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HEMOPHILIA: A GENETIC DISORDER

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ABSTRACT: Hemophilia is an inherited bleeding disorder where one of the blood clotting proteins is absent or present in a reduced amount. People with Hemophilia, do not bleed faster than anyone else; but will bleed continuously at the normal rate until they are treated. As this is a genetic disorder no complete cure is possible as of now. The available treatment for Hemophilia is by replacing the missing clotting factor in the blood through an intravenous infusion of clotting factor concentrate. Several new technologies are also being implemented to advance Hemophilia, treatment. The present review provides an overview of hemophilia.

KEYWORDS: Hemophilia, mutations, bleeding.

INTRODUCTION:

Hemophilia is an X-linked congenital bleeding [1] disorder caused by a deficiency of coagulation factor VIII (FVIII) (in hemophilia A) or factor IX (FIX) (in hemophilia B). The deficiency is the result of mutations of the respective clotting factor genes. Hemophilia has an estimated frequency of approximately one in 10,000 births. Hemophilia A is more common than hemophilia B, representing 80-85% of the total hemophilia population. Hemophilia generally affects males on the maternal side. However, both *F8* and *F9* genes are prone to new mutations, and as many as 1/3 of all cases are the result of spontaneous mutation where there is no prior family history. Estimations based on the World Federation of Haemophilia's(WFH's) annual global surveys indicate that the number of people with Hemophilia in the world is approximately 400 000. Bleeding disorders are due to defects in the blood vessels, the coagulation mechanism, or the blood platelets [2]. An affected individual may bleed spontaneously or for longer than a healthy person after injury or surgery. When coagulation factors are missing or deficient the blood does

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not clot properly and bleeding continues. Bleeding is common into joints such asknees, ankles and elbows. This may be caused by injury, but in severe Hemophilia, can begin spontaneously [3].

CLASSIFICATION OF HEMOPHILIA[4]

- **Hemophilia-A (Classic hemophilia)**

It is "X"linked recessive disorder occurred due to the absence or deficiency of clotting factor VIII (FVIII). Hence it affects only males and females are carriers. Carrier females usually are asymptomatic but can have bleeding symptoms when they have significant reductions in factor VIII levels, which are caused by the extreme inactivation of the normal FVIII gene, compared with the hemophilic FVIII gene, during early embryogenesis. The occurrence of hemophilia A is 1: 5000-10000.

- **Hemophilia B (Christmas disease)**

It is also an "X" linked recessive disorder occurring due to the absence or deficiency of the clotting factor IX. The inheritance pattern and the symptoms of hemophilia B are same as that of the classic hemophilia. The occurrence of hemophilia B is 1: 20000-34000.

- **Hemophilia C**

It is an autosomal recessive disorder exhibits bleeding symptoms because of the absence /deficiency of the factor XI. For inheriting the disease both parents must carry the defective gene. Factor XI deficiency affects males and females in equal numbers. The occurrence of the Hemophilia C is 1:100000.

SYMPTOMS [5]

- **Hemophilia A**

Spontaneous bleeding to joints, muscles and soft tissues, hemarthrosis, deep muscle hematomas Intracranial bleeding in the absence of major trauma, neonatal cephalo hematoma or intracranial bleeding, prolonged oozing or renewed bleeding after initial bleeding stops following tooth extractions, mouth injury, or circumcision, prolonged bleeding or renewed bleeding following surgery or trauma unexplained GI bleeding or hematuria,

menorrhagia, especially at menarche, prolonged nosebleeds, especially recurrent and bilateral, excessive bruising, especially with firm, subcutaneous hematomas

- **Hemophilia B**

The symptoms are same as hemophilia A.

- **Hemophilia C**

Mostly same as that of the mild hemophilia. Individuals are not likely to bleed spontaneously, and hemorrhage normally occurs after trauma or surgery. Certain procedures carry an increased risk of bleeding such as, dental extractions, tonsillectomies, surgery in the urinary and genital tracts and nasal surgery. Joint, muscle and soft tissue bleeds are uncommon.

REASONS FOR HEMOPHILIA [6-10]

- **Inheritance**

The gene for factor VIII and IX are both located on the "X" chromosome. [Female (XX) male (XY)]. Hemophilia is therefore said to be an "x" linked hereditary disorder. This results in males being affected by the disease while females are carriers.

- **Mutation**

These include point mutations, inversions, deletions, and unidentified mutations. It is of course also possible for a human to acquire it spontaneously (de novo), rather than inheriting it, because of a new mutation in one of their parents gametes. Spontaneous mutations account for about 1/3 of all hemophilia.

DIAGNOSIS OF HEMOPHILIA

1. ***Basic screening tests for hemophilia***
   - Bleeding time
   - Prothrombin time(PT)
   - Platelet count
   - Activated partial thromboplastin time (APTT)

2. ***Correction studies with factor deficient plasma***
3. ***Factor assays***

Individuals with a history of a lifelong bleeding tendency should have specific coagulation factor assays performed even if all the coagulation screening tests are in the normal range. The level of factors VIII, IX and XI depending upon the condition is summarized in table 1 and table 2.

