Genetic Blood and Bleeding Disorders

**What is a Genetic Blood Disorder?**

Stories of excessive or abnormal bleeding have been recorded all the way back to biblical times, such as excusing circumcision for boys who had at least two brothers that died from the procedure. In the 1800’s, papers were published about a condition that mostly affected males and that they could pass on to their daughters, who would not have symptoms. This condition was coined haemorrhaphilia, then later shortened to hemophilia. In the early 1900’s, Finnish doctor Erik von Willebrand wrote about a blood disorder that affected both sexes equally and called it pseudohemophilia, later to be called Von Willebrand Disease. Soon after, many scientific breakthroughs would happen throughout the years including treatments and the discovery of other blood disorders.

To understand how a genetic blood disorder functions, we first have to understand how any blood disease occurs. The blood in the human body is made up of many parts such as red blood cells, plasma, and white blood cells. With multiple elements in the blood, come multiple different types of blood diseases because any one of these tissues can cause its own disease if it malfunctions or is in low supply.

A genetic blood disorder is simply a blood disorder that is passed down from one generation to the next within families. They can be **autosomal**, which means that the mutated gene is located on a non-sex chromosome, or **X-linked**, referring to the X sex chromosome. Autosomal inheritance can either be dominant or recessive. A dominant trait only requires one of the pair of chromosomes to carry the gene with the mutation for the trait to present as a diseased **phenotype**, which is the physiological way a trait presents. Recessive traits however, only present if both have the mutation. An X-linked inheritance means that males are more likely to have the disease because they only have one X chromosome, so if it has the mutation the disease is presented. Females are less likely to show symptoms because with 2 X chromosomes, if one is mutated and not the other, she would be a **carrier** of the disease.

There are many different kinds of genetic blood disorders, with each separate mutation functioning in different mechanisms. In this chapter, we will discuss several genetic blood disorders and explore their cause, symptoms, diagnosis method, treatment, and prevalence.

**Section 1: Von Willebrand’s Disease**

One common hereditary blood disorder is Von Willebrand’s Disease. Also known as VWD, this autosomal disorder can be dominant or recessive depending on type, and is caused by a qualitative or quantitative deficiency in the Von Willebrand Factor. This factor is a crucial element in clotting and **coagulation** because it carries clotting **Factor VIII**. VWD can be diagnosed into 3 different types. The mildest and most common is Type 1 and it is a quantitative deficiency in the Von Willebrand Factor, or VWF. Type 2 can be divided into 4 subtypes and is a qualitative deficiency. The 4 subtypes are 2A, 2B, 2N, and 2M and each one is set apart by either their platelet dependency function or affinity to a specific clotting factor. The last and most severe is Type 3, which like Type 1 is a quantitative deficiency, but to a much greater extent. Each type and subtype contains a specific **multimer** pattern that is different from a person without VWD.

Symptoms and Diagnosis

The symptoms this disorder causes a patient to have depends on the type, but generally it presents with heavy and prolonged bleeding from an injury or in some cases, spontaneous bleeding. In female patients, VWD often causes **menorrhagia**, which is heavy prolonged bleeding with menstruation. Sometimes, it can be diagnosed along with anemia, because the VWD can cause it due to the blood loss. This can result in symptoms including fatigue, lethargy, and feeling faint after standing up too fast or standing too long. These symptoms can become more frequent or severe if the patient does not eat enough. Other symptoms of VWD can include bruising easily and long lasting nosebleeds.

Von Willebrand’s Disease is typically diagnosed by a complicated multi-step process that ultimately determines if the multimer patterns in the blood are normal and if not, what is different. For the type 2 subtypes, a confirmation test using agarose **gel** **electrophoresis** distinguishes between them. However, new research is testing a new method to diagnose, which is faster and more efficient than the traditional way. Instead of needing expertise to handle multiple machines and processes, this method utilizes one piece of equipment to combine all of the tests which will save money and time.

Treatment and Prevalence

Though there is no cure, there are multiple treatment options available for VWD patients to help alleviate some of the symptoms. One is called desmopressin, which is a synthetic version of the **diuretic** drug vasopressin. Diuretics help increase blood circulation, which in turn increases VWF circulation. Another medication available is aminocaproic acid, or amicar, as it is marketed. This drug acts as an **antifibrinolytic**, which means it promotes clotting. In addition, certain oral birth controls that contain estrogen also promote clotting because they regulate menstruation in women and in some cases, can bypass it altogether by not using a placebo. Finally, in the most severe cases, replacement therapy is an option. This is a much more invasive and direct approach to treatment, which infuses VWF and Factor VIII into the bloodstream to increase levels.

