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Treatment and Diagnostics of the Inhibitor Form of Hemophilia in the Republic of Uzbekistan

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ABSTRACT
The production of blocking antibodies to factor VIII and IX drugs is one of the most serious problems in the treatment of hemophilia. The development of an inhibitor leads to insufficient effectiveness of substitution therapy, sharply worsens the quality of life, and significantly increases the cost of treating patients with hemophilia [1]. Inhibitory hemophilia is an acutely developed pathological condition characterized by a violation of blood coagulation as a result of the detection of an inhibitor of disease VIII / IX, spontaneous and / or post-traumatic bleeding, identified in life threatening, in patients without previous cases of hemostasis. The appearance of an inhibitor to factor VIII/IX is considered the most severe complication associated with the treatment of hemophilia. Inhibitors are allo antibodies (IgG) that neutralize exogenous factors VIII/IX.

Introduction

Inhibitors to factor VIII or IX are one of the most severe complications of replacement therapy for hemophilia A or B. The appearance of an inhibitor is mainly manifested by a lack of clinical response to standard therapy with clotting factor concentrates or the appearance of bleeding during prophylactic therapy. The most significant complication of hemophilia that occurs in response to treatment is the development of blocking antibodies (inhibitor) to coagulation factors VIII or IX - the development of inhibitory (complicated) hemophilia. The frequency of inhibitor

development varies widely and, on average, is 10–15%. The greatest chance of developing an inhibitor during the first 20 days after the introduction of drugs of blood coagulation factors VIII and IX. In the future, the risk is significantly reduced, but remains throughout the life of the patient. The inhibitory form of hemophilia presents significant difficulties in providing urgent care to patients suffering from this disease, since repeated administration of antihemophilic drugs causes a rapid increase (from 4–7 days) in antibody titer in them, as a result of which replacement therapy, initially giving some effect, becomes ineffective, develops a number of complications that are difficult to correct [2,5]. At the same time, the appearance of antibodies to factor VIII is noted much more often (in 15-35% of patients) than to factor IX (about 3-5%). In most cases, they are found at the age of 3-6 years. In the world, out of 250 thousand patients with hemophilia, about 9 thousand suffer from inhibitory form [1,2,3]. Although the risk factors provoking the development of inhibitory forms of hemophilia have not yet been established, the severity of hemophilia and the age of the patient probably play an important role in the occurrence of inhibitory complications. A more detailed study of this complication of hemophilia and its timely diagnosis will make it possible to select an adequate dose of deficient factors for replacement therapy at various stages of treatment, as well as reduce the incidence of complications and improve the prognosis of the disease. Determination of the activity of inhibitors to f.VIII and f.IX is most often carried out in cases where the level of the deficient factor is below 5%. Most often, inhibitors appear in patients with severe hemophilia (in 20-30% of patients with severe hemophilia A and in 3-5% of patients with severe hemophilia B). Most often, the inhibitor develops in the first 50 days after the introduction (DV) of the factor and after intensive therapy during surgery.

In severe hemophilia, the appearance of an inhibitor does not affect the amount and location of bleeding. But, since factor replacement therapy becomes ineffective when inhibitors appear, the risk of severe complications and even death from bleeding in these patients is higher.

In moderate or mild hemophilia, an inhibitor can neutralize endogenous FVIII, thereby transforming the patient's phenotype into a severe form.

Pathogenesis. For a long time it was believed that the task of the immune system is to recognize protein molecules as “self” or “foreign”. Since the inhibitor develops in only 30% of patients and does not develop in the rest, it is clear that exogenous factor VIII is not recognized as a “foreign” protein in them. B and T cell clones that interact with body proteins are eliminated in the thymus during the formation of the immune system. In patients with severe hemophilia, this mechanism does not work, since FVIII is not produced in the body. FVIII-specific T and B cell clones persist and can elicit an immune response against exogenous FVIII.

Hazard signals that may lead to the development of an inhibitor:

1. Vaccination or infection (components of the cell wall of bacteria or viruses).
2. Surgical intervention or trauma (internal immune stimulants in case of cell damage).

Autoantibodies to factor VIII / IX: a combination of polyclonal immunoglobulins IgG1 and IgG4, blocking sections of the A2, A3 and C2 domains of the FVIII / FIX protein. The connection of FVIII with FWB, interaction with phospholipids, FIX and FX is broken. In contrast to alloantibodies in hemophilia A and B, there is no linear relationship between inhibitor concentration and degree of suppression of FVIII/FIX activity.

In coagulological tests: 1. Selective prolongation of APTT, with normal PT, TT, FG and the absence of lupus anticoagulant.

