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## Hemophilia A Genetic Disorder: Diagnosis, Treatment And Prognosis

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**Abstract:** Hemophilia a genetic disorder with patient's inability to stop bleeding. There are two main types of hemophilia, hemophilia A due to not enough clotting factor VIII and hemophilia B due to not enough factor IX, and acquired hemophilia A (AHA) caused by autoantibodies against clotting factor VIII (FVIII). AHA is associated with malignancy, autoimmune disorders, and pregnancy. Factor IX deficiency can cause interference of the coagulation cascade. People with more severe hemophilia usually suffer more severe and more bleeds than people with mild hemophilia. Complications of hemophilia include deep internal bleeding, joint damage, transfusion induced infection, adverse reactions to clotting factor treatment, and intracranial hemorrhage. Diagnosis of hemophilia can be confirmed by, coagulation screening test, bleeding scores and coagulation factor assay. Gold standard of treatment is rapid treatment of bleeding episodes decreases damage to the body. Prophylactic treatment although high costs, is more effective than on demand treatment. People with severe hemophilia without adequate treatment have generally shortened lifespans. Gene therapy is not currently an accepted treatment for hemophilia.

**Keywords:** Bleeding, Diagnosis, Factor VIII & F IX, Hemophilia, Treatment.

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### I. Introduction

Hemophilia the word is from the Greek *haima* meaning blood and *philia* meaning *love* [1]. Hemophilia is a mostly inherited, genetic disorder that impairs body's ability to make blood clots, a process needed to stop bleeding [2]. Hemophilia is rare, with only about 1 instance in every 10,000 births (or 1 in 5000 male births) for hemophilia and 1 in 50,000 births for hemophilia B [3]. About 18,000 people in the United States have hemophilia. Each year in the U.S. 400 babies are born with the disorder. Hemophilia usually occurs in males and less often in females [4]. It is estimated that about 2,500 Canadians have hemophilia A and about 500 Canadians have hemophilia B [5]. In the 1800s hemophilia was common within the royal families of Europe [6]. About 45 people in Sabah, Malaysia, and about 1000 people in West Malaysia have hemophilia [7]. There are two main types of hemophilia, hemophilia A due to not enough clotting factor VIII and hemophilia B due to not enough factor IX [8]. They are typically due to inheriting from one's parents an X chromosome with nonfunctional gene [9]. Other types include hemophilia C due to not enough factor XI and parahaemophilia due to not enough factor V [10]. Acquired hemophilia A (AHA) is a rare bleeding disorder caused by autoantibodies against clotting factor VIII (FVIII) [11]. Acquired hemophilia is associated with cancers, autoimmune disorders, and pregnancy [12]. Clinical symptoms include bleeding longer after injury, easy bruising, and increased risk of bleeding inside joints or brain. Bleeding into a joint can result in permanent damage while bleeding in the brain can result in long term headaches, seizures, or a decreased level of unconsciousness [13]. Diagnosis is by testing the blood for its ability to clot and its levels of clotting factors [14]. Treatment is by replacing the missing blood clot factors. Prevention may occur by removing a woman's egg fertilizing it, and testing the embryo before putting it back in the uterus [14]. The paper summarizes the current literature, diagnosis, treatment and outcome of hemophilia.

### II. History and Discovery Of Hemophilia

The first medical professional to describe the disease was Abulcasis. In the tenth century he described families whose males died of bleeding after only minor traumas [15]. In 1803, John Conrad Otto, a Philadelphia physician, wrote an account about "hemorrhagic disposition existing in certain families" in which he called the affected males "bleeders" [16]. He recognized that the disorder was hereditary and it affected mostly males and was passed down by healthy females. His paper was the second paper to describe important characteristics of an X-linked genetic disorder (the first paper being a description of color blindness by John Dalton who studied his own family). Otto was able to trace the disease back to a woman who settled near Plymouth, NH in 1720. The

idea that affected males could pass the trait onto their unaffected daughters was not described until 1813 when John F Hay, published an account in the New England Journal of Medicine [17].

