrix is impaired);

• Willebrand's disease (VW) (deficiency or defect in VWF, which plays an important role in the initial adhesion of platelets to collagen and other extracellular matrix proteins when the subendothelial surface is damaged).

2. Violation of platelet aggregation:

• Glantsman's thrombasthenia (deficiency or defect of GP 2b-3a, binding of fibrinogen to the cell membrane is disturbed, "crosslinking" of platelets with fibrinogen necessary for their aggregation does not occur);

• hereditary afibrinogenemia (deficiency or defect of a11bb3, fibrinogen).

3. Impaired release and deficiency of granules:

• α-granule storage pool deficiency (grey platelet syndrome, APC syndrome, Quebec platelet syndrome, Pari-Trousseau syndrome), 5-granules (dense granule deficiency, Hermansky-Pudlak disease, Chediak-Higashi syndrome, TAP syndrome), and - and 5-granules (deficiency of dense and a-granules).

4. Violation of the formation and deficiency of signaling pathways:

• defects in agonist receptors: thromboxane A.

Acquired (symptomatic):

1. With hemoblastoses.

2. With MPD and essential thrombocythemia.

3. With vitamin B12 deficiency anemia.

4. With uremia (violation of the adhesive-aggregative function of platelets, less often clot retraction).

5. With multiple myeloma, Waldenström's disease, gammopathy (blockade of platelets by macro- and paraproteins).

6. With cirrhosis, tumors and parasitic diseases of the liver (disturbances in the adhesive-aggregation function of platelets due to metabolic disorders, sequestration of platelets in the portal system, consumption of platelets in the development of DIC).

7. With scurvy (impaired interaction with the endothelium and ADP-aggregation).

8. With hormonal disorders - hypoestrogenism, hypothyroidism.

9. Medicinal and toxigenic forms (in the treatment of aspirin and other NSAIDs, antibiotics, tranquilizers, nitrofurans, cytostatics, etc.).

10. With radiation sickness.

11. With massive blood transfusions and infusions of rheopolyglucin.

12. With large thrombosis and giant angiomas (consumption thrombocytopathy).

Qualitative platelet dysfunction should be suspected when:

• pathological time of capillary bleeding;

• normal values of APTT, prothrombin and thrombin time;

• normal platelet count.

OAK

• Evaluation of platelets in manual mode in a blood smear with Romanovsky-Giemsa staining.

• Counting the number of platelets (most thrombocytopathies are characterized by a normal number).

• Evaluation of platelet morphology.

• Evaluation of the morphology of leukocytes (the presence of large basophilic inclusions in granulocytes and monocytes is a marker of the MYH9 group of syndromes).

• Evaluation of erythrocyte morphology (the presence of morphological abnormalities may indicate diseases associated with GATA-l gene mutation).

Morphological analysis of platelets will provide additional information regarding the number and size of platelets, the presence of their conglomerates and other features: the absence of alpha granules and the general gray color of platelets indicates gray platelet disease.

The study of functional disorders of platelets.

• prolongation of capillary bleeding time (Duke, Ivey tests) and PFA-100 (automatic platelet

function analyzer).

Determination of the duration of capillary bleeding. According to Duke (most often used in clinical practice, earlobe puncture with a scarifier). Normally it is 2-4 minutes. The lengthening of time indicates a decrease in the tone of the vascular wall, thrombocytopenia or thrombocytopathy.

Evaluation of platelet function. The method of optical aggregometry (light transmission aggregometry - LTA) was recognized as the "gold standard" for assessing the functional activity of platelets. The method is based on the photometer assessment of the light transmission capacity (% aggregation) of citrate platelet-rich plasma when an aggregation agonist (ADP, epinephrine, collagen, arachidonic acid, thromboxane) is added to it. Platelet agglutination induced by ristocetin, which activates VWF binding to GP 1b-IX-V, is also measured by LTA. Ideally, testing should be done at least once to confirm a platelet aggregation disorder. In addition, when assessing the functional activity of platelets, it is necessary to collect a detailed history of taking medications and homeopathic preparations that can affect the test results.

Treatment

Hereditary thrombocytopathies are observed in specialized hematological centers. With the development of moderate and severe bleeding, systemic administration of drugs is necessary: antifibrinolytic agents (tranexamic acid), desmopressin (DDAVP) and activated recombinant blood coagulation factor VII (rVIIa). Life-threatening conditions often require platelet transfusions to compensate for their congenital dysfunction.

RANDU-OSLER DISEASE

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Randu disease, is a rare hereditary disorder that results in the formation of easily bleeding telangiectasias on the surface of the skin and mucous membranes. It is associated with the presence of arteriovenous congenital malformations in the systems of many organs, which can cause dangerous complications. Synonyms of the disease are generalized angiomatosis, hemorrhagic familial angiomatosis, hereditary hemorrhagic telangiectasia, familial hemorrhagic telangiectasia.

The frequency of this disease is 1-2 per 1 million people. Both sexes are equally affected.

Etiopathogenesis

There is no single point of view on the origin of vascular changes. Bleeding is explained by pathological restructuring of the vascular wall and is always localized in areas of vascular expansion - telangiectasias.

The disease is inherited in an autosomal dominant manner, the probability of gene manifestation is 97%. In some families, a mutation has been observed in the gene encoding a receptor for a transforming growth factor called endoglin. Genetic heterogeneity has been demonstrated, suggesting the involvement of other transforming growth factor receptors. This may explain the differences in the clinical manifestations of the disease. Arteriovenous congenital malformations, capable of reaching a diameter of several centimeters, consisting of thin-walled vascular cavities with one or more feeding arteries, can appear in any organ, but mainly in the lungs, liver and brain.

In the last decade, a link between the disease and chromosomal changes has been established. There are mutations in the genes involved in angiogenesis, or pathogenetic variants of the genes involved in the TGF-B/BMP signaling cascade:

- ENG — gene encoding cell surface endoglin coreceptor;
- ACVRL 1 (formerly ALK 1) - the gene encoding the cell surface receptor;
- SMAD 4 — gene encoding an intracellular signaling molecule;
- GDF 2 is the gene encoding growth/differentiation factor.

At least two other yet unknown genes take part in the pathological process. Molecular genetic testing of ENG, ACVRL 1, SMAD 4, and GDF 2 detects pathogenic variants in 80-87% of individuals who are clinically diagnosed with hereditary hemorrhagic telangiectasia.

Depending on the gene in which the violation is detected, the following types of disease are distinguished:

- ENG — hereditary hemorrhagic telangiectasia type 1 (HHT-1);
- ACVRL 1 (formerly ALK 1) — hereditary hemorrhagic telangiectasia type 2 (HHT-2);

•SMAD 4 — hereditary hemorrhagic telangiectasia associated with juvenile polyposis;

• GDF 2 - hereditary hemorrhagic telangiectasia type 5 (HHT-5).

The first two types are the most common (53 and 47%, respectively). Mutation of these genes leads to disruption of the structure of the muscular and elastic layers of blood vessels, as well as perivascular connective tissue. Defects in intercellular connections and degeneration of endothelial cells are possible. The presence of areas of absence of the muscle layer leads to dilatation of capillaries and postcapillary venules. Violation of angiogenesis is manifested by the formation of aneurysms, the presence of telangiectasias and arteriovenous shunts. The process of formation of pathological vascular structures is possible throughout the life of the patient.

Clinic

The classic picture of the disease is the familial pattern of telangiectasias and the presence of nosebleeds and characteristic lesions 1 to 2 mm in diameter, consisting of an enlarged vessel on the surface of the skin or mucous membranes, as well as visceral vascular anomalies (angiomas, arteriovenous aneurysms, shunts in the lungs, liver, brain, etc.).

Skin and mucous membranes. Most patients have telangiectasias - dilatation of small skin vessels (capillaries, arterioles, venules) of non-inflammatory genesis, the size of a pinhead or more. The localization of telangiectasias is different (face, auricles, scalp, chest, fingers, mucous membranes of the mouth, tongue, conjunctiva of the eyes, etc.). In almost all patients with an advanced phase of the disease, they can be found in the area of the nasal mucous membranes (more often in the area of the septum, in the Kisselbach zone).

Telangiectasias usually have a punctate, spotted or spider-like appearance, red-purple in color, slightly rise above the surface of the skin and mucous membranes, turn pale when pressure is applied to them (unlike petechiae). They are multiple, their number increases with age, one of their characteristic features is bleeding. Hemorrhagic diathesis is angiomatous type. Subcutaneous hemorrhages are not typical.

