Why Are Humans Vulnerable To Hemophilia?

Hemophilia is a bleeding disorder that is argued to have first appeared in the second century A.D. though others will contest that it can be traced further back to ancient Egypt (Castro, Briceño, Casas, & Rueda, 2014). Despite having been around for centuries, it rose to public attention as the royal disease since Queen Victoria of England was a carrier for hemophilia B and through marriage the disease entered the royal family lines in Germany, Spain, and Russia (Franchini & Mannucci, 2012). Hemophilia affects all ethnicities and is heritable, although “30-33% of the new diagnosed cases of the current X-linked disorder show no family history” (Mansouritorghabeh, 2015). Hemophilia is caused by mutations in the factor VIII (FVIII) and factor IX (FIX) genes on the x-chromosome (Franchini & Mannucci, 2014), which are responsible for making the proteins known as coagulation factors VIII and IX (F8 gene, 2015). It is relatively rare for females to have hemophilia, since females have two x-chromosomes, and if one chromosome has the mutation, there is still a normally functioning chromosome to counteract it. Females with the mutation are commonly carriers. Only if the father has hemophilia and the mother is a carrier will the daughter have hemophilia (How do you get hemophilia?, 2012). Sons have a 50% chance of acquiring hemophilia if their mother is a carrier. There are two variations of hemophilia, hemophilia A and hemophilia B, which are further classified by severity into severe, moderate, and mild depending on the percentage of clotting factor in the blood (Franchini & Mannucci, 2014). “Data collected by the World Federation of Haemophilia indicate that persons with hemophilia rarely live beyond childhood in developing countries” (Peyvandi, 2005). Yet even with the higher death rate for people with hemophilia, the gene mutation continues to exist. For some reason, natural selection has not weeded out the
mutation. This essay discusses the mechanisms, ontogeny, and phylogeny of the blood coagulation system and its factors that contribute to hemophilia before exploring possibilities of why the mutation persists.

Hemophilia is quite variable, from its level of severity to the way that the disorder arises. The severity of hemophilia is determined by how active the clotting factor VIII or IX is (Castro et al., 2014). Mild hemophilia is characterized by 5-40% clotting factor activity, moderate hemophilia is 1-5% activity, and severe hemophilia has less than 1% of activity (Castro et al., 2014). Symptoms of severe hemophilia include impromptu bleeding into muscles, joints, and organs (Antonarakis et al., 1995). More visible symptoms include nosebleeds, excessive bleeding from small cuts, bruises, and blood mixed in with urine (“What Are the Signs and Symptoms of Hemophilia?”, 2013). Hemophiliacs with moderate severity experience bleeding after minor trauma and hemophiliacs with mild severity show symptoms after severe trauma (Antonarakis et al., 1995). Hemophilia A and B are differentiated by the clotting factor that is reduced. Not enough of clotting factor VIII causes hemophilia A and not enough of clotting factor IX leads to hemophilia B (Scott & Lozier, 2012). Comparative studies “suggest that hemophilia B is a less severe disease than hemophilia A” (Melchiorre et al., 2015). Hemophilia B is also rarer than hemophilia A, with 1 in 50,000 being born with hemophilia B in contrast to the 1 in 10,000 born having hemophilia A (How do you get hemophilia?, 2012).

Factor VIII and factor IX are part of the body’s coagulation system, which regulates the formation of clots to stop bleeding (Palta, Saroa, & Palta, 2014). There are two processes in blood coagulation, known as the extrinsic and intrinsic pathways. The extrinsic pathway has two steps and begins with tissue factor combining with the coagulant factor VII to form a unit which then activates FX and FIX (Giuseppe, Franchini, Montagnana, & Favaloro, 2012). Once FX is activated, it combines with activated FV and becomes prothrombinase. Activated FIX combines with activated FVIII to make tenase. Prothrombinase and tenase are necessary for changing
prothrombin into thrombin. Thrombin is responsible for the conversion of fibrinogen to fibrin, which is what forms a clot. In this first step, very little thrombin is created. The second step is necessary for forming enough fibrin to build a strong clot to stop the bleeding. It begins when thrombin starts what is known as the coagulation cascade, where the coagulant factors activate in a chain reaction (Giuseppe et al., 2012). Insufficient quantities of the proteins in the intrinsic pathway have little to no causation of bleeding disorders, leading to the belief that the intrinsic pathway is a small part of hemostasis and it is the extrinsic pathway that is largely responsible for coagulation (Tapper & Herwald, 2000). It is when there is a problem with the proteins in the extrinsic pathway that coagulation does not function properly. The most common mutation for people who have severe hemophilia A is an inversion in intron 22 (Peyvandi, 2005). Deletions and point mutations are also frequent causes of hemophilia. These gene mutations reduce the efficacy of the coagulation factors VIII and IX by creating “an abnormal version” of the factors or reducing “the amount of [the] protein” (F8 gene, 2015; F9 gene, 2015).