In 1924, a Finish doctor discovered a hereditary bleeding disorder similar to hemophilia localized to in the “Aland Islands”, southwest of Finland. The bleeding disorder is called “Von Willebrand Disease” [18]. The term “hemophilia” is derived from the term “hemorrhaphilia” which was used in a description of the condition written by Friedrich Hopff in 1828, while he was a student at the University of Zurich [16]. In 1937, Patek and Taylor, two doctors from Harvard, discovered anti-hemophilic globulin [19].

Hemophilia has featured prominently in European royalty and this is sometimes known as “the royal disease”. Queen Victoria passed the mutation for hemophilia to her son Leopold and, through two of her daughters, Alice and Beatrice, to various royals across the continent, including the royal families of Spain, Germany, and Russia [20].

### **Contaminated blood transfusion**

Prior to 1985 there were no laws enacted within the U.S. to screen blood. As a result many people with hemophilia that received untested and unscreened clotting factor prior to 1992 were at extreme risk for contracting HIV and hepatitis C via blood products. It is estimated that more than 50% of the hemophilia population, i.e. over 10,000 people, contracted HIV from the tainted blood supply in the United States alone [21]. As a direct result of the contamination of the blood supply in the 1970s and early/mid 1980s with viruses such as hepatitis and HIV, new methods were developed in the production of clotting factor product. The initial response was to heat-treat (pasteurize) plasma-derived factor concentrate, followed by the development of monoclonal factor concentrates, which use a combination of heat treatment and affinity chromatography to inactivate any viral agents in the pooled plasma from which the factor concentrate is derived. The Lindsay Tribunal in Ireland investigated, among other things, the slow adoption of new methods [21].

### **III. Genetic Factors**

Hemophilia A is inherited as an X-linked recessive trait, and occurs in males and homozygous females (only possible in the offspring of a carrier female and a hemophilic male [22]). However, mild hemophilia A is known to occur in heterozygous females due to X-inactivation, so it is recommended that levels of factor VIII and IX be measured in all known potential carriers prior to surgery and in the event of clinically significant bleeding [23].

Hemophilia B the factor IX gene is located on X chromosome (Xq27.1-q27-2). It is an X-linked recessive trait, which explains why, as in hemophilia A, usually only males are affected [24]. In 1990, George Brownlee and Merlin Crossley showed that two sets of genetic mutations were preventing two key proteins from attaching to the DNA of the people with a rare and unusual form of hemophilia B *hemophilia B Leyden*—where sufferers experience episodes of excessive bleeding in childhood but have few bleeding problems after puberty [25]. This lack of protein attachment to the DNA was hereby was turning off the gene that produces clotting factor IX, which prevents excessive bleeding [25].

### **Hemophilia and its severity**

There are numerous different mutations which cause each type of hemophilia. Due to differences in changes to the genes involved; people with hemophilia often have some level of active clotting factor. Individuals with less than 1% active factor are classified as having severe hemophilia, those with 1-5% active factor have moderate hemophilia, and those with mild hemophilia have between 5-40% of normal levels [26].

### **IV. Pathophysiology**

In terms of mechanism, factor IX deficiency leads to an increased propensity for hemorrhage. This is in response to mild trauma or even spontaneously, such as in joints (hemarthrosis) or muscles. Factor IX deficiency can cause interference of the coagulation cascade, therapy causing hemorrhage when there is trauma. Factor IX when activated activates factor X which helps fibrinogen to fibrin conversion [27]. Factor IX becomes active eventually in coagulation, by cofactor factor VIII (especially IXa). Platelets provide a binding site for both cofactors. This complex (in the coagulation pathway) will eventually activate factor X [28].

### **V. Clinical Manifestations**

Characteristic symptoms vary with severity. In general symptoms are internal or external bleeding episodes, which are called “bleeds”. People with more severe hemophilia suffer more severe and more frequent bleeds, while people with mild hemophilia usually suffer minor symptoms except after surgery or serious trauma. In cases of moderate hemophilia symptoms are variable which manifest along a spectrum between severe and mild forms [29].