Recurrent nosebleeds, observed in 50-80% of patients - this is the first complaint, often noted before the age of 10 years, provoked by intercurrent diseases, insolation, unrest, alcohol intake, spicy foods, but more often occur for no apparent reason at any time of the day.

With age, there is a tendency to increase hemorrhages, and they become more abundant. The usual one-time blood loss from telangiectasias is different - from a few drops to 500 ml or more. Acute massive blood loss can be fatal. Other localizations of bleeding are often noted: gastrointestinal (10-20%), pulmonary (3-5%), renal (1-3%), etc.

Arteriovenous congenital pulmonary malformations, found in 15-30% of patients with NHT, can lead to significant left-to-right shunting and hypoxemia. Serious complications include bleeding with hemoptysis, hemothorax with paradoxical emboli, or only mild dyspnoea.

Arteriovenous congenital malformations of the digestive tract. Loss of blood through telangiectases in the intestine occurs in 10-40% of patients and usually occurs later in life than nosebleeds. In half of patients, a bleeding spot in the form of a small red, well-marked lesion can be determined using endoscopy of the stomach or duodenum; telangiectases in the colon are rare. Sporadic large arteriovenous congenital malformations occur between the hepatic artery and vein, between the portal and hepatic veins, and between the hepatic artery and portal vein, possibly leading to left-to-right shunting accompanied by heart failure with high cardiac output, to hepatic encephalopathy after bleeding in the intestine and to portal hypertension, accompanied by varicose veins of the esophagus. Hepatomegaly or murmur over the liver should prompt further investigation. Computed tomography and color Doppler are sensitive non-invasive detection methods.

The lesion of the liver, termed cirrhosis in NHT, is characterized by abnormally dilated vessels surrounded by a stroma of varying volume, distributed throughout the liver.

Congenital malformations of cerebral vessels are detected in 5-10% of cases and manifest as telangiectasia, cavernous angiomas, aneurysms. They can cause headache, epileptic seizures, and ischemia of surrounding tissues as a result of the steal syndrome. The risk of bleeding appears to be small. Against the background of cerebral angiomas and arteriovenous aneurysms, some patients develop brain abscesses. Spinal lesions are rare and have been described mainly in children. There are reports of cases

of paraplegia due to arteriovenous fistula of the spinal cord.

Cardiac involvement: NHT may present with symptoms of pulmonary hypertension or heart failure with preserved ejection fraction.

Other symptoms: Recurrent blood loss may be the cause of iron deficiency anemia. With lesions of the vessels of the eye, cases of intraocular hemorrhage are described, with telangiectasias of the conjunctiva - bloody tears.

Diagnostics

Diagnosis is based on family history, identification of telangiectasias, absence of platelet pathology and plasma hemostasis.

Certain signs of changes in the blood coagulation system found in some patients in the form of platelet dysfunction, local fibrinolysis, von Willibrand syndrome stigmata and others are secondary and usually do not lead to the genesis of bleeding.

In the diagnosis of telangiectasia, rhinoscopy, gastroduodenoscopy, colonoscopy, bronchoscopy, and cystoscopy help. Visceral vascular malformations can be detected using ultrasound research methods, computed tomography and magnetic resonance method, angiography. X-ray examination is often informative in the presence of lung malformations.

Current examination practice is to measure paO2 using accurate reference values (paO2 = 104-0.24 x age) in combination with chest x-ray. In the event of a hypoxemic discharge, the measurement is carried out using the 100% oxygen method. If the shunt fraction is abnormal, or if there is any suspicion on a chest x-ray, then intravenous digital primary angiography is done.

MRI is probably the best screening method.

Differential diagnosis of HHT is carried out with diseases accompanied by hemorrhagic manifestations and with those diseases in which there are vascular changes such as telangiectasias. Arteriovenous malformations of the internal organs are differentiated with various diseases: with localization of vascular changes in the lungs - with neoplasms, tuberculoma, cysts, sarcoidosis, and with localization in the liver - with primary or metastatic cancer, cirrhosis-cancer, etc.

Treatment

In the presence of active bleeding, anticoagulants are contraindicated. However, given the risk of increased thrombus formation and thromboembolism, a significant number of patients require this group of drugs.

Antibiotic prophylaxis is recommended for patients with NHT for any invasive and dental procedures.

The use of bevacizumab, an anticancer agent, monoclonal antibodies, is being investigated. The drug interferes with the process of angiogenesis, the growth of a network of blood vessels in the tumor.

Dangerous blood loss from intestinal telangiectasias can be treated with a combination of low doses of estrogen and progestogen, the mechanism of action of which is unknown, but has been shown to reduce the need for blood transfusion when used.

For bleeding, antifibrinolytics are used, for anemia - iron preparations, laser ablation, sclerotherapy, endoscopic procedures, segmental surgical resections. With symptomatic large arteriovenous malformations, the main method of treatment is embolization, if it is ineffective, surgical methods.

The results of endoscopic laser treatment are not as expected, and the treatment of large liver malformations should be conservative. There is doubt as to whether asymptomatic lesions of the nervous system should be treated, as various assumptions have been made regarding the relationship between bleeding risk and surgical risks.

HEMANGIOMAS

Hemangiomas are benign vascular tumors that arise as a result of abnormal vascular formation, with significant dysregulation of angiogenesis.

Congenital and acquired vascular anomalies, including neoplasms and malformations (malformations), are often found in infancy and childhood, in 3-10% of newborns.

Hemangiomas of the outer integument are observed in children from 50 to 80% and in adults up to 20%. Ultrasound examination (ultrasound), CT and MRI of the abdominal cavity reveals hemangiomas in

approximately 5-20% of cases in both men and women, autopsy - in 0.4-20% of cases.

Classification

Hemangiomas are divided into true and false.

Of the true hemangiomas, there are:

• capillary (simple);

• cavernous;

• combined.

There are both single and multiple hemangiomas (in approximately equal proportions).

Simple hemangiomas are located above the surface of the skin. They have a red or blue-purple color, clearly defined reliefs, grow mainly to the sides. Such formations affect the skin and capture several millimeters of subcutaneous fatty tissue. The surface of simple hemangiomas is often smooth, but there is a rough, uneven surface. When pressed, the hemangioma turns pale with the restoration of its color after the cessation of exposure. This type of hemangiomas is painless.

Cavernous hemangioma (cavernoma) is formed under the skin as a result of the development of skin vessels, subcutaneous fatty tissue and underlying soft tissues. Cavernomas can occur after systematic injury to a simple hemangioma. With a cavernoma, which is a nodular formation of a soft and elastic consistency, massive cavities filled with blood are determined in the tumor tissues. Lymphatic vessels may also be involved in the formation of such a tumor. Cavernous hemangioma has bluish hues and looks like bruises and hematomas. When pressed, the hemangioma turns pale (there is an outflow of blood), when coughing - it increases as a result of blood flow. As a rule, cavernous hemangioma is accompanied by a symptom of temperature asymmetry: the tumor is hotter to the touch than the surrounding healthy tissue.

Combined hemangioma is a combination of simple and cavernous. It has subcutaneous and subcutaneous parts. The clinical manifestations of such formations depend on the predominance of one or another part of the vascular tumor.

These vascular neoplasms do not have a capsule, in some cases they are able to grow rapidly, aggressively grow into the surrounding tissues, lead to their destruction, causing both cosmetic and functional disorders.

Etiopathogenesis

Opinions on the origin and pathogenesis of hemangiomas differ in the literature. Some authors refer them to dysplastic processes, others to neoplastic ones (that is, to benign vascular tumors).

A number of epidemiological predisposing factors for the development of hemangiomas have been identified. So, the risk of their development is greater in girls (the sex ratio is from 3:1 to 5:1 and even up to 9:1); in persons of Caucasian race, with prematurity and low birth weight; burdened family history of juvenile hemangiomas (infantile hemangiomas), as well as previous multiple births in mothers. Children born to mothers who underwent chorionic villus biopsy are also at increased risk of developing hemangiomas.

There are a number of hypotheses regarding the probable causes of endothelial cell proliferation and the development of hemangiomas.

A specific marker for all stages of development of infantile hemangiomas is the glucose transporter GLUT1, which is normally detected in the endothelium of the brain, retina, placenta, and endoneurium and is absent in normal skin and other vascular tumors or in abnormalities.

The occurrence of hemangiomas is associated with a defect in the regulation of angiogenesis at an early stage of pregnancy (6-10 weeks), with a characteristic activation of signals that induce neoangiogenesis or adversely affect apoptosis, and inhibition of factors that limit the development of new vessels and the proliferation of endothelial cells.

