Sickle Cell Disease And Thalassemia

Introduction:

Sickle Cell Disease, abbreviated as (SCD), are part of genetically inherited blood disorders that causes the body to produce abnormal Hemoglobin beta chains, while Thalassemia are a group of inherited genetic blood disorders that causes decreased Hemoglobin production. These two diseases can cause many complications and problems in the human body due to their effect on blood flow, oxygen and nutrients delivery, which can lead to damage and injuries in multiple different organs such as the brain and the heart, and they are increasing in numbers especially in Africa and the Middle East. This report will talk about what causes the Sickle Cell Disease, how it is inherited from the parents, its clinical presentations, symptoms, complications and the reasons behind them, what organs it affects and how these organs are affected, the appropriate way to treat a pregnant woman with SCD during labor. We will also talk about the different types of Hemoglobin during the human development cycle, and the disease variants of Hemoglobin, as well as the types and subtypes of Thalassemia and their effect on Hemoglobin Production.

Details:

Inheritance Map of SCD: Sickle Cell Disease results from a mutation in the sixth position of the DNA coding for the ?-globin chain in chromosome 11, which leads to an amino acid change from glutamic acid (codon GAG) to valine acid (codon GTG), and the abnormal ?-globin chain will form instead of the normal ?-globin chain found in normal Hemoglobin, which is different in configuration and makes the red blood cells develop into the sickle cell shape. And if both of the ?-globin chain genes are affected, a form of SCD known as Sickle Cell Anemia will form. because Sickle Cell Disease is autosomal recessive, a person must inherit two copies of the abnormal gene, one from each parent, in order to have SCD and its symptoms, if a person inherits only one copy of the abnormal gene, then they will be a Carrier of the disease, also known as having a “Sickle Trait”, and will not have any symptoms but they will have some sickle-shaped red blood cells.

If the parents are both normal, then all of the children will be normal. If only one of the parents is a Carrier, then ½ of the Children will be Carriers and ½ will be normal. If only one of the parents has SCD, then all of the Children will be carriers. If both of the parents are carriers of SCD, then ½ of the Children will be Carriers, ¼ will have SCD and ¼ will be normal. If one of the parents is a Carrier and the other has SCD, then ½ of the Children will have SCD and ½ will be Carriers. If both of the parents have SCD, then all of the Children will have SCD.

Clinical Presentations of SCD:

Sickle Cell Disorders can be classified into 2 types, Symptomatic Sickle Cell Disease and Asymptomatic Sickle Cell Trait who are the carriers and usually have no symptoms and increased resistance to Malaria infections. Sickle Cell Disease has a wide variety of symptoms but they do not show up until the age of 4-6 months old because of the dominant Hemoglobin F during that age while adults have very little of it and have Hemoglobin A and A2. The severity of SCD changes over time and is different for every person.

Early childhood symptoms include dactylitis, which is a painful swelling of the digits, characterized by “sausage shape digits”, but it can also affect the hands and feet, it occurs because blood flow is easily blocked in these small bones. Sickle Cell Anemia can result in the destruction of healthy Red Blood Cells, and when the body lacks enough of them, it can lead to Fatigue, Weakness, Tiredness and Pain. Delayed Growth and Puberty may also result if the Red Blood Cells are not able to supply the body with adequate amounts of Nutrients and Oxygen needed for growth. Bacterial Infections especially by Encapsulated Bacteria Types can occur if the Sickle Cells damage the Spleen and its functions. A condition of yellowing of the Skin and White of the Eye known as Jaundice can occur due to a yellow-orange bile pigment called bilirubin that results from the frequent breakdown of Red Blood Cells due to the shorter Red Blood Cell lifespan in Sickle Cell Anemia.

