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A Review on Hemophilia

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ABSTRACT

Hemophilia is a hereditary draining problem. Hemophilia An or B is treated by recombinant coagulating factor VIII or factor IX and immunosuppressives to forest all arrangement of alloantibodies and inhibitors. Development of inhibitors to these elements represents a challenge in treating hemophila. Plasma determined initiated prothrombin complex concentrate and actuated recombinant element VII are utilized to treat patients with inhibitors. Treatment additionally differs with circumstances, for example, pregnancy, medical procedure, and danger, as these trigger expanded hazard of dying. This audit delineates the different etiologies of hemophilia, strategies for conclusion, more current treatment choices accessible for hemophilia, treatment in extraordinary conditions and the eventual fate of hemophilia treatment. In the present times, durable and longlasting remedy for hemophilia isn't accessible. Substitution by factors gives a brief fix for hemophilia. Super durable fix might lie toward quality treatment or undeveloped cell treatment which is a work in progress. Few victories are accomplished by quality treatment in past examinations giving fix enduring to numerous months without need for recombinant factor substitution. Further adjustments of treatment are expected to accomplish dependable and extremely durable solution for hemophilia.

Keywords:Heamophilia, Bleeding disorders, Treatment of Hemophilia.

INTRODUCTION

Hemophilia got from the Greek haima (Blood) furthermore, philia (Love),is a hereditarydraining problem brought about by the lack of thickening element VIII (Hemophilia-A) orfactor-IX (Hemophilia-B) or variable XI (Hemophilia C). Hemophilia A (otherwise called work of art hemophilia) and B (otherwise called Christmas sickness) are X-connected latent characteristic with flawed F8 and F9 qualities in long arm of X chromosome with rate of one of every 5,000 what's more, one out of 30,000 guys individually while Hemophilia C (otherwise called plasma thromboplastin predecessor (PTA) inadequacy or Rosenthal condition) has autosomal latent legacy with flawed quality in chromosome 4 and has rate of one out of 1,00,000 guys and is more normal in Jews of Ashkenazi.Hemophilia can likewise be procured because of the turn of events of autoantibodies coordinated against the thickening variables.Procured hemophilia is exceptionally uncommon with frequency of one in 1 million persons.1-3 In Hemophilia there is inward or outer draining which might be unconstrained or with trifling injury. It can prompt inconveniences like constant weakness, haemarthrosis,intracranial drain and compartment disorder. Early analysis and theexecutives is expected to forestall the improvement of these complications.4 The executives changes in unique circumstances, for example,pregnancy, significant medical procedures, and danger. This audit points in introducing the ongoing advances in analysis and treatment of hemophilia and the new suggestions in the administration of extraordinary circumstances or systems in hemophiliacs.

Types Of Hemophilia

There are several different types of hemophilia. The following two are the most common:

- Hemophilia A (Classic Hemophilia)

This type is caused by a lack or decrease of clotting factor VIII.

- Hemophilia B (Christmas Disease) This type is caused by a lack or decrease of clotting factor IX.

Signs and Symptoms

Common signs of hemophilia include:

- Bleeding into the joints. This can cause swelling and pain or tightness in the joints; it often affects the knees, elbows, and ankles.
- Bleeding into the skin (which is bruising) or muscle and soft tissue causing a build-up of blood in the area (called a hematoma).
- Bleeding of the mouth and gums, and bleeding that is hard to stop after losing a tooth.
- Bleeding after circumcision (surgery performed on male babies to remove the hood of skin, called the foreskin, covering the head of the penis).
- Bleeding after having shots, such as vaccinations.
- Bleeding in the head of an infant after a difficult delivery.
- Blood in the urine or stool.
- Frequent and hard-to-stop nosebleeds.

CAUSES OF HEMOPHILIA

At the point when there is injury to the vein, the platelets are actuated at the site of injury which prompts initiation of the coagulating elements and development of fibrin blood clump by the 'Inborn pathway' of coagulation. Factor VIII and factor IX are expected to enact consider X which turn actuates prothrombin activator which changes over prothrombin to thrombin. Thrombin helps in change of fibrinogen to fibrin which traps the platelets and structures cluster. Factor XI is expected to actuate factor IX.5 The variables VIII, IX or XI are hereditarily moved to the posterity through X chromosome (F8 and F9) and chromosome 4 (F11). Any imperfection in these qualities causes nonattendance or decreased creation of these variables.In some cases antibodies named as 'inhibitors' to these variables might create. Inhibitors might create as a reaction to treatment with the thickening elements in hemophiliacs or idiopathically in typical subjects without any hereditary deformity. In these patients, even after treatment with thickening variable, initiated incomplete thromboplastin time (aPTT) and prothrombin time (PT) are prolonged.6 Different systems are proposed in the beginning of hereditary deformity or inhibitor arrangement.

