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HEREDITARY DEFICIENCY OF FACTOR XIII – LACKY-LORANDE FACTOR

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Resume. *Congenital factor XIII (FXIII) deficiency is a rare bleeding disorder characterized by muscle or mucocutaneous bleeding with life-threatening intracranial hemorrhage (ICH), especially in severe cases. Although FXIII deficiency is rare, it is characterized by varying bleeding manifestations depending on the magnitude of the deficiency. Congenital FXIII deficiency with a level of less than 1% can be found in children with prolonged bleeding from the umbilical cord stump, as well as with prolonged bleeding after trauma. Factor XIII (FXIII) is activated by thrombin to produce transglutaminase (FXIIIa), which stabilizes clot formation by cross-linking fibrin monomers and antifibrinolytic proteins. The molecular basis of FXIII deficiency is characterized by a high degree of heterogeneity, which results in variable clinical manifestations of the disease. More than 60 FXIII mutations have been identified in the current literature.*

INTRODUCTION

Factor XIII (FXIII) deficiency is one of the extremely rare coagulopathies with an estimated prevalence of about 1 in 3 million [1]. FXIII (fibrin-stabilizing factor) is a progamma-transglutaminase that circulates in plasma as a heterotetramer (FXIII-A2B2) consisting of 2 carrier subunits (FXIII-B2) and 2 catalytic subunits (FXIII-A2) [2]. This peptide is present in a large number of cells, including platelets, megakaryocytes, and monocytes. In addition to its main function, participation in the coagulation cascade, FXIII plays an important role in angiogenesis, wound healing, bone metabolism, as well as pregnancy maintenance and cardioprotection [3]. The main function of FXIII is to covalently bind fibrin strands and thus stabilize the fibrin clot. Activation of the fibrin-stabilizing factor is caused by thrombin, as well as calcium ions and fibrin [4]. The half-life is 9–12 days. The gene responsible for the A-subunit is located on the 6th chromosome, occupies a region of 160 kb and contains 15 exons separated by 14 introns, the gene responsible for the B-subunit is located on the 1st chromosome, occupies a region of 28 kb and contains 12 exons separated by 11 introns [5].

The clinical manifestations of this deficiency are extremely heterogeneous. Severe factor deficiency is characterized by bleeding that is detected in the neonatal period: bleeding from the umbilical cord, intramuscular hematomas, bleeding in the joints. The frequency of intracranial hemorrhages is quite high, about 30%, which are the main cause of death and disability in patients [6]. A feature of FXIII deficiency is the presence of a correlation between the activity of the factor and the severity of bleeding: the lower the activity, the more pronounced the hemorrhagic syndrome. Also, one of the distinctive features is not only hematological manifestations, but also prolonged wound healing, defective formation of scar tissue, as well as repeated episodes of miscarriage in women [7]. Factor XIII deficiency. Coagulation factor XIII, a fibrin-stabilizing factor, is a progammatransglutaminase that circulates in the 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.

Severity of rare coagulopathy.

Clotting factor	Form of the disease (by activity of blood coagulation factors, %)		
	Heavy	moderate severity	mild
FII	not defined	< 10%	>10%
FV	< 1%	5 – 10%	>10%
FVII	< 10%	10 – 20%	>10 %
FX	< 10%	10 – 40%	>40%
FXI	< 1%	5 – 10%	>10%
FXIII	1-5%	5 – 10%	>30%

Scientific novelty

Early detection and improvement of diagnosis and treatment of patients with FXIII deficiency in the Republic of Uzbekistan, as well as reduction of disability and mortality among them.

