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Treatment And Incidence Of Von Willebrand's Disease In The Republic Of Uzbekistan

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Summary. Von Willebrand disease (VW) is the most common coagulopathy caused by quantitative and qualitative von Willebrand factor (vWF) deficiency. BV affects about 1% of the population. However, most patients with VWD usually have no symptoms. The number of patients with BV who need ongoing treatment is comparable to that of hemophilia. Approximately 70% of patients with VWD have a mild disease, while the remaining 30% of patients have a moderate or severe disease [1]. The most characteristic and specific symptom in von Willebrand disease is bleeding from the mucous membranes of the mouth, nose, and internal organs. Symptoms of bleeding vary from moderately severe to extremely severe, proceeding mainly according to the microcirculatory type. Patients with severe factor VIII deficiency experience profuse and prolonged bleeding (nasal, gingival, uterine), as well as hemorrhages in muscles and joints. In addition, prolonged bleeding may occur with injuries, tooth extractions, and operations. In childhood, there are often bleeding from the mucous membranes of the oral cavity, nosebleeds, 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 in the presence of an infection is a violation of vascular permeability. The most likely trigger for bleeding in the presence of an infection is a violation of vascular permeability. As a result, spontaneous bleeding of the diapedetic type appears.

Key words: von Willebrand disease, menorrhagia, petechiae, hemorrhagia.

Introduction

von Willebrand disease is an inherited blood disorder characterized by the occurrence of 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 according to an autosomal recessive type (types 2 and 3 of the disease). The cause of bleeding is a violation of blood clotting due to insufficient activity of von Willebrand factor, which is involved in platelet adhesion to collagen and protects factor VIII from proteolysis. In von Willebrand Factor VIII deficiency, the factor undergoes proteolysis and its plasma levels decrease. In von Willebrand's disease, the microcirculatory type of bleeding predominates, petechial-bruising hemorrhages in the skin, recurrent nosebleeds, profuse menorrhagia, causing significant anemia in patients. Gastrointestinal bleeding, hematuria, hemarthrosis, and intracranial hemorrhage are much less common in von Willebrand disease. Recurrent gastrointestinal bleeding without an ulcerative history may be due to Heyde's syndrome, in which there is a comorbidity: aortic stenosis, angiodysplasia, and gastrointestinal bleeding. The cause of bleeding is the deposition of large VWF multimers on damaged aortic valves in the area of altered blood flow and constant increased load. The process of blood coagulation - hemostasis is quite complicated and consists of a number of successive stages. The end result is the formation of a thrombus, which reliably clogs the site of damage to the vessel. 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 the fixation of platelets between 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 trauma 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

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sufficient. The prevalence of von Willebrand disease is about 120 per 1 million. Severe forms are observed in about 1-5 people out of a million.

There are three types of von Willebrand disease: Type I is due to a partial quantitative deficiency of the von Willebrand factor. At the same time, its multidimensional structure is preserved. There is a decrease in the procoagulant activity of factor VIII, platelet aggregation induced by ristocetin, ristocetin cofactor activity, von Willebrand factor antigen. The frequency of this form is from 75% to 80% of all cases of von Willebrand's disease. Inheritance is autosomal dominant.

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

Type III is the most severe form with complete von Willebrand factor deficiency. This form is characterized by the absence of von Willebrand factor in plasma, platelets and the vascular wall. Factor VIII levels below 10%. Inheritance is autosomal recessive. The disease manifests itself in homozygotes with the same 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 platelet receptor glycoprotein Ib gene, which increases the sensitivity of this receptor to high-molecular-weight multimers of von Willebrand factor. The phenotype is similar to subtype 2B.

Table 1. The incidence of hereditary (hemophilia A, B, C and von Willebrand disease) coagulopathy in the Republic of Uzbekistan (%)

Coagulation 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%)

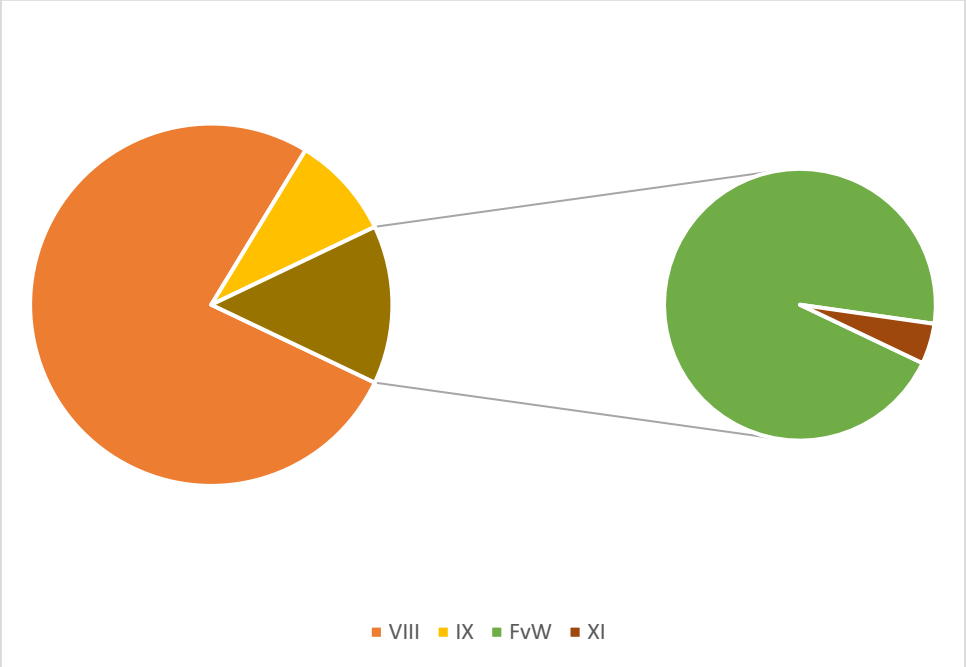

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Table 2. Replacement prophylactic therapy for vWF

