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Hemophilia throughout the life cycle

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Abstract

Hemophilia is an inherited X-linked coagulopathy defined by a deficiency or abnormality in the clotting function of factor VIII (hemophilia A) or factor IX (hemophilia B). The continuous improvement of the treatment has made possible to monitor the patient through their life cycle with the inherent transition of care, initially by caregivers in childhood and later by the patient himself. Alterations associated with age added to chronic diseases are a constant challenge in the comprehensive treatment of the patient. One of the main results related to the use of factors VIII and IX is the development of inhibitors, which are IgG alloantibodies directed to exogenous coagulation factors. The likelihood of developing inhibitors varies from one person with hemophilia to another and depends on the interaction between genetic and environmental factors. This review offers a better understanding of the physiological alterations that allow a comprehensive assessment of the patient with hemophilia.

Keywords: *Hemophilia A; Hemophilia B; Inhibitors; Hemophilia life cycle*

INTRODUCTION

Hemophilia is an inherited X-linked coagulopathy defined by a deficiency or abnormality in the clotting function of factor VIII (hemophilia A) or factor IX (hemophilia B). The estimated prevalence of hemophilia A is one case in 5,000 live male births, and one case per 30,000 male births in hemophilia B[1]. In about 70% of cases, boys affected by this condition inherit the genetic mutation from carrier mothers. However, 30% of cases have no family history and originate from *de novo* mutations, a phenomenon that can occur in the mother or fetus. These cases are sporadic. Daughters of a man with hemophilia will be obligate carriers of the mutation. Very rarely, hemophilia can occur in women as result of descent from a carrier mother and a father with hemophilia. However, the most frequent cause of decreased levels of factor VIII or factor IX in women related to the inactivation of the normal X chromosome, a phenomenon called lionization. The clinical presentation of hemophilia A and B is indistinct, characterized by the presence of abnormal bleeding: intra-articular (hemarthrosis), mucocutaneous or in other tissues or cavities. The frequency and severity of bleeding episodes varies according to the residual clotting activity of factors VIII or IX, which determines the severity of hemophilia (Table 1). In severe hemophilia, spontaneous or post-traumatic hemarthrosis or muscular hematomas are common. In moderate cases, bleeding is usually associated with trauma, being rarely spontaneous, and may be prolonged after procedures, even if minor. In mild hemophilia, bleeding is usually caused by major trauma or procedures[2,3].

Table 1: Classification of hemophilia severity in relation to clotting factor level[3].

Classification	Clotting factor level
Severe	< 1 IU/dL (< 0.01 IU/mL) or < 1% of normal
Moderate	1-5 IU/dL (0.01-0.05 IU/mL) or 1-5% of normal
Mild	5-40 IU/dL (0.05-0.40 IU/mL) or 5-< 40% of normal

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DIAGNOSIS

The diagnosis of hemophilia is possible whenever spontaneous or post-traumatic abnormal bleeding is present. The typical laboratory presentation includes prolongation of APTT (partially activated thromboplastin time) with normal PT (prothrombin time). The diagnostic confirmation is made by measuring the coagulant activity of factor VIII (hemophilia A) or factor IX (hemophilia B)[2].

HEMOPHILIA OVER THE LIFE CYCLE

Most new cases of hemophilia can be predicted by the presence of a positive family history. Given the X-linked recessive inheritance pattern, females heterozygous for this condition are called carriers. About 70% of boys born with this condition are descendants of possible or obligatory carriers, with the remaining cases being sporadic and arising from de novo mutations. Female carriers of this condition are expected to have plasma levels of factor VIII or factor IX corresponding to approximately 50% of that predicted for healthy individuals, which usually guarantees adequate hemostasis. However, a great variation in these values occurs in practice, from very low values, similar to those of affected male individuals, to values in the upper limit of normal. This broad spectrum of phenotypes can be explained by phenomena such as lionization, the random inactivation of one of the X chromosomes that occurs early in embryonic life, but also by other genetic factors, such as ABO typing, and environmental factors, such as the use of oral contraceptives. A study in Netherlands contacted all women undergoing testing for hemophilia status and followed 274 women confirmed as carriers and 245 women evaluated but not diagnosed with this condition. The median clotting factor level in carriers was 60 IU/dL (ranging from 5 to 219 IU/dL), compared to 102 IU/dL (ranging from 45 to 328 IU/dL) in non-carriers. Sixty-two carrier women and none of the non-carriers had clotting factors at levels below 40 IU/dL, compatible with the diagnosis of hemophilia[4].