Materials and methods of research. The diagnosis is based on medical history: signs of increased bleeding in other family members (both male and female); clinical signs of the disease and laboratory data. Conducting coagulological screening, if hemorrhagic conditions are suspected, the first stage includes activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen concentration (according to Clauss), bleeding time (BT) using a standardized method and platelet count according to Fonio. A distinctive feature of FXIII deficiency is that this pathology does not affect the performance of standard coagulation tests. Determination of FXIII activity and antigen is required according to the International Society of Thrombosis and Haemostasis criteria. Depending on the ratio of FXIII-A and FXIII-B antigen activity, 3 types of deficiency are distinguished: Type I – when there is a decrease in FXIII activity due to a small amount of A-subunit antigen; Type II – when there is a sufficient amount of A-subunit antigen, but it is functionally inactive; and type III – when there is a decrease in FXIII activity due to a small amount of B-subunit [8]. This rather labor-intensive classification is required to select the desired concentrate. About 95% of all mutations are in the A subunit [9]. Table 1.

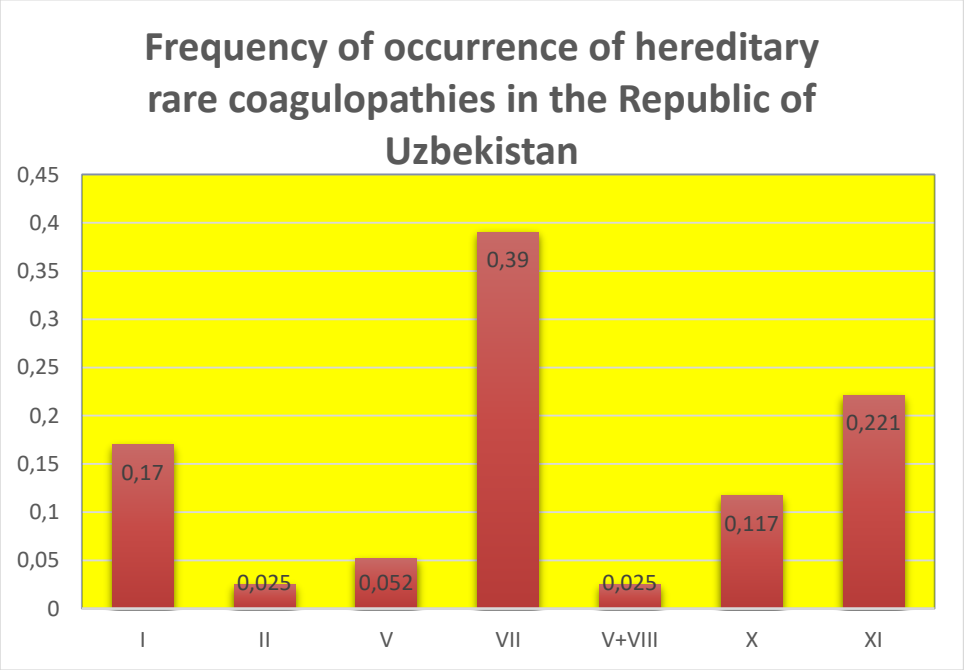
Classification of FXIII deficiency [8]

deficiency	Plasma FXIII activity	Antigen FXIIIA2B2 in plasma	Antigen FXIII-A in plasma	Antigen FXIII-B in plasma	FXIII activity on platelets	Antigen FXIII-A on platelets
FXIII-A Type I	↓↓↓	↓↓↓	↓↓↓	> 30 %	↓↓↓	↓↓↓
FXIII-A Type II	↓↓↓	↓-N	↓-N	> 30 %	↓↓↓	↓-N
FXIII-B	↓↓	↓↓↓	↓↓	↓↓↓	N	N

Results and discussion.