1. F8 gene mutation

Hemophilia An is brought about by changes in the F8 quality. In hemophilia A, there are enormous DNA transformations like intron 22 and intron 1 reversal and numerous little transformations like missense changes, rubbish transformations and frameshift mutations.7 Factor 8 comprises of 2332 amino acids and has spaces A1, A2, A3, B, C1, and C2. Seriousness of the sickness is connected with the sort of transformation in these domains.8 As per Ryan et al, a point change causing amino corrosive replacement N1922S in A3 space of F8 quality prompts blemished collapsing of A3 which eventually stops the creation of variable VIII.9 There may likewise be Arg2150His replacement in C1 space of component 8 which results in decreased restricting of element 8 to Von Willebrand factor which prompts diminished solidness of variable VIII.10

2. Lack of f8 mRNA

In some hemophiliacs no defects were found in DNA. There is defective mRNA or lack of mRNA in some of them which prevents the relay of message.11-13 In these patients, RT-PCR did not give any mRNA corresponding product which is specific for factor 8. This can be due to swift degradation of mRNA due to an unidentifiable

3. F8 inhibitors

Inhibitor to factor VIII develops as a complication to therapy of hemophiliaA, mostly in patients with deletion or nonsense mutation in F8 gene.Alloantibodies develop against the replaced factor VIII and bind to A2 and C2 domain of F8 and inactivate F8 completely.6 The incidence of inhibitor development is directly proportional to age of the individual. This may be due to decline of immune regulation function in old age.15 According to Viel et al, mismatched factor VIII replacement by giving H1 and H2 types of factor VIII (present in white population) to black population in whom H3, H4 and H5 are present increases the incidence of developing alloantibodies to factor VIII in black population.16 These patients don't respond or respond poorly to therapy.

In Acquired Hemophilia, autoantibodies mostly of IgG class are present against factor VIII in subjects who have normal factor VIII gene. It can be idiopathic or can accompany other conditions like autoimmune diseases, cancer and drug ingestion.17 They bind to A2, A3 or C2 domain of factor VIII and inactivate factor VIII incompletely.6 This results in reduced function of factor VIII and increased aPTT even after therapy.

4. Defect in tissue factor pathway

Tissue factor (TF) can initiate an alternate pathway of coagulation in the absence of factor VIII, IX or XI by forming TF-factor VII complex. This becomes TF-Factor VIIa complex which activates factor X to Xa. Absence of factors VIII, IX or XI is more significant when there is deficient TF concentration.1-18

DIAGNOSIS OF HEMOPHILIA

Diagnosis of hemophilia is made on the basis of clinical suspicion and laboratory tests. Mutation in a particular gene may be detected which helps in development of newer modalities of treatment like gene therapy.

a.Clinical diagnosis

Clinical conditions, such as hemarthrosis, intracranial bleeding, excessive bleeding in trivial trauma, prolonged bleeding after surgery and menorrhagia point strongly towards a diagnosis of hemophilia.19 Bleeding can be spontaneous in severe cases or only as a response to trauma in mild cases and these are correlated with the

b.Lab diagnosis

Hemophilia can be diagnosed by coagulation factor assays or activated partial thromboplastin time. Bleeding time, prothrombin time and thrombin time are normal in Hemophilia. Bleeding time is not affected as it shows only platelet function. Prothrombin time is not affected as it depends only on extrinsic pathway of coagulation and factors I, II, V, VII and X. Thrombin time is normal because it depends on fibrinogen.

Activated partial thromboplastin time

This measures the integrity of intrinsic pathway and common pathway.20 In Hemophilia, there is prolongation of aPTT. As factors VIII, IX and XI are part of intrinsic pathway of coagulation along with other factors, aPTT is prolonged in all 3 types of Hemophilia.21

Coagulation factors F8/F9 assays

The type of hemophilia and degree of factor activity can be assessed by factor assay. The normal value of factor VIII is 50-150% and factor IX is 50-150%.22 In hemophilia these values are reduced. Knowledge of the exact amount of activity of clotting factors help in grading the severity of the disease and its precise management.19

Thrombin generation assay

This measures the ability of blood to form thrombin. This is valuable in assessing the response to therapy in hemophiliacs with inhibitors as the conventional coagulation profiles are not useful in them.23 It shows the overall assessment of hemostasis while aPTT shows only the time taken to form a clot.24 Thrombin generation (TG) maximum peak and lagphase time are used to find the severity of hemophilia.25,26 Severity determined byconventional methods show discrepancies as many severe hemophiliacs may not have severe symptoms and bleeding.27 This is because other pro-thrombotic factors play a role in bleeding in hemophiliacs which can be detected by TG assay.28

Thromboelastography

The integrity of coagulation can be assessed by thromboelastography. R-time and K-time shows the integrity of clotting factors.29 R- time shows the time taken for onset of clotting. PT and aPTT show the integrity of coagulation till this point only. K time is the time taken from end of R until the clot reaches 20mm and it shows the speed of clot formation.30 This helps in monitoring of patients on therapy.

c.Genetic diagnosis

Genetic testing helps in confirmation of diagnosis and identification of carriers. This can increase the index of suspicion and aid in early prenatal diagnosis of fetuses.