In both hemophilia A and B, there is spontaneous bleeding but a normal bleeding time, normal prothrombin time, normal thrombin time, but prolonged partial thromboplastin time. Internal bleeding is common in people with severe hemophilia and some individuals with moderate hemophilia. The most characteristic type of internal bleed is a joint bleed where blood enters into the joint spaces [30]. This is most common with severe hemophilia and can occur spontaneously (without evident trauma). If not treated promptly, joint bleeds can lead to permanent joint damage and disfigurement. Bleeding into soft tissues such as muscles and subcutaneous tissues is less severe but can lead to damage and requires treatment [30].

Children with mild to moderate hemophilia may not have any signs or symptoms at birth especially if they do not undergo circumcision. Their first symptoms are often frequent and large bruises and hematomas from frequent bumps and falls as they learn to walk. Swelling and bruising from bleeding in joints, soft tissue, and muscles may also occur. Children with mild hemophilia may not have noticeable symptoms for many years. Often, the first sign in very mild hemophiliacs is heavy bleeding from a dental procedure, an accident, or surgery. Females who are carriers usually have enough clotting factors from their one normal gene to prevent serious bleeding problems, though some may present as mild hemophiliacs [30].

### **Hemophilia and its complications**

Severe complications are much more common in cases of severe and moderate hemophilia. Complications may arise from the disease itself or from its treatment [31]. Frequent complications include:

- a) Deep internal bleeding, e.g. Deep muscle bleeding, leading to swelling, numbness or pain of a limb.
- b) Joint damage from hemarthrosis (hemophilic arthropathy), potentially with severe pain, disfigurement, and even destruction of joint and development of debilitating arthritis.
- c) Transfusion transmitted infection from blood transfusions that are given as treatment.
- d) Adverse reactions to clotting factor treatment, including the development of an immune inhibitors which renders factors replacement less effective.
- e) Intracranial hemorrhage is serious medical emergency caused by the buildup of pressure inside the skull. It can cause disorientation, nausea, loss of consciousness, brain damage, and death.

Hemophilic arthropathy is characterized by chronic proliferative synovitis and cartilage destruction [32]. If an intra-articular bleed is not drained early, it may cause apoptosis of chondrocytes and affect the synthesis of proteoglycans. The hypertrophied and fragile synovial lining while attempting to eliminate excessive blood may be more likely to easily re-bleed, leading to a vicious cycle of hemarthrosis-synovitis-hemarthrosis. In addition, iron deposition in synovium may induce an inflammatory response activating the immune system and stimulating angiogenesis, resulting in cartilage and bone destruction [33].

Hemophilia C, also known as plasma thromboplastin antecedent (PTA) deficiency or Rosenthal syndrome, is a mild form of hemophilia [34]. In terms of signs and symptoms of hemophilia C, unlike individuals with hemophilia A and people affected by it are not the one to bleed spontaneously. In these cases, hemorrhages tend to happen after a major surgery or injury [35]. However, people affected with hemophilia C might experience symptoms closely related to those of other forms of hemophilia that includes: oral bleeding, nose bleeds, and blood in the urine [36].

## **VI. Diagnosis**

The diagnosis for hemophilia B can be done by the diagnostic tests include: [37].

- i) Coagulation screening test.
- ii) Bleeding scores.
- iii) Coagulation factor assay.

Differential diagnosis for this inherited condition is the following hemophilia A, factor XI deficiency, von Willebrand disease, fibrinogen disorders and Bernard-Soulier syndrome [25].

The diagnosis of hemophilia A may be suspected as coagulation testing reveals increased PTT in the context of a normal PT and bleeding time. PTT tests are the first blood test done when hemophilia is indicated [24]. However diagnosis is made in the presence of low levels of Factor VIII. A family history is frequently present, although not essential. Recently, genetic testing has been made available to determine individual's risk of attaining or passing on hemophilia. Diagnosis of hemophilia A also includes a severity level which can range from mild to severe based on the amount of active and functioning factor VIII detected in the blood. Factor VIII levels do not typically change throughout an individual's life. Severe hemophilia A is the most common form occurring in the majority of the affected people. Individuals with mild hemophilia often experience often experience few or no bleeding episodes except in the case of serious trauma (i.e. tooth extraction and surgery) [23].