2. Decreased activity of FVIII/FIX.

3. Identification of the FVIII/FIX inhibitor and determination of its titer by the Bethesda method. 1 BU - the amount of antibodies capable of reducing the activity of FVIII / FIX in normal plasma by 50% during a 2-hour incubation with the patient's plasma at 37 degrees.

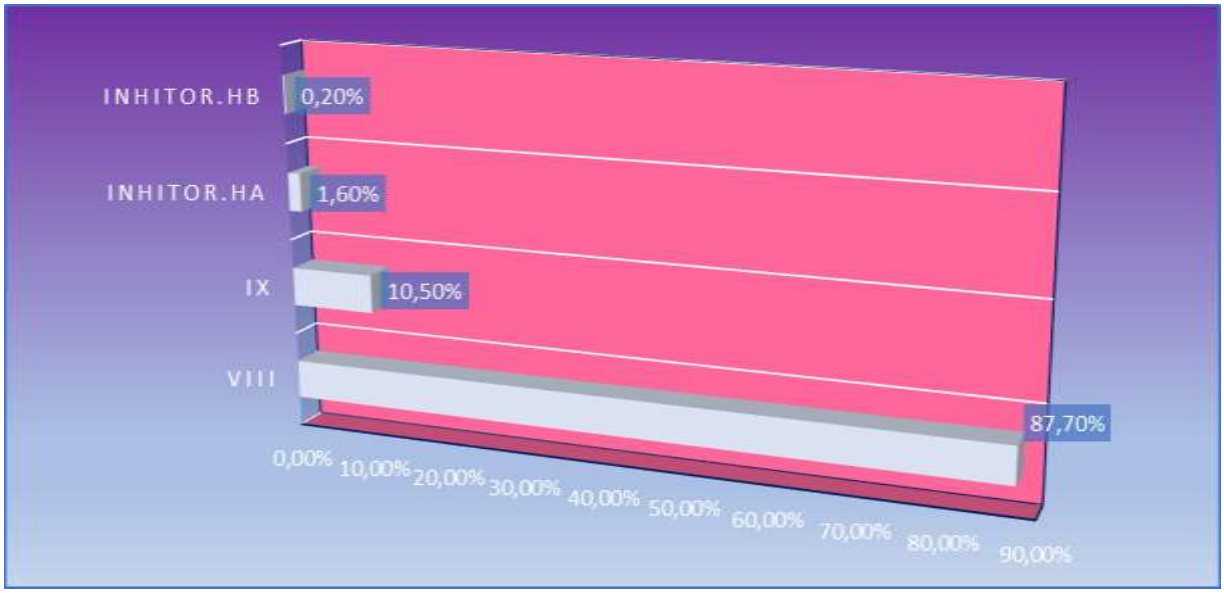
Classification of inhibitors: 1. Inhibitor titer < 5 BU - inhibitor in low titer (low responsive).

2. Inhibitor titer ≥ 5 BU - inhibitor in high titer (highly responsive).

Low titer inhibitors may be transient and disappear within 6 months. High titer inhibitors are usually permanent. With a long absence of replacement therapy, their titer may decrease, but when therapy is resumed, anamnestic reaction after 3-5 days. At a very low titer (<0.6 BU), the inhibitor may not be detected by the Bethesda method, but may cause a shortening of the period half-life and recovery factor. Up to 50% of patients with inhibitory hemophilia B may have severe allergic reactions, including anaphylaxis, while receiving FIX. Such reactions are often the first symptom of inhibitor development.

The frequency of occurrence of hereditary (hemophilia A, B, and inhibitory form of Hemophilia A and B) coagulopathy in the Republic of Uzbekistan (%): F VIII-1580 (87.7%), F IX-189 (10.5%), inhibitory form of Hemophilia A (28-1.6%) and Hemophilia B (0.2%). The number of registered cases of hemophilia A in the Republic of Uzbekistan significantly exceeds the number of cases of hemophilia B, 87.7% and 10.5%, respectively (ratio 5, 2:1), 1.8% of total hemophilia was the inhibitory form of hemophilia (Fig. 1).

Fig. 1



The frequency of occurrence of Hemophilia A / B and the inhibitory form of Hemophilia A / B in the Republic of Uzbekistan.

