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Hemophilia in Children - Modern Paradigms of Treatment and Prevention

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Abstract: World Hemophilia Day is celebrated on April 17. The date is timed to coincide with the birthday of Frank Schneibel, founder of the World Hemophilia Federation. Both on this day and on other days, the medical community is called upon to draw attention to the problems of people suffering from blood clotting disorders — one of the central problems in hematology. Although hemophilia is one of the most common genetically determined disorders of blood clotting, it is considered a rare (orphan) disease. The disease manifests itself in early childhood, has clinically the two most common variants of the disease: hemophilia A and hemophilia B. Diagnosis requires mandatory genetic confirmation or laboratory confirmation of a decrease in the concentration of factor VIII for hemophilia A and factor IX for hemophilia B. The introduction of domestic recombinant coagulation factors in recent years has made it possible to significantly optimize replacement therapy in children with hemophilia, and in the face of growing Western sanctions, to provide Russian children with the necessary urgent care and prevention tools that are not inferior to the best foreign analogues. New principles of therapy that radically change management include non-active drugs and gene therapy options for both hemophilia Aand hemophilia B.

Key words: children, hemophilia, inhibitor, substitution therapy, non-factorial drugs.

Introduction

The problem of hemophilia is as relevant today as it was decades ago. Modern doctors have learned how to stop bleeding in the most severe cases of the disease, and have received reliable information about the mechanisms of pathology developmentand its inheritance. Only methods of complete cure of patients have not been found, but they are also at the stage of clinical development. Hemophilia in children is a hereditary disease in which blood does not clot well and often there is heavy bleeding. Congenital pathology is associated with a small number of coagulation factors in plasma (the liquid part of the blood) and occurs with a frequency of 10-14 per 100 thousand boys[1].

According to the International Classification of Diseases (ICD-10), hemophilia in children is encoded as D66.0 (hemophilia A, hereditary factor VIII deficiency) and D67.0 (hemophilia B, hereditary factor IX deficiency)[2]. Hemophilia A is diagnosed four times more often than hemophilia B. Initial symptoms of the disease usually appear in the first year of life. Sometimes, already in the newborn period, hemorrhages on the scalp (cephalohematomas), umbilical bleeding soon after the umbilical cord remains fall off, and subcutaneous hematomas are detected [3]. Older children still have a tendency to bleed. It takes more severe forms due to the expansion of the child's motor activity. During a long-term follow-up of families with a diagnosis of hemophilia in children, scientists noticed that [3]:

- in the vast majority of cases, only boys are ill, and girls are carriers of the pathology;

- in the family, boys can be both sick and healthy;
- adult men with hemophilia pass it on to their grandchildren through female conductors [4].

In isolated cases, carriers of the pathological gene (girls) there are also unusually heavy bleeding events. To stop them, specialized medical care is required [5].

Reasons. Hemophilia A and B are diseases in which factors VIII or IX are missing among the 13 plasma coagulation factors, less often factors I, XI, XII, and XIII. Diseases in 75 % of cases are inherited from parents in the female line, transmitted recessively, through the X chromosome. The remaining 25 % of diseases occur accidentally as a result of mutations in one of the loci of the X chromosome. The mutation that has occurred is fixed and passed down in the future[6].

Experts of the World Health Organization report that in recent decades, the number of patients and carriers of hemophilia has been constantly increasing. At the same time, hereditary, rather than random forms of the disease, increase. Experts explain this situation by a significant reduction in child mortality from hemophilia, the effectiveness of modern methods of therapy. Patients with hemophilia live to middle age and older, marry healthy women, and raise daughters who are carriers of the pathological gene [7].