Two of the most common differential diagnosis are hemophilia B which is deficiency in Factor IX and von Willebrand Disease which is a deficiency in von Willebrand factor (needed for proper function of Factor VIII) [38], hemophilia is also a possible, differential diagnosis [39].

## **VII. Treatment**

Clotting factors are usually not needed in mild hemophilia[40].In moderate hemophilia clotting factors are typically only needed when bleeding occurs or prevent bleeding with certain events[40].In severe hemophilia preventive use is often recommended two or three times a week and may continue for life[40].Rapid treatment of bleeding episodes decreases damage to the body[40].Factor VIII is used in hemophilia A and Factor IX in hemophilia B.Factor replacement can be either isolated from human blood serum,recombinant, or a combination of the two. Some people develop antibodies (inhibitors) against the replacement factors given to them, so the amount of factor has to be increased or non-human replacement products must be given, such as porcine factor VIII[40].If a person becomes refractory to replacement coagulation factor as a result of circulating inhibitors, this may be partially overcome with recombinant human factor VII[40].In early 2008,US Food and Drug Administration (FDA) approved anti-hemophilic factor, genetically engineered from the genes of Chinese hamster ovary cells[40].

Clotting factors are either given preventively or on-demand. Preventive use involves the infusion of clotting factor on a regular schedule in order to keep clotting levels sufficiently high to prevent spontaneously bleeding episodes. On-demand (or episode) treatment involves treating bleeding episodes of boys (< 30 months) with hemophilia A with prophylactic treatment (infusion of 25IU/kg body weight of Factor VIII every other day)in respect to its effect on the prevention of joint-diseases. When the boys reached 6 years age, 93% of those in the prophylactic group and 55% of those in the episode-therapy group had a normal index joint-structure on MRI[41].Prophylactic treatment, however, resulted in average costs of \$300,000 per year. The editor of an editorial published in the same issue of the NEJM supports this idea that prophylactic treatment is more effective than on demand treatment but also suggest that starting after the first serious joint-related hemorrhage may be more cost effective than waiting until the fixed age to begin[42].

#### **Alternative drugs and side effect of anticoagulants**

Desmopressin(DDAVP) may be used in those with mild hemophilia A[40].Tranexamic acid or epsilon aminocaproic acid may be given along with clotting factors to prevent breakdowns of clots[40].Pain medicines, steroids, and physical therapy may be used to reduce pain and swelling in an affected joint[40]. Anticoagulants such as heparin and warfarin are contraindicated for people with hemophilia as these can aggravate clotting difficulties. Also contraindicated are those drugs which have “blood thinning: side effects. For instance, medicines which contain aspirin, ibuprofen or naproxen sodium should not be taken because they are well known to have the side effect of prolonged bleeding[43].Also are contraindicated are activities with a high likelihood of trauma, such as motorcycling and skateboarding. Popular sports with high rates of physical contact and injuries such as American football, hockey,boxing,wrestling,and rugby should be avoided by the people with hemophilia[43].Other active sports like soccer ball, basketball also have high rate of injuries, but overall less contact and should be undertaken cautiously and only in consultation with a doctor[43].

### **VIII. Prognosis and Future Directions**

Like most aspects of the disorder, life expectancy varies with severity and adequate treatment. People with severe hemophilia who don't receive adequate, modern treatment have greatly shortened lifespans and often do not reach maturity. Prior to 1960s when effective treatment became available, average life expectancy was only 11 years [30].By the 1980s the life span of the average hemophilia receiving appropriate treatment was 50 -60 years [30].Today with appropriate treatment, males with hemophilia typically have a near normal life with an average lifespan approximately 10 years shorter than an unaffected male[44].

Since the 1980s the primary leading cause of death of people with severe hemophilia has shifted from hemorrhage to HIV/AIDS acquired through treatment with contaminated blood products [30].The second leading cause of death related to severe hemophilia complications is intracranial hemorrhage which today accounts for one third of all deaths of people with hemophilia. Two other major causes of death include hepatitis infections causing cirrhosis and obstruction of air or blood flow due to soft tissue hemorrhage [30].

