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Overview of hemophilia A in pediatrics

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Abstract
Hemophilia A is a rare congenital, recessive X-linked disorder caused by lack or deficiency of clotting factor VIII. The defining clinical feature is bleeding into key joints including the ankles, knees, and elbows, which can lead to the development of arthropathy, particularly in severe instances that go untreated. Before the 1960s, the median life expectancy was about 30 years. However, a paradigm shift has occurred due to a better understanding of the disorder and the development of effective therapy based on prophylactic replacement of the missing factor. As a result, people with hemophilia can now anticipate a quality of life and life expectancy that is almost normal. However, for a significant number of patients, the possibility of developing inhibitory antibodies to infused factor remains a significant obstacle to overcome. Finally, gene therapy for hemophilia has progressed remarkably and could soon become a reality.

Keywords: Hemophilia A, FVIII, prophylaxis, inhibitors

Epidemiology

There is no ethnic group on our planet where hemophilia is not common. In 2022, 427,685 patients were identified with hemophilia globally (1). Hemophilia A, not hemophilia B, affects 80% to 15% of the population. It was present in 1% of live male infants. The disease tends to cluster in nations with high rates of consanguineous marriage, such as Egypt, due to its X-linked inheritance pattern. Recent advances in diagnosis and treatment have given patients hope for a normal lifetime (2).

Etiology

A deficiency in blood clotting factors is the hallmark of hemophilia, a disorder that tends to run in families. The clotting factor gene is almost always at blame in these cases. The study discovered that out of over a thousand changes in the genes that code for factor VIII, around 30% are due to random mutations. On the long arm of chromosome X, factor VIII encoding gene is found. Hemophilia A is an X-linked recessive illness, meaning it solely affects females and has no effect on boys born to carriers. A female carrier mother has a 50% chance of bearing affected sons and carrier females. It is also possible for females to be affected when the X chromosome is inactivated or missing, as in lyonization or Turner Syndrome, or when the defective gene is present in both parents (2).

Pathophysiology

The development of blood clots is facilitated by two pathways: the contact pathway and the extrinsic tissue factor (TF) pathway. Both pathways include a cascade of enzyme activation events that activate platelets and crosslink fibrin monomers, resulting in the formation and stabilization of a blood clot. Extrinsic pathway initiation occurs upon endothelium degradation and subsequent exposure of subendothelium tissue factor (TF). After VIIa and tissue factor are activated, they form a complex that activates factors IX and X, respectively, leading to IXa and Xa. To activate the intrinsic pathway, blood factor XII, prekallikrein, and high-molecular-weight kininogen must come into touch with a synthetic surface. A conformational change in factor XII results in the small creation of factor XIIa, which in turn activates kallikrein and factor XII to XIIa in the opposite direction. In order to make factor XIIa, factor XI must first be activated. This triggers the transformation of factor IX into factor IXa. When factor Xa is produced, both paths converge. Thrombin is produced when factor Xa converts factor II, prothrombin, into factor IIa (3).

The first step in the chain reaction is the activation of factor VIIa by thrombin, which in turn releases factor VIII from the von Willebrand factor. After that, thrombin releases phospholipids that bind IXa, which in turn activates factor XIII into factor XIIIa. This, in turn, helps stabilize clots by cross-linking fibrin monomers. A large amount of factor X is attracted to and activated by the tenase complex, which consists of factor IXa, factor VIIa, calcium, and phospholipids. The process continues with the formation of the prothrombinase complex by factor Xa, calcium, and phospholipids. This complex facilitates the conversion of prothrombin to thrombin. Thrombin then facilitates fibrinogen's hydrolysis into fibrin monomers. Clot formation is insufficient due to a lack of or issue with factor VIII and factor IX, which hinder the intrinsic pathway of the coagulation cascade from being properly activated (2).