Carrier detection

This is imperative in genetic counseling and in vigilant care of pregnant mother and possibly hemophilic child. Hemophilia A carrier women have wide variation in levels of FVIII and rarely may show mild bleeding tendencies.19 This is because of Xinactivation in women during embryonic life.34 Hemophilia carrier women are at risk for post partum hemorrhage and hemophiliac child is at risk of intracranial hemorrhage. Inverse PCR (I-PCR) or inverse shifting PCR (IS-PCR) can be used to detect intron 1 and intron 22 inversions.35,36

Prenatal diagnosis

Prenatal diagnosis of fetuses with hemophilia is crucial during management of labour. It is done by assessing chorionic villous sampling at 11-14 weeks of gestation or amniocentesis after 15 weeks of gestation or cordocentesis after 20 weeks of gestation.37 This is beneficial in fetuses with a

strong family history of moderate to severe hemophilia. In early 1980s hemophilia was prenatally diagnosed mainly by immunoradiometry, factor VIII:CAg and factor VIIIR:Ag assays.

MANAGEMENT OF HEMOPHILIA

Initially in early 1960's concentrates of antihemophilic globulin46 and glycene precipitated factor VIII were used in the treatment of hemophilia.47 Then in 1970's and 80's plasma derived products and cryoprecipitate were used to treat hemophilia.48 But this increased the incidence of HIV and Hepatitis A and B in hemophiliacs and increased the development of antibodies to factors VIII and IX.4951By the beginning of 1990, recombinant-DNA derived antihemophilicfactors were used to treat hemophilia.Following that desmopressin and immunosuppressive therapy were used.54,55 Activated prothrombin complex concentrate was used to treat patients with inhibitors.56 In patients with liver cirrhosis or hepatitis due to transfusion, liver transplantation was done which provided good results and cured factor VIII and factor IX deficiencies.

ADVANCES IN MANAGEMENT

In recent times, many advances are made in the treatment of hemophilia. They include modification of time old therapy or breakthrough of new drugs.

a.Immunosuppressives

Steroids alone or steroids with cyclophosphamide or rituximab or cyclosporine are used as first line therapy. People who did not have complete remission with first line are given second line therapy with steroids, cytotoxics and rituximab. According to Collins et al, first line therapy with combination of steroids and cyclophosphamide gives a stable remission.60

b.Gene therapy

Gene therapy may provide complete lifelong cure for hemophilia. Gene therapy for hemophilia B using adenoassociated viral vector shows promising results in some studies. It provides remission temporarily and further studies are required to achieve permanent cure.61,62 There are some limiting factors to its use like humoral and cellular immune response, toxicity and safety issues which must be rectified in future.63 There is development of antibodies to recombinant proteins in hemophilia A. This can be prevented by giving adenoviral vector expressing factor VIII to neonates as their immune system is immature.

c.Therapy under development

Many new treatment options are tried in the recent times. Bone marrow transplantation and hematopoietic stem cell transplantation are being tried in mice.65,66 In vitro studies are done using solulin to increase clot stability in whole blood.67 Further studies are required to achieve long lasting and permanent cure for hemophilia.

Complications

Development of inhibitors and the role of immune tolerance induction and monoclonal antibodies Musculoskeletal Complications

Another critical complication of hemophilia is hemophilic arthropathies from repeated musculoskeletal bleeding. About 90% of patients with severe hemophilia who have had repeated musculoskeletal bleeds end up having chronic degenerative changes in major joints like ankles, knees, and elbows in their 20s and 30s. The only way to prevent these arthropathies is to prevent spontaneous intraarticular hemorrhage by providing prophylactic treatment; however, subclinical hemorrhages can still occur despite prophylactic treatment. Management of joint bleeds has been discussed extensively in the treatment section.[51]

Pseudotumors

Pseudotumor is a life, and limb-threatening condition due to inadequately treated soft tissue bleeds, usually in muscles adjacent to the bones. It is most commonly seen in long bones or pelvis. If not treated timely and adequately, pseudotumors can rapidly enlarge and lead to neurovascular compromise by pressure on adjacent structures. It can also cause pathologic fractures and create fistulas through the skin. Clinical examination and imaging studies are essential in diagnosis. Small pseudotumors can be monitored, while larger ones can receive aspiration or surgical ablation. Factor concentrate infusion is necessary and should occur for at least six weeks, followed by repeat imaging to document a decrease in the size. Large pseudotumors that have failed conservative management and those that are rapidly expanding may require limb amputations. Abdominal pseudotumors require surgery as soon as possible.[52]

