Hemophilia Disorders

Definition of Disease

Hemophilia (pronounced ‘hee-moe-FEE-lee-uh’) is a group of inherited bleeding disorders caused by lack of protein factors needed for normal blood clotting action. These proteins interact with platelets to cause clotting, thus prolonged and often devastating bleeding occurs. There are two types, Hemophilia A and B, with no known cure.

Brief History

Documentation of a severe bleeding disorder of the male population occurred in the Babylonian Talmud approximately 2,000 years ago. Male infants from families where a male had previously died from circumcision were exempted from the religious ceremony. The term ‘Hemophilia’ first appeared in medical literature in 1828 in Zurich, Switzerland, and soon became known as the “Royal Disease” (hemophilia.org), as it was promulgated through Queen Victoria of England’s descendants, and throughout royal families all over Europe and Russia. The most famous royal with Hemophilia was Alexei Romanov, an heir to the Russian throne in the early 1900s. Until the cause of hemophilia was discovered, it was thought that hemophilia was caused by fragile blood vessels. By the 1930s to 1940s, physicians had discovered they could remedy hemophilia with plasma without platelets, which led to isolating the different clotting factor deficiencies that were named Hemophilia A and B. Through the early 1960s, treatment for hemophilia consisted of icing joints and areas of bleeding, and with transfusion of whole blood or plasma if needed. Death was common from internal bleeding, with chronic pain and grave disability prevalent due to severe joint damage. Through the 1980s, extensive exposure to blood products rendered many hemophiliacs Hepatitis C+ and HIV+. Since then, many scientific advances have made factor replacement much simpler and safer. Currently, most patients can live more normal lives with much less risk of disability.

Detailed pathophysiology at cellular, tissue, organ, and system levels.

Human blood clotting is a remarkably complex process involving many participant chemicals. When bleeding or tissue injury occurs, platelets congregate at the site and form a platelet plug, which is a temporizing measure until the stronger fibrin clot can be formed. Once platelets congregate, tissue factors are released and many substances act on others to lead to bleeding cessation. Factors VIII and IX participate in the middle portion of the intrinsic clotting pathway and are required in order to form a stable fibrin clot. Factor VIII & IX are required to convert factor X into Factor Xa, which then accelerates converting Prothrombin to Thrombin. Thrombin is then responsible to activate Fibrinogen and convert it into Fibrin. Lack of either Factor VIII or IX will interrupt this mechanism, and cause an incomplete or incompetent fibrin plug to form at the site of bleeding/tissue injury. Thus, slow bleeding or oozing continues. The organ systems involved most generally involve joints, but bleeding can occur anywhere, including internally and intra-cranially. Sequelae from bleeding into the joints or muscles cause most of the pain and disability associated with hemophilia. Blood is heavy, loaded with iron, and takes a great deal of time to be removed from tissue and joints, which interrupts normal function. Many patients can have iron staining in the skin over muscles and joints from chronic bleeding.

Genetics

There are 2 main hemophilia disorders: A and B. They are largely inherited as sex-linked, autosomal recessive genetic disorders. However, in 30% of cases, hemophilia is related to spontaneously occurring genetic mutations. Hemophilia only affects males, and women are the carriers, as the genetic defect occurs on the X chromosome. The sons of a male with Hemophilia A or B are not affected, but his daughters will be obligate carriers. Women carry the disease on 50% of their X chromosomes, so the disease manifests in males, due to passing an affected x-chromosome to the child. Statistically, a female carrier can expect 50% of her male offspring to have Hemophilia, and 50% of her daughter to be carriers. Approximately 10% of carrier females have less than normal factor levels, and can manifest a mild case of the condition, which becomes apparent with heavy menstruation, childbirth, surgery or a tooth extraction. There is currently no cure for Hemophilia. Researchers are striving to find a genetic cure. The genetic mutation that causes Hemophilia is on the F8 gene for Hemophilia A and the F9 gene for Hemophilia B. The instructions for making the proteins Factor VIII and Factor IX are on genes F8 and F9, respectively. They are attributed to two types of defects: “gene deletions and point mutations” (McCance, 2010, p. 1079). These mutations serve to produce a reduced amount of these vital coagulation proteins. Hemophilia A is the most common, with severity depending on the amount of circulating Factor VIII a patient has. It is commonly known as Factor VIII deficiency or classic hemophilia. Hemophilia B, or Factor IX deficiency, is also known as “Christmas disease,” and is caused by a deficiency of factor IX. Acquired hemophilia is rare and not due to genetics. It develops due to an illness wherein the body makes auto-antibodies that inhibit clotting factors from working normally. Some cases are attributed to pregnancy, cancer, drug reactions, or immunological problems. In others, the cause remains unknown. A third type, Hemophilia C, was discovered later and is a separate disease that is autosomal dominant and occurs equally in males and females. It is a deficiency of Factor XI, and bleeding is usually less severe than Hemophilia A or B (McCance, 2010, p. 1079). It is not discussed herein.

Epidemiology

1. The occurrence of the Hemophilia A & B vary worldwide:

    A. Hemophilia A = 1 in 5,000 to 10,000 males worldwide
    B. Hemophilia B = 1 in approx 30,000 to 50,000 males worldwide
    C. Males are exclusively affected due to X-linked inheritance; however, the rare female cases that occur are linked to “lyonization (random inactivation of the normal X chromosome), homozygosity, mosaicism, or Turner syndrome” (online.epocrates.com).

2. There are approximately 400 hemophiliac births annually in the US.
3. Both occur in all races and socio-economic strata.
4. The condition has equal worldwide prevalence.
5. 33% of infants born with hemophilia have no known family history, and it occurs as a spontaneous genetic mutation.