Evaluation

Hemophilia is most often diagnosed with a high index of suspicion based on laboratory testing, clinical symptoms, and family history. A person should be tested if he has a family history of bleeding disorders, has had excessive bleeding after surgery or trauma, or is a carrier for the gene. Chorionic villous sample or amniocentesis genetic testing is usually administered to families with a history of hemophilia during pregnancy. Hemophilia prenatal testing for families also has the option of genetic counseling. Among other things, a complete blood count, prothrombin time (PT), partial thromboplastin time (PTT), and bleeding time (BT) may be part of the first laboratory testing following pregnancy. Excessive bleeding following a blood transfusion, circumcision, or delivery should prompt a hemophilia examination in persons without a family history of the condition. Hemophilia A patients often have normal PT and BT, but a prolonged PTT because the intrinsic pathway is interrupted. The potential PTT duration exceeds the high normal range by a factor of two to three. Any mixing research worth its salt will adhere to a definitively lengthened PTT. It is recommended that the PTT should be normalized if a mixing analysis suggests a possible factor deficiency. After the mixing experiment, factor VIII test should be conducted. When factor activity drops below 40% of the normal level a hemophilia diagnosis is usually established. Molecular genotyping will be administered as a subsequent step to validate the diagnosis and provide a more accurate prognosis. The works cited include those of Zimmerman et al. (2), Srivastava et al. (4), and Peyvandi et al. (5).

The frequency and severity of symptoms of the hemophilia A depends on the level of factor present at the plasma level: Mild deficiency (5–40% FVIII activity) which usually presenting with bleeding after surgical procedures; moderate deficiency (1 to 5% FVIII activity) and severe deficiency (<1% FVIII activity) which is characterized by the presence of spontaneous bleeding more frequently and severe bleeding phenotype (5).

When patients present with symptoms that might suggest internal bleeding, it can be challenging for healthcare providers to identify and treat hemophilia. Rapid evaluation and diagnostic testing are required to rule out potentially life-threatening bleeding, such as that which might occur in the brain or abdomen. Patients exhibiting changed mental state, disorientation, cognitive dysfunctions, or repeated falls are often prescribed a brain CT scan or MRI to rule for intracranial bleeding. This is especially crucial in the early years of life, when patients may not be able to provide a complete history, such as in neonates, babies, and children. Brain magnetic resonance imaging (MRI) is required for the evaluation of silent cerebral microbleeds caused by hemophilia, which may lead to unusual symptoms in adulthood, such as cognitive impairment (5).

Hemophilic arthropathy is a blood-induced joint damage caused by repetitive intra-articular bleeding in the joint which leads to the deposition of hemosiderin in the synovial tissues inducing hypertrophy, neovascularization and fibrosis of the latter. Patients with recurrent joint bleeding may be able to monitor the progression of hemophilic arthropathies with the use of ultrasound imaging done at the time of therapy (6). Imaging studies that include the chest and abdomen, such as CT or MRI scans, may be used to assess the severity of abdominal or thoracic bleeding (7).

Treatment / Management

The primary goals of treating hemophilia are acute bleeding management and prophylaxis.
Blood Transfusions for intense bleeding achieving aggressive hemostasis as rapidly as possible and correcting coagulopathy is the major goal of acute bleeding management in hemophilia, preferably within two hours of symptoms presenting. Regardless of the status of pending diagnostic tests or the absence of physical symptoms, these actions should not be postponed. Hospitalization and treatment of individuals experiencing severe bleeding must adhere to the standards set out by the World Federation of Hemophilia.
In the event of a severe acute bleeding episode in a hemophilia patient, it is crucial to promptly provide factor VIII as a high-dose clotting factor concentrate (CFC) when the location and severity of the bleeding have been determined. It is advised to provide 50 international units of factor VIII per kilogram of body weight. If the patient has a brain hemorrhage, airway compromise from a bleed in the neck or throat, severe bleeds in the chest or belly, or compartment syndrome with large hematomas in the muscles, the patient may need to undergo urgent surgery or therapy. Prior to or concurrent with the planned procedure or surgery, high-dose CFC replacement is required, unless cardiopulmonary resuscitation (CPR) is necessary (8).