Pathogenesis. The hemophilia gene is located on the X chromosome. In girls, the sex set consists of two X chromosomes, so if there is an anomaly in one of them, the clinical signs of the disease do not appear, they are suppressed by the normal chromosome [8]. Scientists have proved that carriers of the pathological gene have significantly reduced the content of VIII and IX clotting factors, but pathological bleeding does not occur, because clotting disorders appear when the number of necessary factors decreases to 20% or lower. Boys have only one X chromosome in their sex set. У-хромосомеThere are no genes responsible for the coagulation system on the Y chromosome[9]. If the X chromosome contains an abnormal gene, the child has hemophilia. The following cases of inheritance of an anomaly are possible:

- Sons from a father with hemophilia and a healthy mother are also born healthy. The normal X chromosome is passed on to them by the mother, so the inheritance of pathology stops. If daughters are born, they are all healthy, but there is a pathological gene dormant on their X chromosome. In the future, it will be inherited by the sons, that is, the grandchildren of the sick father[10].
- From the marriage of a healthy father and a mother гемофилическогоwho carries the hemophilic gene, both sick and healthy sons are equally likely to be born. Similarly, daughters from such a marriage carry the disease gene or it is absent.
- Extremely rare cases of female hemophilia are associated with the transfer of genetic information to a girl who was born from the marriage of a hemophiliac father and a carrier mother. Both daughters and sons from such a union have the same chances of both getting sick and staying healthy[11].

Basic knowledge of genetics is important for parents who have relatives with hemophilia in their family. To stop the inheritance of pathology, families where the father is ill, you need to limit the birth of sons (all of them will be healthy).

For an individual consultation, you can contact a Medical Center and get detailed information about the disease and its type of inheritance[12].

Symptoms. Themain symptoms of hemophilia in children are external and internal bleeding[13], hemorrhages in the joints (hemarthrosis) and internal organs, and a tendency to bleed during and after surgical operations:

- the blood does not stop for a long time even after small scratches, cuts and abrasions, with any damage to the skin, you have to wait a long time for the bleeding to stop;

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- accumulations of blood inside the knee, elbow joints, as well as the joints of the hands and feet are quickly formed during falls and bruises;
- the appearance of extensive subcutaneous hematomas is difficult to associate with any serious injury;
- when a tooth is removed, any gum damage, or teething occurs in infants, bleeding occurs that does not stop on its own;
- an impurity of blood is often found in the urine and intestinal contents;
- nosebleeds are typical, and it is also quite difficult to stop them.

The peculiarity of the disease in children under 3 years of age is the absence of hemarthrosis. Hemorrhagic syndrome in them is most pronounced on the mucous membranes. They are injured by children's toys and any objects that get into their mouths. The most severe bleeding at this age occurs during respiratory infections with coughs and runny nose. With false croup, when the child loses his voice, bleeding from the laryngeal mucosa is very dangerous.

As soon as the baby starts to get up and walk, the likelihood of injuries increases. On the face and torso, a lot of bruises are formed, which clearly do not correspond to the injuries received. After three years, the most characteristic sign of hemophilia appears – hemorrhages in the joints. In the future, they predominate in the clinical picture of the disease:

- The joint quickly increases in volume, and the skin above it is hot to the touch.
- The pain gradually increases, and it becomes impossible to move your arm or leg. Adults notice that children spare the limb on the affected side.
- In mild cases, the blood resolves in 1-1. 5 weeks, the joint function is restored. In more severe situations, rehabilitation lasts 3-4 weeks.

An analysis of blood clotting and the presence of certain coagulation factors in it helps to understand the exact cause of bleeding. The earlier the treatment of hemophilia is started, the less likely it is to cause serious complications of the disease.

Methodology

Classification and stages of the disease. Depending on the missing coagulation factor, there are 3 types of the disease:

Hemophilia A. This is the classic and most common form of the disease. In 85% of cases of abnormal coagulation system, the blood lacks factor VIII. This is an anti-hemophilic protein-globulin, which is normally formed in sufficient quantities by liver cells, participates in the formation of a blood clot when the vascular wall is damaged.емофилияHemophilia B. In 10 % of cases of the disease, the cause of blood clotting is associated with a deficiency of factor IX (Christmas disease). Pathology is inherited in the same way. According to clinical signs, their age-related changes and complications, it exactly corresponds to hemophilia A. The difference is in therapy – the need to introduce other drugs to stop bleeding. GEmophilia C (Rosenthal's disease). This is also a hereditary pathology, it is rare. It is associated with a combined lack of several factors of the coagulation system at once-XI, XII, XIII and I. The type of inheritance differs from hemophilia A and B, both boys and girls are ill. Neverthelessменее, the disease proceeds more easily, bleeding occurs only with extensive injuries.