Fractures

Fractures can occur in patients with hemophilic arthropathy. Immediate treatment of a fracture is replacement with factor concentrate to raise the levels to almost 50% and maintain them at that level for at least 3 to 5 days. Surgical management depends on the location and severity of the fracture, and splints or external fixators may be necessary. Immobilization for a necessary duration with early initiation of physical therapy is crucial.[53]

Blood-borne Infection-related Complications

In the 1980s, factor concentrates got contaminated with viruses like HIV and HCV, and patients who received those got infected with HIV and hepatitis C. This resulted in high mortality rates in patients with hemophilia in the 1980s and early 1990s. Today, many studies show that HIV and HCV transmission through factor concentrate has been almost eliminated due to careful selection of donors, screening techniques, viral elimination process during manufacturing, and advancement in diagnostic procedures to detect these viruses early. Higher usage of recombinant factors has dramatically decreased the risk of infection. However, new challenges from non-lipid enveloped viruses and prion diseases are emerging. Also, currently available anti-HIV medications are all safe for use in patients, with no contraindications. For patients with hepatitis C and hemophilia, pegylated interferon and ribavirin are the treatment.[51]

Treatment

The best way to treat hemophilia is to replace the missing blood clotting factor so that the blood can clot properly. This is typically done by injecting treatment products, called clotting factor concentrates, into a person's vein. Clinicians typically prescribe treatment products for episodic care or prophylactic care. Episodic care is used to stop a patient's bleeding episodes; prophylactic care is used to prevent bleeding episodes from occurring. Today, it's possible for people with hemophilia, and their families, to learn how to give their own clotting factor treatment products at home. Giving factor treatment products at home means that bleeds can be treated quicker, resulting in less serious bleeding and fewer side effects. The main treatment for severe hemophilia involves replacing the clotting factor you need through a tube in a vein.

This replacement therapy can be given to treat a bleeding episode in progress. It can also be given on a regular schedule at home to help prevent bleeding episodes. Some people receive continuous replacement therapy.

Replacement clotting factor can be made from donated blood. Similar products, called recombinant clotting factors, are made in a laboratory, not from human blood. Other therapies include:

- **Desmopressin.** In some forms of mild hemophilia, this hormone can stimulate the body to release more clotting factor. It can be injected slowly into a vein or used as a nasal spray.
- **Emicizumab (Hemlibra).** This is a newer drug that doesn't include clotting factors. This drug can help prevent bleeding episodes in people with hemophilia A.
- **Clot-preserving medications.** Also known as anti-fibrinolytics, these medications help prevent clots from breaking down.
- **Fibrin sealants.** These can be applied directly to wound sites to promote clotting and healing. Fibrin sealants are especially useful for dental work.
- **Physical therapy.** It can ease signs and symptoms if internal bleeding has damaged your joints. Severe damage might require surgery.
- **First aid for minor cuts.** Using pressure and a bandage will generally take care of the bleeding. For small areas of bleeding beneath the skin, use an ice pack. Ice pops can be used to slow down minor bleeding in the mouth.

Treatment Medications

Clotting Factor Products

The two main types of clotting factor concentrates available are:

1.Plasma-derived Factor Concentrates

2. **Recombinant Factor Concentrates**

*1.**Plasma-derived Factor Concentrates***

Plasma is the liquid part of blood. It is pale yellow or straw-colored and contains proteins such as antibodies, albumin, and clotting factors. Several factor concentrate treatment products are available that are made from human plasma proteins. All blood and parts of blood, such as plasma, are routinely tested for viruses. The plasma is collected from many people, and then it goes through several processes to separate it into components, such as clotting factors. The clotting proteins are then made into a freeze-dried product, which is tested and treated to kill any potential viruses before it is packaged for use.

2.Recombinant factor Concentrates

Until 1992, all factor replacement products were made from human plasma. In 1992, the U.S. Food and Drug Administration (FDA) approved recombinant factor VIII (8) concentrate, which does not come from human plasma. This concentrate is genetically engineered using DNA technology. Commercially prepared factor concentrates are treated to remove or inactivate bloodborne viruses. Additionally, recombinant factors VIII (8) and IX (9) do not contain any plasma or albumin, and therefore, cannot spread any bloodborneviruses.Some people who infuse with clotting factor concentrates may develop.

CONCLUSION

In conclusion, early diagnosis of hemophilia and early management helps in improving the quality of living of the patient and prevents early development of complications. Replacement of factors provides effective control of hemophilia for short term. Newer research based options are required to provide long lasting and complete cure for hemophilia which may be possible by gene therapy in the near future.

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