Placental hypoxia is considered one of the initiating factors for the development of hemangiomas. According to the theory of dysembryogenesis, hemangiomas occur where islands of embryonic angioblast tissue cannot make normal contact with the rest of the developing vascular system.

The monoclonal nature of hemangioma endothelial cells was established, which suggests the existence of a single precursor cell, the appearance of which occurred as a result of a somatic mutation and is associated with a high mitotic activity of cells, against which mutations easily occur. Therefore, we

can assume the existence of a somatic mutation in the genes that control the proliferative activity of endothelial cells.

So, the cause of the development of hemangiomas can be mutations in the chromosome regions responsible for the synthesis of growth factors and regulatory molecules that interact between growth factors and blood vessel cells. Endostatin, which normally inhibits the migration of endothelial cells, in hemangioma tissues not only does not suppress, but also activates this process.

Thus, despite the existence of various hypotheses of the origin of hemangiomas, in all cases, conditions develop that lead to dysregulation of angiogenesis.

Clinic

Frequent localization of hemangiomas, which can be single or multiple, is the skin of the head, neck, parotid region.

Most hemangiomas less than 4 cm in diameter are asymptomatic. Larger hemangiomas may present clinically and in rare cases (less than 1% of cases) require treatment, usually surgical resection. Although other options are possible - puncture sclerosis, arterial or local ferromagnetic embolization.

Depending on the size of hemangiomas, they are divided into:

• small - less than 1.5 cm;

• medium - 1.5-5.0 cm;

• large - more than 5 cm.

Telangiectatic hemangioma is a flat purple-colored spot consisting of many dilated capillaries that intertwine and are located in the surface layer of the skin. The edges of such a hemangioma are blurred, and the purple color gradually turns into the color of normal skin.

Tuberous hemangioma is a bright red or purplish-bluish formation protruding above the surface of the skin, with clear, even or scalloped edges. Its surface is smooth or rough.

Subcutaneous hemangioma is a hemispherical swelling with a smooth surface and without clear boundaries, covered with unchanged skin. The bulk of the tumor is located in the subcutaneous adipose tissue at various depths.

Combined hemangioma is a hemispherical or ovoid vascular formation without clear boundaries, located in the skin and subcutaneous tissue. The color of the formation depends on the color of the superficial part and the depth of the tumor.

Superficial hemangiomas are most prone to spontaneous regression, while subcutaneous and combined hemangiomas may spontaneously disappear at a later date or remain stable.

In adult patients, hemangiomas of muscles, bones or internal organs (liver, spleen) are found.

Along with hemangiomas, hemangiomatosis of the liver is isolated on the skin, which is a process of unknown nature, characterized by diffuse replacement of the parenchyma with hemangiomatous foci, similar in histological structure to cavernous hemangiomas. From multiple or giant hemangiomas, hemangiomatous foci differ macroscopically by the fuzziness of the boundaries, and microscopically by the presence of unevenly expanded and non-anastomosing vascular spaces against the background of normal hepatic parenchyma, lined with a single-layer squamous endothelium without cellular atypia.

Diagnostics

On ultrasound, small hemangiomas (less than 3 cm in diameter) look like hyperechoic formations with a cellular structure and clear bumpy contours. Some hemangiomas appear as hypo- or isoechoic masses. This can make it extremely difficult to differentiate from metastases (if intravenous contrast is not used with special ultrasound contrast agents).

On CT, hemangiomas (natively) do not have noticeable features in their display and look like rounded formations of various sizes with a homogeneous structure of reduced density and clear even or wavy contours. Without intravenous contrasting, differential diagnosis with other focal liver tumors is practically impossible. However, with intravenous contrast (both with CT and MRI), one can detect signs that are very characteristic of hemangiomas: clear wavy contours of a focal formation, a homogeneous internal structure. In the arterial phase of contrasting, the appearance of large nodular areas of contrasting is noted only along the periphery of the formation. In the venous phase - a significant increase in the size of these areas. In the delayed phase, there is a further increase in the size of the contrasting areas and their almost complete fusion in the absence of contrasting of the central parts of the formation.

On MRI, hemangiomas are uniformly hypointense at T1 and uniformly hyperintense at T2 (but to a lesser extent than cysts). Their shape is round, the contours are clear and even. In large hemangiomas, the contours may be wavy.

In recent years, diffusion-weighted MRI has been actively used in the diagnosis and differential diagnosis of focal lesions in the liver, which has established itself as an effective and promising method in various departments of diagnostic radiology, primarily in neuroradiology.

Difficulties in differential diagnosis are possible with small adenomas, nodules of hepatocellular cancer and hypervascular metastases (1-1.5 cm), which can be contrasted quickly and relatively uniformly (already in the arterial phase), outwardly resembling the display of hemangiomas. However, it should be remembered that the state of "strengthening" of the listed formations lasts only about 1-2 minutes (but not 10 minutes, as with hemangiomas).

Discussing the issue of diagnosis and differential diagnosis of hemangiomas, one should mention the high information content of the radionuclide method using labeled erythrocytes. Using this method, it is possible to confidently recognize hemangiomas with a diameter of 1-2.5 cm (depending on their localization in the liver). The use of fine needle biopsy for the diagnosis of hemangiomas is currently considered irrational.

Treatment

One of the very serious problems is the treatment of ulcerated hemangiomas, accompanied by infection and bleeding.

Sometimes, under the influence of minor injuries, hemangiomas are damaged, infected and, having ulcerated, are difficult to respond to traditional methods of treatment.

Currently, there are various ways to treat hemangiomas:

- surgical;
- sclerosing;
- electrocoagulation;
- radiation;
- hormonal;
- laser;
- cryogenic, etc.

The presence of a large number of treatment methods indicates that none of them is universal, and their diversity makes it difficult to choose a method of treating a particular patient.

Von Willebrand disease (VW) is a heterogeneous group of hereditary and acquired coagulopathies caused by impaired synthesis or qualitative anomalies of VWF.

BV (Table 3) affects about 1% of the population (more often the disease is mild, in about 70% of patients; the remaining 30% of patients have a moderate or severe form of the disease).

Table 3 - BV classification (Scietificand Standardization Committee of International Societyon Thrombosisand Haemostasis, 2006)

Тип	Характеристика
I	Partial quantitative deficiency of VWF
II	Quality deficiency VWF
II A	Qualitative VWF deficiency with decreased VWF-dependent platelet adhesion and isolated deficiency of high molecular weight VWF multimers
II B	Qualitative VWF deficiency with increased platelet affinity for GPIb
II M	Qualitative VWF deficiency with decreased VWF-dependent platelet adhesion without isolated deficiency of high molecular weight VWF multimers
II N	Significant reduction in the ability of VWF to bind to FVIII
III	Virtually no VWF

BV type I is the most common, accounting for 55 to 70% of all diagnosed cases. In type I VWF, the amount of VWF is somewhat reduced, but the function of each molecule is preserved.

BV type II — qualitative defects in VWF are observed, which in most patients are expressed in a disproportionate decrease in VWF: RCo or VWFTVnffi in relation to the amount of VWF determined by its antigen (VWF:Ag).

Classification of the subtype of BV type II is the most difficult task, due to the heterogeneity of functional and structural defects.

Subtype II A - there is an isolated deficiency of high molecular weight VWF multimers and reduced VWF-dependent platelet adhesion. This is due to hypersensitivity to the ADAMTS-13 metalloproteinase, which cleaves ultra-high molecular weight VWF multimers, or defects in the assembly of VWF multimers due to impaired dimerization or multimerization.

Subtype II B - includes various variants of a qualitative defect in VWF, expressed in its increased affinity for platelet GPIb. Due to the increased affinity of VWF for GPIb, the binding of large high molecular weight VWF multimers to platelets is more efficient, so they are more rapidly cleaved by ADAMTS-13 metalloproteinase. The consequence of this is a decrease in the number of large VWF multimers. Rarely, increased affinity of VWF for GPIb is not accompanied by loss of high molecular weight VWF multimers and a normal triplet structure of VWF multimers is found.

BV type IIB is characterized by increased ristocetin-induced platelet aggregation under the influence of low concentrations of ristocetin. Patients often present with varying degrees of thrombocytopenia, which may be exacerbated by stress or DDAVP.

