

# Deep Vein Thrombosis and Pulmonary Embolism in Sickle Cell Disease

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## Abstract

Sickle Cell Disease (SCD) is considered a group of genetic red blood cell (RBC) disorders. Healthy red blood cells (RBC) are round in shape and migrates throughout the body to carry oxygen in the small blood vessels. In SCD, the RBC turns into hard and sticky, and the shape is similar to a C-Shaped tool called "SICKLE." Because of the early death of the sickle cells, a constant shortage of red blood cells arises. Because of the typical shape of the sickle cells, their movement in the blood vessel is not as smooth as normal RBC and get stuck and clog the blood flow leading to anemia. The changes in shape make the cells more easily destroyed, causing anemia. Defective hemoglobin is the primary cause of SCD.

**Keywords:** deep vein; thrombosis; pulmonary embolism; sickle cell disease

## Introduction

Sickle Cell Disease (SCD) is considered a group of genetic red blood cell (RBC) disorders. Healthy red blood cells (RBC) are round in shape and migrates throughout the body to carry oxygen in the small blood vessels. In SCD, the RBC turns into hard and sticky, and the shape is similar to a C-Shaped tool called "SICKLE." Because of the early death of the sickle cells, a constant shortage of red blood cells arises. Because of the typical shape of the sickle cells, their movement in the blood vessel is not as smooth as normal RBC and get stuck and clog the blood flow leading to anemia. The changes in shape make the cells more easily destroyed, causing anemia. Defective hemoglobin is the primary cause of SCD. Hemoglobin has different combinations of chains. Hemoglobin A (HbA) made up of two Alpha and two Beta globin peptide chains. It is the primary hemoglobin affected in Sickle cell Disease. Patients suffering from SCD inherit two Sickle cell genes (HbSS) [1]. In SCD, a Sickle cell gene ("S") is inherited from one parent, abnormal hemoglobin called ("C") hemoglobin is inherited from another parent. The latter protein is responsible for carrying oxygen to all parts of the body. In the group of SCD, this form is milder than other forms of SCD. Some SCD patients inherit one Sickle cell gene ("S") from one parent and one gene for Beta-Thalassemia, another type of anemia from the other parent. There are two types of Beta-Thalassemia ("0") and "(+)." Patients with the genotype of HbS beta 0-thalassemia usually present a severe form of SCD. People with HbS beta "+" thalassemia tend to have a milder form of Sickle Cell Disease [2].

Sickle cell disease is an Autosomal Recessive Disease. Mutation of both HbB and HBSS leads to get the Disease Homozygote. If a person has one copy of the mutation and one normal HbB gene, then they are Sickle Cell carriers or also called as Sickle cell trait. Sickle cell trait does not have health problems unless they get exposed to extreme conditions like High Altitude regions, dehydration. It does decrease the severity of infection by Plasmodium falciparum (Malaria) like Africa and some parts of

Southern Asia. Those with Sickle trait actually have an evolutionary advantage. This phenomenon is called a heterozygote. It unfortunate consequence is a high rate of Sickle cell Anemia for those parts of the world. The mutations in SCD is missense mutation with Non-conservative pattern [3].

## Epidemiology

SCD is present predominantly in blacks. It also is found in the eastern Mediterranean, and Middle East population's population with much less frequency, Individuals of Central African Republic descent are at an increased risk for renal failure. In the United States statistic, about 8% of black Americans possess the sickle gene. As per the recent study of child prevalence of sickle cell anemia at birth is 1 in 625 in the United States. Early mortality affects the actual reported incidence. About 2 million people with the ancestry of African Americans in the United States carry the sickle gene, homozygous HbS disease patient counts up to 30,000patients [4].