Table 1. Incidence of hereditary rare coagulopathies in the Republic of Uzbekistan (%)

Clotting factor deficiency; % of patients in the group of rare hereditary coagulopathy in the Republic of Uzbekistan.						
I	II	V	V+ VIII	VII	X	X I
13 (17,0%)	2(2,5%)	4(5,2%)	2(2,5%)	30 (39,0%)	9(11,7%)	1 7(22, 1%)



Thus, to make a diagnosis of Rare Coagulopathies, a careful assessment of clinical data and the presence of a well-equipped laboratory are required. Clinical studies for rare factor deficiencies are limited by their low prevalence in the population. Hemorrhagic manifestations of RC are varied, and at the moment it is not possible to identify a specific symptom indicating a specific factor deficiency. Compared with hemophilia, with rare deficiencies of coagulation factors, a higher frequency of nosebleeds and bleeding from the umbilical cord is observed, while hemarthrosis and bleeding into the muscles are much less common.

A feature of this deficiency (FXIII) is the high frequency of severe bleeding: Bleeding from the umbilical cord occurs on average in 80% of newborns, intracranial hemorrhage reaches 30%, the only generally accepted measure for the prevention of intracranial hemorrhage is prophylactic therapy in order to maintain FXIII activity

above 5%. This measure allows you to avoid severe neurological complications and achieve a satisfactory quality of life [2].

Treatment for FXIII deficiency:

To stop bleeding, replacement therapy with clotting factor concentrates should be used. When carrying out specific replacement therapy, preference should be given to the use of recombinant or highly purified virus-inactivated plasma concentrates of blood coagulation factors in relation to FFP; Effective doses of clotting factor concentrates should be used immediately. Therapy with insufficient doses will not stop bleeding, will lead to loss of time, an increase in hemorrhagic syndrome and unreasonable consumption of an expensive drug;

Hemostatic therapy must be started as early as possible (if possible within the first 2 hours after injury, the onset of bleeding or the appearance of the first subjective signs of hemorrhage), therefore the basis for starting therapy may be the patient's subjective sensations or the fact of injury. It is advisable to stop bleeding or hemorrhage before significant clinical manifestations develop;

1. Treatment of mild and moderate bleeding should be carried out at home by the patient or his relatives in accordance with the recommendations of the hematologist. If life-threatening bleeding develops, therapy should be started as early as possible (at home) and continued under the supervision of a hematologist on an inpatient or outpatient basis; If life-threatening bleeding develops, therapy should be started as early as possible (at home) and continued under the supervision of a hematologist on an inpatient or outpatient basis;

2. A key aspect of improving health and quality of life when treating FXIII deficiency is the prevention of bleeding: hemarthrosis, life-threatening bleeding and hemorrhage (in the central nervous system (CNS), gastrointestinal tract (GIT), etc.).

3. The basis of treatment is the use of FXIII concentrates; it is also possible to use cryoprecipitate and, in extreme cases, fresh frozen plasma (FFP). Considering the severity of hemorrhagic manifestations and the high probability of life-threatening bleeding, the following is recommended. For the treatment of acute bleeding and for perioperative prophylaxis in patients with FXIII deficiency, therapy with cryoprecipitate is indicated: 1 dose per 10 kg; in its absence, FFP at a dose of 15–25 ml/kg [10,11]. The use of cryoprecipitate is preferable, since the content of fibrinogen in it is approximately 3 times higher than in FFP, respectively, and the volume required for infusion will be 3 times less [12]. All patients with FXIII activity <1% require mandatory prophylactic treatment. In patients with FXIII activity between 1 and 5% and severe bleeding, prophylaxis is also strongly recommended [10]. The goal of prevention is to achieve an increase in factor activity above 5%, which avoids life-threatening, especially intracranial, bleeding [13].

1. For prophylaxis, cryoprecipitate is used, 1 dose per 10 kg every 4–6 weeks, or FFP 15–25 ml/kg every 4–6 weeks [10].

2. At the moment, there are 2 types of concentrates in the world: plasma and recombinant. The advantage of plasma concentrate is that it contains both A and B subunits, making it suitable for all patients with FXIII deficiency. The recombinant concentrate was developed for patients with a defect in the A subunit, which accounts for about 95% of all cases of decreased FXIII activity [16, 17]. These drugs are not registered in Uzbekistan.

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