Subtype II M - includes various variants of a qualitative defect in VWF, expressed in a decrease in VWF-dependent platelet adhesion without an isolated deficiency of high-molecular-weight VWF multimers. The functional defect is caused by mutations that result in impaired VWF binding to platelets or subendothelium. Reduced platelet binding reduces the availability of VWF multimers for cleavage by metalloproteinase ADAMTS-13, and therefore the distribution of VWF multimers by molecular weight remains unchanged after their secretion by endothelial cells. Most patients with BV type II M have a disproportionately low VWF: RCo relative to VWF: Ag. Subtype II N - there is a defect in VWF at the binding site to FVIII. As a result, the VWF-FVIII complex cannot be formed. This BV variant is determined using the VWF-FVIII binding assay.

VW type III (occurs rarely in 1-3% of patients) is the most severe form of the disease, since VWF is almost completely absent. Since one of the functions of VWF is to bind to FVIII and protect it from premature proteolysis, patients with VW type III are characterized not only by the absence of VWF, but also by very low FVIII:C.

The clinical picture of BV is variable, from mild (with minor hemorrhagic syndrome) to severe (with heavy bleeding).

Usually, bleeding begins in early childhood, followed by alternating exacerbations and remissions. There is a tendency to decrease in hemorrhagic manifestations with age. Nosebleeds are the most common manifestation of the disease in men and women, can often recur and be very pronounced. Frequent recurrences of nosebleeds are due to a certain extent to vascular dysplasia (often observed in BV).

In a mild form of the disease, a moderately pronounced hemorrhagic rash on the skin and bleeding of the mucous membranes (a reflection of a violation of primary hemostasis) is observed. In a severe form of the disease, extensive subcutaneous hemorrhages, intramuscular hematomas and hemarthroses are observed.

Severe form - manifested by heavy bleeding after injuries, tooth extractions, surgical interventions, severe gastrointestinal bleeding is possible. Rarely observed renal bleeding and intracerebral hemorrhage.

BV is often combined with diseases in which there is connective tissue dysplasia and vascular dysplasia - with Rendu-Osler disease, Marfan's syndrome (VWF and its antigen are produced in endothelial cells, and therefore VWF synthesis is impaired in vascular dysplasia and dysmesenchymosis). Often, when examining patients with BV, signs of connective tissue dysplasia are revealed in the form of skin hyperextensibility and joint hypermobility.

BV laboratory data:

General blood analysis. There are no characteristic changes. In severe form of the disease, frequent bleeding develops hypochromic anemia.

General urine analysis. There are no characteristic changes. In rare cases, with a severe form of the disease, hematuria is observed, the appearance of erythrocyte cylinders is possible.

Biochemical blood test (BAC). There are no specific changes. With the development of chronic iron deficiency anemia, the content of iron in the blood decreases.

Research of system of a hemostasis. The severity and direction of changes in the hemostasis system depend on the type and severity of BV. The most characteristic changes in the hemostasis system are as follows:

• prolonged bleeding time (only in type I, in some patients, this indicator is normal);

• normal or extended activated APTT (indicators of this test are closely related to the level of factor VIII.C in the blood plasma of patients);

• significant change in indicators of ristocetin-induced platelet aggregation;

• changes in the level of VWF in blood plasma and the balance of its multimers depending on the type of disease;

• change in the level of VWF antigen in the blood and VWF: RCoF depending on the type of disease;

• normal indicators of blood clotting time (with the exception of type III disease).

The leading laboratory methods for diagnosing BV are ristocetin-induced platelet aggregation and quantitative determination of VWF in the blood plasma of patients. A more accurate method for determining VWF is the ELISA method. In recent years, a highly specific and sensitive method for the determination of VWF in plasma, which is based on its affinity for collagen, has been used (soluble type III collagen obtained from human placenta is used, which is immobilized on microplates; polyclonal antibodies to VWF are used for titration, and collagen binding is recorded photometrically). A radioimmunoassay method for determining VWF is also used.

Instrumental studies:

• FGDS, ultrasound of the pelvic organs, bronchoscopy, colonoscopy - detection of the source of bleeding;

• radiography of the joints - determination of organic changes in the bone structures of the joint;

• Ultrasound of the joints - determination of the volume of outflowing blood, the condition of the synovial membrane, signs of compression of the surrounding tissues.

Treatment for BV:

The goal of treating BV is to increase or replace the missing clotting factors. Treatment may be prophylactic or on demand for acute bleeding. Patients with VWD receive less regular prophylactic treatment than patients with hemophilia. However, for recurrent joint bleeding or gastrointestinal bleeding, a prophylactic regimen may be the best treatment for patients with VWD.

Not all patients diagnosed with VWD require therapy (Table 4).

The criteria for initiating therapy are:

1. diagnosis of BV (VWF and FVIII levels);

2. clinical situation: spontaneous bleeding, surgery, recurrent bleeding (reducing the quality of life).

Depending on the type of BV, various therapeutic approaches are used (Table 4):

1. Desmopressin acetate (DDAVP) is a synthetic analogue of vasopressin (antidiuretic hormone) with modifications aimed at reducing the pressor (causing an increase in blood pressure) activity of vasopressin. DDAVP increases VWF concentration and FVIII activity in healthy individuals, in patients with mild or moderate VWD, and in patients with mild hemophilia A. DDAVP causes the release of VWF and FVIII from endothelial cells.

Absolute contraindications to the appointment of DDAVP: progressive atherosclerosis, heart failure, epilepsy, pregnancy. The criterion of effectiveness is an increase in the procoagulant activity of FVIII > 50%.

Desmopressin is administered slowly by intravenous drip at a dose of 0.3 μg/kg, in 50 ml of saline for 30 minutes. Injections are repeated after 12-24 hours, however, after 3-4 injections, the therapeutic effect decreases. Repeated treatment is carried out after 7-10 days. The drug (undiluted) can be administered as

a subcutaneous injection or intranasally as a spray.
2. Hormones. In women, FVIII and VWF increase with the introduction of estrogen, and the use of oral contraceptives containing estrogen and progesterone, vaginal rings, or intrauterine devices may be sufficient to control moderate menorrhagia. Hormones can be prescribed for a long time to reduce the duration and abundance of menstrual flow.
3. Antifibrinolytic agents: ACC and tranexamic acid prevent the lysis of formed clots by binding to the active sites of plasminogen, which prevents its interaction with fibrin and penetration into the forming thrombus. Antifibrinolytics are often used topically or systemically to control oral bleeding, epistaxis, bleeding after dental extractions, and menorrhagia. Antifibrinolytics can be combined with DDAVP or F.
4. Replacement therapy with VWF/FVIII concentrates.
In the absence of the effect of DDAVP, virus-inactivated concentrates are the drug of choice for the treatment and prevention of BV.
VWF/FVIII, which contain a large amount of VWF with a distribution of multimers as close as possible to that of normal human plasma.
Table 4 — Therapeutic approaches depending on the type of BV

Тип заболевания	Препарат выбора	Альтернативные методы и дополнительное лечение
I	Десмопрессина ацетат	Антифибринолитические средства, эстрогены, концентрат VWF/FVIII
IIa	Концентрат vWF/FVIII	Антифибринолитические средства, эстрогены
IIb	Концентрат vWF/FVIII	
iim	IIM Концентрат vWF/FVIII	
iin	IIN Концентрат vWF/FVIII	
iii	Концентрат vWF/FVIII	Концентрат VWF/FVIII или тромбоконцентрат

HEMORRHAGIC VASCULITIS

Hemorrhagic vasculitis (Schonlein-Henoch disease) is a vasculitis characterized by the deposition in the walls of small vessels (arterioles, capillaries, venules) of IgA-containing immune complexes with characteristic symmetrical hemorrhagic rashes, arthritis, abdominal syndrome and GN.

HV affects children and young people more often; it ranks first in prevalence among systemic vasculitis.

Etiology of hepatitis B: insect bites, drug allergy, use of serums and vaccines, cold allergy, food idiosyncrasy. Infectious agents (often P-hemolytic streptococcus group A, mycoplasmas, viruses) are only a resolving factor, not a causative one.

HV pathogenesis: immunocomplex inflammation with the formation of CEC with IgA -> deposition of CEC in the microvessels of the skin and internal organs -> destructive and destructive-productive microvasculitis with multiple microthromboses, an increase in the permeability of the vascular wall with the release of proteins and erythrocytes from the vascular bed.

The clinical picture of hepatitis B is characterized more often by an acute onset, general weakness, and subfebrile temperature.