There are also many other complications and types of crisis caused by SCDs, the term “Sickle Cell Crisis” can be used to refer to them, they generally last between 5 to 7 days. Vaso-Occlusive Crisis is one of the most common symptoms of SCDs, the severity and management of it varies a lot, it happens due to obstruction of circulation in blood vessels by sickled Red Blood Cells and can cause pain, necrosis, ischemia, injury and organ damage. The Spleen is frequently affected by Splenic Sequestration Crisis in SCD, a large volume of blood accumulates in the Spleen and causes it to become enlarged and painful, and after repeated exposure the Spleen can become scarred, damaged and not as effective for infections. Hemolytic Crisis causes lower Hemoglobin levels in the blood because of the rapid breakdown of the Sickled misshapen Red Blood Cells due to their decreased lifespan from the normal healthy 90-120 days to 10-20 days. Acute Chest Syndrome can be defined by many symptoms including Chest Pain, Fever and Breathing Difficulty, it happens as a result of lower oxygen levels in the lung due to sickling in its blood vessels and damage of the lung tissue.

Organs Affected in SCD:

any major body organ can be affected. A Stroke can result in the Brain if the Sickled and misshapen Red Blood Cells block any major blood vessels that supply the Brain with Oxygen and can cause severe Brain damage. The Eye’s Blood Vessels can get blocked, bleed or overgrow due to the Sickled Blood Cells and that can damage and detach the Retina which causes vision loss or impairments. Many Heart problems may result such as Ischemic Heart Disease if the Heart does not get enough blood, oxygen and is stressed to pump blood, this can cause damage to the blood vessels, bad circulation and high blood pressure in the Lungs due to damage in the pulmonary arteries which is a condition known as Pulmonary Hypertension. Sickling in the Bones and Joints can raise complications due to decreased oxygen flow and results in avascular or aseptic necrosis.

Men can get Priapism, a prolonged erection of the penis due to blocked blood flow out of the penis by Sickled Blood Cells. Women with Sickle Cell Disease have an increased risk for blood clots, high blood pressure and pregnancy related complications such as miscarriages and low birth weight babies.

Dealing with an SCD Women in Labor:

normally, Women lose blood during labor but in the case of Sickle Cell Disease, extra care is needed in case if the hemoglobin levels drop below the normal baseline levels. unless if there

are any obstetric contraindications or fetal complications, pregnancy should be allowed to progress normally through spontaneous labor and normal vaginal delivery, the woman needs to be kept warm and should be given the adequate fluids and oxygen. And the fetus should be monitored during this period. Analgesia should be prepared specifically to the woman taking into account her usual Analgesia plan in case of Acute Sickle Cell Crisis Pain as well as the degree of opioid tolerance from past exposures. Pethidine increases risk of fits and should be avoided for women with SCD. Prior to caesarean section, Blood Transfusion is not recommended unless if the hemoglobin levels drop to below 70g/l or drops more than 20 g/l from the patient's baseline, then this option should be considered. If the patient has red cell alloantibodies, then blood should be cross-matched early, in anticipation of the requirement.

After Labor, the patient is recommended to maintain adequate hydration, oxygenation and analgesia and should have daily medical assessment by the hematology team, especially for the chest because the risk of acute chest crisis is high during this period, Blood Transfusion for several months might also be required after delivery if the patient needed Blood Transfusion during labor especially if she had recurrent painful crisis during labor.

Types of Hemoglobin:

normal human development shows several different variants of Hemoglobin, abbreviated as (Hb), over time, there are 7 normal variants through the normal human development cycle, the Embryo Hemoglobin types include Gower 1 (?2?2), which is composed from two zeta(?) and two epsilon(?) chains. Gower 2 (?2?2), which is composed from two alpha(?) and two epsilon(?) chains. Portland I (?2?2), which is composed from two zeta(?) and two gamma(?) chains. And Portland II (?2?2), which is composed from two zeta(?) and two beta(?) chains. Once the Embryo develops into a Fetus, a new type of Fetal Hemoglobin, Hemoglobin F (?2?2) is produced, which is composed from two alpha(?) and two gamma(?) chains. Hb F remains in the body during the fatal period of 4-6 months old, but after birth, two new adult Hemoglobin replace most Hemoglobin F, Hemoglobin A (?2?2), which is composed of two alpha(?) and two beta(?) chains, and it accounts for about 95% of the body's Hemoglobin. the second adult Hemoglobin A2 (?2?2), is composed of two alpha(?) and two delta(?) chains, and it accounts for a small 1.5-3.5% of the total body's Hemoglobin. While the Fetal Hemoglobin F is usually very low in the adult human body, it can be elevated for people with SCD or beta-thalassemia in order to decrease the effects of these diseases as Hemoglobin F is not affected by them because it has no beta chain.