#### **Future directions**

In those with severe hemophilia, gene therapy may reduce symptoms to those that a mild or moderate person with hemophilia might have. The best results have been found in hemophilia B.As of 2016 early stage human research is ongoing with a few sites recruiting participants. It is not currently an accepted treatment for hemophilia [40].

### **IX. Conclusion**

Hemophilia is mostly an inherited genetic disorder that impairs body's ability to make clots, a process needed to stop bleeding. Clinical symptoms include longer bleeding after injury, and bleeding inside joints or the brain.Diagnosis by confirming the low Factor VIII level. Treatment is by replacing the blood clot factors. Prophylactic treatment is more effective than episode treatment

## References

- [1]. Douglas Harper. Online Etymology Dictionary. Retrieved 10 October 2007.
- [2]. Hemophilia Facts. CDC. August 26, 2014. Retrieved 8 September 2016.
- [3]. World Federation of Hemophilia Frequently Asked Questions About Hemophilia ([http://www.wfh.org/index.asp?lang=EN&url=2/1/1\\_1\\_1\\_FAQ.htm](http://www.wfh.org/index.asp?lang=EN&url=2/1/1_1_1_FAQ.htm)).
- [4]. U.S. National Library of Medicine. Retrieved 2 December 2007.
- [5]. Canadian Hemophilia Society FAQ (<http://www.hemophilia.ca/en/10.php>).
- [6]. Wynbrandt James, Ludman Mark D. (1 January 2009). The Encyclopedia of Genetic Disorders and Birth Defects. InfoBase Publishing. p.194. ISBN 978-1-4381-2095-9. Retrieved 25 August 2013.
- [7]. Personal Communication, Ministry of Health Sabah, Malaysia, 2016.
- [8]. What is Hemophilia ?. NHLBI. July 13, 2013. Retrieved 8 September 2016.
- [9]. What Causes Hemophilia ?. NHLBI July, 2013. Retrieved 10 September 2016.
- [10]. Franchini M, Mannucci PM. Inhibitors of propagation of coagulation (factors VIII, IX and XI): a review of current therapeutic practice. *Brit J Clin Pharm*. 2011; **72**(4):553-62.
- [11]. Mulliez SM, Vantiborgh A, Devreese KM. Acquired hemophilia: a case report and review of literature. *Int J Lab Hematol*. 2014; **36**(3):398-407.
- [12]. Franchini M, Mannucci PM. Acquired hemophilia A: a 2013 update. *Thromb Haemost*. 2013; **110**(6):1114-20.
- [13]. What are the Signs and Symptoms of Hemophilia ?. NHLBI. July 13, 2013. Retrieved 8 September 2016.
- [14]. How is Hemophilia Diagnosed. *NHBI*. July 13, 2013. Retrieved 10 September 2016.
- [15]. The case of the week 175. University Utah Medical Library. Achieved from the original on 19 May 2011.
- [16]. Nilsson IM (1994). Hemophilia—then and now. *Sydsvenskamedicin historiska sällskapets årskrift*. **31**:33-52. PMID 11640407.
- [17]. Digitised Early Papers and Books on Human and Medical Genetics. (<http://www.genmedhist.imfo/Articles%20andpapers/GeneticsandMedicineHistoricalNetwork,CardifUniversity>).
- [18]. Hemophilia Special Issue: von Willebrand Disease: a Report from a Meeting in the Aland Islands. Retrieved 22 November 2012.
- [19]. Chapter 38 Coagulation Factors V and VIII GC White and GE Gilbert (<http://books-google.com/books?id=H85dwxYTKLwC&pg=RA1195&1pg=RA-PA1195> in Blood principles and practice of hematology: 2<sup>nd</sup> edition 2003. Eds. Robert I. Handin Samuel E Lux, Thomas P, et al. ISBN 978-0-7817-1993-3.
- [20]. Micheal Price (2009). Case Closed: Famous Royals Suffered From Hemophilia. Science NOW Daily News. AAAS. Retrieved 9 October 2009.