The appropriate imaging studies should be conducted to detect possible bleeding sites depending on the location and magnitude of the hemorrhage. The next step is to refer the patient to the appropriate specialty for further care. Whether or whether the bleeding stops, it is crucial to keep giving high-dose CFC as required for healing. It is essential to test variables often to ensure they remain at the correct levels. After hemostasis has been accomplished and coagulopathy has been treated, the assessment for bleeding may commence. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) are not recommended for the management of pain due to their effects on platelet function and the possibility of increased bleeding. Both acetaminophen and certain COX-2 inhibitors are considered safe to use. In addition, wherever possible, it is recommended to refrain from injecting anything into a muscle (8).

Hemophilia Prevention

In addition to managing acute bleeding, prophylaxis is another therapeutic option for individuals with hemophilia. Going for preventive treatment has several upsides. Reducing the frequency of hemarthroses episodes may minimize the severity of hemophilic arthropathy and the need for corrective joint surgery. Additional advantages of preventative treatment include a decrease in hospitalizations and a reduction in brain and muscle hemorrhage. Improved quality of life is a result of fewer medical interventions and less time away from work for patients (9). In accordance with their guidelines, the World Federation of Hemophilia categorizes prophylaxis as either primary or secondary, and as continuous or intermittent. Continuous prophylaxis is when preventive therapy begins with a 52-week treatment duration and continues for at least 45 weeks of that duration (9).

Each year, the maximum duration of intermittent prophylaxis should not exceed 45 weeks. Therapy should be delivered as required or as the situation demands if bleeding is obvious in a clinical environment. Prior to the child reaching the age of three and two clinically apparent major joint bleeds, primary continuous prophylaxis is initiated in the event that osteochondral joint disease develops. Tertiary prophylaxis starts once a patient is diagnosed with osteochondral joint disease, whereas secondary prophylaxis starts after a patient has had two or more significant joint bleeds but before they are three years old. Two preventive regimens, the Malmo protocol and the Utrecht protocol, are now in use, although the perfect regimen has not been identified. It is standard practice to begin preventative medicine once or twice weekly before significant bleeding develops, often between 12 and 18 months of age (10). The frequency is gradually increased until the maximum primary prophylactic dose is reached (10).

Schedules, Objectives, and Dosage Calculations for Factor VIII

Although maintaining factor levels above 1% to 2% is the desired goal, the optimal dosing schedule is dependent on factors such as factor shortfall, patient, bleeding rate, and IV access. Patients with hemophilia A may be given factor VIII infusions (15–30 units/kg, three times weekly) or 25–40 units/kg, three times weekly, according to the procedures developed in Malmo and Utrecht, respectively. After multiplying the patient's kilogramme weight by the required rise in factor VIII, add 0.5 units/kg to get the correct dose of factor VIII. Measuring factor levels fifteen minutes after infusion is the gold standard for verifying the predicted dose. A proper dosage is established by considering that factor VIII has a half-life of about 8 to 12 hours and that an infusion dose of 1 unit/kg results in an average increase of 2% in plasma levels. Adults should not provide more than 3 milliliters per minute of infusion, and young children should not receive more than 100 units per minute. How much factor VIII is best depends on where and how much blood is flowing. Keep levels at 30% for small hemorrhages, 50% for medium-sized ones, and 80% to 90% for large, potentially fatal ones. The recommended dosage is 40% to 50% for a minimum of 7–10 days after bleeding stabilization. Due to its 8 to 12 hour half-life, factor VIII is usually given 6 to 8 hours after the first dose and half of the first predicted dose is given 8 to 12 hours later. It takes many more doses for major hemorrhages and 1 to 3 doses for minor hemorrhages to maintain levels between 40% and 50% for at least 7 to 10 days. Continuous infusions could be required in severe hemorrhage or after major surgery. When choosing to stop prophylaxis, it is important to take the patient's symptoms and worries into account. McEney-King and colleagues as well as Castaman and Linari stated that patients should attentively monitor their symptoms before deciding whether to lower the frequency of their dosages or quit prophylaxis completely (11); (12).

