HEMOPHILIA

Dharitri Parmar

Professor and Head, Department of Physiology, Government medical college, Surat

Address of Correspondance: Dr. Dharitri Parmar, Department of Physiology, Government Medical College, Surat, E-mail: dharitri@hotmail.com

To continue learning during these pandemic days, sharingour(my PG students and my) experience of being affiliated with one of the top Hemophilia care Centre in India. Prevalence of the disorder is 1:10000 in population. At GMCS nearly 628 hemophilic are registered out of which 69 are of type B .The affiliation has been an opportunity for physiologists at GMCS to learn physiology of coagulation disorder clinically,recent advances in its therapyand a little contribution to the society as doctor.

Hemophilia is the disorder of hemostasis due to deficiency or dysfunction of Coagulation factors which are necessary to prevent excessive bleedingwhen there is injury to tissues. It is usually the inherited genetic disorder but may be acquired also due to production of auto antibodies against the coagulation factors.

Jewish writings of 2ndcentury AD States that a woman's third son was exempted from being circumcised, if two elder brothers had died of bleeding after circumcision. It can be considered as earliest diagnosisabout hemophilia/bleeding disorder.In 1803, by DrJohn Otto,the first article about hemophilia was published titled "An account of a hemorrhagic disposition existing in certain families". It was a case of a woman carrier where sex-linked inheritance and premature death were noted.

There are different types of hemophilia. Apart from clinical classification as per severity, they can be as

1. Hemophilia A (Clotting Factor VIII deficiency)
   Von Willebrand factor deficiency is milder type of hemophilia where a part of molecule of factor VIII is reduced
2. Hemophilia B (Clotting Factor IX deficiency),
3. Hemophilia C (Clotting Factor XI deficiency),
4. Para hemophilia (Clotting Factor V deficiency).

Hemophilia A and B are Inherited as X-linked recessive pattern but later are Autosomal recessive pattern. The "Royal disease"isof hemophilia B type.Hemophilia came to spotlight as "Royal disease" during the reign of Queen Victoria(1837 to 1901) ,who was a carrier of hemophilia B. She had transmitted disease to thee of nine offspring. This Disease was transmitted to Russian and Spain royal families through marriages of princesses Alice and Beatrice as they gave birth to carrier daughters and affected sons.

To understand the pathogenesis of hemophilia, it is precondition to studyphysiology of hemostasis. Hemostasis is the natural mechanisms occurring in the body to prevent the excessive blood loss during injury and to maintain the flow of the blood.

Injury to blood vessels, causes vasospasmdue to vasoconstrictor molecules released from the injured cell wall and platelets. This reduces the amount of blood flow through the vessels to

prevent the loss of blood through damaged area.

Then the platelets will get adhered to the exposed collagen at the site of injury with the help of molecule called von Willebrand factor (part of factor VIII). VW factor is known to lengthen the half-life of factor VIII from 2 hours to 12 hours. This triggers the morphological as well as functional changes in platelets results in platelet aggregation at the site of injury hence the injured site will be sealed temporarily. This is called temporary or primary hemostatic plug which is unstable in nature.The process of stabilization of the hemostatic plug is called as secondary hemostasis in which the clotting factors(*there are 12 coagulation factors available, Initially it was thought to be 13 factors but factor VI was removed from the list as it was activated factor V. The numbers given in the order of the factor's discovery*)will be activated serially called coagulation cascade. Every factor will get activated by the prior one in the cascade. There are two pathways in coagulation cascade, Intrinsic and extrinsic pathways.

Exposure of factor XII to the negatively charged surface will activate the intrinsic pathway.

Followed by that factor XI,IX,VIII and Xwill get activated.

Extrinsic pathway will get activated when factor III (also named as tissue thromboplastin, which is released when there is tissue trauma. This factor will bind with activated factor VII and C alcium to form a complex that can activate factor X.

Both the intrinsic and extrinsic pathway ends when factor X got activated. Hereafter it will be called as common pathway. Activated factor X will combine with Factor V, calcium and phospholipid surface to form a complex which converts prothrombin into thrombin(Factor II).Thrombin Converts the Fibrinogen in to fibrin and also activates factor XIII. This Fibrin is the end product of coagulation cascade which is stabilized by factor XIII. Thus the injury site will be sealed completely and will be allowed to heal.

Initially patients with hemophilia were treated with blood transfusions as the normal person's blood has clotting factor. Plasma,Cryoprecipitate and clotting factor concentrate were separated and infused totreat patients as research and therapy advanced. However, transfusion of blood borne products resulted in transfusion transmissible infectionsi.e.HIV, HBV, HCV. Development of recombinant factors helps us to overcome this problem and they were improved gradually which has no exogenous bovine or human protein. Passing through I, II nd& III rd generations of recombinant factors Monoclonal antibodies are latest treatment considered nowadays namely**Emicizumab**.It is a Bispecific monoclonal antibody mimicking the function of factor VIII (**Subcutaneous injections available)** forHemophilia A patients with or without inhibitors. Recombinant adeno-associated viral (AAV) vectors were used for factor VIII or IX hepatocyte transduction which normalization of factor levels. But transient liver enzymes elevation was reported. (Note: complications and effects of lifelong disease are omitted here)

References:

1. **Acquired haemophilia: an overview for clinical practice**Craig M. Kessler,Paul KnöblFirst published: 17

December 2015.**https://doi.org/10.1111/ejh.12689**

2. **Emicizumab Prophylaxis in Hemophilia A with Inhibitors**Johannes Oldenburg [1], Johnny N Mahlangu [1], Benjamin Kim [1], Christophe Schmitt [1], Michael U Callaghan [1], Guy Young [1], Elena Santagostino [1], Rebecca Kruse-Jarres [1], Claude Negrier [1], Craig Kessler [1], Nancy Valente [1], Elina Asikanius [1], Gallia G Levy [1], Jerzy Windyga [1], Midori Shima [1]PMID: 28691557 ,DOI: 10.1056/NEJMoa1703068.. N Engl J Med**,**2017 Aug 31;377(9):809-818. Epub 2017 Jul 10
3. **Advances and challenges for hemophilia gene therapy.**Paul Batty† and David Lillicrap* Department of Pathology and Molecular Medicine, Richardson Laboratory, Queen's University, Kingston, Ontario, Canada.Human Molecular Genetics, 2019, Vol. 28, No. R1 R95–R101 doi: 10.1093/hmg/ddz157 Advance Access Publication Date: 23 July 2019
4. principles of hematology by Peter.J.Haen.
5. Wintrobe's clinical hematology(14th edition)
6. Textbook of hemophilia 3rd edition,Edited by Christine A. Lee, Erik E. Berntorp, Keith Hoots .**Wiley blackwell**