- [21]. *In re Rhone-Poulenc Rorer Inc*, 51 F.3d 1293, 1296 (7<sup>th</sup> Cir. 1995), Project Posner. Org (<http://www.projectposner.org/case/1995/51F3d1293>). Retrieved 28 January 2008.
- [22]. Nair Preethi S, Shetty S, Ghosh K. A homozygous female hemophilia A. *Ind J Human Genet*. 2012; **18**(1):134-36.
- [23]. Konke BA, Josephson NC, Nakaya FS. Eds. Hemophilia A. Seattle (WA): University of Washington, Seattle. 1993. PMID 20301578. update 2014.
- [24]. OMIM Entry #306900-Hemophilia B: *HEMA.omim.org*. Retrieved 2016-10-07.
- [25]. <http://ghr.nlm.nih.gov/condition/hemophilia>.
- [26]. Hemophilia Overview (<http://emedicine.medscape.com/article/210104-overview>) eMedicine from webMD. Dimitrios P Agaliotis, MD, PhD, FACP, Robert A Zaiden MD, Fellow, and Saduman Ozturk, PA-C. Updated: 24 November 2009.
- [27]. Hemophilia B: Practice Essentials, Background, Pathophysiology. eMedicine. Medscape. 24 August 2016. Retrieved 7 October 2016.
- [28]. Factor IX Deficiency: Background, Pathophysiology, Epidemiology. eMedicine. Medscape. 24 August 2016. Retrieved 7 October 2016.
- [29]. Types of Bleeds (<http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=191&contentid=382&rpname=bleeding>). National Hemophilia Federation.
- [30]. Hemophilia Overview (<http://emedicine.medscape.com/article/210104-overview>) eMedicine from webMD. Dimitrios P Agaliotis, MD, PhD, FACP, Robert A Zaiden, MD, Fellow, and Saduman Ozturk, PA-C. Updated: 24 November 2009.
- [31]. Hemophilia Complications (<http://www.myoclinic.com/health/hemophilia/DS00218/DSECTION=complications>) Myoclinic Staff. 16 May 2009.
- [32]. Rodriguez-Merchan, E. Carlos. Musculoskeleton Complications of Hemophilia. Retrieved 4 April 2014.
- [33]. Valentino LA, Hakobyan N, Rodriguez N, et al. Pathogenesis of hemophilic synovitis: experimental studies on blood-induced joint damage. *Hemophilia*. 2007; **13** Suppl 3:10-3.
- [34]. eMedicine-Hemophilia C: Article by Prasad Mathew, MBBS, DCH (<http://www.emedicine.com/ped/topic964.htm>).
- [35]. Gomes K, Bolton Maggs P. Factor XI deficiency. *Hemophilia*. 2008; **14**(6):1183-1189.
- [36]. Seligshn U. Factor XI deficiency in humans. *J Thromb Hemos*. 2009; **7**:84-87.
- [37]. Konke BA, Josephson NC, Nakaya FS (1 January 1993) Hemophilia B. GeneReview® University of Washington, Seattle. Retrieved 7 October 2016 update 2014.
- [38]. Von Willebrand's Disease. About von Willebrand's Patient. Patient. Retrieved 2016-07-08.
- [39]. Hemophilia A (Factor VIII deficiency) information Patient. Patient. Retrieved 24 June 2016.
- [40]. How is Hemophilia Treated. *NHLBI*. July 13, 2013. Retrieved 10 September 2016.
- [41]. Manco Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episode treatment to prevent joint disease in boys with severe hemophilia. *NEngl J Med*. 2007; **357**(6):535-544.
- [42]. Roosendaal G, Lafeber F. Prophylactic treatment for prevention of joint disease in hemophilia—cost versus benefit. *NEngl J Med*. 2007; **357**(6):603-05.
- [43]. How to Deal With Hemophilia. ([http://kidshealth.org/kidhealth\\_problems/blood/hemophilia.html](http://kidshealth.org/kidhealth_problems/blood/hemophilia.html)) Reviewed by: Larissa Hirsch MD 2007. kidshealth.org by Nemours. Retrieved 23 January 2010.
- [44]. World Federation of Hemophilia ([http://www.wfh.org/en/page.aspx?pid=637#Life\\_expectancy](http://www.wfh.org/en/page.aspx?pid=637#Life_expectancy)) Frequently Asked Questions. 2005..