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VON WILLEBRAND'S DISEASE

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Resume: *The most characteristic and specific symptom of von Willebrand disease is bleeding from the mucous membranes of the mouth, nose, and internal organs. Symptoms of bleeding vary from moderate to extremely severe and occur predominantly of the microcirculatory type. Patients with a severe deficiency of factor VIII experience heavy and prolonged bleeding (nasal, gingival, uterine), as well as hemorrhages in the muscles and joints. In addition, prolonged bleeding may occur due to injuries, tooth extraction, and operations. In childhood, there is often bleeding from the mucous membranes of the mouth, nosebleeds, and bruises on the skin. A more severe course of hemorrhagic diathesis is observed during or shortly after infectious diseases. The most likely trigger for bleeding due to infection is impaired vascular permeability. As a result, spontaneous bleeding of the diapedetic type appears.*

Key words: *von Willebrand disease, menorrhagia, petechiae, hemorrhage.*

INTRODUCTION

Von Willebrand disease is a hereditary blood disorder characterized by episodic spontaneous bleeding, which is similar to bleeding in hemophilia. The disease is inherited according to the principle of autosomal dominance. Inheritance is also possible in an autosomal recessive manner (types 2 and 3 of the disease). The cause of bleeding is a blood clotting disorder due to insufficient activity of von Willebrand factor, which is involved in platelet adhesion to collagen and protects factor VIII from proteolysis. When Von Willebrand Factor VIII is deficient, factor undergoes proteolysis and its plasma content decreases. The process of blood clotting - hemostasis - is quite complex and consists of a number of successive stages. The end result is the formation of a blood clot, which reliably clogs the site of vessel damage. In von Willebrand disease, one of the links of hemostasis is disrupted due to a reduced amount or complete absence of von Willebrand factor, a complex protein that ensures platelet fixation among themselves and on the inner wall of the vessel. The main manifestation of the disease is bleeding of varying severity. In most cases, severe bleeding occurs due to injury or invasive procedures. This is a hereditary disease of an autosomal dominant type: for the development of this pathology, the transmission of a defective gene from one of the parents (the gene responsible for the production of von Willebrand factor) is sufficient. The prevalence of von Willebrand disease is about 120 people per 1 million. Severe forms occur in approximately 1-5 people out of a million. There are three types of von Willebrand disease:

Type I is caused by a partial quantitative deficiency of von Willebrand factor. At the same time, its multimeric structure is preserved. There is a decrease in the procoagulant activity of factor VIII, platelet aggregation induced by ristocetin, ristocetin factor activity,

and von Willebrand factor antigen. The frequency of this form ranges from 75% to 80% of all cases of von Willebrand disease. Inheritance is autosomal dominant.

Type II is caused by qualitative changes in von Willebrand factor associated with impaired formation of multimers, and is divided into subtypes: 2A, 2B, 2M, 2N. The subtype 2A phenotype is the result of a defect in two different mechanisms: a defect in the synthesis of high molecular weight multimers and increased proteolysis of von Willebrand factor. In subtype 2B, there is an increased affinity of von Willebrand factor for the platelet membrane receptor glycoprotein Ib. Subtype 2M is characterized by a disruption of the association of von Willebrand factor with the glycoprotein Ib receptor on the platelet membrane. Subtype 2N is characterized by normal levels of von Willebrand factor and low procoagulant activity, which is caused by a disruption of the relationship between factor VIII and von Willebrand factor. Inheritance of von Willebrand disease type 2 is autosomal dominant, with the exception of subtype 2N, where it is recessive. The frequency of occurrence of these forms ranges from 5% to 15% of all cases of von Willebrand disease.

Type III is the most severe form with complete deficiency of von Willebrand factor. This form is characterized by the absence of von Willebrand factor in plasma, platelets and the vascular wall. Factor VIII levels are below 10%. Inheritance is autosomal recessive. The disease occurs in homozygotes with identical defective alleles or double heterozygotes with two different defective alleles. Patients with type 3 are likely to develop alloantibodies to von Willebrand factor. The incidence of type 3 von Willebrand disease is less than 5%.

In addition, there is a platelet type of von Willebrand disease, which is caused by a mutation in the gene for the platelet receptor glycoprotein Ib, which increases the sensitivity of this receptor to high molecular weight von Willebrand factor multimers. The phenotype is similar to subtype 2B.

Table 1. Frequency of occurrence of hereditary (hemophilia A, B, C and von Willebrand disease) coagulopathies in the Republic of Uzbekistan (%)

Clotting factor deficiency; % of patients in the group of hereditary coagulopathy in the Republic of Uzbekistan.			
VIII	IX	XI	FvW
1580(77,4%)	189(9,3%)	14(0,69%)	257(13,6%)

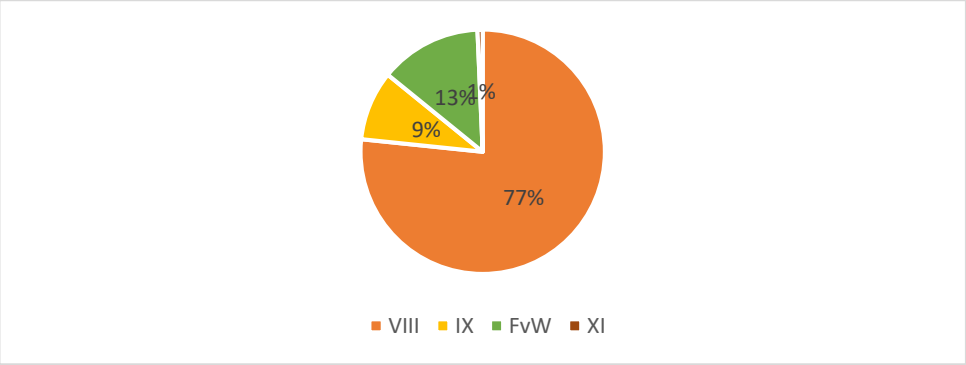

Table 2. Replacement preventive therapy for BV

Indication/location of bleeding	type BW	Dose FVIII+vWF/FVIII, ME/кг массы тела	Mode	Start of prevention
Hemarthrosis	3	10-50(ME)	1-3 times a week	after the first bleeding
Gastrointestinal bleeding	2	20-40(ME)	2-4 times a week	after 2-3 bleeding
Nasal/from the oral mucosa leading to anemia	3	20-50(ME)	1-3 times a week	after 3-4 bleeding per year (usually children)
Menorrhagia	any type	20-50(ME)	daily for 3-4 days during menstruation	women of childbearing age

