Sickle cell anemia: treatment and effects

Sickle cell anemia is an inherited genetic blood disorder characterized by bouts of intense pain, organ damage, infection, depleted oxygen levels and at times premature death. Although it has come to be known as a disease that affects mainly people of African decent; affliction with sickle cell anemia has also been observed in those individuals with ancestry stemming from parts of the Middle East, India, Latin America, the Mediterranean and the Caribbean. The genetic aspect of the disease is as such; one gene for the illness must be inherited from both parents for that person to be determined to have sickle cell disease. Therefore, a person with sickle cell disease has inherited one mutated copy for the trait from both of its parents. The mutated trait that leads to sickle cell disease impacts the creation of hemoglobin by the body. In a normal individual without the sickle cell trait or disease, they create hemoglobin A (HbA).

However, in persons with sickle cell disease, their bone marrow creates a form of hemoglobin called hemoglobin S (HbS). It is the creation of Hb(S) that causes the formation of abnormal red blood cells. In a healthy individual, the red blood cells are usually disc-shaped but with Hb(S), the red blood cells have a stretched out sickle shaped appearance (Figure 1). Although it has been around for hundreds of years, sickle cell anemia was only scientifically observed in the early 1900s when in 1910 Dr. James B. Herrick noted the presence of “ sickle cells” in the blood of Walter C. Noel. Further scientific study showed that the sickling of the red blood cells was related to low blood oxygen.

Major advancements into the study of sickle cell anemia were first achieved in 1949 by Dr. Linus Pauling who postulated that the hemoglobin produced

by those with sickle cell disease was abnormal and secondly by Vernon Ingram who in 1959 discovered that the difference between Hb(S) and Hb(A) was " a single amino-acid substitution in the Î²-polypeptide chain (Î²6Glu â†' Val)"(Wikipedia). Other scientists followed this line of thinking (Figure 2) and found that this switch in the Î²-polypeptide chain was due to " a substitution of thymine for adenine in the DNA codon for Glu (GAG â†' GTG). This was the first example in any species of the effects of a mutation on a protein" (ibid).

Genetics of Sickle Cell

Sickle cell anemia, like other traits such as height, hair and eye color is an inherited attribute. Both parents must be carriers of these particular traits in order to pass on copies of these genes to their offspring. In the case of sickle cell which is an inherited autosomal recessive point mutation (see Figure 3), the hemoglobin beta gene (HBB) that is located on chromosome 11p. 15. 5 is affected. The mutation that affects this gene is the direct result of a glutamate being substituted for a valine. This exchange of the Î²-globin gene occurs in the sixth codon of the HBB gene and signifies that the disorder is caused by a single mutation in the nucleotide, an A to T changeover resulting in a GAG to a GTG sequence (see Figure 4). The substitution of the glutamate for valine causes a

Figure 4change to the structure and the function of the HBB gene and causes it to produce " structurally abnormal hemoglobin (Hb), called hemoglobin S; HbS (National Center for Biotechnology)." The importance of Hb is that it serves as " an oxygen carrying protein that gives red blood cells their characteristic color" (ibid). As previously stated, " the allele responsible for causing sickle cell anemia is autosomal recessive and can be found on the

short arm of chromosome 11” (Wikipedia). This means that an individual that has been diagnosed with sickle cell disease has received both copies of the mutated gene from their parents who each carry one copy of the mutated gene.

Sickle Cell Anemia and the Malaria Influence

In understanding the genetics of sickle cell anemia, it is important to recognize the role in which the mosquito born disease malaria played in the high incidences of sickle cell trait. With the introduction of malaria into areas of sub-Saharan Africa over 4000 years ago, “ naturally occurring genetic defense mechanisms have evolved for resisting infection by malaria” (Tishkoff, 2001). One such defense has been the sickle cell trait.

How is this possible? The initial answer comes from the relationship between the two. As illustrated in figure 5, areas hit hardest by malaria, where the disease is endemic, also show a high frequency of individuals that carry the Hb(S) gene. The data also indicates that in areas where malaria occurs at a much lower rate, such as in cooler drier climates, the gene expression of the sickle hemoglobin is greatly reduced or nonexistant.

In West Africa, where malaria is so common that most children are infected with the disease, the incidences of sickle cell trait are as high as 40%. Though many suffer symptoms that are severe enough to warrant trips to the hospital, for most, the disease is not fatal. The key to their resistance is in their genes. Genes are all paired with each parent supplying one half of each pair. If either hemoglobin gene undergoes a mutation, the hemoglobin it makes will be changed. This particular mutation called the sickle cell gene

is tiny but it is enough to change the shape of the hemoglobin molecules it makes.

In areas where malaria is endemic, carriers of the Hb (S) gene have gained some resistance to malaria. This resistance results from the red blood cells that the Hb (S) carriers have. When the malaria parasite attempts to infect the red blood cells of an Hb (S) carrier, the abnormal hemoglobin present tends to sickle and this causes it to rupture. The rupturing prohibits the malaria parasite from reproducing. Due to their sickle shape, the infected cells die, are processed in the spleen and are then eliminated out of the body. “ The frequency of sickle-cell genes is around 10%. The existence of four haplotypes of sickle-type hemoglobin suggests that this mutation has emerged independently at least four times in malaria-endemic areas, further demonstrating its evolutionary advantage in such affected regions”(The Medical News).