Disease described

Hemophilia A and B are disorders that can remain dormant for long periods of time in that no symptoms are present if there is no bleeding. It occurs due to injury / trauma or surgery in the milder forms, and can present spontaneously in moderate to severely factor-deficient patients. It responds immediately to infused factor products that correct the factor deficiency. The long-term sequelae are related to the area of the body where bleeding is experienced, and is dependent on the amount of blood in the affected tissue or joint. While the bleeding can be stopped with factor, the pain and tissue damage from bleeding take much longer to resolve. Patients with blood product exposures that have led to Hepatitis C or HIV/AIDS have additional problems.

Sign and Symptoms

Signs and symptoms are identical for Hemophilia A and B, and are directly related to the site and severity of bleeding. There are virtually no outward signs that an individual has hemophilia, until they bleed excessively. Hemophilia presents as excessive and/or prolonged bleeding, either spontaneously or in relation to and injury or surgery. The symptoms are generally isolated to the specific site of bleeding initiation or injury. Long-term damage to the joints is the most common clinical manifestation for hemophiliacs. In the case of muscle bleeds, distention of the tissue can put pressure on nerves and joints causing additional symptomatic pain and loss of movement.

Diagnosis

Hemophilia A and Hemophilia B are the same in terms of bleeding and approach to diagnosis. Diagnosis is initiated by testing related to genetic expectation, or suspicion created by severity or length of a bleeding episode. Determining the factor assays (quantity of factor found in the blood) makes the diagnosis. This difference is significant because it determines which type of factor is needed for treatment. Several other blood tests are helpful: 1) the activated partial thromboplastin time (aPTT) is prolonged in moderate and severe Hemophiliacs; and often normal for mild factor deficient patients; 2) Prothrombin time (PT) is usually normal, but always part of the testing regime; 3) a Fibrinogen Test is done, which helps determine the patient’s clot-forming ability. This test is generally ordered when the aPTT is abnormal; and, sometimes, 4) a bleeding time, which determines how long it takes for the blood to clot.
Diagnosis includes assessing the level of Hemophilia, determined by amount of factor found in blood. Testing factor levels can also be detected in utero. Normal Factor VIII and IX levels vary from 50% to 150%. There are three main categories of Hemophilia A or B:

Mild -- These patients will have 6% to 49% (Hemophilia A) or 5% to 30% (Hemophilia B) of the normal amount of factor VIII or IX, respectively. Patients with levels on the higher end of this will often not be diagnosed until they experience injury or surgery with resultant excessive bleeding.
Moderate -- These patients have 1% to 5% of the normal amount of factor VIII. They make up 15% of hemophiliacs. They have significant bleeding episodes with injury and can have spontaneous (non-injury related) bleeds as well.
Severe -- This group consists of 60% of hemophiliacs, and they have <1% Factor VIII. These patients have serious and frequent muscle and joint bleeds. Many patients must be maintained on daily infusions of factor to prevent bleeding; or will pre-treat before activities likely to cause bleeding.

While factor levels determine category diagnosis, it is important to note that symptom severity is somewhat variable between levels. Some patients with mild hemophilia can have bleeding more frequently as per the moderate level of Factor deficiency (nhlbi.nih.org; hemophilia.org). Since severe hemophilia generally causes serious bleeding in infants, it tends to be diagnosed in the first twelve months of life. Milder forms are usually detected by age 6.

Treatment

Treatment for both types of Hemophilia consists of factor replacement; factor VIII for Hemophilia A and factor IX for Hemophilia B, which are given intravenously to allow normal clotting. Treatment is generally given as needed for bleeding. The amount of factor given depends on the patient’s normal factor level and the severity and location of

bleeding. Repeated infusions are required over days to weeks depending on location and severity of bleeding. Some patients receive prophylactic intravenous factor infusions for certain activities, or if they have a severe factor deficiency. Gradually decreasing doses are administered following surgeries. Clotting factor concentrates can be made from human blood, with the blood being treated to prevent the spread of diseases, such as hepatitis. Current blood bank methods significantly reduce the risk of getting an infectious disease from factor replacement. Additionally, there are recombinant or synthetic factors that completely eliminate that risk. Many patients can self-infuse synthetic factor at home, with monitoring by local or regional hemophilia centers. In the event of acute injury, serious trauma or large-scale bleeding, Emergency Room treatment is required. Synthetic, recombinant factor remains the most common treatment for Hemophilia today. Some patients are able to use Desmopressin (DDAVP) as a slow IV infusion as part of their treatment protocol. DDAVP causes the release of the body's own stored clotting factor to inhibit bleeding. DDAVP can be administered by nasal spray for those patients that respond to it (genome.gov). In addition to factor replacement, Amicar is used for dental procedures. Amicar is an anti-fibrinolytic which prevents the chemicals in saliva from breaking down the needed clotting in the mouth.

Links to evidence based practice or reliable websites

1. Centers for Disease Control --

    A. Hemophilia facts: http://www.cdc.gov/ncbddd/hemophilia/facts.html
    B. Hemophilia diagnosis: http://www.cdc.gov/ncbddd/hemophilia/diagnosis.html

2. National Hemophilia Foundation:

    A. Hemophilia A: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=179& content id=45&rptname=bleeding
    B. Hemophilia B: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx? menuid=181&contentid=46&rptname=bleeding

3. National Heart, Lung, and Blood Institute: https://www.nhlbi.nih.gov/health/health-topics/topics/hemophilia/treatment.html
4. Hemophilia Treatment Centers: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx? menuid=203&contentid=385

Related current articles

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