Since Von Willebrand’s Disease tends to be underdiagnosed, the prevalence of this disorder is difficult to calculate. This is because many of the symptoms are not severe enough for some to cause concern and get tested, so it is much more prevalent than statistics appear. However, it is estimated that every 1 in 100 to 10,000 people are affected by VWD.

**Section 2: Hemophilia**

A similar bleeding disorder to VWD is Hemophilia. Also deficient in Factor VIII or Factor IX depending on the type, this bleeding disorder can also be acquired later in life. The type deficient in Factor VIII is Hemophilia A, sometimes called Classic Hemophilia. The other type deficient in **Factor IX** is Hemophilia B, and is often called Christmas Disease. This disorder’s inheritance pattern is X-linked, so if a male has the gene, he will have the disease and present symptoms. But for females, if only one of her sex chromosomes have the gene for it, she might not present symptoms and instead would be a carrier that can still pass on the gene while being seemingly healthy.

Symptoms and Diagnosis

The symptoms involved with this bleeding disorder are similar to those of VWD, since the causes are essentially the same. Symptoms such as bruising, frequent and prolonged nosebleeds, and excessive bleeding with injury present with both bleeding disorders. However, Hemophilia symptoms also include bleeding into joints which can cause pain and **edema**, which is swelling, as well as blood in urine or stool and bleeding after shots. And similarly to VWD, the severity of symptoms depends on the severity of clotting factor deficiency.

Oftentimes patients with Hemophilia will have their sons tested for the disease shortly after birth because of the inheritance mechanism. But sometimes newborns will present with Hemophilia symptoms when none of the family members have the disease due to a new mutation, so doctors will also test for it then. The diagnostic process is similar to that of VWD, and involves certain blood tests to determine clotting efficiency. If the results are not normal levels, clotting factor tests are performed to determine what the issue is and what type.

Treatment and Prevalence

The most effective treatment for Hemophilia is replacement therapy, such as the previously discussed method used for VWD. Because these infusions need to be administered frequently to make a significant difference, patients can learn how to do it themselves, rather than going to a doctor every time. Though some of the treatment options for VWD other than replacement therapy may also work, the severity of Hemophilia typically is worse than that of Von Willebrand’s Disease, so the more direct method is more effective to treat the clotting deficiencies.

Hemophilia has the potential to affect any and all racial and ethnic groups, and since it is X-linked, mostly affects males. Specifically, it occurs in 1 in every 5,000 males. In addition, Hemophilia A is much more common than Hemophilia B, with the former 4x as common than the latter.

**Section 3: Sickle Cell Anemia**

Sickle Cell Anemia, unlike the previous two disorders, is not caused by a clotting issue, but instead a form malfunction where the red blood cells are misshapen like crescents or sickles as shown in Figure 1. Normally, in a healthy person, red blood cells are round and have an indent in the center for **hemoglobin** to attach to and transport oxygen throughout the body. In Sickle Cell patients, the hemoglobin is mutated which causes the red blood cells to become distorted in shape so that it is difficult for the hemoglobin to attach. This sickle form makes the cells rigid and prone to premature breakdown. This disease is autosomal recessive, so both chromosomes in a pair must have the mutation for Sickle Cell to present.

A close up of a logo

Description automatically generatedFigure 1.

Symptoms and Diagnosis

Symptoms for Sickle Cell Anemia usually include fatigue, shortness of breath, and delayed development in children due to the low red blood cell count. The premature breakdown of cells can also cause signs of **jaundice** such as yellowing of the eyes and skin. Because of the rigidity of the sickle shape, they can form an **embolus**, which is a clot stuck in a blood vessel which causes pain and insufficient blood flow to organs. Other symptoms can include frequent infections, signs of malnutrition, and bone deformities due to the delayed and slow growth.

The main mechanism for diagnosing Sickle Cell Anemia is screening newborns using a method called **liquid** **chromatography** and/or **isoelectric** **focusing**. The former term is a form of separating components of a compound mixture such as blood using density to separate the components. The latter does a similar process, but instead uses pH to distinguish. These are all different forms of the genetic testing that determines if a person has the disease or not.

