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Frequency of Occurrence and Laboratory Features of Rarecoagulopathies Republican Specialized Scientific and Practical Medicalcenter of Hematology of the Ministry of Healthof Therepublic of Uzbekistan

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Abstract: ***Blood clotting is a process that converts normal liquid blood into a clot that closes the damaged vessel and prevents bleeding. The external and internal pathway of thrombus formation proceeds with the participation of coagulation factors. This process involves the formation of fibrin, a protein that forms the basis of a blood clot. Fibrin as a scaffold gives the thrombus strength. With coagulopathy, due to a lack of coagulation factors, fibrin formation does not occur. Without fibrin, a thrombus is not able to reliably anchor at the site of injury. Uncontrolled bleeding occurs, which can lead to death.***
The purpose of this review was to assess the frequency, clinical presentation, genetic basis, possibilities and difficulties in diagnosing these deficiencies. Rare blood clotting disorders (RBCD) include monogenic coagulopathies caused by a deficiency of plasma proteins involved in hemostasis, not related to von Willebrand disease and hemophilia A or B. RBCD include hereditary deficiencies or abnormalities of fibrinogen, prothrombin (factor II), coagulation factors V, VII, X, XI, XII, XIII. All these violations in the overwhelming majority of cases lead to violations of fibrin formation. The reasons for the development of RBCD are, as a rule, recessive inheritance of unique or rare nucleotide changes in genes encoding coagulation factors, or in proteins required for post-translational modifications of these factors. RBCD are most common in ethnic groups in which closely related marriages are accepted, due to the greater likelihood of homozygous carriage of the gene defect.

Key Words: ***Rare Blood Clotting Disorders,Hemarthrosis, Coagulopathy, Hemorrhage, Blood Coagulation.***

1. INTRODUCTION

Fibrinogen deficiency. There are 2 types of fibrinogen deficiency. Type I, or quantitative deficiency, is afibrinogenemia or hypofibrinogenemia, when fibrinogen is absent or its amount is reduced. Type II - dysfibrinogenemia, a qualitative defect of fibrinogen, when the fibrinogen

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antigen can be reduced or it is within the normal range, but its activity is disproportionately reduced. The incidence of afibrinogenemia is approximately 1 in 1,000,000 in the population. The incidence of hypofibrinogenemia is much higher, up to 1 in 500. Dysfibrinogenemia is inherited in an autosomal dominant manner, therefore, it is rather problematic to assess its real

frequency. The clinical picture is quite variable, from an asymptomatic course to severe bleeding, most patients with afibrinogenemia make their debut in the neonatal period with bleeding from the umbilical cord, but there are also frequent cases of a later onset of hemorrhagic syndrome in the form of hemarthrosis, postoperative bleeding, bleeding from the mucous membranes.

Hereditary coagulation factor II (prothrombin) deficiency is an autosomal recessive disorder. Characteristics: FII is a glycoprotein, formed in the liver in the presence of vitamin K. Under the influence of activated blood coagulation factor X (FXa) in the initiating phase of the coagulation cascade and the prothrombinase complex (amplification phase), it transforms into thrombin. Thrombin, in turn, activates other plasma coagulation proteins and platelets with the final formation of a fibrin clot. In addition, thrombin is involved in the activation of blood coagulation inhibitors and in the regulation of fibrinolysis. FII deficiency is due to variations in the F2 gene that codes for prothrombin. There is no direct correlation between the F2 genotype and disease phenotype. The hemostatically sufficient FII level is about 40%. FII half-life is about 60 hours. The prevalence of hereditary coagulation factor II (prothrombin) deficiency in most countries is 1 in 2,000,000 of the population.

Factor V deficiency. Factor V, proaccelerin, or labile factor, is a glycoprotein synthesized in the liver and consists of 2,224 amino acids, including a long signal peptide (consisting of 28 amino acids) and a maternal single-chain polypeptide (consisting of 2196 amino acids). The half-life of factor V is about 16-36 hours. Clinical picture.Homozygotes or compound heterozygotes may have moderate to severe bleeding; heterozygotes are usually asymptomatic. In patients with severe factor deficiency, perioperative bleeding, bleeding into the central nervous system (CNS), gastrointestinal bleeding, bleeding from the umbilical residue, spontaneous hematomas have been described.

Hereditary coagulation factor VII deficiency is an autosomal recessive disorder. The physiological role of FVII is to initiate the process of blood coagulation in the area of damage to the vascular wall. In combination with tissue factor, FVIIa activates FX and FIX, which are involved in thrombin generation. The half-life of FVII is 4-6 hours. Sufficient hemostatic level is at least 10%. In severe trauma, clinically significant bleeding may occur when FVII levels are greater than 20%. The clinical picture with factor VII deficiency is most often manifested by recurrent nosebleeds (60%), bleeding from the mucous membranes (34%), spontaneous occurrence of ecchymosis (36%), menorrhagia (69% of women). In this case, severe bleeding includes hemarthrosis (19%), gastrointestinal bleeding (15%), hemorrhages in the central nervous system (2.5%). The prevalence of hypoproconvertinemia is 1: 300,000 - 500,000 of the population.

Hereditary coagulation factor X deficiency is an autosomal recessive disorder. FX activation occurs in the initiation phase of blood coagulation with the participation of the tissue factor - FVIIa complex and in the amplification phase with the tenase complex. Activated FX (FXa) and its co-factor, coagulation factor V (FV), are part of the prothrombinase complex, which activates prothrombin. The half-life of FX is 30 to 50 hours. Patients with factor X deficiency are characterized by a high incidence of severe bleeding, such as hemorrhages in the central

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nervous system - 21%. Bleeding can debut at any age and is nonspecific. As a rule, if the FX activity is less than 1%, the debut of hemorrhagic syndrome is observed in the first year of life

in the form of severe bleeding from the umbilical cord, hemarthrosis and bleeding in the central nervous system, gastrointestinal bleeding. The average prevalence of sporadic forms of hereditary deficiency of blood coagulation factor X is 1 patient: 1,000,000 population.