Alternative Pharmacological Choices

Several drugs, not limited to coagulation factor concentrates, have shown promise in the treatment of hemophilia. The three substances in question are tranexamic acid, desmopressin, and epsilon aminocaproic acid (13).

Desmopressin, or DDAVP for short, is a synthetic vasopressin that functions similarly. By stimulating the secretion of von Willebrand factor (VWF), it raises plasma concentrations of endogenous factor VIII by a factor of three to five. Without a factor concentrate, it can treat mild to moderate hemophilia A, which is less expensive and less likely to trigger inhibitor development in people. It may be given intravenously or intranasally, however subcutaneous administration is the most common method (13).

The second medicine is an antifibrinolytic combination of epsilon aminocaproic acid and tranexamic acid, which increases clot stability. A less prevalent option is epsilon aminocaproic acid, which is less effective, has a shorter half-life, and is more hazardous. Nonetheless, they prove useful in averting epistaxis, heavy periods, and bleeding during dental procedures by lining the mucocutaneous passages. Patients experiencing hematuria should not use these medications since they may lead to obstructive uropathy by inhibiting the disintegration of urine clots; also, they should not be used as a sole treatment for musculoskeletal bleeding. Patients undergoing thoracic surgery should not use it since it has the potential to induce the formation of intractable hematomas (14).

Innovative Treatments for Hemophilia

First, Genetic Medicine

Cloning the gene not only made gene therapy a possibility for treating the disease, but it also made recombinant factors possible to produce. A little increase in clotting factor activity may substantially reduce bleeding episodes and improve quality of life, making hemophilia a promising option for gene therapy due to its genetic nature. The outcomes of the phase I and phase II investigations are encouraging. Children, those with liver illness, and individuals with pre-existing factor antibodies are among the categories for whom gene therapy presents unique challenges. On the other hand, further studies and research are underway to broaden the reach of this therapy (14).

Section II. Customized Antibodies

In addition to gene therapy, the development and usage of monoclonal antibodies like emicizumab and concizumab to treat hemophilia has generated a lot of excitement. Because it lacks structural and immunological similarities with factor VIII, the monoclonal antibody emicizumab is unaffected by inhibitors while mimicking the action of activated factor VIII molecules. It has several benefits, including a low yearlyized bleeding rate with higher dosages, a long half-life of four to five weeks, and the option to be administered subcutaneously. It is also highly safe and well-tolerated. Furthermore, no anti-drug antibodies were found throughout the studies. But more studies are being run to look at how well treatment works and whether or not it has any negative side effects in patients who are expected to have negative results. Because monoclonal antibodies have the potential to radically change the treatment of hemophilia, emicizumab was named a breakthrough therapy (15).

Balkaransingh and Young stated that the production of inhibitors is the greatest treatment difficulty for people with hemophilia. Inhibitors are human immunoglobulin G alloantibodies that bind to and suppress the action of factor VIII and factor IX. This is the worst possible adverse effect of any medication for hemophilia. Inhibitors are likely to blame if a patient who has responded to clotting factor infusions in the past continues to bleeds following the operation. Inhibitors further decrease the effectiveness of injected factor concentration by shortening its half-life. The prevalence of inhibitors is greater in hemophilia A than in hemophilia B; in severe hemophilia, the frequency is 20% to 30%, while in mild hemophilia it is 5% to 10%. The creation of inhibitors usually happens around the age of 30 in mild to moderate hemophilia, whereas in severe hemophilia, it happens no later than three years. Mucocutaneous sites account for the vast majority of inhibitor-induced bleeding in moderate to severe hemophilia. To verify the existence of an inhibitor, the Nijmegen-modified Bethesda test is used (16)