According to the severity, there are three types of hemophilia:

1. Severe form. The activity of clotting factors is less than 1 %. Various manifestations of hemorrhagic syndrome are detected at a very early age. Soon after birth, extensive cephalohematomas form, the umbilical wound does not heal for a long time and bleeds. In the future, bleeding is accompanied by eruption of milk and permanent teeth, hemarthrosis, hemorrhages in internal organs and muscles occur early.

2. Medium-heavy. The plasma contains from 1 to 5 % of the required amount of clotting factors. At birth, there may be no symptoms of the disease, but with the expansion of the baby's motor activity, the first serious bleeding appears. Preschoolers already have hemorrhages inside the joints, and all the typical complications of the disease are gradually developing.
3. Easy form. Clotting factors are only 5-50% active. The child and his parents learn about the presence of pathology when preparing for surgery or after serious injuries. Bleeding occurs less frequently and is not as intense as in hemophilia A and B. Transfusions of donor blood are rarely required, usually in the case of operations or injuries.

Up to 70% of all established cases of the disease occur in severe forms, in which it is difficult to understand the cause of bleeding. They develop with minor bruises that are invisible to a healthy person, so such episodes of bleeding are called spontaneous.

Depending on the presence of an inhibitor in the blood (a substance that inhibits the activity of clotting factors), they speak of: uncomplicated hemophilia (typical symptoms of the disease are stopped with the introduction of drugs saturated with clotting factors);inhibitory form, in which the activity of the immune system is directed against its own clotting factors, and the administered donor blood preparations are destroyed by the immune system.

Result

Complications. Abnormal blood clotting most often causes 3 types of complications: Hemorrhages damage organs and tissues. Hematomas form under the skin, in the muscles and intermuscular spaces. Often, large accumulations of blood squeeze the branches of nerves or main blood vessels, which disrupts sensitivity in these areas of the body, makes it difficult for the muscles to work. Even with awkward movements, intramuscular hematomas occur, which resolve for a long time, are accompanied by fever, pronounced soreness.Foreign bleeding depletes the body, blood loss affects the general condition of the child. The children look pale and have a thin build. Because of low hemoglobin, they often feel dizzy and have a headache. Periodically there is bleeding from the urinary tract, stomach and intestines. They are accompanied by pain in the lower back or in the abdomen. Hemorrhages in the brain are rare, but they are very difficult. With the formation of hematomas in the spinal cord, the prognosis is more favorable.Intra-овторяютсяarticular hemorrhages recur. They form foci of chronic inflammation, destroy joint surfaces, deform joints, and disrupt their functions. With age, joint disorders progress. Lesions of the musculoskeletal system become multiple. They predominate over all other symptoms of the disease and largely determine the degree of social adaptation of a person.

More rare complications of hemophilia in children are disorders in the hematopoietic system. Due to frequent blood loss, the bone marrow is depleted, and the formation of blood cell elements decreases. In such children, a reduced platelet count is found, which further worsens the blood clotting properties, a decrease in the number of white blood cells. Deficiency of white blood cells leads to secondary immune disorders, weakening of the body's anti-infective defenses. The consequence of hemophilia is also kidney damage. Amyloidosis of the renal tissue (deposition of a pathological type of protein in it) and chronic inflammation ultimately lead to chronic kidney failure, constant intoxication with products of their own metabolism. A very dangerous condition in hemophilia is pathological reactions to transfusions of antihemophilic drugs. In addition to fever and allergic skin rash, an inhibitory form of the disease develops, in which medications lose their effectiveness. Replacement therapy with drugs from donor blood in this complication ceases to help.

