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Hereditary Deficiency of Blood Coagulation Factor I - Afibrinogenemia, Clinical Observation Medical Center of Hematology of the Ministry of Health of The Republic of Uzbekistan.

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Abstract: Afibrinogenemia is a congenital hemorrhagic syndrome with an autosomal recessive mode of transmission, which occurs due to a lack of synthesis of factor I (fibrinogen) and is clinically characterized by the occurrence of large post-traumatic bleeding. It is characteristic of a patient with afibrinogenemia that his tendency to bleed is never spontaneous; it is always a consequence of some trauma (sometimes so minor that it can go unnoticed). The first manifestation of the disease occurs at the very moment of the birth of the patient, that is, when the umbilical cord is cut off; this surgical trauma causes severe hemorrhage with a very high mortality rate. The significant frequency of this early onset of afibrinogenemia (70-80% of cases), compared with such a low frequency in hemophilia (3-4%), is due to the fact that maternal antihemophilic globulin, which has a small molecule, passes through the placenta and protects the hemophilic fetus at birth; on the contrary, maternal fibrinogen, which has a large molecule, cannot pass through the placental barrier to protect the afibrinogenamic fetus. In addition, the umbilical cord is very rich in tissue thromboplastin, which can cause blood coagulation (externally) in a hemophilic fetus, but without any effect in the case of an afibrinogenemic fetus. The same hemorrhagic episode occurs on the occasion of circumcision, in male children of the Jewish or Moslem religion; here the frequency is the same as in hemophilia. Hemorrhagic episodes are more frequent during childhood, with its inevitable trauma, in the adult they are much thinner.

Key words: afibrinogenemia, rare hereditary coagulopathy, congenital fibrinogen deficiency, hereditary disorders of fibrinogen formation.

Introduction

Rare hereditary coagulopathies include deficiencies of I, II, V, VII, X, XI and XIII coagulation factors; they make up 3-5% of all hereditary disorders of plasma hemostasis. Among them, fibrinogen deficiency occurs in 8–12% of patients [1]. allocate a quantitative and qualitative violation of the formation of fibrinogen [2,4]. Quantitative include hypofibrinogenemia (fibrinogen level less than 1.8 g / l) and afibrinogenemia (fibrinogen level less than 0.1 g / l - traces). Qualitative disorders are characterized by a change in the structure of the fibrinogen molecule and are called dysfibrinogenemia. In addition, hypodysfibrinogenemia is distinguished, in which changes in the structure of the fibrinogen molecule are combined with a decrease in its content in plasma. fibrinogen - a glycoprotein with a molecular weight of 340 kDa, is the largest protein in the hemostasis system along with coagulation factors V, VIII and XIII. Synthesized mainly in the liver, it is also found in megakaryocytes and platelets. The normal content in plasma is 1.8 - 4.0 g / l; half-life is 4-5 days. Fibrinogen synthesis is encoded by 3 genes: FGA, FGB, FGG, localized on the long arm of the 4th chromosome [3,5,7]. The protein structure of fibrinogen is completely deciphered. It is a symmetrical structure - a hexamer, consisting of three pairs of identical chains: α, β and γ. in the fibrinogen molecule, a central E domain and two extreme D domains are isolated. The domains contain polymerization centers and centers of interaction with various proteins, such as tissue plasminogen activator, thrombospondin, fibronectin. The fibrinogen molecule has elasticity and extensibility, its dimensions can change by 2-3 times or more.

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The final step in blood clotting is the conversion of fibrinogen to fibrin. The initial stage of this process is the proteolytic cleavage of fibrinopeptide A (FPA) and fibrinopeptide B (FPB) from the N-terminal parts of the respective chains under the action of thrombin. thus, fibrin monomers with 4 free bonds are formed. then, in the presence of calcium ions, fibrin monomers are converted into dimers, tetramers, and oligomers. Due to the chains α and β, linear and lateral polymerization of molecules occurs. After that, under the action of blood coagulation factor XIIIa, transverse polymerization occurs due to γ chains. in this way, the fibrin polymer turns into a stable insoluble clot [2]. The functional role of fibrinogen in the body is diverse. It is involved in the processes of blood coagulation, being a substrate of blood coagulation factors II and XIII. the interaction of fibrinogen with the fibrinogen receptor on activated platelets leads to platelet aggregation and the formation of a platelet clot. By binding to tissue plasminogen activator and plasminogen, it mediates the processes of fibrinolysis, preventing thrombosis. It also promotes wound healing by forming the basis for the growth of fibroblasts and histiocytes; is an acute phase response protein [1–5]. About 350 mutations associated with impaired fibrinogen formation have been described in the literature. Mutations are more commonly found in the FGA and FGG genes. in the FGB gene, they are approximately 1.5 times less common. these are mainly missense and nonsense mutations, but there are also splicing mutations, frameshift mutations, and rare violations in the regulatory regions of genes. Mutations leading to reduced formation of fibrinogen disrupt protein synthesis, assembly, and secretion. Mutations that qualitatively change the structure of fibrinogen are associated with a slowdown or absence of FPA/FPB cleavage; slowing down or accelerating the polymerization of molecules, disruption of cross-linking of molecules [2, 3, 5]. Afibrinogenemia was first described by German doctors F. Rabe and S. Solomon in 1920 in a 9-year-old boy [2, 8].
The prevalence of the disease is 1:1,000,000. The incidence of the disease is increased by 8–10 times in regions where consanguineous marriages are typical (Iran, South India) [1, 5]. Afibrinogenemia has an autosomal recessive mode of inheritance. About 80 mutations leading to Afibrinogenemia have been described. Clinical symptoms of the disease can debut both from the moment of birth (bleeding from the umbilical cord in 85% of patients), and at a later age. The clinical phenotype of the disease is represented by post-traumatic bleeding, skin hemorrhagic syndrome, poor healing of surgical wounds, gastrointestinal bleeding, hemarthrosis, spontaneous rupture of the spleen, hemorrhage into the central nervous system (which is the main cause of death in these patients). Obstetric and gynecological manifestations of AfGE are menometrorrhagia/menorrhagia, spontaneous abortions (mainly in the first trimester of pregnancy), hemoperitoneum due to rupture of the corpus luteum/follicle during ovulation [1, 8].