Hemophilia A was diagnosed at an earlier age (mean age at diagnosis was 1.8 years) than hemophilia B (mean age at initial diagnosis was 2.6 years), due to the milder course of hemophilia B. Severe hemophilia (factor level less than 1%) was diagnosed in 29% of the subjects, moderate severity of the disease (factor level 1–5%) - in 42%, mild hemophilia (factor level more than 5%) - in 29%. Of 1,580 men with hemophilia A, most had moderate disease (42%), 30% mild, and 28% severe. Of 189 patients with hemophilia B, 39% were diagnosed with moderate severity, 38% with severe, and 23% with mild severity of the disease. Thus, there was more often a decrease in plasma coagulation factors, corresponding to the moderate severity of

hemophilia, regardless of its variant.

The aim of this work is to study the level of factor VIII/IX in patients with an inhibitory form of hemophilia during replacement therapy with plasma and recombinant preparations of blood coagulation factors.

Scientific novelty

Timely diagnosis of the presence of an inhibitor makes it possible to correct the patient's treatment, which helps to control the disease phenotype, prevent the development of arthropathy and improve the quality of life of patients, which reduces the risk of complications.

Materials and research methods. In the course of the study, clinical and laboratory data of 107 patients who were hospitalized in the Republican Specialized Scientific and Practical Medical Center of Hematology with a diagnosis of Hemophilia A and B, a severe form of the course, were used. Patients were hospitalized for hemarthrosis of the knee joints. All male patients, age at the time of the study ranged from 1 to 50 years (mean 31.4 years). 94 patients had hemophilia A (39 children aged 1 to 18 years, 55 adults aged 22 to 50 years), 13 had hemophilia B (4 children aged 9 to 18 years, 9 adults aged 23 to 48 years).

All patients were examined by clinical, biochemical and coagulological research methods.

In the coagulation laboratory, to determine the titer level of the inhibitor of VIII and IX blood coagulation factors, a programmable coagulometer of the Sysmex-CA 660 type was used, which is an analyzer of hemostasis indicators designed to study the plasma hemostasis subsystem by clotting methods (i.e., based on recording the time of formation of a fibrin clot).

Coagulation factor inhibitors were determined by the Bethezda unit method modified by Nimegan with normal plasma buffering. The acceptable level of inhibitor to plasma factors VIII and IX is 0.6 BU/ml. The activity of plasma coagulation factors was determined using the Siemens reagent kit. The values of factor VIII content in plasma are 50-200%, factor IX - 50-200% are taken as the norm.

Results and discussion. The inhibitory form of hemophilia was diagnosed in the examined patients (n = 31) with Hemophilia A-28, Hemophilia B-3, in 6.5% of patients with hemophilia B and in 93.5% with hemophilia A. The inhibitor level was determined in the range from 1, 3 to 7.9 BU/ml (median 3.5 BU/ml). At the same time, the content of the deficient plasma coagulation factor varied from 0 to 5%, with a median of 2.0%. The medians of the studied parameters and the significance of their differences depending on the type of hemophilia are presented in Table 1.

Indicators of the coagulation link of hemostasis in patients with hemophilia and inhibitory form of hemophilia (before and after the introduction of plasma and recombinant blood coagulation factors) (M±m)

Coagulogram indicators	Patients with hemophilia (n=107)			
	Hemophilia A and B (n=76)		Inhibitory form of hemophilia A and B (n=31)	
	Before introduction	**After the introduction**	**Before introduction**	**After the introduction**
APTT	93,05± 10,34	42,78± 8,16*	128,78± 8,16	78,71± 6,54

PTI,%	106,78±1,33	112, 89±1,40	108,56 ±1,42	113, 61±1,32
TV, sec.	18,2±0,32	16,6±0,28	20,8±0,23	17,2±0,28
fibrinogen	6,48±0,28	4,89±0,30	7,89±0,16	6,56±0,30
Tolerance to heparin, min.	>20±1,31	18±3,14	>20±1,50	20±0,55
F.VIII, % (n=94)	4,8±1,55	148±3,48%*	0,3±2,48	8,3±2,48
F. IX, % (n=13)	3,2±0,38	163±5,42%*	0,5±1,48	11,8±0,48

To obtain comparative clinical and laboratory characteristics, patients with inhibitors were divided into groups depending on the type of hemophilia: with hemophilia A (n = 28), with hemophilia B (n = 3); and also depending on the inhibitor level: up to 5 BU/ml (n = 18) and above 5 BU/ml (n = 13). Table 2.