Several leading syndromes:

The skin syndrome (present in all patients) is a small-spotted (-3 mm in diameter), symmetrical, confluent hemorrhagic rash that is easily identified visually and palpably. Localization of the rash is more often on the extensor surface of the upper and lower extremities, on the buttocks, less often on the trunk. Skin syndrome disappears 2-3 days after the onset. Often, several waves of rashes are characteristic (from two to five), in such cases, old and new elements of a hemorrhagic rash are present on the skin. Confluent purpura can lead to the formation of hemorrhagic blisters, which then open with the formation of deep erosions and ulcers.

Articular syndrome (more often in adults) is a symmetrical lesion of large joints, mainly of the lower extremities (knee, ankle) with periarticular edema, pain, limited function, but no bone changes. Duration about 1-2 weeks. Often there is a combination of arthritis with myalgia and swelling of the lower extremities.

Abdominal syndrome (occurs in patients) - develops due to edema and hemorrhages in the peritoneum, intestinal wall (more often the small intestine, less often the large intestine, esophagus and stomach are affected). There are pronounced cramping pains in the abdomen of the type of intestinal colic, localized in the mesogastrium. May be accompanied by nausea and vomiting. Sometimes typical gastrointestinal bleeding develops with tarry stools.

Complications of hepatitis B: intestinal obstruction, perforation with peritonitis, intussusception (more often in children).

Renal syndrome (more often in adults, usually develops in the fourth to sixth week after the onset of the disease) - GN. Isolated gross hematuria or its combination with moderate proteinuria is characteristic, nephrotic syndrome and arterial hypertension are not characteristic. Persistent hematuria and proteinuria can lead to CKD.

Pulmonary syndrome (capillaritis of the interalveolar septa with hemorrhages in the alveoli) is characterized by hemoptysis, shortness of breath and cough with a scant amount of sputum. Inconsistency of the meager picture of auscultation of the degree of radiographic changes (multiple infiltrates in the middle and lower sections), rarely hemorrhagic pleurisy.

Heart damage - hemorrhagic pericarditis, hemorrhages in the endocardium, infarction changes are possible on the ECG.

Damage to the central nervous system - paroxysmal headaches, dizziness, tearfulness, irritability, with swelling of the membranes - meningeal symptoms and epileptiform seizures.

Clinical variants of HV:

a) fulminant form - death a few days later from a stroke or intestinal bleeding;

b) acute form - from several weeks to several months; in the outcome - recovery or recurrent course;

c) relapsing course - characterized by relapses with periods of remission of varying duration (from several months to a year or more).

Diagnosis of HV:

1. Laboratory data are non-specific.

Complete blood count: moderate leukocytosis with a shift to the left, increased ESR (in the abdominal form and especially in GN); often eosinophilia up to 10-15%, platelets are normal.

Urinalysis: hematuria, proteinuria (with GN).

Biochemical analysis of blood: in the acute period, dysproteinemia due to an increase in IgA.

The analysis of feces for occult blood in abdominal syndrome is positive.

2. Instrumental research:

Skin biopsy and its immunohistochemical examination - perivascular leukocyte infiltrates, deposition of IgA-containing immune complexes.

FGDS - detection of erosions in the esophagus, stomach, duodenum, etc.

Treatment of HV:

The main stages of treatment:

1. Strict bed rest.

2. Diet therapy (exclude foods that cause allergies and increase blood clotting). It is not recommended to use in food: coffee, cocoa, sweets, eggs, hot spices, mayonnaise, red varieties of berries;

fried, smoked meat and fish dishes.

3. Heparin therapy: 300 U / kg / day subcutaneously (evenly distribute the dose over several injections every 4-6 hours). Under the control of TV (optimal) or clotting time (less sensitive indicator). It is important to achieve their elongation by 2 times.

4. If the effect of heparin is insufficient, you can use:

• fresh frozen plasma 300-400 ml intravenously (to replenish antithrombin III);

• nicotinic acid intravenously drip with physical. solution (to stimulate fibrinolysis);

• pentoxifylline / trental intravenous drip with physical. solution (improves microcirculation in areas of impaired circulation);

- NSAIDs or short courses of corticosteroids, with rapidly progressive GN, pulse therapy with methylprednisolone 1000 mg / day intravenously for 3 days is used;

• with a high level of the CEC, a long-term persistent course of HV, plasmapheresis and immunosuppressants are indicated.

HEMOPHILIA

Hemophilia is a group of coagulopathies caused by a genetically determined deficiency of blood plasma F VIII, IX - the most important links in the hemostasis system. Hemophilias are classified according to AHG deficiency: hemophilia A is a factor VIII (FVIII) deficiency; hemophilia B (Christmas disease) - deficiency of factor IX (FIX). Very rarely, concomitant hemophilia is detected: a simultaneous deficiency of FVIII and FIX, often accompanied by a violation of color vision.

The prevalence of hemophilia in most countries is 1,520 per 100,000 males, or 1:10,000 newborn boys. An estimate based on the World Hemophilia Federation's annual global survey puts the number of people with hemophilia in the world at approximately 400,000. The ratio of hemophilia A to hemophilia B is 4:1. In the Republic of Belarus, the prevalence of hemophilia A is 12-16 cases per 100 thousand of the male population, and hemophilia B is 1.2-1.6 per 100 thousand of the male population.

For the first time in written sources, hemophilia is mentioned in the holy book of the Jews - the Talmud. In the 12th century Abu al Qasim, a physician who served at the court of one of the Arab rulers of Spain, was the first to describe the symptoms of hemophilia. However, modern knowledge and scientific research on hemophilia dates back to the 19th century. For the first time the term "hemophilia" was introduced in 1828 by the Swiss physician Hopf. Literally, it means "love of blood." Hemophilia is called the “royal” disease, because the English Queen Victoria is considered the first high-ranking carrier of the disease. As a "legacy" from her, this disease was received by the royal families of Germany, Spain and Russia.

Understanding the cause of increased bleeding in hemophilia is associated with the names of two American researchers Pateck and Talor, who in 1936 for the first time showed that a violation of blood coagulation in this disease is due to the absence of a certain protein in the blood, which they called “antihemophilic globulin”. After 17 years, using the thromboplastin formation method, it was found that hemophilia is not homogeneous and includes two types of the disease: hemophilia A and hemophilia B.

The gene encoding the factor VIII level is located on the long arm of the X chromosome at the q28 locus. The gene encoding the level of factor IX is also located on the long arm of the X chromosome at the q27 locus. Therefore, the nature of inheritance of hemophilia A and B is recessive, linked to the X chromosome. It has now been established that genetic defects leading to hemophilia are point mutations, as a result of which a change in the amino acid composition of the protein occurs in the factor VIII or IX gene, which leads to the synthesis of an incomplete protein. The hereditary (family) nature of hemophilia is noted in 70-90% of patients. In 30-10% of cases, hemophilia is sporadic, resulting from the realization of latent heterozygous carriage or as a result of spontaneous genetic mutations.

Hemophilia only affects men. conductors (transmitters) diseases are women. Women carriers of the hemophilia gene do not have clinical manifestations, but they can give birth to sick sons. Sons of female carriers have a 50% risk of being born with hemophilia, and daughters have a 50% risk of being carriers of the hemophilia gene (Figure 2).

