

REVIEW ARTICLE

HEMOPHILIACARE: THE WAY FORWARD

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INTRODUCTION

Hemophilia is an inherited X linked disorder due to deficiency or dysfunction of coagulation factor VIII causing hemophilia A and factor IX causing hemophilia B. As per the global survey of the World Federation of Hemophilia, the prevalence of hemophilia is 1 in 5000 male births and 1 in 30,000 male births in hemophilia A and B respectively. It is estimated that there are more than 400,000 people with hemophilia (pwh) in the world. There are more than 3000 mutations in the factor VIII and IX genes causing varying clinical severity of the disorder. Around 70% of patients have a positive family history. However, in one third of the pwh, a spontaneous mutation can cause the disorder when there will be no prior family history. Hemophilia A and B are clinically indistinguishable heterogeneous disorders. Their clinical manifestations are identical, with an increased tendency for musculoskeletal, soft tissue and mucocutaneous bleeding. Bleeding into other organs can also occur. The severity of bleeding symptoms correlates with the coagulant activity of the deficient factor.

This article is intended to provide a brief account of the present management strategies, complications and advances in hemophilia care with a note on the present Indian scenario.

Diagnosis

A correct diagnosis is essential to ensure that the patient is treated appropriately. Different bleeding disorders may have similar symptoms though their product for treatment is different. A prolonged activated partial thromboplastin time (APTT) with measurement of factor VIII or factor IX clotting factor activity in

blood is required for the diagnosis of hemophilia. The clotting factor activity is needed to calculate the dose of the factor to be infused and also to monitor the response to treatment. The clotting factor activity of factor VIII /IX can be assessed by one stage, two stage, or chromogenic assays using automatic coagulation analysers. Recent methods of testing also include thrombin generation tests and global assays.

Based on the coagulant activity of factor VIII or IX, hemophilia is classified into 3 types- severe, moderate and mild. Patients with coagulation factor level of less than 1 IU/dl (<1% of normal) are classified as severe and constitute about half of the diagnosed cases. Moderate haemophilia is defined as factor levels of 1–5 IU/dl (1–5% of normal), and mild disease has factor VIII levels of 6–40 IU/dl (6–40% of normal). The normal level of factor VIII/IX is 50 to 150%. It has been found that there is heterogeneity in about 30% of patients where the severity of the disease is not concurrent with the clotting factor activity by the different methods of testing.

Genetic analysis

Genetic analysis to identify the causative mutations is recommended in all patients as it helps to identify female carriers in the family. More than 2000 unique molecular defects have been described in the factor VIII gene of which inversions of intron 22 and intron 1 are the common mutations. In the factor IX gene about 1095 unique mutations have been described. DNA based mutation analysis is now available in many centres. Prenatal diagnosis is usually offered when termination of pregnancy would be considered if the fetus is found to be affected. Genetic counselling prior to prenatal testing is imperative. Prenatal testing by

chorionic villi sampling is best done between 9 to 14 weeks of gestation or amniocentesis can be done at 15 to 17 weeks of gestation. Preimplantation genetic diagnosis also provides an opportunity for selection of embryos without the specific mutation so that couples or carriers can have pregnancy with an unaffected child.

Management of hemophilia

The primary aim of hemophilia care is to prevent and treat bleeding with administration of the deficient clotting factor or the specific factor concentrate. The factor replacement therapy protocols include episodic (on demand) treatment when infusions are given at the time of clinical bleeding. The dose, frequency and number of infusions depend on the severity of the bleed. Prophylaxis is treatment with intravenous infusions 2 to 3 times a week to prevent bleeding and joint damage. Primary, secondary and tertiary prophylaxis is long term treatment before 2 years, before joint disease or after onset of joint disease respectively. Low dose prophylaxis as is practised in developing countries including India with limited supply of concentrates is by infusion of 10 – 20 IU/kg once or twice a week. However there are uncertainties regarding prophylaxis about the age of initial treatment, duration of treatment, dosing regimens and long term outcomes.

Treatment products

The World Federation of Hemophilia (WFH) recommends the use of virally inactivated plasma derived or recombinant concentrates in preference to cryoprecipitate and fresh frozen plasma as replacement therapy for hemophilia. However cryoprecipitate and frozen plasma are being used in countries around the world where it is the only available or affordable option. The short half-life of factors (8-12 hours for factor VIII and 18-24 hours for factor IX) requires that the factor infusions need to be given frequently.

Bioengineering technology has increased the half-life of recombinant factors by processes like PEGylation whereby the half-life of recombinant factor IX has been improved 3-6 times and factor VIII 1.5-1.6 times. Clinical research is underway of technologies to enhance hemostasis by products other than replacement factor concentrates. There are also ongoing clinical trials on subcutaneous administration

of products which would simplify prophylaxis in children with poor venous access.

Other pharmacological products which are useful include

1. Desmopressin (DDAVP) synthetic analogue of vasopressin that boosts plasma levels of factor VIII and von Willebrand factor. It is used in the treatment of mild or moderate hemophilia A and also in the treatment and prevention of bleeding in carriers.
2. Tranexamic Acid is an antifibrinolytic agent used as an adjuvant in the control of bleeding from skin, mucosal surfaces and oral bleeds.