Characteristics of inhibitory forms of the disease depending on the variant of hemophilia

Index	Patients with hemophilia with an inhibitor (n=31)						
	Hemophilia A (n=28)			Hemophilia B (n=3)			authenticity
	Me	25%	75%	Me	0,5%	95%	P
Age, years	28	17	46	27	6	38	0,49
Factor level,%	2	1	3	1	0,1	2,3	0,23
Inhibitor level, BU/ml	3,5	4,1	7,25	3	6,8	3,2	0,1

As can be seen from the data presented in Table 3, there were no differences in patient age, factor level, inhibitor level in hemophilia A and hemophilia B. Correlation analysis according to Spearman between the inhibitor level, the factor level, and the age of patients did not reveal a significant relationship ($\rho = -0.07$; $p = 0.63$).

According to the level of inhibitors, it is customary to single out “low responsive” (inhibitor level less than 10 BU/ml) and “highly responsive” (inhibitor level more than 10 BU/ml) [5,6]. Since the maximum inhibitor level in our study was 7.9 BU/ml, in order to obtain comparative characteristics, patients with the inhibitor form were divided into two groups according to the inhibitor level. Table 3.

Characterization of inhibitory forms of hemophilia with an inhibitor level up to 5 BU/ml and above 5 BU/ml

Index	Patients with hemophilia with an inhibitor (n=31)						
	Inhibitor level, <5BU/ml n=18 (58%)			inhibitor level, >5BU/ml n=13 (42%)			authenticity
	ME	25%	75%	ME	25%	75%	P
Age, years	25	17	42	22	15	19	0,59
Factor level,%	2,3	1,1	4	1,1	0,1	2,3	0,04

The development of the inhibitory form of hemophilia as a whole does not depend on the patient's age, the level of the deficient factor, the variant of hemophilia, which indirectly confirms, first of all, the effect of ongoing replacement therapy on the formation of inhibitors of plasma coagulation factors.

The following plan for examining patients with inhibitory forms of hemophilia is proposed. "Low responding" patients (inhibitor level less than 5 BU/ml) to determine the inhibitor: in the event of severe bleeding and hemorrhage in the joints; repeated single determination of the inhibitor level a week after replacement therapy; before performing invasive diagnostic manipulations and surgical interventions; once every 6 months on an outpatient basis in the absence of severe clinical manifestations.

"Highly responsive" patients (inhibitor level more than 5 BU/ml) to determine the inhibitor: in the event of bleeding and hemorrhage in the joints; repeated double determination of the level of the inhibitor after one and three weeks, since a high level of inhibitory antibodies in them can persist for a long time after the replacement therapy; before performing invasive diagnostic manipulations and surgical interventions; once every three months on an outpatient basis in the absence of severe clinical manifestations. Since the presence of a high titer of inhibitory antibodies may accompany the presence of autoimmune complications, patients in this group can be recommended to conduct an immunological study once a year to determine the level of IgG, circulating immune complexes, antinuclear antibodies, complement levels, the ratio of T-helpers / T-suppressors.

Thus, timely diagnosis of the presence of an inhibitor allows for a correction of the patient's treatment, which contributes to the control of the disease phenotype, the prevention of the development of arthropathies, and the improvement of the patient's quality of life. In order to choose the tactics of therapy, dynamic monitoring of patients with an inhibitory form of hemophilia is necessary. The timing and extent of laboratory testing should be adjusted depending on the initial inhibitor level.

Treatment. The choice of drug for treatment should be based on inhibitor titer, clinical response to therapy, and bleeding pattern. In patients with a low inhibitor titer, bleeding can be stopped by administering factor concentrate at doses 3 times the standard dose. If there is no effect, it is necessary to use bypass drugs. Treatment of bleeding in patients with a high titer of the inhibitor should be carried out only with bypass drugs. Currently, there are 2 groups of bypass drugs: AICC and activated recombinant factor VII (Eptacog alfa).

However, there are data on the individual characteristics of the patient's response to each of the drugs, which must be considered when choosing a drug. Dosing of drugs with a bypass mechanism of action for the relief of bleeding:

1. AICC is administered at a dose of 50-100 U/kg every 12 hours. Maximum daily dose 200 U/kg.

2.Eptacog alfa (activated) is prescribed at a dose of 90-120 mcg/kg every 2-4 hours until bleeding stops. Possible single injection day at a dose of 270 mcg / kg. It is possible to carry out prophylactic therapy for hemophilia complicated by an inhibitor.

Long-term prophylactic therapy is carried out by AICC in the following mode.

1. At a dose of 50 - 100 U / kg every 12 hours during IIT (induction of immune tolerance), until reduced

inhibitor titer less than 2 BU;

2. Outside IIT at a dose of 50 - 100 U / kg 3 times a week or every other day. Short-term (within 3 months) prophylactic therapy can be carried out with eptacog alfa in the regimen of 90 mcg/kg 1 time per day.

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