NIH and Centers for Disease Control and Prevention (CDC) describe in the United States, sickle cell anemia is one of the most prevalent inherited blood disorders. As per the recent statistics, approximately 100,000 current cases of SCD patients have been recorded in the United States. In the Hispanic-American births, SCD is reported in about 1 of every 16,300; however, a higher sickle cell trait rate of 1 in 13 reported for African Americans. Fewer than 1% of all new cases SCD accounts for end-stage renal disease (ESRD) in the United States. Factors that are known to portend a higher likelihood of progression are renal failure, hypertension, nephrotic-range proteinuria, hematuria, and severe anemia. Of about 5-18% of SCD patients develop renal failure. One cohort study suggested that the median age is 23.1 yrs at the time of renal failure in patients with SCD [5].

## Signs and Symptom

At about five months of age, SCD patients present initial signs of the condition. The symptoms and complications of SCD vary for each person, and range could vary from mild to severe [6].

#### Hand-Foot Syndrome

Swelling in hands and feet usually is the first symptom of SCD. The sickle cells get stuck in the blood vessels and block the flow, and particularly in the lower and upper limbs leading to swelling.

#### Pain Crises

One of the most common complications associated with SCD is Pain, considered as the primary reason for SCD patients seeking immediate medical attention. When the sickle cells could not move in the blood vessel freely and blocking the flow of blood, it could initiate milder pain but suddenly progressing to severe pain.

#### Anemia

Anemia is a prevalent complication with SCD; the RBC life is shortened. The number of healthy RBC is reduced considerably and reducing the ability to carry oxygen throughout the body. When this happens, a person might

Demonstrate tiredness, irritability, dizziness and lightheadedness, fast heart rate (Tachycardia), difficulty breathing, pale skin color, jaundice, slow growth, and delayed Puberty.

#### Infections

Infants and children are particularly at higher risk for infections among SCD patients. This may be severe in bacterial infections with spleen damage. In infants and young children with SCD, the leading cause of death is Pneumonia.

#### Acute chest Syndrome

Acute chest syndrome is considered life-threatening and should be brought into the immediate attention of a physician. The symptoms and signs of acute chest syndrome are similar to those of Pneumonia.

The signs and symptoms of acute chest syndrome include chest pain, coughing, difficulty breathing, and fever.

#### Spleen Sequestrations

Spleen Sequestrations can also be a life-threatening condition and should also be treated immediately. When a large number of abnormal sickle cells are trapped in the spleen, it causes enlargement of the spleen. In this condition, the symptoms are fast breathing, pale lips, extreme thirst, abdominal (belly) pain on the left side of the body, sudden weakness, and rapid heartbeat. Parents of a child with SCD should be trained to identify the symptoms by feeling and measuring the spleen size of the SCD child periodically. If the spleen is enlarged, they should seek immediate medical attention.

#### Vision loss

One of the other complications associated with SCD is the loss of vision, blindness is an aftereffect of sickle cells blocked in the blood vessels in the eye and the retina and damage of the retina. Some patients develop new blood vessels in the eye from the lack of oxygen.

#### Deep Vein Thrombosis and Pulmonary Embolism

Deep Vein Thrombosis (DVT) may arise by sickling of red cells and increase blood coagulation and induce an increased risk of the blood clot and also may cause lung Pulmonary Embolism (PE) in the cases where the blood clot moves from the deep veins. SCD patient has a very high

chance of developing DVT or Pulmonary Embolism. DVT and or PE can cause severe illness disability and, in some cases, death [7, 8].

#### Stroke

Barin also can be affected in the SCD patients leading to stroke, when the sickle cells clog the blood flow by getting stuck in the brain blood vessels. Asymptomatic stroke is seen in about 10% of SCD patients. Stroke can cause learning problems and lifelong disabilities.