Gene therapy

A curative treatment for hemophilia is possible with gene therapy whereby there can be clinical/phenotypic improvement and increase in in-vivo coagulation activity. Various vector delivery systems were in use of which adeno associated virus (AAV) mediated approach attracted attention in spite of limitations. The promising results in hemophilia B whereby patients treated with gene therapy had a stable expression of factor IX levels for about 5 years without side effects is the hope for a cure for hemophilia A too.

Inhibitor development

The major complications of hemophilia include chronic hemophilic arthropathy, inhibitor development and transfusion transmitted diseases.

Inhibitors are polyclonal IgG antibodies against the clotting factors. It is suspected when a patient fails to respond clinically to the administered clotting factors. It is frequently encountered in patients with severe hemophilia compared to moderate or mild hemophilia. The incidence or lifetime risk of inhibitor development is 20-30% in severe hemophilia and about 5-10% in mild disease. In hemophilia B it is much rarer, the risk being less than 5%. The risk factors for inhibitor development include

- a. Patient related factors like severity of hemophilia, factor VIII gene mutation, family history of

inhibitors, black ethnic origin and polymorphisms of immune-response genes like IL-10 and TNFA.

- b. Treatment-related factors like number of exposure days, intensity of exposure, product type ie plasma derived versus recombinant, age at first exposure and prophylaxis with factor replacement therapy.

The screening for inhibitors is done using APTT mixing where factor VIII inhibitor is a delayed type of inhibitor (APTT with pooled normal plasma mix remains not corrected after 2 hours of incubation). The confirmation and quantification of inhibitor is done using the Nijmegen modified Bethesda Assay.

Inhibitor testing needs to be done in children more frequently according to the exposure days to factors. In adults, inhibitor testing is done in non-responsiveness to factors, intense treatment of more than 5 days or at 6-12 monthly review after more than 150 exposure days.

Inhibitor level that are persistently less than 5 BU/ml (Bethesda unit/ml) are low responding inhibitors whereas in high responding inhibitors, the level is \geq 5 BU/ml. Low responding inhibitors may be transient and may respond to high doses of factor concentrates which will neutralise the inhibitor with the excess factor activity. High responding inhibitors may be persistent and respond to bypassing agents which circumvent the need for factor VIII or factor IX by generating thrombin through other mechanisms. Bypassing agents available are activated prothrombin complex concentrate (APCC, FEIBA) and recombinant activated factor VII (rFVIIa). Eradication of inhibitors in severe hemophilia A is possible through immune tolerance induction therapy.

Comprehensive care

Hemophilia though rare is a complex disease to manage. Optimal care is not just about treating acute bleeds. Being a lifelong disease, improvement of health and quality of life of pwh is a necessity.

This includes treatment of bleeding, prevention of joint damage, management of complications, physiotherapy and exercise to maintain joint health, psychosocial support and oral health. Education about the disease and monitoring quality of life are all of

utmost importance to the patients' health. These needs of the pwh can be met through comprehensive care delivered through a multidisciplinary team of health care professionals. The core team members include a medical expert (hematologist, paediatrician, physician), orthopaedic surgeon, physiotherapist/ occupational therapist, laboratory specialist and psychologist/ social worker. The pwh need to be evaluated by the comprehensive care team at least yearly whereby the problems and complications can be adequately addressed. The comprehensive team is also responsible for the education of the pwh, their families and monitoring the outcome of the disease.

The Indian scenario

In India, there is an estimated 1,00,000 people with haemophilia of which only about 16,000 have been identified. The Hemophilia Federation of India (HFI) is the registered national patient member organisation founded in 1983 working for the welfare of pwh through its 79 chapters in the four regions of the country. HFI in New Delhi is affiliated to the World Federation of Hemophilia (WFH) located in Montreal, Canada. HFI aims to reach out to pwh and provide total quality care, education, help to make treatment available at affordable cost, psycho-social support and economic rehabilitation. It also helps to locate undiagnosed persons with hemophilia and provide proper information on hemophilic care to both pwh, their families and the medical fraternity.

In India, progress is being made to achieve these goals. While there are centres of excellence in government and private sector, there is no uniformity of care at the grass root level. The lobbying of the organisation have helped to muster governmental support for factors. It is

heartening to note that about 20 states in India are having funds allotted through the government for hemophilia care so that factor concentrates are available in the district hospitals mostly free of cost. Many comprehensive care centres too are now being established.

Conclusion

To summarise haemophilia is the genetic disease that is treatable but not yet curable. The advance in research is facilitating the treatment with newer

recombinant products and products of long life. However complications due to inhibitors is on the rise and problems of the ageing population of hemophilia patients is also increasing. Prevention of hemophilia through genetic counselling is the need of the hour.

The collective efforts of the health care professionals along with patient organisations can help to realise the vision of Hemophilia Federation of India “Haemophilia without disability and children free of pain.”

▼ *References*

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