3.1.3

Inherited (Primary) Disorders NOT Involving Platelets

Hemophilia A and B

Hemophilia is a condition where affected individuals have an impaired ability to form fibrin clots through the clotting cascade. Hemophilia A occurs due to a gene mutation that results in a deficiency in clotting factor VIII. If a person is born with one mutated gene and a second normal gene, they can generally produce adequate amounts of factor VIII. However, hemophilia A is X linked, which means that the gene for factor VIII is on the X chromosome. Since males only have one X chromosome, they are at much greater risk of expressing this disease because they don't receive a second X chromosome that might have a normal gene. Females have two X chromosomes and can frequently be carriers of the condition but won't manifest the disease unless they inherit a mutated gene from both their mother and their father.

Hemophilia B is similar to type A except that the mutation produces a deficiency in factor IX. The factor IX gene is also on the X chromosome and so hemophilia B is also X linked and seen mostly in males.

There is no cure for hemophilia. The disease must be managed by replacing the deficient clotting factor (VIII for A and IX for B). These factors are delivered by injection or IV when bleeding occurs or if bleeding is expected to occur (such as with a surgery). It is possible to treat patients prophylactically with daily injections of the necessary clotting factor, but the cost is excessive for most patients.

It is not uncommon for spontaneous bleeding to occur in and around joints as part of the trauma of everyday living in those who have hemophilia. Individuals with this disease often have early onset of joint destruction and the need for reconstruction.

Factor V Deficiency

Factor V deficiency occurs when a patient is predisposed to hemorrhage because they do not have enough factor V. This condition results in symptoms of a mild hemophilia. There are many variants of this condition but all are related to mutations of the factor V protein that affect its availability or function. Treatment for factor V deficiency is usually only necessary if a severe bleed occurs. Small day to day bleeds can generally clot even though it does take longer than normal to do so. If a severe bleed does occur, fresh frozen plasma from a donor can be used. Upon administration, it will provide factor V to the recipient.

Factor V Leiden

There is one type of mutation to the factor V protein that does not affect its function but does render it difficult to be broken down by Protein C. In this case, an opposite problem occurs than with factor V deficiency. The inability to break down factor V leaves excessive amounts of it in circulation which contributes to a relatively hypercoagulable state of the blood. Individuals with this condition do not generally receive any ongoing treatment. However, they may be at increased risk of blood clots throughout their life and they may be given anticoagulant drugs when they are involved in things that tend to increase clotting risk (such as surgery or systemic trauma). This condition is commonly called factor V Leiden disease because it was discovered in a Dutch city named Leiden.

Prothrombin Thrombophilia

In this condition, mutations in the prothrombin gene cause prothrombin to be overproduced. This leads to a hypercoagulable state that seems to be manifested most often by the onset of an insidious deep vein thrombosis (DVT) and possible pulmonary embolism (PE).

Hyperhomocysteinemia

Homocysteine is a naturally occurring amino acid produced in the body. Hyperhomocysteinemia occurs when homocysteine levels become excessively high. One reason for this is a genetic mutation where a person is missing a functional enzyme that can convert homocysteine to methionine. This condition can also be acquired as it may be found with some nutritional deficiencies (such as low vitamin B-12 or folic acid). Homocysteine at high levels tends to cause blood vessel damage and lead to clot risk. This damage is a product of the ability of homocysteine to contribute to free radical generation and diminish NO production.

Vascular Disorders

Vascular disorders can be very harmful because they may cause bleeding. **Hemorrhagic telangiectasia** is a vascular disorder characterized by malformations of various blood vessels that can potentially result in bleeding. This condition is an autosomal dominant trait and can result in life threatening arterial venous malformations (AVM) in the brain. There are other inherited diseases that influence connective tissue in the body and sometimes these connective tissue mutations affect surface tissue of blood vessels and can weaken them. **Ehlers-Danlos syndrome** can affect connective tissue and is known to be common in people who are excessively flexible. Some patients with Ehlers-Danlos can bruise more easily as blood vessel strength is diminished.