PERINATAL PERIOD

The maternal carriers have a 50% chance of having a male newborn diagnosed with hemophilia, or a female carrier. Previous maternal knowledge of the carrier condition allows for better management of pregnancy, childbirth and the immediate neonatal period, aiming to reduce the increased risk of bleeding for the mother and the fetus. The testing and determination of fetal sex is adequate, and, in male fetuses, amniocentesis can be performed in the third trimester to confirm the diagnosis. The most suitable mode of delivery for a fetus with a possible diagnosis of hemophilia remains a matter of debate, given the uncertainties regarding the risks of intracranial and extracranial bleeding. There is relative consensus that instrumented vaginal delivery should be avoided, and the option of an elective cesarean section can be considered[4,5].

The presence of bleeding episodes in babies with hemophilia in the neonatal period are usually iatrogenic. Venipuncture, sample collection for neonatal screening or intramuscular application of vitamin K are possible causes and the treatment is urgent. Concentrates of recombinant factors are the best choice and should be applied immediately, considering that neonates may require higher doses and the applied factor may have a shorter half-life than in other age groups. Prophylactic administration of clotting factor concentrates would be a possible approach in an attempt to reduce the risk of intracranial hemorrhage or other severe bleeding in the neonatal period, but this strategy has not been the subject of any systematic evaluation. Among the potential disadvantages, the risk of trauma related to the administration of the concentrate, the prolongation of hospital stay, but, mainly, a possible increase in the risk of the development of inhibitors related to very early exposure to clotting factors. Potentially newborn carrier girls appear to have a low risk of bleeding in the neonatal period without reports of relevant complications in this patient population. These children should receive obstetric and neonatal management considered usual[4,5].

An American population-based survey with 547 children with hemophilia found that 70% of them have diagnosis within the first month of life, those 82% with hemophilia A. Of these, 40% of the mothers were known carriers, 23% had another positive family history, and 35% the diagnosis was confirmed due to bleeding. During the first two years of life, 81% had some bleeding episode, the most common being of soft tissue origin, oral or resulting from circumcision, or secondary to head trauma. 46 episodes of intracranial hemorrhage were found in 37 babies (7%), most commonly in order of frequency: 18 spontaneous, 14 related to childbirth, 11 traumatic, 2 related to other procedures, and one cause not described. The development of inhibitors occurred in 109 (20%) of the babies, who had a higher frequency of intracranial bleeding[6].

The personalized assessment of the bleeding phenotype is important for therapeutic decisions such as initiating and scaling primary prophylaxis with factor concentrates, as well as others related to the care of the person with hemophilia. Although the association between clotting factor activity and bleeding frequency is well known, it is not linear. A theoretical model demonstrated an 18% reduction

in bleeding frequency for each UI/dL increase in residual factor VIII activity[7].

INFANCY AND CHILDHOOD

Infants with hemophilia are prone to bleeding as they become active (crawling as well as getting up to stand and cruise), common complications include soft tissue/ intramuscular hematomas, oral/nasal bleeding, head injuries, and joint bleeds. Parents should be informed of the options to prevent and control bleeding in their children, as well as with the assistance of health professionals they are tasked with helping children achieve a good quality of life and maintain joint health until adult age. Primary prophylaxis is the gold standard to optimize results and it is recommended to start before 2 years of age[8].

In the social context, adapting to school life is a challenge that causes suffering in childhood due to the prohibition of common games considered risky such as cycling and soccer. Parents also have difficulty disciplining and balancing discipline with healthy siblings, as described in a cohort of 15 children aged 6 to 12 years old with hemophilia, where school absence was also identified despite good adherence to treatment. Encouraging self-care, requires a partnership between health professionals, family members, school and child in the construction of therapeutic plans that consider the child's active participation[9].