#### Cause

Sickle cell Disease denotes all genotypes containing at least one sickle gene in which HbS makes up at least half the hemoglobin present. Major sickle genotypes described so far include HbSS disease or Sickle Cell Anemia, which is the most common form of the homozygote for S-globin, with usually a severe or moderately severe phenotype and with the shortest survival. HbS/b-0 thalassemia is the double heterozygote for HbS and b-0 thalassemia clinically indistinguishable from sickle cell anemia (SCA). HbS/b+ thalassemia is mild-to-moderate severity with variability in different ethnicities and HbSC disease – Double heterozygote for HbS and HbC characterized by moderate clinical severity; HbS/hereditary persistence of fetal Hb (S/HbF) – Very mild or asymptomatic phenotype; HbS/HbE syndrome - Very rare with a phenotype usually similar to HbS/b+ thalassemia; and rare combinations of HbS with other abnormal hemoglobins such as HbD Los Angeles, G-Philadelphia, HbO Arab, and others.

#### Pathophysiology

The mutation in Sickle cell is a non-conservative missense mutation with a change of amino acid valine in the place of glutamic acid as the sixth amino acid of beta-globin. A hemoglobin tetramer with 2<sup>nd</sup> globin and Z mutated beta-globin proteins is called hemoglobin can carry O<sub>2</sub>. However, when it is deoxy-Hbs changes its shape, which allows it to aggregate with other Hbs proteins and forms long polymers that distort. The RBC'S into a crescent shape

Conditions favoring to sickling are acidosis and dehydration, hypoxia, and infections. Repeated sickling of RBC's change their cell membranes and promotes premature destruction. Since this happens in the vasculature, it is called intravascular hemolysis leading to anemia. But also hemoglobin spilling out to free hemoglobin in the plasma is bound by a molecule called haptoglobin and gets recycled. A low haptoglobin load is a sign of intravascular hemolysis. This leads to unconjugated bilirubin can which further may advance to sclera icterus, jaundice, and bilirubin gall stones. To counteract the developed anemia, the bone marrow makes an increased number of reticulocytes, which are immature RBC'S. This ends up causing new bone formation, which causes frontal nosing and prominent cheek bones. Crew cut appearance on X-ray of the skull. Extramedullary hematopoiesis is RBC's production acts side bone marrow, which can cause hepatomegaly. Vaso occlusion in sickle cells is stuck in sickle RBCs in capillaries, which causes dactylitis. In other bones, pain crises, necrosis occurs.

RBC's can clog up in spleen can lead to infarct of the spleen. Interact leads to auto splenectomy down to fibrosis. Vaso-occlusion in cerebral vasculature causes a stroke. Blood vessels of lungs lead to acute chest syndrome, which can lead to hypoxic vasoconstriction. In renal papillary necrosis causes hematuria and proteinuria.

#### Diagnosis

A typical clinical presentation of chronic hemolytic anemia and vaso-occlusive crisis is the initial suggestion for SCD. The presence of homozygous HbS can be confirmed by a molecular biology technique using electrophoresis, and this method could be used for other hemoglobinopathies (e.g., HbSC, HbS-beta+ thalassemia) [9].

In the United States, a mandatory infant screening for HbS helped in the early diagnosis of SCD. Prenatal testing is also available, which uses chorionic villus sampling. A series of biochemical tests are available for SCD, such as CBC count with differential and reticulocyte count, Hemoglobin electrophoresis, Hemoglobin solubility testing, Serum electrolytes, Pulmonary function tests (transcutaneous O<sub>2</sub> saturation), Peripheral blood smear. Other tests such as renal function test (creatinine, BUN, urinalysis) and Hepatobiliary function tests for ALT, fractionated bilirubin, and CSF examination are performed. In febrile children with neurologic symptoms of neck stiffness, focal deficits, and Brudzinski/Kernig signs, lumbar puncture (LP) is considered [10].

## Treatment

Hydroxyurea is a drug of choice which increases fetal hemoglobin in children with sickle cell disease. Hydroxyurea is established as a safe and effective drug for an effective treatment for SCD. This drug acts by increasing the total and fetal hemoglobin in children with SCD. An increase in fetal hemoglobin inhibits gelation and the sickling of RBCs. The other associated mechanism of hydroxyurea is by reducing the number of circulating leukocytes and therefore reducing the adherence of neutrophils to the vascular endothelium. These synergistic effects of hydroxyurea minimize the pain episodes and also acute chest syndrome episodes.