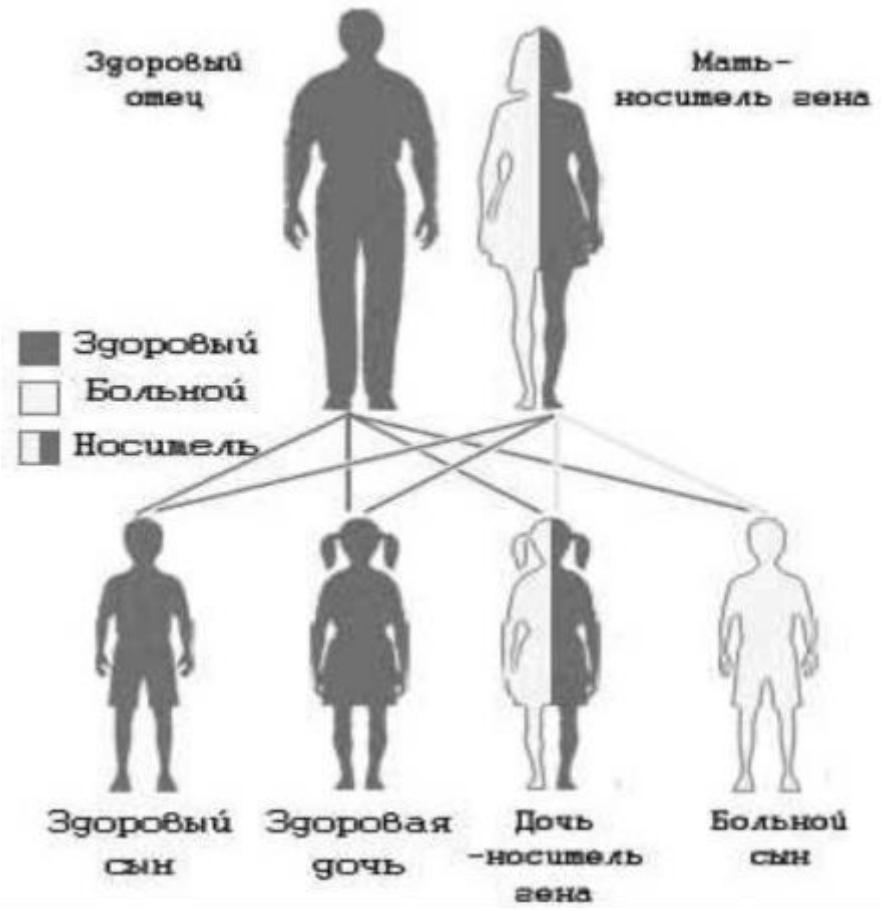

Figure 2 - Scheme of inheritance of hemophilia

All daughters of a patient with hemophilia are obligate carriers of abnormal genes, all sons are healthy. Homozygous true hemophilia A can occur in a girl whose father has hemophilia and whose mother is a carrier. In this case, we are talking about the double inheritance of the hemophilia gene. Usually such cases of development of hemophilia are observed in marriages between blood relatives. A mild form of factor VIII deficiency (greater than 5%) with little bleeding may occur in women carriers of hemophilia from hemophilic families. The development of hemophilia A in these women is explained by the fact that the abnormal factor VIII produced by the hemophilic X chromosome inhibits the function of the allelic gene on the second normal X chromosome.

In hemophilia, antihemophilic globulin (FVIII or FIX) is absent or its activity is sharply reduced; or it is functionally defective and cannot take part in blood coagulation. Factors FVIII or FIX are key participants in the first phase of plasma hemostasis (prothrombin formation phase). Their deficiency causes a violation of the formation of the complex: factor IXa + factor VIIIa + Ca ++

+ platelet phospholipid, which is necessary for the activation of factor X and the formation of prothrombinase, which ultimately leads to hypocoagulation and the formation of a syndrome of increased bleeding.

main clinical symptoms. Clinical manifestations of hemophilia A and B are identical and are characterized by hematoma type of bleeding: hematoma, hemarthrosis, bleeding.

Since FVIII and FIX do not cross the placenta, a bleeding tendency may appear already in the early neonatal period (cephalohematomas, hemorrhages in the buttocks, bleeding from the umbilical wound). However, most often the first manifestations of hemophilia are observed by 8-12 months, when children begin to walk and, of course, often fall. There are hemorrhages in the joints, as well as extensive hematomas in the buttocks, abdomen, head. Often there are prolonged, long-lasting bleeding from intramuscular injection sites. Bleeding of the mucous membranes of the oral cavity, nose is rare.

One of the most characteristic clinical manifestations of hemophilia are hemorrhages in large joints (hemarthrosis) of the upper and lower extremities: knee, elbow, ankle, shoulder, hip. Acute hemarthrosis can occur both after a minor injury and spontaneously, it is characterized by sharp pain, a rapid and

significant increase in the volume of the joint, and smoothness of the articular contours. The skin over the joint becomes hyperemic and hot to the touch, tense and shiny. With volumetric hemorrhages, fluctuation can be determined. Patients try to create rest for the affected joint and take a forced position, usually the joint is slightly bent. Recurrent hemarthroses gradually lead to the development of hemophilic arthropathy with the formation of contractures and ankylosis of the affected joints, muscle atrophy.

The second place in frequency and significance in the clinical picture of hemophilia is occupied by hemorrhages in soft tissues (hematomas) of various localization: subcutaneous, intermuscular, intramuscular, subfascial and retroperitoneal. Especially dangerous are hematomas in the area of soft tissues of the submandibular region, neck, pharynx, pharynx, mediastinum, as they can lead to the development of acute asphyxia. Hematomas, as a rule, are accompanied by intense pain due to compression of nearby nerve trunks. In the area of the hematoma, the skin becomes tense, shiny, and its palpation is painful. Large hematomas are palpated as tumor-like formations and may fluctuate. At first, the color of the skin in the area of the hematoma does not change, in the future, the blood imbibes not only the subcutaneous tissue, but also the skin, which changes its color, “bruises” of a blue-violet color appear, which subsequently become greenish-yellow. Extensive hematomas are accompanied by hyperthermia, chills, severe anemia, a drop in blood pressure, and leukocytosis. In the period of resorption of hematomas, moderate unconjugated hyperbilirubinemia is noted. The hematoma can become infected, suppurate, and lead to severe sepsis.

An important clinical manifestation of hemophilia is bleeding. The source of gastrointestinal bleeding is usually a peptic ulcer of the stomach or duodenum; erosive gastritis. The clinical picture of the gastrointestinal tract bleeding is typical and is manifested by hematemesis, chalk, and a drop in blood pressure. Intramural intestinal bleeding (into the intestinal wall) is of great danger. These are diapedetic capillary bleeding of unknown origin, while the intestinal wall is saturated with blood for a long time. Intramural bleeding can lead to the development of intestinal intussusception, intestinal obstruction and cause death. Hemorrhages in the intestinal wall, as well as in the mesentery, omentum and subserosis are almost always accompanied by intense abdominal pain, fever, peripheral blood leukocytosis, symptoms of peritoneal irritation, which mimics acute diseases of the abdominal organs.

The cause of renal bleeding can be trauma to the lumbar region, acute pyelonephritis, taking analgesics. Renal bleeding is more typical for adult patients and is manifested by severe gross hematuria. In this case, dysuric phenomena are often observed with difficulty urinating, pain in the lumbar region, along the ureters and urethra. Usually there is an intense urge to urinate, after which blood clots depart.

Hemorrhage into the subarachnoid space, into the brain and spinal cord is rare, usually provoked by trauma and accompanied by appropriate neurological symptoms: intense sudden headache, loss of consciousness, symptoms of irritation of the meninges, the development of paresis, disturbances in the rhythm of breathing and cardiac activity, etc.). Hemorrhages of this localization can cause an unfavorable outcome.

Prolonged recurrent bleeding after trauma and surgery is a characteristic feature of hemophilia. Even after minor injuries and damage to the skin (cuts during shaving, light scratches, abrasions) and mucous membranes, prolonged, difficult to stop bleeding can develop. Extraction of teeth, tonsillectomy, minor surgical interventions may be accompanied by heavy and prolonged (sometimes many days) bleeding. It is characteristic that bleeding is often delayed, does not occur immediately after surgery, but after 30-60 minutes, sometimes after 2-4 hours. This is especially important during abdominal operations, after which heavy bleeding into the abdominal cavity may begin, although bleeding during surgery was weakly expressed.

Complications of hemophilia: hemophilic arthropathy; secondary rheumatoid syndrome; pseudotumors; posthemorrhagic iron deficiency anemia; inhibitory form of hemophilia.

Diagnosis of hemophilia:

• Family history.

• Hemorrhagic history.

• Laboratory Diagnostics:

=> Postnatal Diagnosis of Hemophilia:

• prolongation of activated APTT with normal prothrombin, thrombosed time and fibrinogen

amount;

• decrease in the activity of factors VIII, IX in blood plasma (normal values for factor VIII - 60-250%; for factor IX - 60-140%).

Depending on the content of AGH in the blood, it is customary to distinguish three degrees of severity of hemophilia: less than 1% - severe; 1-5% - moderate form; more than 5% - mild form.

=> Prenatal Diagnosis of hemophilia and identification of carriers: gene analysis by PCR. Chorionic villus sampling (CVS) or biopsy is the main method of prenatal diagnosis; carried out between 9 and 14 weeks. pregnancy.

Treatment. There is no cure for hemophilia! The main goals of medical care are the prevention and treatment of bleeding; prevention of arthropathy progression; improving the quality of life of patients.

The main principle of hemophilia treatment is KAGH replacement therapy.

Drugs for replacement therapy of hemophilia. Purified factor VIII concentrates: Hemophil M, Immunat, Coate-DWI, Emoclot DI, Octanat, etc. Factor IX concentrates: Immunin, Octanight F, Imafix DI, Octanaim.

Substitution therapy rules: as early as possible - up to 2 hours; administration of an adequate dose; sufficient duration of treatment: until the signs of hemorrhagic manifestations disappear; clinical and laboratory control. F blood concentrates are administered intravenously by bolus.