Table 3. Depending on the type of BW, different therapeutic approaches can be chosen.

Type of disease	Drug of choice	Alternative Methods and Complementary Treatments
I	Desmopressin acetate	Antifibrinolytic agents, estrogens, vWF/FVIII concentrate
IIA	vWF/FVIII concentrate	Antifibrinolytics, estrogens
IIB	vWF/FVIII concentrate	Antifibrinolytic agents, estrogens, desmopressin
IIM	vWF/FVIII concentrate	Antifibrinolytic agents, estrogens, desmopressin
IIN	vWF/FVIII concentrate	Antifibrinolytic agents, estrogens, desmopressin
III	vWF/FVIII concentrate	vWF/FVIII concentrate or platelet concentrate

Scientific novelty

Modern replacement therapy with factor VIII drugs (containing von Willebrand factor) clotting will reduce the severity of clinical symptoms of the disease, as well as improve the quality of life of patients, which reduces the risk of complications.

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.

Von Willebrand factor antigen. The method is used for the quantitative determination of von Willebrand factor in the blood. In type I disease, the level of this indicator is reduced. In type III, von Willebrand factor is practically absent; in type II, its level may be slightly reduced, but its functional activity is impaired.

Platelet aggregation with ristocetin in plasma. This study shows the effectiveness of von Willebrand factor. Ristocetin is an antibiotic that stimulates platelet aggregation (sticking together). In von Willebrand disease it will be reduced.

APTT is the time during which a clot forms after adding special reagents to the blood plasma. This indicator is of great importance for identifying the deficiency of certain coagulation factors. In von Willebrand disease, this time is increased, which indicates a decrease in the ability to form a blood clot. Determination of coagulant (clotting) activity of factor VIII. In von Willebrand disease it can be normal or reduced. Bleeding time is the interval from the start of bleeding until it stops. Increased in von Willebrand's disease.

Patient K., 7 years old, first applied to the RSSPM of Hematology. Clinical picture of the patient with hemorrhage in the skin, mucous membranes, nasal and gingival bleeding. Denies his parents' consanguineous marriage. There was no family history of bleeding. At the age of 1 year, he received a lip injury, severe bleeding was noted, was hospitalized, and electrocoagulation was performed for hemostatic purposes.

Results. Laboratory data before treatment:

APTT 61 sec., fibrinogen 4.0 g/l, prothrombin according to Quick 108%, FVII 102%, FII 98%, FV 100%; FVIII 44%, FIX 98%, FX 96%, FXI 79.9%, FW 13%, FXII 101%, XIIa-dependent fibrinolysis 6 min, platelet aggregation with ristomycin 65%, platelet aggregation with collagen 73%, platelet aggregation with ADP 69%. The absence of an inhibitor to FW allowed us to exclude acquired FW deficiency. In the general blood test, the patient's hemoglobin was 87 g/l, erythrocytes 3.2 x 1012/l, platelets 190 x 109/l; leukocytes 6.8 x 109/l; in the biochemical blood test - total protein 69 g/l, albumin 40 g/l, alanine aminotransferase 42 units/l, aspartate aminotransferase 29 units/l, creatinine 85 μmol/l.

Laboratory data after treatment:

APTT 38 sec., fibrinogen 3.4 g/l, prothrombin according to Quick 115%, FVII 105%, FII 103%, FV 100%; FVIII 104%, FIX 98%, FX 106%, FXI 91.0%, FW 95%, FXII 101%, XIIa-dependent fibrinolysis 6 min, platelet aggregation with ristomycin 75%, platelet aggregation with collagen 78%, platelet aggregation with ADP 69%. In the general blood test, the patient's hemoglobin increased by 112 g/l, erythrocytes 3.8 x 1012/l, platelets 202 x 109/l; leukocytes 7 x 109/l;

Taking into account the anamnestic, clinical and laboratory data, the patient was diagnosed with von Willebrand disease (type 2). Emoclot transfusions were continued at a dose of 40 IU/kg body weight; after stabilizing the patient's condition, he was discharged from the Russian Scientific and Practical Center for Hematology 7 days later.

Thus, treatment of von Willebrand disease is conservative. It is aimed at increasing the amount of von Willebrand factor in the blood and restoring blood clotting parameters. The following groups of drugs are used: 1. Drugs containing blood coagulation factor VIII

and von Willebrand factor - serve to compensate for the deficiency of von Willebrand factor and can be used for any form of the disease.

2. Drugs that enhance the release of von Willebrand factor reserves from the vascular wall can be effective in type I and some forms of type II disease.

3. Hormonal contraceptives (estrogens contained in birth control pills help increase the amount and activity of von Willebrand factor) - can be used for prolonged menstrual bleeding caused by von Willebrand factor deficiency.

4. Antifibrinolytic drugs - drugs that slow down the destruction of blood clotting factors, this helps preserve already formed blood clots, can be prescribed before and after surgical procedures, tooth extraction and other invasive procedures.

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