A randomized controlled trial showed that the initiation of prophylaxis prior to age 2.5 years avoid joint damage of patients with severe hemophilia, as demonstrated by comparing prophylaxis initiated before age 2.5 years vs after age 6 years. Those who have delayed prophylaxis initiation continued with greater bleeding frequency and subsequent arthropathy development after prophylaxis initiation. The Index joint magnetic resonance imaging scores progressed more rapidly prior to age 14 years in children in delayed prophylaxis. This demonstrates the importance of bleeding on bone and cartilage development during the growing years. Joint physical examination scores increased progressively through childhood and adolescence but were consistently higher in participants on delayed prophylaxis[10].

ADOLESCENCE AND YOUNG ADULT

Adolescents with hemophilia face all the usual challenges of this age group, in addition to the issues inherent to their chronic disease. Adolescents may not feel capable of assuming the responsibilities related to their therapeutic plan, making the change from family-centered to individual-centered care very challenging. Ideally, this change should occur in a planned and gradual manner[11].

A Scandinavian study showed that the median age at which patients start taking responsibility for their care is 14 years. However, at age 17, approximately 25% of patients still require parental assistance for their care. The same study showed that 41% of young people did not fully follow their prescribed prophylaxis plan[12]. Another study showed that the perception of high adherence to the prophylaxis regimen (greater than 90%) drops from 59% at age 0-12 years to 13% at 13-18 years and 6% from 19 to 28 years old. Factors perceived as relevant to lower adherence include lack of understanding of the benefits of the prophylaxis regimen, denial of the disease, poor venous network, scarce parental or family support, "teenage rebellion" or lack of time. The lack of adherence in this age group can lead to recurrent joint bleeding with great loss in functional aspects and those related to quality of life[13].

THE ELDERLY ADULT

In the 1970s, hemophilia shifted from a potentially life-threatening condition to a chronic disease[14]. Due to the increasing availability of clotting factor concentrates, especially in developed countries, the life expectancy of people with hemophilia has increased from less than 30 to more than 60 years of age[15,16]. This favorable evolution interrupted by the devastating effect of HIV and hepatitis C infections in the 1980s and 1990s. With the development of effective methods of viral inactivation in plasma-derived factor concentrates, as well as clotting factors produced from recombinant DNA technology, infections transmitted by blood components are no longer a threat, and the treatment of viral infections by HIV and HCV has become a reality[17].

Older patients who grew up initially without the availability of treatment, or with episodic treatment subject to a shortage of factor concentrates are invariably afflicted with chronic hemophilic arthropathy. Joint damage increases linearly with age, even in patients affected by moderate forms of the disease[18]. Joint instability, decreased range of motion, muscle contractures and atrophy, chronic synovitis and resulting balance disorders also occur frequently. Thus, 70% of elderly hemophiliacs are at increased risk of spontaneous falls. Individuals with hemophilia also have a 7× higher rate of total joint replacement surgery when compared to the general population[19].

A retrospective analysis of 382 people with hemophilia demonstrated a significantly increased risk of fractures when compared to the general population, with a relative risk of 10.7, also correlated with hemophilia severity and age. In individuals with hemophilia, 24.8 fractures/1000 patients/year observed, against 9.6 fractures per 1000 patients/year in the general population. Individuals with hemophilia older than

31 years already have a fracture risk 2× greater than that of the general population, and this risk increases by 1.3% with each increment of one year of age[20].

Although the benefit of prophylaxis among elderly patients is clear, some situations related to this age group may reconsider its use. The decrease in motor activity, often evidenced at this stage, can reduce the frequency of bleeding, and the limited capacity of self-infusion caused by the decrease in visual acuity or dexterity, poor venous network or even neurological or psychiatric conditions, can make impossible this therapeutic strategy[21].

Studies also demonstrate the benefit of the prophylaxis regimen for adult patients with established arthropathy. In addition to musculoskeletal outcomes, an additional benefit may be the reduction in the risk of intracranial hemorrhage. In people with hemophilia, this risk increases from 40 to 50 years of age, with a risk ratio of 3.7[22]. There is also a growing interest in brain microhemorrhages. Evidences suggests a correlation with increased risk of clinically significant intracerebral hemorrhage, reduced cognitive function, and dementia from any cause. Among people with hemophilia, the presence of brain microbleeds was associated with older age, hepatitis C infection, cardiovascular risk factors and the presence of inhibitors[23].

