

Sickle Cell Disease with Special Emphasis to African Americans: An Overview

Sunny Mandal¹, Sudhish Mishra² and Prabir K Mandal^{3*}

¹Department of Cell Biology, Microbiology, and Molecular Biology, College of Arts and Sciences, University of South Florida, 4202 East Fowler Avenue, Tampa, FL 33620, USA

²Translational Science and Molecular Medicine, Michigan State University, Grand Rapids, MI 48202, USA

³Biology Program, Edward Waters College, Jacksonville, FL 32224, USA

*Corresponding author: Prabir K Mandal, Professor, Biology Program, Edward Waters College, Jacksonville, FL 32224, USA, Tel: +904-470-8091; Fax: +904-470-8047; E-mail: prabir.mandal0807@ewc.edu

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Introduction

September is sickle cell awareness month which dictated us to write an overview. The term Sickle Cell Disease (SCD) describes a group of inherited red blood cell (erythrocytes) disorders. People with SCD have abnormal haemoglobin, called haemoglobin S or sickle haemoglobin, in their red blood cells. SCD is a serious blood disorder that affects the red blood cells, which use a protein called haemoglobin to transport oxygen from the lungs to the rest of the body [1]. Mutations in the haemoglobin gene cause sickle cell disease. SCD is the most common genetic disorder in the United States with higher frequency in African Americans when compared to other populations. About one in 500 African American babies are born with sickle cell anemia and one in 12 African American people carry the gene for this trait or disease. About 100,000 Americans are thought to be living with SCD, and every year another 1,000 babies are born with the disease. Approximately 3 million Americans including 10% of African American population carry one gene for SCD (i.e. sickle cell trait). SCD has several recognized forms including sickle cell anaemia, sickle cell haemoglobin C disease and sickle cell thalassemia disease. The red blood cells of patients with SCD don't live as long as healthy red blood cells. So people with this disorder often have low red blood cell counts (anemia), which is why this disease is commonly referred to as sickle cell anaemia. Affected patients characteristically are asymptomatic until approximately 4 to 6 months of age. The median age at death is approximately 42 years for men and 48 years for women [2,3].

Aetiopathogenesis of Sickle Cell Disease

The haemoglobin molecule, the oxygen carrying protein in red blood cells, has two parts: an alpha and a beta. Children typically inherit one copy of the normal haemoglobin beta chain gene (haemoglobin A) from each parent. But some children instead inherit one or two mutated haemoglobin genes (viz., haemoglobin S, C, D, E, or O). It is an autosomal recessive single gene defect in beta-globin chain of normal adult haemoglobin (HbA) that produces a mutant form of haemoglobin known as sickle cell haemoglobin (HbS). Both HbA and HbS have 574 amino acids and are grouped in four subunits [4]. The alpha subunits have 141 amino acids each and are identical to each other. The beta subunits have 146 amino acids and are also identical with each other. The HbA and HbS in the beta subunits of the protein are different from each other by an amino acid. HbS is formed by the substitution of valine for glutamic acid in position six of the beta globin chain of haemoglobin. This modified haemoglobin, when not

carrying oxygen, tends to clump with other deoxygenated haemoglobin, deforming red blood cells and causing blood to clot throughout the body. Fever, chest pain, shortness of breath, increasing tiredness, abdominal swelling, dark urine, unusual headache, any sudden weakness or loss of feeling, sudden vision change are the signs and symptoms of SCD. If the disorder is not detected at birth, a blood sample can be used in a test called haemoglobin electrophoresis. This test will determine whether a person has sickle cell disease or carries the faulty haemoglobin gene. 4,000 to 5,000 pregnancies are at risk for sickle cell disease each year in the U.S [5-7].

Red blood cells are made in the spongy marrow inside the larger bones of the body. Bone marrow is always making new red blood cells to replace old ones. Normally, red blood cells are round and flexible so they can travel freely through the narrow blood vessels (capillaries) of the peripheral blood system. Unlike normal red blood cells (pliable, smooth, disk-shaped), which can live for 120 days, sickle-shaped cells (crescent or sickle) live only 10 to 20 days. The bone marrow can't make new blood cells fast enough to replace the dying ones. These irregularly shaped cells get stuck in the blood vessels and are unable to transport oxygen effectively, causing pain and damage to the organs. Because of this painful process (known as vaso-occlusion), it can lead to life-threatening complications including painful episodes (crisis), anemia (low haemoglobin), organ damage, infections, lung problems, leg ulcers, bone damage, painful inflammation of the fingers and toes (sickle cell dactylitis), pale color of the tongue and lips, strokes etc. The organ damage, enlarged spleen (splenomegaly), enlarged liver (hepatomegaly), yellow appearance of the eyeballs (scleral icterus), heart murmurs and other complications often shorten patient lives by about 30 years [8].