Treatment. Treatment of hemophilia in children is carried out by a hematologist with donor blood clotting factors. Such therapy is substitution, because the missing protein compounds are introduced into the patient's body. All drugs are administered intravenously or applied topically to the bleeding surface. Intramuscular administration of any medications is contraindicated in patients with hemophilia. If it is necessary to introduce a vaccine into the muscle, preliminary preparation is carried out with donor blood preparations. For hemarthrosis, intravenous replacement therapy is also

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prescribed. At the same time, the affected arm or leg is fixed immobile for 2-5 days. You can not apply cold to the joint, it worsens the prognosis. Immediately after removing the fixing bandage, physical therapy begins to restore movement in the joint. If there are wounds, they are treated and sutured by surgeons under the cover of antihemophilic drugs. It is not recommended to apply pressure bandages to the wound.

Rehabilitation. Rehabilitation doctors of the Medical Center select individually for each child physical therapy exercises to expand the range of motion in the joints after hemorrhage in them, give recommendations on acceptable physical exercises to strengthen the musculoskeletal system and prevent cardiovascular diseases. At the stage of experimental development around the world is the therapy of:

- ✓ gene therapy (methods for replacing abnormal genes are being studied).
- ✓ cellular (transplantation of healthy cells and proteins);
- ✓ tissue (transplantation of healthy tissues, transplanting stem cells to eliminate the consequences of the disease).

Discussion

Hemophilia is a genetic disorder that significantly impacts the clotting ability of blood, making even minor injuries potentially life-threatening due to prolonged bleeding. It primarily affects boys, with girls being carriers. Hemophilia is classified into three types: Hemophilia A, B, and C, which are distinguished by the specific coagulation factor deficiencies involved. The two most common types are Hemophilia A and B, with Hemophilia A being the more frequent, occurring in about 85% of cases.

Recent advancements in treatment and prevention have greatly improved the quality of life for children with hemophilia. Recombinant coagulation factor therapy has become a cornerstone of management. This approach replaces the missing clotting factor, significantly reducing the frequency and severity of bleeding episodes. Additionally, with the rising effectiveness of these therapies, children are now living longer and healthier lives, which was not always the case in the past. Substitution therapy is a vital aspect of treatment, and new methods like gene therapy and monoclonal antibody therapies hold promise for more permanent solutions. Gene therapy, which involves inserting a functional copy of the faulty gene, has the potential to provide a long-term cure by addressing the root cause of the disorder. Although still in the experimental phase, gene therapy has already shown promising results in clinical trials, offering hope for a future where hemophilia can be treated permanently rather than managed with lifelong therapies.

A challenge in hemophilia treatment is the development of inhibitors, which occur when the body's immune system attacks the infused clotting factors. This complicates the therapy, making the disease harder to manage. In such cases, more specialized treatments, such as immune tolerance induction therapy or the use of bypassing agents, are required.

Preventive measures are critical in the management of hemophilia in children. Early diagnosis and regular monitoring of clotting factors are essential for avoiding severe bleeding episodes. In addition, parents and caregivers play an important role in preventing injuries by creating a safe environment, avoiding trauma, and engaging in appropriate activities that do not put the child at risk for bleeding.

Despite these significant advances, hemophilia continues to pose a unique set of challenges. However, ongoing research, better therapies, and early intervention strategies are making it increasingly possible to not only manage the disease effectively but also offer hope for a future cure.

Conclusion

In conclusion, Prevention of bleeding is performed by a hematologist. He prescribes substitution therapy, as well as treatment with monoclonal antibodies. They bind clotting factors IX and X to make up for the lack of factor VIII. In this way, it is possible to prevent the most severe forms of

bleeding – hemarthrosis and associated early disability. Parents create a protective regime for a child with hemophilia. Piercing, cutting objects, and potentially dangerous toys are removed from household items. Outdoor games and traumatic sports are restricted as much as possible. From the first years of life, the baby is taught to read, draw, and play board games. Individual swimming sessions with foam paddles to protect the joints are useful.щитками. Professional orientation also starts early. The child is taught an interest in professions related to intellectual work.

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