Risks associated with the regular infusion of clotting factor concentrates or periods of more intensive exposure to clotting factors may be present. Those related to orthopedic or other surgical procedures at older ages may cause the development of inhibitors and are currently the most feared complication related to the treatment of hemophilia. These occur in about 30% of people with hemophilia, and their peak onset occurs within the first 20 to 50 days of exposure to concentrates. After this stage, the emergence of new cases occurs very slowly over time[24].

With aging, people with hemophilia are subject to the same risk factors for the development of atherosclerotic disease as the general population. Studies describe a similar rate between people with hemophilia and controls. However, data indicate that mortality from coronary heart disease among people with hemophilia is between 0.2 and 0.6 of that expected for the general population, indicating a protective effect of this condition[25,26]. A possible explanation for the finding of the same prevalence for cardiovascular risk factors, but lower associated mortality, is that reduced thrombin generation at the atherosclerotic plaque rupture point results in a reduced risk of arterial occlusion[27]. There is no data evaluating the impact of prophylaxis regimens on cardiovascular mortality in older people with hemophilia[21]. The risk of cancer increases with age, affecting the population with hemophilia. This is also correlated with the individual's serological status (hepatitis C and HIV)[28].

The increase in life expectancy of people with hemophilia makes imperative that treatment centers are aware of the common comorbidities of aging. Young people with hemophilia are treated with safe products in the basis of regular prophylaxis. This new generation will likely age without significant joint damage, and free from HIV and HCV infections. The comorbidities that will come with aging are likely to constitute the therapeutic challenge in this new generation of people with hemophilia[21].

BONE AND JOINT HEALTH

Prior to the availability of clotting factor concentrates, the natural history of hemophilia is recurrent joint bleeding and progression to joint damage and destruction. The main alterations observed in the synovium are hypertrophy and hypervascularization, resulting from the presence of iron in the synovial fluid, which has pro-inflammatory and angiogenic actions. The neovascularization predisposes to bleeding, as the new vessels are friable. A vicious circle of bleeding, iron accumulation, synovial hypertrophy and hypervascularization originates, leading to new bleeding and progressive joint damage. Therefore, it is of paramount importance that patients undergoing prophylaxis or episodic treatment have joint bleeding treated quickly and effectively, with the aim of minimizing synovial proliferation, a key factor in hemophilic arthropathy[29].

Although prophylaxis is the recommended treatment modality, some patients continue with episodic (on demand) replacement therapy, in which sporadic or post-traumatic bleeding is common. In patients on prophylaxis, trauma is the most common cause of breakthrough bleeding, but inadequate plasma levels of the factors, missed doses, the presence of underlying synovitis, or established joint damage are also contributing factors to the condition. Prompt treatment of bleeding episodes is potentially capable of preventing permanent damage, hence the importance of availability of doses for home use and their use at the slightest sign or symptom of bleeding[30].

The term "target joint" is defined by the International Society of Thrombosis and Hemostasis (ISTH) as the presence of three or more episodes of spontaneous bleeding in the same joint, within a period of 6 consecutive months. Target joint resolution occurs when fewer than two bleeds occur in this topography during a period of 12 consecutive months[31].

Radioisotope synovectomy, also known as radiosynoviorthesis, offers a conservative alternative to surgical synovectomy for patients affected by a target joint, whose intensive management with factor concentrates has ineffective. It is a particularly attractive option for patients with inhibitors or who do not have the clinical conditions for a traditional

surgical approach. The radioactivity emitted by the isotope causes atrophy and fibrosis of the synovium, and consequent reduction of the bleeding tendency. A study described the Brazilian experience in the use of radioactive synovectomy with the isotope I^{90} (yttrium citrate^{90}) in the treatment of 245 joints of 190 patients diagnosed with hemophilia or von Willebrand disease, from 2003 to 2007. Of these, 36 joints of 22 patients with factor VIII inhibitors underwent the procedure. There were no lesions related to radioisotope extravasation, nor procedure-related hemarthrosis. The mean annual number of hemarthrosis fell from 19.8 in the period before radioactive synovectomy to 2.6 in the first and 2.2 in the second year after the procedure, respectively. Pain reduction occurred in most patients, and joint range of motion maintained or increased one year after the procedure, demonstrating the relevance of this therapeutic modality[32].