Thus, people that had one copy of the gene were able to survive the malaria infection. They were able to grow up, get married and have children and pass the genes on to the next generation. This is selective pressure; that gene had an advantage in that particular environment for those carriers. We all have lots of small gene mutations; they mostly go unnoticed but if the environment changes, one may suddenly show unforeseen effects – both good and bad. In this case, one copy of the gene is beneficial but two can be disastrous. “ In the USA, where there is no endemic malaria, the prevalence of sickle-cell anemia among blacks is lower (about 0. 25%) than in West Africa (about 4. 0%) and is falling” (National Center for Biotechnology). As such, the sickle cell trait is gradually being selected out of that population.

Inheritance of Sickle Cell Trait/Disease

Figure 6In order to inherit the sickle cell trait one parent must be “ a carrier of the HBB, Î²-globin S mutation and the other a carrier of an HBB mutation such as Î²-thalassemia” (M. A. Bender). A person develops the disease when they receive a copy of the defective gene from both parents. An individual that is heterozygous for the trait; in which they have one mutated and one healthy allele will remain healthy, but will be able to pass on the disease to their offspring. As such, this person is referred to as a carrier. Take for example two parents who are carriers (Rr) for sickle cell trait. Were they to have a child, there is a 25 percent chance that their child will develop the disease and a 50 percent chance of that child being a carrier. These examples as well as the other statistical possibilities are depicted in Figure 6. “ Individuals that are heterozygous for the sickle cell trait have a higher fitness than either of the homozygotes. This is known as heterozygote advantage” (Brigham and Women’s Hospital). As this has remained a favorable adaptive advantage, the high prevalence of carriers in areas where malaria is still widespread brings to the forefront the reality that sickle cell disease is still pervasive in those regions.

Hemoglobin: the story of Sickle Cell

“ I had the idea in 1945 that sickle cell anemia might be a disease of the hemoglobin molecule. No one had ever suggested the idea of a molecular disease before. As soon I had this idea, I thought it must be right. From what I know of the properties of these patients I believed that this is a disease of the molecule; that if we looked at the blood of these patients we shall find

that the hemoglobin molecules are different from other people.” Linus Pauling

Figure 7. Linus Pauling. BioRichUSALinus Pauling began his research into sickle cell disease by paying particularly close attention to the role that hemoglobin played in its manifestation. Hemoglobin is an oxygen carrying protein found inside red blood cells. Pauling theorized that the hemoglobin that characterizes sickle cell disease is abnormal. His studies showed that sickle cell Hb (S) does differ from Hb (A) in that it has a lower negative charge and pH. “ In sickle cell anemia, which is a common form of sickle cell disease, hemoglobin S replaces both beta-globin subunits in hemoglobin” (Genetics Home Reference).

Further inspection into the nature of hemoglobin shows that the hemoglobin protein produced in adults is divided into four sub-units that are joined together. These grouped sub-units are known as protein chains. Two types of these protein chains exist: 1) the ‘ alpha (Î±) globin chain’ and 2) the ‘ beta (Î²) globin chain’. Hemoglobin protein is made up of two alpha globin chains and two beta globin chains. It is important to note that the genetic information used by the body to make the two hemoglobin chains can be found “ in two different hemoglobin genes located on two different chromosomes” (Barlow-Stewart, 2001). The two identical Î±-globin genes that code for Î± globin chains is located on chromosome 16.

Figure 8The Î²-globin gene codes for the beta (Î²) globin chain is located on chromosome 11 (see Figure 8). Two copies of each of these chromosomes can be found in body cells. “ Everyone therefore has four copies of the alpha

globin gene and two copies of the beta globin gene in their body cells” (ibid). According to statics posted by the World Health Organization, it is estimated that five percent of adults are carriers for a hemoglobin condition with approximately 2. 3% of that number accounting for those adults diagnosed with sickle cell disease. Interestingly enough, there is a correlation between a person’s ancestry and the influence it has on the likelihood of that person being a genetic carrier for a hemoglobin condition such as sickle cell anemia.

Detection and Treatment

Detection of sickle cell disease can take place in one of two ways – amniocentesis and blood testing. Blood testing on newborns is now conducted in more than 40 states. The use of pre-implantation genetic diagnosis (PGD) is also being utilized to help those parents that are undergoing in vitro fertilization and are also carriers of the sickle cell trait identify those embryos that have the defective sickle cell hemoglobin. In so doing, this allows the parents to choose only to implant those embryos that are free of the defect. The treatment of sickle cell disease has taken on the form of prescribing hydroxyurea, an antitumor drug that aids in the creation of fetal hemoglobin. Increased production of fetal hemoglobin helps to prevent the hemoglobin from sickling. New therapies have begun to be developed to treat sickle cell disease at the genetic level. Since December 2001, scientists have conducted research into looking at curing sickle cell disease by correcting the defective hemoglobin; further testing needs to occur to determine the effectiveness of these genetic treatments.

Conclusion

Sickle cell is a uniquely fascinating disease in that it is one of a few genetic abnormalities that actually have a positive effect: it can be immensely beneficial protecting its carriers from facing the full brunt of the malicious malaria virus, as it renders the cells the virus invades as inhospitable. On the other end of the spectrum, however, it can also be a devastating affliction that leaves its victims with lives marked by constant pain crises and frequent stays in hospitals. Unfortunately, for those suffering from particularly severe sickle cell disease, there is no guaranteed cure for it, but there are potential treatments that scientists are researching to determine their plausibility.