Indication/localization of bleeding	тип БВ	Dose FVIII+vWF/FVIII, IU / kg of mass тела	Regime	Start of prevention
Hemarthrosis	3	10-50(IU)	1-3 times a week	after the first bleeding
Gastrointestinal bleeding	2	20-40(IU)	2-4 times a week	after 2-3 bleeding
Nasal/oral mucosa leading to anemia	3	20-50(IU)	1-3 times a week	after 3-4 bleeding per year (usually children)
Menorrhagia	any type	20-50(IU)	daily for 3-4 days during menstruation	women of childbearing age

Scientific novelty

Modern replacement therapy with factor VIII drugs (containing von Willebrand factor) coagulation will lead to a decrease in the severity of the clinical symptoms of the disease, as well as an improvement in the quality of life of patients, which reduces the risk of complications.

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.
Willebrand factor antigen. The method is used to quantify the von Willebrand factor in the blood. In type I disease, the level of this indicator is reduced. In type III, the von Willebrand factor is practically absent; in type II, its level may be slightly reduced, but its functional activity is impaired.
Plasma platelet aggregation with ristocetin. This study shows the effectiveness of the von Willebrand factor. Ristocetin is an antibiotic that stimulates the aggregation (gluing) of platelets. With von Willebrand's disease, it will be reduced.
APTT is the time it takes for a clot to form after the addition of special reagents to the blood plasma. This indicator is of great importance for identifying a lack of certain clotting 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's disease, it can be normal or reduced. Bleeding time - the interval from the start of bleeding to its stop. Increased in von Willebrand's disease.
Patient K., 7 years old, first applied to the RSSPMC Hematology. The clinical picture of the patient is bleeding into the skin, mucous membranes, nasal and gingival bleeding. Consanguineous marriage of parents denies. There was no family history of bleeding. At the age of 1 year, he received a lip injury, severe bleeding was noted, he was hospitalized, electrocoagulation was performed for hemostatic purposes.

Results. Laboratory data before treatment:

APTT 71 sec, fibrinogen 4.0 g/l, Quick prothrombin 108%, FVII 102%, FII 98%, FV 100%; FVIII 14%, FIX 98%, FX 96%, FXI 79.9%, FW >1%, FXII 101%, platelet aggregation with ristomycin 5%, platelet aggregation with collagen 73%, platelet aggregation with ADP 69%. The absence of an inhibitor to FW made it possible 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 a biochemical blood test - total

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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 115%, FVII 105%, FII 103%, FV 100%; FVIII 124%, FIX 98%, FX 106%, FXI 91.0%, FW 95%, FXII 101%, platelet aggregation with ristomycin 58%, platelet aggregation with collagen 78%, platelet aggregation with ADP 69%. In the general analysis of blood in a patient, hemoglobin rose by 112 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 von Willebrand's disease (type 3). Bioclot A transfusions were continued at a dose of 40 IU/kg of body weight; after stabilization of the patient's condition, he was discharged from the RSSPMC of Hematology 7 days later.

After the introduction of BioClot A, a significant increase in the activity of factor VIII and F.VWF to the required hemostatic level was noted: factor VIII from 14% to 124%, F.VWF from >1% to 95% ($p<0.001$), platelet aggregation with ristomycin: c 5% to 58% ($p<0.001$), shortening of APTT from 71.0 to 38.0 sec. ($p<0.01$).

Thus, the plasma factor BioClot A makes it possible to obtain a therapeutic effect in the provision of highly specialized care to von Willebrand patients with hematoma and prolonged bleeding.

It was shown that the restoration of the activity of factor VIII and F.VWF in plasma after the administration of BioClot A occurs in accordance with the calculated values. Plasma factor BioClot A is a highly effective hemostatic agent in the treatment of von Willebrand's disease, increasing the level of the deficient factor.

Treatment of von Willebrand disease is conservative. It is aimed at increasing the amount of von Willebrand factor in the blood and restoring blood coagulation parameters. The following groups of drugs are used:

1. Drugs containing coagulation factor VIII and von Willebrand factor - serve to compensate for the deficiency of von Willebrand factor and can be used in any form of the disease.
2. Drugs that enhance the release of von Willebrand factor reserves from the vascular wall - can be effective in I and some forms of type II disease.
3. Hormonal contraceptives (estrogens contained in birth control pills increase the amount and activity of von Willebrand factor) - can be used for prolonged menstrual bleeding due to von Willebrand factor deficiency.
4. Antifibrinolytic drugs - drugs that slow down the destruction of blood clotting factors, this helps to preserve already formed blood clots, can be prescribed before and after surgical procedures, tooth extractions and other invasive procedures.

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