The radiosynovectomy may be the first approach in the treatment of chronic hemophilic synovitis. Although radiosynovectomy and chemical synovectomy using rifampicin or tetracycline have similar results, radioablation of the synovium is much less painful than the chemical procedure. Ideally, synoviorthesis performed in young patients with moderate synovial hypertrophy. In more advanced cases, the expected results with this approach are worse. If, after three procedures within a 6-month interval, failure of this approach is evident, arthroscopic synovectomy should indicated. Depending on the therapeutic regimen and adherence, joint destruction between the second and fourth decades of life occurs. Surgical approaches such as arthroscopic debridement, alignment osteotomy, arthrodesis and total arthroplasty with prosthesis are therapeutic options in these cases[33].

Bone mass in adults is the result of peak bone mass achieved around age 18 to 25 years, subtracted from subsequent bone loss. The peak bone mass is primarily determined by genetic factors, with the important contribution of factors such as general health status, nutrition, physical activity, concurrent comorbidities and use of medications during growth[34]. Studies show that low bone density occurs more commonly in adults with hemophilia than in the general population[35]. Although a decrease in bone density in children is also observed, as showed in a meta-analysis of 69 boys where low bone mass was present in 37%, 42% and 21% of children with severe, moderate, or mild hemophilia, respectively[36]. However, it is still unclear whether this is due to failure to acquire bone mass, premature loss of bone mass, or both mechanisms[35].

Physical condition, muscle strength, aerobic and anaerobic endurance reduced in people with hemophilia. Established muscle atrophy and joint instability increase the risk of injury and establish a vicious circle of joint pain, immobility, atrophy, joint instability, and new episodes of bleeding. In previous decades, physical activity was a relative contraindication for people with hemophilia. However, with the greater availability of clotting factor concentrates, and especially with the advent of prophylaxis regimens, some modalities such as regular physical exercise and rehabilitation with physiotherapy are essential, particularly in countries where replacement therapy is not readily available[37].

INHIBITORS

The presence of inhibitors in hemophilia concerns the detection of IgG alloantibodies directed to exogenous clotting factors, factor VIII or factor IX. These are able to counteract the function of the infused factors[3]. For this reason, they are also known as neutralizing antibodies. There are significant differences between hemophilia A and B in terms of the development of inhibitors frequency, with studies reporting incidences of 1.5-10.2% in hemophilia B resulting in a rare event, compared to 25-35% in hemophilia A. In patients with severe hemophilia B, inhibitors are associated with significant morbidity and is practically exclusive to the severe cases. They are related to bleeding complications, severe allergic reactions (anaphylaxis) and nephrotic syndrome. The latter can complicate immune tolerance induction (ITI) and could be one of the reasons for the low success rates of 30-35%[38,39]. In a Chinese cohort of 4485 patients, allergic/anaphylactic reactions occurred in 59.1% and nephrotic syndrome in 16.7% of patients during ITI[40].

Risk factors for development of inhibitors in severe hemophilia A involves interactions between genetic and non-genetic factors, the former including mutations in the *F8* gene, single nucleotide polymorphisms in the HLA locus, mutations in the immunomodulatory gene, race and family history, and these factors are the basis and a prerequisite for the production of inhibitors. The non-genetic factors includes triggerings such as age of first exposure, intensity of treatment, type of FVIII preparation, presence of infection and history of surgery. The RODIN study found that in previously untreated patients with severe hemophilia A, intensive treatment with high-dose FVIII increases the risk of inhibitors and prophylactic treatment with FVIII decreases the risk, especially in patients with low-risk *F8* mutations[41].

In contrast to severe hemophilia A, patients with moderate/mild have a lower but life-long risk of inhibitor development[42]. In hemophilia B, inhibitors occur primarily in patients with *F9* deletions, frameshifts, and nonsense mutations, resulting in truncated or absent factor IX protein. Only one missense variant

and two splice variants have been reported in patients with inhibitors[43].

In situations of major bleeding or after surgery, exposure to high doses of factor VIII occurs in association with inflammation and tissue damage and repeated exposure to high doses of factor VIII in this context has been associated with an increased risk of inhibitor development[44-47]. Otherwise, in prophylaxis regimens, infusions occur with lower frequency and dosage, and outside the context of tissue damage. In this way, immune tolerance can be induced by the generation of regulatory T lymphocytes from naïve cells, or even trigger the anergy of previously "primated" T cells[48]. Observations that prophylaxis regimens may be associated with a reduced risk of inhibitors support this hypothesis[44,49,50].