These mutations can be detected and used to diagnose hemophilia in the first trimester (Ljung, 1996). In a healthy human fetus, coagulation factors appear after ten weeks of gestation but continue to increase in concentration over time (Campbell & Bolton-Maggs, 2015). A neonate does not reach adult coagulation factor levels until they are six months old (Campbell & Bolton-Maggs, 2015). FVIII is distinct in that it reaches adult levels by the time of birth but then decreases in the following six months (Andrew et al., 1987), at least in healthy neonates. A lower than adult level of factor VIII in a newborn is another indicator, besides checking for a mutation, that the infant has hemophilia A. Hemophilia B is not as easy to predict since “Factor IX activity can be as low as 15% in a healthy term infant and does not reach normal levels until late in the first year of life” (Saxonhouse & Manco-Johnson, 2009). Despite the lower levels of most coagulant factors, there is no evidence that infants are at a greater risk of bleeding than adults (Monagle, Ignjatovic, & Savoia, 2010).
As a child ages, their coagulation proteins change. One example is fibrinogen. An infant's fibrinogen has more sialic acid in it than an adult's (Monagle et al., 2010). Sialic acid is thought to be involved in “the stabilization of molecules and membranes, as well as modulating interactions with the environment” and “are reported to modulate processes involved in transmembrane signaling, fertilization, growth, and differentiation” (Varki & Schauer, 2009). The developmental changes that take place as a child ages are conjectured to be “driven by the function of coagulation proteins in other physiological systems such as angiogenesis, inflammation and wound repair” (Campbell & Bolton-Maggs, 2015).

One form of treatment for hemophilia is the injection of plasma or recombinant factor VIII or IX. A major drawback to infusion treatment is the development of inhibitors, which produce an immune response to the injected coagulant factor (AlFadhli & Nizam, 2014). Gene transfer experiments on fetal sheep have shown that the immune system of a fetus is more receptive to foreign substances and can develop tolerance to the infusions during this period of growth (Porada, Rodman, Ignacio, Atala, & Almeida-Porada, 2014). There is hope that gene therapy in utero could cure the mutated gene or at least lessen its severity.

It is not too surprising that transfusions to fix the blood coagulation system can result in an immune response, seeing as “the simultaneous activation of the inflammatory response and the coagulation system after injury is a phylogenetically ancient, adaptive response that can be traced back to the early stages of eukaryotic evolution” (Opal, 2000). The clotting of blood at an injury site is not only to prevent the organism’s insides from coming out, but also the outside from coming in. Both the immune system and clotting system are able to “recognize surface features of microbial pathogens that differ from human cell membranes. This results in the generation of a network of early host response signals that alarms the host to the presence of a potential microbial threat” (Opal, 2000). The implications of this will be explored further on after examining the evolutionary history of the coagulation system.
The coagulation system is not specific to humans, or even mammals. It is present in all vertebrates. “The 11 human coagulation factors (FG, FII-FXIII) have been identified across all vertebrates, suggesting that they emerged with the first vertebrates around 500 Ma” (Rallapalli, Orengo, Studer, & Perkins, 2014). Another study suggests factor VIII and factor IX developed “within the 50-100-million-year window between the appearance of protochordates and vertebrates” (Doolittle, 2009). A study that examined selective pressures on these proteins as they evolved showed positive selection for FVIII and FIX in mammals and for FVIII in primates (Rallapalli et al., 2014). Additionally, proteins that were positively selected were “less likely to be associated with disease-causing mutations” (Rallapalli et al., 2014). This only means that mutations were less likely to occur in positively selected proteins, not that they wouldn’t, since clearly the hemophilia mutation exists.

Doolittle (2009) speculates that the complexity of the mammalian blood clotting system is the result of “regulating the response under a wider spectrum of environments. Higher blood pressure, more complicated cardiovascular systems, higher metabolic rates, and new organs such as lungs or the placenta all introduce more challenges for maintaining the balance between liquidity and gelation.” This balance is easily disrupted if there are irregular amounts of the coagulation proteins. In regards to factor VIII, too much can be just as dangerous as too little and is “associated with increased risk of deep venous thrombosis” (Sugita et al., 2013), which in layman’s terms is a blood clot in a vein. It also impacts development. Higher than normal levels of FVIII were present in the mothers of growth-retarded babies (Scholtes, Gerretsen, & Haak, 1983). Of course, there are drawbacks to low levels of FVIII and FIX as well.