Genetics of Sickle Cell Disease

Patients with sickle cell disease have a mutation in a gene on chromosome 11 that codes for the beta subunit of the haemoglobin protein. As a result, haemoglobin molecules don't form properly, causing red blood cells to be rigid and have a concave shape (like a sickle used to cut wheat). People are born with SCD, it does not develop in adulthood, and it is not contagious [9]. SCD is inherited in an autosomal recessive pattern. This means that a child will not inherit the disease unless both parents pass down a defective copy of the gene. People who inherit one good copy of the gene (A) and one mutated copy (S) are carriers (always more A than S). They are clinically normal, but can still pass the defective gene to their children (corresponding change in codon 6 of the beta-globin gene GAG to GTG). While most people with sickle cell trait are unaffected carriers who don't experience SCD symptoms or complications, a very small

number can develop problems when they are exposed to factors viz., high altitude, yellow eyes or jaundice, increased atmospheric pressure, low oxygen, early gallstones, lung blockage, delayed growth, eye damage, kidney damage, priapism (painful erection in men), sequestration (blood blockage in spleen or liver), and severe dehydration.

SCD occurs more often among people from parts of the world where malaria is or was common. Africa is the area of the world most threatened by malaria because it has the most efficient vectors, the *Anopheles gambiae* complex. Sickle cell trait or disease offers a protective effect against malaria. Individual with sickle cell anaemia are resistant to the parasite that causes malaria. The malarial parasite cannot live in a sickled celled red blood cell because the body sends red blood cells to the spleen. The spleen is an organ that helps filter the blood of infections. Sickle cells get stuck in this filter and die. If a parasite is in the cell, it also is destroyed. As the cell membrane become porous, the sickle cell leaks nutrients, viz., potassium (the parasite needs to survive) and the parasite dies due to lack of much needed nutrient. In malaria-endemic regions, this has led to positive selection of the genetic mutation. Because the U.S. does not have a problem with malaria, the incidence of sickle cell anaemia has decreased in African American population [10].

Disease Modifying Therapies

Sickle cell anaemia accounts for 60% to 70% of sickle cell disease in the U.S. 8% to 10% of African American neonates in the U.S. are carriers of the sickle cell trait. SCD is chronic but treatable and is not a death sentence. Patients with SCD require comprehensive care. Taking the vitamin folic acid (folate) daily to help make new red blood cells, butyric acid (food additive that may increase normal haemoglobin), nitric oxide (may make sickle cells less sticky and keep blood vessels open), decitabine/5-Azacytidine (increases haemoglobin F levels which carries more oxygen), drinking plenty of water daily, avoiding too hot or too cold temperatures, getting plenty of rest, and avoiding over exertion and stress are general guidelines to keep the sickle cell patient healthy. Newborn screening for haemoglobinopathies has been a successful form of population screening for SCD. Babies and young

children with sickle cell disease must take a daily dose of penicillin to prevent potentially deadly infections. Patients also take folic acid, which helps build new red blood cells. Hydroxyurea may be the first drug to effectively address SCD and is the first FDA (Food and Drug Administration)-approved medication for this genetic disease [11]. People with more severe cases of the disease can be treated with a bone marrow transplant. While bone marrow/stem cell transplantation appears to have successfully cured a small number of SCD patients, the vast majority of people with SCD are not candidates for this costly and high risk procedure. Researchers at Harvard Medical School and MIT, supported by National Institute of Health (NIH), announced that they had corrected sickle cell disease in mice using gene therapy (correcting the defective gene and inserting it into the bone marrow of those with sickle cell to stimulate production of normal haemoglobin). Though the only cure to SCD is bone marrow transplantation, gene therapy offers promise of a cure.

References

1. American Society of Hematology (2015) Sickle Cell Anemia.
2. Center for Disease Control and Prevention (2015) Sickle Cell Disease Data and Statistics.
3. Huff post Healthy Living (2014) Black Americans with Sickle Cell Trait at increased risk of kidney disease.
4. John Hopkins Medicine (2015) Sickle Cell Disease.
5. Life Source (2014) Sickle cell awareness month.
6. National Heart, Lung, and Blood Institute (2009) Disease and conditions index. Sickle cell anemia: who is at risk? US Department of Health and Human Services, National Institutes of Health.
7. National Human Genome Research Institute (2014) What do we know about heredity and sickle cell disease?
8. National Library of Medicine, National Institute of Health (2015) Sickle cell disease.
9. National Newborn Screening and Genetics Resource Center (2006) Current newborn screening (NBS) conditions by state. U.S. National Newborn Screening Status Report. Austin, TX, USA.
10. National Organization for Rare Disorders (2006) Sickle cell disease.
11. Sickle Cell Information Center (2011) Information Center Sickle Cell Disease.