Hydroxyurea is usually prescribed by hematologists using rigorous selection criteria. Indications for hydroxyurea include frequent painful events (six or more per year) [11]. The history of acute chest syndrome; the history of other severe unremitting chronic pain: severe symptomatic anemia; severe vaso-occlusive events that cannot be controlled with conservative measures. That SCD patient who doesn't respond positively to hydroxyurea, an alternate therapy option of repeated transfusions for a limited period, is considered. Management of constant pain is challenging, and expert advice should be obtained.

## Transfusion

For the common anemia or episodes of pain in SCD patients, transfusions are not recommended. Conditions like acute splenic sequestration, parvovirus B19 infection, or hyperhemolytic crises may lead to severe anemia in the SCD patients requiring urgent replacement of blood. The transfusion is also a choice of treatment in perioperatively, acute chest syndrome. In pregnancy, transfusion could be considered [12]. Use of acute red cell exchange transfusion is indicated in these situations: severe acute chest syndrome; acute infarctive stroke; right upper quadrant syndrome; priapism that does not resolve after adequate hydration and analgesia; multiorgan failure syndromes.

Children with SCD may develop primary and secondary stroke, and for prevention, regular blood transfusions are used for. There are many complications associated with transfusions, such as iron overload, infection, and alloimmunization. The newly available oral chelators are efficient in the treatment of iron overload. The HbS concentration alone or combined concentration of HbS and HbC in SCD patients with complications and undergoing retinal surgery needs must be lowered to 30%, which will enhance to hemoglobin A level to 70%. Based on the nature of the complication of the procedure and other underlying medical conditions, a personalized treatment plan must be deduced. In the case of adult SCD patients with a predisposition to stroke risk factors, management of the disease must be followed according to the set guidelines for primary stroke prevention in 2014 AHA/ASA [13]. These organizations are also responsible for guidelines for other stroke-related conditions to prevent stroke in patients with stroke or transient ischemic attack. Additionally, guidelines for the prevention of secondary strokes recommend controlling associated risk factors and the use of antiplatelet agents. In SCD adult patients with recurrence of cerebral ischemic attacks,

alternate therapy may be considered to prevent attack with regular blood transfusions to lower the HbS below 50% of total hemoglobin. Hydroxyurea is a choice of drug, and also bypass surgery may be a choice for advanced occlusive disease.

This transfusion therapy aims to lower the HbS proportion below 30%, is helpful in the treatment of SCD, and now used in practice for the prevention of primary and secondary stroke. In a clinical trial for Stroke Prevention Trial in Sickle Cell Anemia, the study suggested that regular transfusion of blood reduced the first stroke to less than 90% in asymptomatic high-risk children. These children had 2 abnormal transcranial Doppler (TCD) studies with velocities of 200 cm/s or higher. As per the primary stroke prevention guidelines set by 2014 AHA/ASA, blood transfusion has been reported to be beneficial in managing strokes in the children with higher stroke risk. During the blood transfusion, most of the subjects enrolled in the TCD study showed improvement to or toward normal. However, on termination of the blood transfusion, TCD reversion was seen as the patients to high risk and also to actual strokes. A new method, Erythrocytapheresis, has gained success as a comparable alternative to simple blood transfusion. This apheresis procedure successfully reduces HbS concentrations quickly to less than 30%, with the advantage of a non-significant increase in total hemoglobin concentration post-transfusion.