Currently, cryoprecipitate and fresh frozen plasma are not used as antihemophilic drugs, since they do not meet the basic requirements for drugs for lifelong replacement therapy.

Three methods of substitution therapy are used: prophylactic, treatment at home, treatment after the occurrence of a hemorrhagic episode.

The prophylactic method is the most progressive, since the prevention of various hemorrhages and their consequences is more important than their treatment. The goal of preventive treatment is to turn a severe form of hemophilia into a milder one. Treatment should be started as early as possible, i.e. from 1-2 years old, when the joints are still intact. The optimal regimen is 25-40 IU factor per kilogram of body weight 3 times a week for hemophilia A and 2 times a week for hemophilia B. Preventive treatment lasts at least up to 20 years, and sometimes longer. In the Republic of Belarus, the preventive method is carried out for children with severe hemophilia.

Treatment at home. For home treatment, the patient's parents or the patient must be trained in the technique of intravenous administration of KAGH and always have the drug at home.

The goals of home treatment are:

1. Prevent massive bleeding by providing immediate assistance as soon as bleeding occurs.

2. Save time and costs for the arrival of ambulance crews or transportation of the patient to the hospital.

3. Save expensive antihemophilic drugs, the consumption of which is much less with immediate help.

4. Reduce school absenteeism or sick leave cases.

5. Release the patient from permanent addiction so that he can live a normal life.

Treatment for bleeding. The administered doses of KAGH in specific cases of hemorrhagic manifestations are different and, depending on the clinical situation, can range from 10 to 100 IU/kg per day. When calculating the dose, take into account the fact that the introduction of KAGH at a dose of 1 IU/kg of the patient's body weight increases the activity of FVIII by an average of 2%, and FIX - by an average of 1%. The dose can be calculated using the formula:

dose of FVIII concentrate (IU) = body weight x (required activity - basal activity) x 0.5;

dose of FIX concentrate (IU) = body weight x (required activity - basal activity).

It should be remembered that the half-life of FVIII is individual and ranges from 8 to 18 hours, while that of FIX is 2 times longer. Therefore, when providing urgent care, FVIII preparations should be administered 2-3 times a day, and FIX preparations - 1-2 times a day.

Treatment depending on the location of the hemorrhagic syndrome. Acute hemarthrosis: temporary immobilization of the joint in a physiological position (no more than 3-5 days); cold on the affected joint; early replacement therapy with KAGH at doses of 20-40 IU/kg. Joint punctures with aspiration of the contents are indicated for: hemarthrosis with pain syndrome, in the presence of a large volume of blood in

the joint cavity, with signs of the development of purulent arthritis, the development of neuromuscular disorders against the background of hemarthrosis. At the same time, in order to stop secondary inflammation, hydrocortisone is injected into the joint cavity.

With subcutaneous hemorrhages, hemorrhages in soft tissues and intermuscular hematomas that are not life-threatening, substitution treatment with KAGH at a dose of 20-25 IU/kg per administration for 56 days is prescribed. With hemorrhage m. iliopsoas replacement drugs are administered at a dose of 40 IU/kg every 8-12 hours for 5-6 days against the background of the patient's bed rest and limitation of physical activity.

Extraction of teeth is performed after a single injection of KAGH at a dose of 10-15 IU/kg to remove incisors and 20 IU/kg to remove large molars. Hemostatic therapy is continued for 2-3 days after the intervention. The use of local and systemic anti-fibrinolytic agents, fibrin glue is recommended, a strict sparing diet and cold drinks are indicated.

In case of renal bleeding, hemostatic therapy is carried out with KAGG preparations at a dose of 40 IU/kg per administration until macrohematuria is stopped. It is desirable to maintain a deficient factor level of 40%. At the same time, a short course (5-7 days) is prescribed prednisone orally at a dose of 1 mg / kg per day, followed by rapid withdrawal. It should be remembered that in case of renal bleeding, the administration of s - ACC is contraindicated, due to the risk of developing acute tumors with blockade of fibrinolysis!

With gastrointestinal bleeding, it is desirable to maintain the level of AGG 60-80%. KAGH preparations are administered at an initial dose of 4050 IU/kg, then every 8-12 hours at a dose of 20-30 IU/kg for 7-9 days. Also shown are the active use of fibrinolysis inhibitors, the generally accepted therapy for erosive and ulcerative diseases of the stomach and intestines.

Life-threatening bleeding, cerebral hemorrhage, major surgical interventions require the administration of KAGH at the rate of 50-100 IU / kg 1-2 times a day until the signs of bleeding stop and subsequent maintenance therapy at lower doses until the wound heals. The use of fibrinolysis inhibitors is also indicated. Next, hemostatic therapy is carried out according to the scheme of preventive treatment for 6 months.

After stopping the acute period, physiotherapy is applied to the area of the affected joint, hematoma: UHF, electro- and phonophoresis of hydrocortisone succinate, dimexide, magnetotherapy. All procedures are carried out against the background of factor replacement therapy. After the end of physiotherapy treatment, exercise therapy is indicated.

Nonspecific therapy. Desmopressin (not registered in the Republic of Belarus) is a derivative of antidiuretic hormone, a synthetic analogue of natural vasopressin. The drug rapidly increases the plasma level of factor VIII due to its release from the endothelium. Patients with a factor VIII level of more than 5%, i.e., with a mild form of the disease, respond best to the administration of the drug. Desmopressin is ineffective in hemophilia B. Desmopressin is administered intravenously at a dose of 0.3 mg/kg of body weight in 50 ml of saline. Undiluted drug can be administered subcutaneously and intranasally. A single injection is sufficient.^{s} - ACC at a daily dose of 100 mg / kg can be used orally or topically for nasal, gingival, gastrointestinal, menstrual bleeding, tooth extraction. Another effective antifibrinolytic agent is tranexamic acid. As mentioned above, fibrinolysis inhibitors are absolutely contraindicated in patients with hemophilia with hematuria. Blockage of the tubular tubules of the kidney, ureters, and bladder with clots that have lost their ability to lyse after the administration of antifibrinolytics can initiate the renal form of renal failure.

Treatment of inhibitory form of hemophilia. In 5-25% of patients with hemophilia, its inhibitory form develops as a result of the formation of antibodies to FVIII/FIX. These antibodies are produced by the patient's own immune system and block the functional activity of the patient's own clotting factors, or those administered as part of KACG. The appearance of an inhibitor is mainly manifested by the absence of a clinical response to standard therapy with clotting factor concentrates or the appearance of bleeding during prophylactic therapy. The diagnosis of this complication is based on the determination of inhibitors to F, which are measured in Bethesda. It has been established that 1 Bethesda inhibitor is capable of inactivating 50% F. Treatment of bleeding in the inhibitory form of hemophilia involves the administration of "bypass" drugs, i.e. drugs that trigger the first phase of plasma hemostasis by an

external mechanism. Currently, two such drugs are used: Feiba and recombinant factor VII (Novoseven). As an induction of immune tolerance, the following are prescribed: high doses of KAGG (100-200 IU / kg); IVIG; immunosuppressants (CF, cyclosporine A); immunosorption sessions.

It is important to remember that antiplatelet agents and anticoagulants are contraindicated in patients with hemophilia; NSAIDs are prescribed with caution; intramuscular injections are contraindicated, if necessary (vaccinations, vaccinations, etc.), they are carried out against the background of replacement therapy for KAGH.