The inhibitors are evaluated by the Bethesda assay, or preferably, by the Bethesda test modified by Nijmegen. The definition of a positive inhibitor is a titer greater than 0.6 Bethesda units (UB) for hemophilia A, or equal to or greater than 0.3 UB for hemophilia B. An inhibitor is considered low-response if it has a titer of less than 5 UB, and high response if the title is equal to or greater than 5 UB. Most low-response inhibitors are transient. A transient inhibitor is defined as a positive inhibitor whose titers fall below the threshold of positivity within 6 months of its detection, in the absence of changes in the therapeutic regimen, and in the absence of antigenic challenge with factor concentrates. High response inhibitors tend to be persistent. Their titers may even decrease or become undetectable after long periods without exposure to factor concentrates; however, they increase rapidly within 3 to 5 days of exposure to the concentrates, which is known as the anamnestic response[3].

Routine assessment for the presence of inhibitors is particularly important during the period of greatest risk for their development, that is, every 6 to 12 months after starting factor concentrate replacement and at least annually thereafter. Although some groups advocate more frequent routine assessments, there is insufficient evidence to support this determination[51]. Situations in which testing for inhibitors is indicated include:

- after initial exposures to clotting factor concentrates;
- after intensive exposures, *ie* daily exposures for more than five consecutive days;
- in the presence of persistent bleeding or target joint development, despite adequate therapy with factor concentrates;
- half-life or recovery of the concentrate lower than expected, with lower recovery defined as less than 66% of the expected factor VIII activity 15 min after infusion[41];
- in the presence of a clinical or laboratory response lower than expected in the context of adequate therapy with the factor concentrates[3];
- before surgeries.

The eradication of the inhibitors may occur through the immune tolerance (ITI). Immune tolerance consists of regular and long-term administration of FVIII concentrate, often at high doses, to downregulate the anti-FVIII antibody response and resulting in desensitisation. There are currently several regimens for ITI, with different dosing schedules and combination therapies, such as bypassing agents as prothrombin complex concentrate (aPCC) and recombinant factor VIIa (rFVIIa), non-factor replacement agents (emicizumab) and other therapies (marzeptacog alfa, serpinPC, gene therapy)[52].

In hemophilia A patients with active bleeding and low-responding inhibitors, the FVIII concentrate is recommended and bypassing agent (aPCC or rFVIIa) for those who have high-responding inhibitors[3]. For hemophilia B patients with inhibitors and an allergic reaction/anaphylaxis to factor IX therapy, it is recommended to treat acute bleeds with rFVIIa but is against the use of aPCC as it contains FIX and may cause or worsen an allergic reaction[3]. Also for hemophilia B, the association of ITI protocols with immunosuppressive regimens is an option to achieve the eradication of inhibitors[53,54].

PERSPECTIVES AND NEW TREATMENTS

The management of hemophilia changed in recent years with new treatments including nonfactor and gene therapies. Emicizumab, a monoclonal antibody, recognizes both activated factor IX and factor X, mimics the activity of the cofactor FVIIIa, and is used for the prevention of bleeding in patients with hemophilia A regardless of the presence or absence of inhibitors. It is administered subcutaneously and has a long half-life[55]. Preliminary data on other subcutaneous drugs for the treatment of hemophilia A and B, such as concizumab and marstacimab, anti-TFPI (Tissue Factor Pathway Inhibitor) antibodies, as well as fitusiran, an antithrombin inhibitor, are encouraging, although results of ongoing trials are awaited[56].

CONCLUSION

The frequency and severity of bleeding episodes varies according to the residual clotting activity of factors VIII or IX, which determines the severity of hemophilia. Until the 1950s, hemophilia was

primarily a pediatric condition, with an estimated life expectancy of 27 years. The older patients with hemophilia have a decreased quality of life due to chronic hemophilic arthropathy and age-related joint damage. Currently, the development of inhibitors is the biggest complication related to hemophilia and its treatment, with an impact on morbidity and quality of life. New treatments for hemophilia A and B, including nonfactor and gene therapies, have encouraging results.

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