As per the primary prevention guidelines of AHA/ASA, a non-invasive method such as the drug of choice hydroxyurea or invasive approach using bone marrow transplantation is an accepted option of treatment for children who are at risk of stroke, but RBC-transfusion is contraindicated. In a consortium studying the SCD children with HLA-matched siblings suggested that the recurrence risk of stroke is significantly reduced when allogeneic bone marrow transplantation is performed. This is a suitable alternative to blood transfusion, which generally is for lifelong and also for iron chelation.

## Prognosis

Identification of prognostic factors in SCD is essential; some prognostic factors are used to predict the adverse outcome of SCD. Infants less than one-year-old, hand-foot syndrome (dactylitis) is considered an excellent predictor, the prognosis can also be done when the hemoglobin level drops below 7 g/dL and also Leukocytosis in the absence of infection. SCD children who are younger than 5 years, the hand-foot syndrome is an excellent prognostic predictor for the overall severity of SCD. The hand-foot syndrome affects children younger than 5 years has proved to be a strong predictor of overall severity (i.e., high pain rate, risk of stroke, recurrent acute chest syndrome, and death). If the SCD child patient had an episode before the age of one year, the patient is at high risk of severe clinical course. The risk rate is even more if the hemoglobin baseline of the child is lower than 7 g/dL or also if the baseline count of WBC is higher.

## Pregnancy in SCD

IN SCD, pregnancy holds a particular concern about medical care. Spontaneous abortion in SCD patients are seen causing high fetal loss. Hypoxia and the placental infarction is a common cause for placenta previa and abruption. Generally, the infant is born premature or born with low birth weight.

## Mortality in SCD

In the early childhood age, there is a high rate of death in SCD patients. Penicillin prophylaxis and pneumococcal vaccination are commonly used in SCD patients. Since the use of this prophylactic treatment, a significant reduction in childhood death is reported. The primary cause of death in SCD is acute chest syndrome. Children with SCD are higher predisposed to acute chest syndrome compare to adults; however, the death rate is

higher in adults. The death rate of SCD patients due to severe chest syndrome is 1.8%; however, the frequency is increased by 4 folds in the case of adults. The primary cause of death is due to infection and pulmonary embolism. The projected survival rate is 94% at age 18 years, as suggested by the Dallas newborn cohort study. In another study, the neonatal United Kingdom cohort carried out in both hospitals and communities found that the estimated survival of HbSS children is 99% at 16 years of age. In this study, modern therapy was used, and screening was done using Transcranial Doppler Ultrasonography. In a previous study carried out in 1995 cooperative study of SCD, the median survival was found to be 48 years for women and a lesser age of 42 years in men in SCD patients. The study suggested that life expectancy was significantly lower than African Americans without SCD.

The life expectancy data from Africa are sporadic and incomplete, where many SCD children remain undiagnosed, especially in rural areas. Malaria and other comorbid conditions are frequently associated with deaths in Africa. Recent literature indicates that SCD induced mortality has considerably reduced in the past 30 years. A previous study reported that about half of the SCD patients did not live beyond 20 years of age, and the majority of SCD patients died before 50 years of age. In SCD patients after diagnosed with end-stage renal disease, the median survival time is 4 years, and 27 years is the median age for death after diagnosis. These patients may have received dialysis treatment. With early detection of SCD and various disease-modifying therapies, a significant increase has been reported in both life expectancy as well as the survival of patients. Especially for newborn, neonatal screening was successful and also used pneumococcal immunization, penicillin prophylaxis has reduced the mortality rate. The use of red cell transfusion for selected patients has been beneficial. Chelation therapy and the use of hydroxyurea have gained importance. Education of parent and patient and treatment in comprehensive centers have been proved to contributing to the longevity of SCD patient's life. However, as the SCD patients grow with age, at an older age, new complications are being reported. One of the commonly reported complications is pulmonary hypertension. Pulmonary hypertension is considered as one of the leading causes of death in adults with SCD. In a recent study carried out in France with 398 outpatients with SCD to examine the prevalence of pulmonary hypertension, it was

confirmed that a low positive predictive value for pulmonary hypertension.

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