TESTS FOR "HEMORRHAGIC DIATHESIS"

1. Thrombocytopenia in myeloproliferative diseases can be any of the following, except:

a) tumor

b) reactive

c) immune

d) medicinal

e) toxic

2. Thrombocytopathy is not accompanied by:

a) prolongation of clotting time

b) violation of the formation of prothrombinase

c) K-avitaminosis

3. The mechanism of occurrence of drug thrombocytopenia:

a) immune

b) toxic

c) inhibition of maturation of megakaryocytes in the bone marrow

d) all of the above are correct

e) none of the listed mechanisms

4. Platelets are formed from:

a) plasmablasts

b) myeloblasts

c) fibroblasts

d) lymphoblasts

5. Thrombocytopenia is characteristic of any of the following diseases, except:

a) autoimmune thrombocytopenia

b) aplastic processes

c) paroxysmal nocturnal hemoglobinuria

d) hemorrhagic thrombocythemia

e) all of the above cases

6. The main pathogenetic mechanism of bleeding in hemophilia A:

a) accelerated clot lysis due to fibrinogen defect

b) increased consumption of clotting factors in microclots

c) slowing down the internal pathway of prothrombinase formation due to hereditary factor VIII deficiency

d) slowing down phase II of blood coagulation due to a deficiency of factors.

e) the appearance of pathological anticoagulants

7. A minor function of platelets is:

a) adhesive

b) aggregation

c) angiotrophic

d) ensuring the retraction of the blood clot

e) fibrinostabilizing

8. An informative laboratory test for disorders in vascular-platelet hemostasis is:

a) Lee-White clotting time

b) duration of bleeding according to Duque, Ivy
c) APTT
d) clot lysis time
e) ethanol test
9. Basic laboratory criterion for hemophilia B:
a) a decrease in the level of fibrinogen
b) decrease in the level of factor thrombin VIII
c) decrease in the level of factor V
d) decreased level of factor IX
e) decrease in the level of factor XI
10. Unchanging hemostasiogram index during treatment with heparin:
a) APTT
b) platelet count
c) thrombin time
d) clot lysis time
e) antithrombin III activity.
11. What type of bleeding is typical for thrombocytopenia:
a) hematoma
b) petechial-ecchymatous
c) mixed bruising-hematoma
d) loculo-vasculitic
e) angiomatous
12. . What type of bleeding is typical for DIC:
a) hematoma
b) petechial-ecchymatous
c) mixed bruising-hematoma
methods for stopping bleeding in hemophilia A: - loculo-vasculitic
e) angiomatous
13. What type of bleeding is typical for hemorrhagic vasculitis:
a) gemtoma
b) petechial-spotted
c) mixed bruising-hematoma

d) loculo-vasculitic
e) angiomatous
14. What hemorrhagic rash is typical for thrombocytopenia
a) vasculitic purple
b) localized around the joints
c) petechial-ecchymotic
d) asymmetrically located
15. Indicate effective methods of stopping bleeding in hemophilia A:
a) splenectomy
b) transfusion of cryoprecipitate
c) prednisone
d) transfusion of purified factor VIII
16. Indicate the clinical manifestations of hemophilia:
a) symmetrical red rash in the form of papules and spots on the extensor surfaces
b) bruises and punctate hemorrhages all over the body
c) subcutaneous and intramuscular hematomas
d) incessant bleeding due to injuries, extraction of teeth
e) hemorrhages in the joints
17. Methods for studying vascular-platelet hemostasis include:
a) determination of activated partial thromboplastin time (APTT)
b) determination of prothrombin time
c) Ivy test
d) determination of thrombin time
e) determination of the level of fibronectin

18. Methods for studying the resistance of microvessels include:
a) Konchalovsky's test
b) Duke test
c) determination of time according to Lee - White
d) determination of Quick time (prothrombin time)
e) determination of blood coagulation with efa venom

19. Methods for determining the deficiency of blood coagulation factors include:
a) tests of mixing the patient's blood plasma with plasma in which there is a deficiency of a known factor, based on APTT tests or prothrombin time
b) determination of activated partial thromboplastin time (APTT)
c) determination of the prothrombin index
d) determination of the level of fibrinogen

20. Methods for rapid diagnosis of DIC do not include:
a) quantitative determination of fibrin-monomeric complexes
b) determination of activated partial thromboplastin time (APTT)
c) determination of the prothrombin index
d) determination of euglobulin lysis
e) determination of thrombospondin level

21. Means that affect the vascular component of hemostasis include:
a) aminocaproic acid
b) streptokinase
c) corinfar
d) fresh frozen plasma
e) platelet mass

22. Pathogenetic mechanisms of development of idiopathic thrombocytopenic purpura are:
a) activation of the complement system
b) immune complex syndrome
c) the appearance of autoantibodies to platelets
d) thrombomodulin deficiency
e) hereditary deficiency of the SZv complement subcomponent

23. In hemophilia A, there is a hereditary deficiency of the following blood coagulation factors:
a) X
b) IX
c) VIII
d) VII

24. In hemophilia B, there is a hereditary deficiency of the following blood coagulation factors:
a) X
b) IX
c) VIII
d) VII
e) V

25. Viral hemorrhagic fevers are characterized by all of the following except:
a) infectious-toxic lesions of the central nervous system
b) hemorrhagic capillarotoxicosis
c) bilateral interstitial serous-hemorrhagic nephritis
d) synthesis of autoantibodies to vascular endothelium

26. Hemorrhagic vasculitis (Schonlein-Genoch disease) is characterized by:
a) the development of the disease after a streptococcal or viral infection
b) the presence of antiplatelet antibodies
c) persistent course with mixed cryoglobulinemia, including rheumatoid factor, with cold urticaria and Quincke's edema, Raynaud's syndrome
d) development of arterial and venous thrombosis, thrombocytopenia, false-positive Wasserman reaction, synthesis of antibodies to DNA
e) a) and c) are correct

27. Pathogenetic factors of DIC (disseminated intravascular coagulation) are:
a) release and activation of tissue thromboplastin during cell decay
b) the appearance of antibodies against VIII and IX blood coagulation factors
c) development of the phenomenon of paracoagulation
d) a) and b) are correct
e) true b) and c)

28. The clinical picture of DIC at various stages of the course is characterized by all of the following, except for:
a) hemocoagulation shock
b) the prevalence of hematoma type of bleeding
c) insufficiency of the function of various organs (renal, liver, etc.)
d) development of respiratory distress syndrome

29. Principles of management of patients with suspected DIC:

a) therapy for DIC is carried out according to health indications until it is confirmed using laboratory research methods
b) DIC should be diagnosed earlier than its clinical signs appear
c) diagnosis is based on the appearance of paracoagulation products - fibrinogen degradation products (PDF) and soluble fibrin-monomer complexes (SFMC)
d) all of the above are true
e) true b) and c)

30. Pathogenetic factors of bleeding in DIC, thrombosis in atherosclerosis, coronary heart disease and hypertension include all of the following, except:
a) local activation of platelets
b) deficiency of physiological anticoagulants
c) synthesis of lupus anticoagulant
d) hyalinosis of the vascular wall (with hypertension)

31. The leading criteria for diagnosing hemorrhagic vasculitis are:
a) features of the clinical picture
b) results of histological examination of the skin
c) complete blood count and coagulogram
d) the level of immune complexes in the blood
e) a) and b) are correct

32. Acute thrombocytopenia is a condition in which the number of platelets in the blood rapidly decreases:
a) up to 20 • 109/l
b) up to 50 • 109/l
c) up to 100 • 109/l
d) up to 150 • 109/l
e) up to 190 • 109/l and below

33. The cause of acute thrombocytopenia can be:
a) increased destruction of platelets in the body
b) a sharp decrease in platelet production in the bone marrow
c) a decrease in the lifespan of platelets up to 5-6 days
d) hyperplasia of the megakaryocytic germ
e) a) and b) are correct

34. The etiological factor in the development of acute thrombocytopenia is
a) the appearance of immune complexes in the blood
b) the appearance of autoantibodies to platelets and hapten in the blood and fixation on the surface of platelets
c) microbial infection
d) viral infection

Z5. Antithrombin III is:
a) primary anticoagulant
b) secondary anticoagulant
c) platelet factor
d) fibrinolytic agent
e) plasma coagulation factor

36. The central place in the pathogenesis of DIC is occupied by:

a) hyperthrombinemia
b) thrombocytopenia
c) thrombocytopathy
d) increased levels of antithrombin III

37. Duration of development of the lightning-fast form of DIC:
a) several tens of minutes
b) several hours
c) several days
d) a few weeks

38. Duration of acute form of DIC:
a) several tens of minutes
b) several hours
c) a few weeks
d) months and years

39. In case of DIC, the use of the following is contraindicated:
a) heparin
b) epsilon-aminocaproic acid
c) transfusion of fresh frozen plasma

STANDARDS OF ANSWERS TO TEST QUESTIONS

1. -а	**11. -б**	**21. -в**	**31. - д**
2. -а	**12. -в**	**22. -в**	**32. -д**
3. -а	**13. -г**	**23. -в**	**33. -д**
4. -а	**14. -в, г**	**24. -б**	**34. -б**
5. -а	**15. - б, г**	**25. -г**	**35. -а**
6. -в	**16. - б, в, г**	**26. -д**	**36. -а**
7. -д	**17. - в**	**27. -г**	**37. -а**
8. -б	**18. - а**	**28. -б**	**38. -б**
9. -г	**19. - а**	**29. - г**	**39. -а**
10. -г	**20. - д**	**30. -б**	**40. –**

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