Materials and research methods. The diagnosis is based on the data of the anamnesis: signs of increased bleeding in other family members (both male and female); clinical signs of the disease and laboratory data.
Patient D., 19 years old. The diagnosis of "hereditary coagulopathy: afibrinogenemia" was established in a patient at the age of 1 month at the RSSPMCH of the Ministry of Health of the Republic of Uzbekistan, where he was observed until he reached the age of majority. During the observation period in the RSSPMCH, prolonged bleeding from wounds, soft tissue hematomas, hemarthrosis, and right-sided retroperitoneal hematoma were noted. For hemostatic purposes, he received cryoprecipitate on demand. Patient's coagulogram data: APTT, PTI, TV, fibrinogen are not detected. The main reasons for treatment are recurrent intense nosebleeds, bruises, abrasions, stab wounds of a traumatic nature. With a hemostatic purpose, replacement therapy with cryoprecipitate is carried out on demand. in 2015. Patient D.'s parents are in a consanguineous marriage: the mother's grandmother and the father's mother are half-sisters (they have a common mother). Patient D.'s parents are also in a related marriage: the fathers of the patient's mother and father are cousins.
In our opinion, the most likely cause of the homozygosity of the examined patients for the identified rare mutations was closely related marriages, which was confirmed by genealogical data.

Laboratory data before treatment:
APTT no clot, fibrinogen no clot, Quick prothrombin no clot, FVII 82%, FII 103%, FV 100%; FVIII 104%, FIX 98%, FX 96%, FXI 79.9%, FW 140%, FXII 101%, XIIa-dependent fibrinolysis 9 min, platelet aggregation with ristomycin 78%, platelet aggregation with collagen 74%, platelet aggregation with ADP 75%. The absence of an inhibitor and antiphospholipid antibodies to FI made it possible to exclude acquired

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FI deficiency. In the general blood test, the patient's hemoglobin was 73 g/l, erythrocytes 3.1 x 1012/l, platelets 188 x 109/l; leukocytes 6.8 x 109/l; in a biochemical blood test - total protein 69 g/l, albumin 40 g/l, alanine aminotransferase 42 U/l, aspartate aminotransferase 29 U/l, creatinine 85 µmol/l.

Laboratory data after treatment:
APTT 38 sec., fibrinogen 3.4 g/l, Quick prothrombin 92%, FVII 108%, FII 115%, FV 100%; FVIII 114%, FIX 98%, FX 106%, FXI 91.0%, FW 150%, FXII 101%, XIIa-dependent fibrinolysis 6 min, platelet aggregation with ristomycin 85%, platelet aggregation with collagen 73%, platelet aggregation with ADP 79%. In the general analysis of blood in a patient, hemoglobin rose by 102 g/l, erythrocytes 3.8 x 1012/l, platelets 202 x 109/l; leukocytes 7 x 109/l;
Considering the anamnestic, clinical and laboratory data, the patient was diagnosed with a hereditary F I deficiency (afibrinogenemia). Transfusions of FFP were continued at a dose of 700 ml/day (15 ml/kg of body weight), after stabilization of the patient's condition, the daily dose of FFP was reduced, and he was discharged from the RSPC of Hematology 9 days later.

Conclusion. Afibrinogenemia is a disease that leads to the development of life-threatening bleeding, which requires timely and adequate hemostatic therapy. In some cases, the course of the disease does not correspond to the severity of hypocoagulation disorders of plasma hemostasis, which is probably due to the multifactorial role of fibrinogen. Genetic studies are needed to verify the disease. In addition, when establishing a diagnosis, it is necessary to take into account genealogical data. Currently, there are no registered fibrinogen preparations in Uzbekistan and FFP and cryoprecipitate are used for treatment.
Treatment is reduced to stopping the bleeding that has arisen by transfusion of media containing fibrinogen (factor I) (plasma, serum, cryoprecipitate, etc.), until the level of fibrinogen rises to 2.0–4.0 g/l of normal. Transfusions, given the short half-life of the deficient factor, should be given every 4 to 8 hours until bleeding stops.
The clinical effect of the transfusion usually lasts for three weeks, although laboratory deficiency of the factor is again detected after a few hours.
For the relief of light bleeding or in the case of a minor surgical intervention, it is possible to prescribe tranexamic acid at a dose of 15-20 mg / kg of the patient's body weight or 1 g x 4 times a day.

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

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