Table 1: Conditions of hemophilia A and B depending upon the factor level present in the plasma

Condition	Factor level (VIII/IX)
Normal	50-150%
Mild	5-30%
Moderate	1-5%
Severe	< 1%

Table 2: Conditions of hemophilia C depending upon the factor level present in the plasma

Condition	Factor level (XI)
Normal	60-140 %
Mild –moderate bleeding	0-15% of normal factor level
Problems only after surgery	15-70% of normal level

4. ***Molecular genetic testing***
   - Sequence analysis
   - Targeted sequence analysis
   - Deletion and duplication analysis
5. ***Linkage analysis (Mutation analysis)***
   - Tracking an unidentified mutation
   - Identifying the origin of a de novo mutation
6. ***Carrier detection***
   - Factor assay
   - DNA analysis
   - Phenotype analysis
   - Genotype
7. ***Prenatal diagnosis***
   - CVS (Chorionic villous sampling)
   - Amniocentesis

TREATMENT FOR HEMOPHILIA[11-19]

1. ***Factor concentrates***
   - **Plasma derived factor concentrates**

Plasma derived virus inactivated factor VIII, IX, and XI concentrates can be used to treat hemophilia. Generally dose is given 250-1000 IU for factor activity. Bleeding can be controlled rapidly after intravenous infusions of factor concentrates.

- **Recombinant factors**

Plasma derived products are more susceptible to viral infections (HIV, Hepatitis).Hence Recombinant factors are used to treat hemophilia. It contains only the corresponding factors.

2. Cryoprecipitate

It is prepared from the pooled blood and contains factor VIII, von willebrand factor, fibrinogen and factor VIII activity and should have at least 80 IU of factor VIII activity and should be used as a replacement therapy in factor VIII deficiency.

3. Fresh frozen plasma (FFP)

If the plasma obtained from the donor within 6 hours, it can be considered as fresh plasma and contain the entire clotting factor in near normal quantities.

4. Fresh whole blood

When no other products are available, fresh whole blood can be used as it contains all clotting factors. The infusion should be continued until the bleeding stops.

5. Adjuvant therapies

- **Tranexamic acid**

It is an anti-fibrinolytic drug that competitively inhibits the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin. Tranexamic acid is mainly used to control mucosal bleedings. It is contraindicated to upper hematuria, due to the risk of forming of blood clots in the ureter and hydronephrosis.

- **Desmopressin (DDAVP)**

It is a synthetic analog of the anti-diuretic hormone vasopressin (1-deaminocys-8D arginini-vasopressin). It is useful in mild hemophilies who have a base line of factor FVIII>10% as it releases the stored FVIII from endothelial cells.

- **Fibrin Sealant**

It is made by mixing fibrinogen and thrombin which mimics the last step in the blood coagulation cascade. A semi rigid to rigid fibrin clot consolidates and adhere to the application site and acts as a fluids tight sealing agent able to stop the bleeding. It is available as sprays and can be used on open wounds or for surgical homeostasis.

- **Factor eight inhibitor by pass activity (FEIBA)**

FEIBA is an activated prothrombin complex concentrate available as FEIBA –TM-4 prepared from pooled human plasma contains small amount of activated factors II,VII,IX and X.

- **Recombinant activated factor VIIa (RFVIIa)**

RFVIIa is licensed by the US Food and Drug Administration for the treatment of bleeding in individuals with hemophilia A and B with acquired inhibitors.

- **Anti-spasmodic analgesics**

For the management of pain during the bleeding episode analgesic like Paracetamol, Dextropropoxyphene , Buscopan, Codeine Buprenorphine, Tramadol can be used. Aspirin should be avoided because it increases the bleeding by inhibiting the platelet aggregation .

- **Corticosteroids**

Prednisone is a corticosteroid drug with predominantly glucocorticoid and low mineralocorticoid activity, making it useful for the treatment of a wide range of inflammatory and auto-immune conditions. It is highly recommended for the treatment of macroscopic upper hematuria.

- **Calcium alginate**

It is a polysaccharide that can be extracted from brown seaweed made in to fibers for swab. When this material is in contact with biological fluids, calcium alginate exchanges its calcium ion and gels.

PREVENTION

The transmittance of the hemophilia to the next generation can be prevented by the following methods.

- Prenatal intrauterine diagnosis with termination of pregnancy as an option.
- Pre implantation genetic diagnostic testing (PGD)
- IVF with egg/sperm donation.

CONCLUSION:

Hemophilia is a bleeding disorder that results from genetic alteration in production of coagulation factors that are important to maintain hemostasis. Hence it is widely anticipated that new technologies will develop to diagnose and treat the patients of Hemophilia and study continue to evolve and expand in many areas of Hemophilia. As technologies are developed

hemophilia can be treated with ease and even complete cure possible. The transmittance of the hemophilia to the next generation can be prevented by using suitable technique.

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