Hemophilia is not only distinguished by slow clotting times that result in a greater loss of blood. Bleeding happens inwardly, into the joints and muscles as well. Hemarthrosis, the bleeding into joints, is symptomized by “pain, inflammation, inflation, elevation of organ temperature, and motion restriction” (Mansouritorghabeh, 2015). The primary joints affected are
the wrist, elbow, ankle, and knee (Mansouritorghabeh, 2015). As the patient ages, hemarthrosis happens with less frequency, due to less physical activity. Hematoma is the bleeding into muscles and “is regarded as the major cause of disability in hemophilia” (Mansouritorghabeh, 2015). It too is associated with pain and inflammation. Joint problems as well as the risk of injury limit the degree of physical exertion a patient with hemophilia can expend. As a result, they have less bone density and are more susceptible to osteoporosis (Mansouritorghabeh, 2015). Along with hemarthrosis, hematoma, and osteoporosis, patients with hemophilia have a greater risk of hypertension and cardiac mortality (Berntorp, Mauser-Bunschoten, Jiménez-Yuste, & Spears, 2015). Instances of hypertension increase with age, and since new treatment options have extended the life expectancy of patients with hemophilia, hypertension occurs in more than 80% of patients who are 60 or older (Berntrop et al., 2015).

Despite these negatives, it is possible that mutations in the FVIII and FIX genes have persisted because they are beneficial in certain circumstances. There is already a precedent with sickle cell anaemia, where the hemoglobin β gene mutation protects the host to some degree against malaria (Rallapalli et al., 2014). Positive selection of the coagulation factors could indicate that a host-pathogen interaction occurred in our past, since traits that improve a host's fitness will be positively selected. “Positive selection for FIII and FVII is attributed to a host-pathogen interaction with the herpes virus family” (Rallapalli et al, 2014). No definitive host-pathogen interactions have been associated with FVIII or FIX yet, but it is possible that there is one since FIII and FVII, which were also positively selected, have a host-pathogen relationship. One such possible relationship is with falciparum malaria. Those who died from this type of malaria had thrombosis, which is the clotting of blood, in the kidneys and brain (Dennis, Eichelberger, Inman, & Conrad, 1967). Low levels of FVIII lead to low levels of thrombin generation and cause hemorrhaging instead of thrombosis. Perhaps mutations of FVIII persist to balance the risk of thrombosis caused by this type of malaria. Examining the effects that a
blood coagulation inhibitor had on blackwater fever “provided preliminary evidence that accelerated intravascular coagulation added to the morbidity of falciparum malaria” (Dennis et al., 1967). The faster the blood clotted, the likelier the patient was to die from this type of malaria.

The hemorrhaging that results from low FVIII activity defends against the pathogen by flushing it out of the body. Rallapalli, et al. (2014) speculated that “the coagulation system in vertebrates was under strong selective pressures, perhaps to adapt against blood-invading pathogens.” When the falciparum parasite gets into red blood cells, it will “localize specifically in the vascular beds of organs such as the brain, a process called sequestration. Sequestration aids in parasite survival by avoiding clearance by the spleen” (Francischetti, Seydel, & Monteiro, 2008). The curative properties of blood loss have been around for centuries and bloodletting was a common method up until 150 years ago for curing all types of illnesses, since an abundance of cases “unequivocally showed that most sick patients survived after a simple bloodletting” (Nickel, 2011). Pathogens can be swept out of the host through the blood, so the slower clotting time in hemophiliacs can be seen as a defense, giving more time for the pathogens to be swept out before the injury site is closed. This would only be beneficial in extreme cases, which malaria can be considered.

Another possible association is with sepsis. Sepsis is a “systemic illness caused by microbial invasion of normally sterile parts of the body” (Lever & Mackenzie, 2007). “In sepsis, toxins cause direct activation of coagulation” which forms thrombin, but in these instances, “thrombin not only produces clots, but also inhibits their removal” (Dellinger, 2003). As mentioned before, too much thrombin is dangerous. Unfortunately, sepsis is “associated with activation of both the coagulation and inflammatory cascades” which “function in a positive feedback loop” and “has the potential to lead to progressive organ dysfunction and death” (Dellinger, 2003). Current studies are exploring antithrombotic approaches to sepsis in
the hopes of increasing survival chances. The hemophilia mutation is itself antithrombotic. The low thrombin generation levels caused by the mutated FVIII or FIX genes are once again useful in counteracting the risk of thrombosis.

A final variation of hemophilia, which I did not mention before because it is too removed from the main disease, is acquired hemophilia (AHA). It is “characterized by autoantibodies directed against circulating coagulation factor (F) VIII” and patients will either have sudden bleeding symptoms or none at all (Huth-Kühne et al., 2009). Whereas the other two forms of hemophilia develop in a fetus, although they may not show symptoms until later in life, “patients with AHA are often elderly” (Huth-Kühne et al., 2009). It is interesting to note that “an underlying medical condition can be identified in up to 50% of patients, including autoimmune diseases” (Huth-Kühne et al., 2009). That percentage of correlation is too large to ignore. Although little is known about AHA, its development after a pre-existing condition, especially one that involves the immune system, could possibly be the result of a countermeasure.

More research needs to be done if we are to uncover an unequivocal relationship with a pathogen. All that can be said at this time is that the slow clotting time and reduced risk of thrombosis that is associated with hemophilia may act as a defense in certain circumstances, but these potential benefits come with their own risks.
Works Cited