Factor XI deficiency. Factor XI is a proenzyme for serine protease XIa. It circulates in plasma at a concentration of about 30 nM (15-45 nM) almost completely as a non-covalent complex with a high molecular weight kininogen. The half-life is about 52 hours. It is synthesized in the liver. In most cases, factor XI deficiency is characterized by induced bleeding, while spontaneous bleeding, with the exception of severe menorrhagia, is rare. Mostly bleeding occurs during trauma or surgery.

Factor XII deficiency - Hageman factor. Factor XII - Hagemann's factor deficiency was first described by Oscar Ratnoff and John Kolopi in 1954. They examined a 37-year-old Hageman patient who was about to undergo surgery. According to the results of routine screening, the patient showed a significant increase in the Lee-White clotting time, while he did not have symptoms of increased bleeding. The prevalence of this deficiency is approximately 1 in 1,000,000.

Factor XIII deficiency. Coagulation factor XIII, a fibrin-stabilizing factor, is a progammatransglutaminase that circulates in plasma as a heterotetramer (FXIII-A2B2), consisting of 2 subunits: a carrier (FXIP-B2) and 2 catalytic subunits. It is synthesized partly in the liver, partly in monocytes, macrophages and megakaryocytes. The half-life is 9-12 days. With a deficiency of factor XIII, there is a correlation between factor activity and hemorrhagic syndrome. So, hemorrhagic syndrome in patients with factor activity below 1% is quite pronounced: in most patients, as a rule, the debut of bleeding is observed in the neonatal period in the form of bleeding from the umbilical cord (80%), intracranial hemorrhage (30%), bleeding from mucous membranes (30%).
Combined deficiency of V and VIII factors is an extremely rare coagulopathies, occurring with a frequency of 1 in 1,000,000. It is inherited autosomal recessively, characterized by a simultaneous low level of both factor V and factor VIII (usually activity is from 5 to 20%). In contrast to the true deficiency of factor V and factor VIII, associated with a violation of their synthesis, the combined deficiency of factors V and VIII is associated with a violation of the intracellular traffic of these glycoproteins. Lectin that binds mannose 1 and the protein of multiple deficiency of coagulation factors 2 together with Ca2 + form a complex that transfers factors V and VIII from the endoplasmic reticulum to the Golgi apparatus, respectively, if the structure of this complex is disturbed, the transport of factors will be disrupted, which leads to a decrease in the level of factors V and VIII, however, a part is still tolerated, and the activity of the factors is not lower than 5%.Simultaneous reduction of V and VIII factors does not increase the hemorrhagic syndrome in comparison with individual deficiencies of these factors. Hemorrhagic manifestations vary widely, with the prevailing manifestations of moderate bleeding: cutaneous hemorrhagic syndrome, more often in the form of ecchymosis, recurrent nasal, gingival bleeding, menorrhagia and bleeding after surgery, trauma; severe bleeding is extremely rare.

Combined deficiency of vitamin K-dependent factors.

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Vitamin K-dependent factors - II, VII, IX, X, as well as proteins C, B and Z. All these factors require y-carboxylation of glutamic acid residues to ensure binding with calcium and attachment to phospholipid membranes. The process of γ-carboxylation is catalyzed by hepatic γ-glutamyl carboxylase, which requires reduced vitamin K as a cofactor. During γ-carboxylation, KH2 is converted into vitamin K epoxide, which is reduced to KH2 using the vitamin K-epoxide reductase complex. Hereditary dysfunction of γ-glutamyl carboxylase or vitamin K-epoxide reductase complex leads to the secretion of weakly carboxylated vitamin K-dependent coagulation factors, as well as proteins C, B, Z and proteins involved in the construction of the skeleton - osteocalcin and matrix protein 01a. The combined deficiency of vitamin K-dependent factors is an extremely rare autosomal recessive coagulopathy, about 30 cases have been described worldwide. There are 2 known genes that are responsible for the deficiency of vitamin K-dependent factors: the gene encoding γ-glutamyl carboxylase is located on chromosome 2p12 and the gene responsible for vitamin K-epoxide reductase is located on chromosome 16p11.2.

Hemophilia is a hereditary hemorrhagic diathesis of coagulation genesis, caused by a deficiency or molecular abnormalities of VIII, IX and XI coagulation factors. The main manifestation of the disease is extensive hemorrhages in large extremities, deep subcutaneous, intermuscular and intramuscular hematomas, hemorrhages in the brain, retroperitoneal hematomas, profuse and prolonged bleeding after tooth extraction and injuries. The prevalence of hemophilia A is 1: 10,000, hemophilia B is 1: 30,000-50,000 males.

2. CONCLUSION

Typical for RBCD are bleeding / bleeding into muscles / soft tissues (hematomas), from the mucous membranes of the oral cavity, nose, urinary system, less often - bleeding into the joints (hemarthrosis). These types of bleeding / hemorrhage are severe. For the diagnosis of Rare Coagulopathies, a thorough assessment of clinical data and a well-equipped laboratory are required. Clinical studies for rare factor deficiencies are limited by their low prevalence in the population. Hemorrhagic manifestations of PK are varied, and at the moment it is not possible to single out a specific symptom indicating a specific factor deficiency. In comparison with hemophilia, with rare deficiencies of clotting factors, there is a higher frequency of nosebleeds, bleeding from the umbilical cord, while hemarthrosis and bleeding into the muscles are much less common.

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