Adults and children alike should undergo frequent screenings for inhibitor development. Children should have screenings every five days during the first twenty days of exposure, every ten days during the second twenty-one to fifty days of exposure, twice annually for the following fifty days, before surgery, or when altering factors focus. All patients who have had a five-day rigorous treatment should have them measured within four weeks of their last infusion. If the response to on-demand therapy is not satisfactory in instances of postoperative bleeding, it is important to assess the presence of inhibitors. Inhibitors may also be grouped

according to their efficacy. Long half-lives are common for inhibitors that work. While the levels may go unnoticed or even decrease without treatment, they will reactivate upon infusion of the factor concentrate, rendering the infusion potentially ineffective. If the patient is exposed to factor products again within three to five days, even when titers go down, they can go up again. Inhibitors with a low response titer tend to have a limited half-life; after six months, they cease to function and will not reactivate, regardless of whether the patient is exposed to factor products again (17).

Acute bleeding episodes in patients with inhibitors need prompt medical attention at a hemophilia center. Activated recombinant factor VII, prothrombin factor complex concentrates, porcine factor VIII, and larger doses of factor are among the therapy options. According to Srivastava et al., patients with hemophilia A may be able to eliminate inhibitors via the process of immunological tolerance training. So far, the elimination of inhibitors has been successfully achieved by immune-tolerance induction. Factor VIII is infused many times each day as part of this therapy. Daily dosages of factor concentrate are often given to patients undergoing immune-tolerance treatment over a period of weeks or even years. Immunosuppressive drugs may also be prescribed to certain patients during therapy, increasing their vulnerability to infections. Tolerance of the factor infusions and prevention of an immune response by downregulating an existing antibody response are the primary goals of this treatment. About 70% of hemophilia A patients and 30% of hemophilia B patients may have their inhibitors removed by immune-tolerance induction (17). Monoclonal antibodies are another potential therapeutic option; they are currently being under research and have shown great promise in treating people with inhibitors. Because emicizumab and other monoclonal antibodies imitate the action of activated factor VIII molecules, they are resistant to inhibitors because they do not structurally or immunologically resemble factor VIII (15).

Looking ahead

Prior to the invention of factor concentrates, the life expectancy of individuals with severe hemophilia was a dismal 11 years in the 1950s and 1960s. Intracranial haemorrhage or bleeding within important organs was the leading cause of death for most severely hemophilic children and adolescents. Judith Pool made a huge discovery in 1964 when she isolated the plasma fraction cryoprecipitate, which contained abundant factor VIII concentrate and greatly enhanced the treatment of hemophilia. Before it, the only options for treating hemophilia were whole blood or fresh plasma, neither of which had enough factor VIII or IX proteins. The availability of lyophilized plasma concentrates of coagulation factors in the 1970s greatly enhanced therapy (17).

Prevention of serious bleeding episodes and arthropathy sequelae was the result of primary prophylaxis, which originated in Sweden and was later adopted by other nations. Scientists discovered desmopressin in 1977. As a result, patients had access to a more effective, less dangerous, and cost-effective therapy alternative, and the danger of blood-borne illnesses from using plasma-derived products repeatedly was reduced. In the 1980s, when coagulation factors infected patients with severe hemophilia with HIV and hepatitis C, techniques were developed to screen blood for viruses and inactivate them. This greatly improved the safety of plasma-derived products. Industrial manufacture of recombinant factor VIII and IX became possible once DNA technology advanced.

The lifestyle of hemophilia patients has been greatly enhanced by the widespread availability of replacement therapy for active bleeding prevention and treatment, new methods for viral inactivation, surveillance for the management of blood-borne infections, and newer treatment options for hepatitis C and HIV. If a patient responds well to therapy and is otherwise healthy, their life expectancy is now comparable to that of the general population in industrialized nations. As a result of limited healthcare access and treatment resources, the death rate in underdeveloped nations is about double that of the general population (18);(19); (20); (21).

Conclusion

Much focus has been devoted to risks of inhibitor development associated with genetics, type of concentrate and dosing aspects, but still a high risk of inhibitor incidence remains. Further clinical exploration of protocols with combined immunosuppression is required for this population; it is hoped that new non-replacement therapies will further improve the situation for this patient group.

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