Other than the normal variants, we do have some Hemoglobin Variants that cause disease, Hb H (?4), which is composed of four beta(?) chains, and Hb Barts (?4), which is composed of four gamma(?) chains, may be present in variants of ?-thalassemia. The Hb found in patients with SCD is Hb S (?2?S2), which is composed of two alpha(?) and two mutated beta(?S) chains. Carrier patients with Sickle Trait are heterozygous and have one adult gene and one SCD gene and form a variant known as Hb AS. Two variants Hb C (?2?C2) and Hb E (?2?E2) result from variation in the beta chain gene and both of them can cause a mild chronic hemolytic anemia. Hb SC is a compound heterozygous form between Hb S and Hb C. another variant of Hb Hopkins-2 results from mutations in the alpha chain genes. A variant of Hb D called Hb D-Punjab is found in the Punjab regions of India and Pakistan and China's Xinjiang region.

Types of Thalassemia:

Thalassemia are inherited genetic blood disorders that decrease hemoglobin production and it has two main types, alpha thalassemia and beta-thalassemia. Each of which has multiple different subtypes. However, there is a third less common type known as delta thalassemia.

Alpha Thalassemia involves mutations of the Hb A1 and Hb A2 genes, it is an autosomal recessive disease. Since we have two genetic loci for the alpha-globin, four alleles exist in our diploid cells, two of the alleles are maternal and come from the mother, and the other two alleles are paternal and come from the father. The severity of the ?-thalassemia depends on the number of altered alleles for the alpha globin, severity and risk increase as the number of affected alleles increase. Alpha Thalassemia decreases the production levels of alpha chains and causes excess beta(?) chains to be produced in adults and excess gamma(?) chains to be produced in newborn children which produces Hb H and Hb Barts respectively, which are not as stable as the normal Hemoglobin variants. The types of alpha thalassemia are determined by the number of affected alleles as shown in the table.

Number of missing Alleles Type of Alpha Thalassemia Symptoms

1. Silent Carrier No Symptoms
2. Alpha Thalassemia Trait Minor Anemia
3. Hb H disease Mild to Moderate Anemia
4. Hydrops Fetalis (Hb Barts) Fetal death usually at birth

Beta Thalassemia involves mutations of the Hb B genes on Chromosome 11, it is an autosomal recessive disease. We only have one genetic loci for Hb B, so only two alleles exist in our diploid cells, one is maternal and comes from the mother, one is paternal and comes from the father, the severity of ?-thalassemia is dependent on the number of altered alleles as well as the nature of the mutation. The mutated alleles have two types, one of them is called (?+) if the allele is partially functional or fully functional but produced in lower quantities. The other allele is called (?o) if there is no functional protein at all. The combination of these two mutated alleles produces the subtypes.

Genotype Type of Beta Thalassemia Symptoms

- ?o/?o ?-thalassemia Major Severe form, no Hemoglobin A
- ?+/?o or ?o/?+ ?-thalassemia Intermediate Some Hemoglobin A is made
- ?/?o or ?/?+ ?-thalassemia Minor Might be Asymptomatic

Conclusion:

Sickle Cell Disease can be identified by many symptoms but they do not show up until the age of 4-6 months old due to the dominant Hemoglobin F, early symptoms include Dactylitis due to blocked blood flow, Fatigue, Tiredness, Pain and delayed growth which results from insufficient delivery of nutrients and oxygen due to the blockage of blood flow, as well as many types of Crisis and Organ Damage due to the decreased blood flow. Blockage in Major Blood Vessels and decreased circulation can result in damage to many body organs including the Heart, Eyes, Lungs and Sickling in the Bones and Joints can cause avascular or aseptic necrosis. Pregnant Women with SCD will need extensive care, Analgesia, fetus monitoring and may need a blood transfusion during Labor. Humans have 7 normal variants of Hemoglobin during the

development including Hb A1, A2, F, Gower 1 and 2, Portland I & II, but mutations in those variants can cause disease variants such as Hb S, AS, H, C, E and D. Thalassemia has two main types, alpha and beta, their subtypes and severity of disease are determined by the amount of alleles they affect and the nature of their mutation, they both affect Hemoglobin production rates and their functions.