Treatment and Prevalence

There is a way to cure this disease through a bone marrow transplant. However, many patients may not be willing to go through with treatment so invasive or expensive as the surgery is, so constant symptom treatment is more common. Sickle Cell Anemia treatment usually revolves around alleviating pain, preventing a crisis, and increasing the quality of life the patient can have with the disease. Therefore, many of the medications taken are typical pain decreasing drugs such as morphine in severe cases and over-the-counter ones such as **acetaminophen**. Other treatments include antibiotics for the infections, taking special care to vaccinate including for the flu, folic acid supplements to aid in red blood cell count, and a drug called **hydroxyurea**, for severe chest pain in adults.

Sickle Cell Anemia affects people all over the world and is the most common genetic blood disorder in the U.S., and affects approximately 75,000 Americans of various ethnicities. However, Sickle Cell is more common in descendants from Africa, occurring in 1 in 500 African Americans compared to about 1 in 12,000 Hispanic Americans.

**Section 4: Thalassemia**

       The last blood disorder we will discuss in this chapter is Thalassemia. This is caused by a hemoglobin production deficiency that results in fewer red blood cells. This also decreases the amount of oxygen in the blood which alone can cause other problems. There are two different types of this disease, which are alpha thalassemia and beta thalassemia. The difference between the two is based on which subunit of the hemoglobin protein the mutation is located in. The alpha subunit is composed of HBA1 and HBA2 genes, so if the mutation is on one of these, it will cause alpha thalassemia. Alternately for the beta subunit, the mutation would be located on the HBB gene to cause beta thalassemia.

Symptoms and Diagnosis

The type and severity of Thalassemia determine what symptoms occur in a patient, if any. With a minor alpha type, the patient would experience small red blood cells, a mild form of anemia, or no symptoms at all. Similar symptoms would present with a minor beta type, as well as symptoms of iron-deficient anemia, with normal iron levels. However, with a major alpha or beta type, the anemia can be much more severe and life threatening, and can also cause other health problems especially if not treated properly.

A Thalassemia diagnosis comes from genetic testing for abnormalities in the HBA1, HBA2, and HBB genes. It involves a series of blood tests including a complete blood count, or CBC, and iron count to distinguish from iron-deficient anemia. This method can diagnose postnatally and prenatally. In addition to testing specifically for the disease, the method can also be used to diagnose carriers for known at-risk family members. However, this is only possible if the specific mutation in the family is known, so it can be searched for.

Treatment and Prevalence

Similarly to Sickle Cell Anemia, Thalassemia can be cured using a bone marrow transplant if caught early enough, even though it is more invasive and expensive than constant treatment. In addition, folic acid supplements increase red blood cell count for both diseases successfully. Thalassemia treatments typically include blood transfusions for more severe cases and **chelation** therapy with an iron-binding agent. The latter treatment is a pill taken daily along with a liquid medicine taken sub dermally to prevent the iron buildup that occurs due to the blood transfusions. Lastly, new research being done involves the possibility of inserting healthy hemoglobin genes into stem cells in bone marrow for another treatment option or a cure.

Thalassemia is most common in people of Italian, Greek, Middle Eastern, Southern Asian, and African descent, so in the melting pot of the U.S., it has the potential to be very prevalent in America.

**Concept Check!**

Check your understanding of the previously discussed disorders by going through Table 1!

Table 1

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | VWD | Hemophilia | Sickle Cell Anemia | Thalassemia |
| Deficiency | VWF, clotting Factor VIII | Clotting Factor VIII, IX | Hemoglobin, oxygen | RBC’s, hemoglobin |
| Heredity | Autosomal dominant or recessive | X-linked | Autosomal recessive | Autosomal recessive |
| Fatigue as a symptom? | possibly | No | Yes | Yes |
| Pain as a symptom? | No | Possibly | Yes | Yes |
| Able to be acquired? | Yes | Yes | No | No |

Tab

**Vocabulary Words:**

* Autosomal
* X-linked
* Phenotype
* Carrier
* Coagulation
* Factor VIII
* Multimer
* Menorrhagia
* Gel Electrophoresis
* Diuretic
* Antifibrinolytic
* Factor IX
* Edema
* Hemoglobin
* Jaundice
* Embolus
* Liquid Chromatography
* Isoelectric Focusing
* Acetaminophen
* Hydroxyurea
* Chelation

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