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# SICKLE CELL ANEMIA

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## ABSTRACT
Sickle-cell disease is one of the most common severe monogenic disorders in the world. Haemoglobin polymerisation, leading to erythrocyte rigidity and vaso-occlusion, is central to the pathophysiology of this disease, although the importance of chronic anaemia, haemolysis, and vasculopathy has been established. Clinical management is basic and few treatments have a robust evidence base. One of the main problems of sickle-cell disease in children is the development of cerebrovascular disease and cognitive impairment, and the role of blood transfusion and hydroxycarbamide for prevention of these complications is starting to be understood. Recurrent episodes of vaso-occlusion and inflammation result in progressive damage to most organs, including the brain, kidneys, lungs, bones, and cardiovascular system, which becomes apparent with increasing age. Most people with sickle-cell disease live in Africa, where little is known about this disease; however, we do know that the disorder follows a more severe clinical course in Africa than for the rest of the world and that infectious diseases have a role in causing this increased severity of sickle-cell disease. More work is needed to develop effective treatments that specifically target pathophysiological changes and clinical complications of sickle-cell disease.

**KEYWORD:** Sickle cell disease, Sickle cell anaemia, pathophysiology, Genetics of Sickle cell anaemia, Inheritance[1], Crisis and Management.

## INTRODUCTION
Sickling Phenomenon was first described by Herrick in 1910. And Pauling showed that the abnormality resided with hemoglobin in 1949.[2]

Hemoglobin is the red coloring matter of blood, which is present in red blood cells.

It is a conjugated protein consisting of heme and the protein globin. It has molecular weight of 64,450. It can combine with oxygen and acts as the transport mechanism for oxygen with in blood. It contain 4 gm atom of iron per mole in the ferrous (Fe++) state.

Let us see the structure of heme. It is a chromo protein consist of two part 96% is a specific simple protein known as globin (histone) and other 4% is a non specific prosthetic group an iron. Containing pigment called heam.[2]

Heam is a metalloporphyrin where the metal is iron. The iron content of hemoglobin is about 0.34% and about 3gm of iron is present as hemoglobin in the total amount of blood of an adult. Iron remains in ferrous (Fe++) form.

Globin helps heam to keep the iron ferrous state and to combine loosely and reversibly with molecular oxygen.

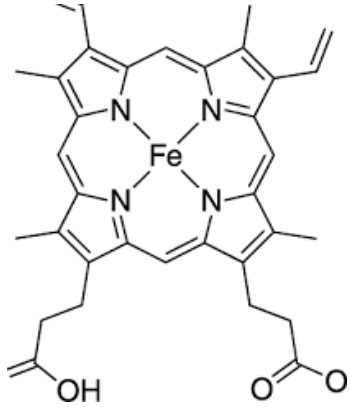


**Fig. 1: Diagram of Heme group.**

Sickle cell anemia (Hbs) is the most common form of abnormal hemoglobins. It is so named because the erythrocytes of this patients adopt a sickle shaped (Crescent like).

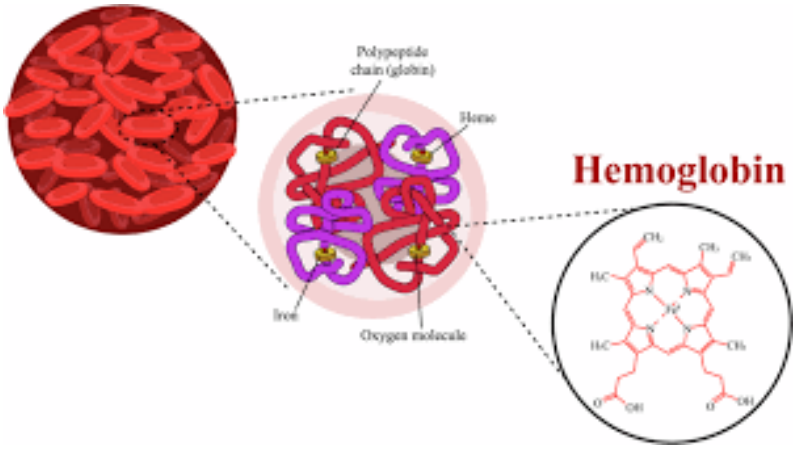


**Fig. 2: Diagrammatic representation of hemoglobin with 2a (alpha) and 2B (beta) shade Synonyms of sickle cell anemia are – heme.[3]**

- Hemoglobin SS Diseases. Hbs.
- Sickling disorder due to Hemoglobin S.
- Hemoglobin S diseases.
- Sickle cell disorders
- SCD.

The structure of hemoglobin (as described all ready) contains two alpha and two beta globins chain. In case of sickle of anemia the hemoglobin (Hbs) has two normal alpha globins and two abnormal (mutant) beta globins chain. This is due to difference in a single amino acid. In Hbs, glutamate at sixth position of beta chain is replaced by valine[3] (Glu B6 à Val).

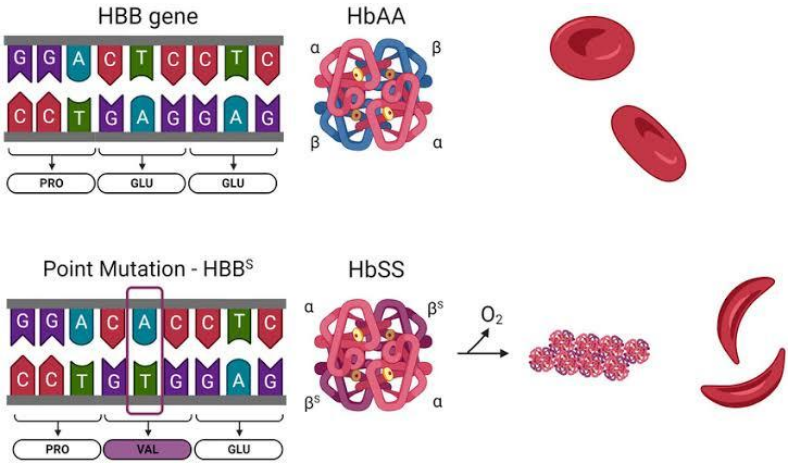


**Fig. 3: Sickle cell anemia is due to a change (missense - mutation) in the single nucleotide (thymine - adenine) of beta globin gene.**

This error causes the formation of altered codon (GUG in place of GAG) which leads to incorporation of valine instead of glutamate at the sixth position in beta chain.[3]

Sickle cell anemia affects millions of people worldwide. It's most common people whose families come from Africa, South or Central America (Specially panama) Caribbean islands, Mediterranean countries (Such as Turkey, Greece and Italy) INDIA and Saudi Arabia. In united State Sickle cell anemia affects about 70000 peoples. It mainly affects African, American with the condition occurring in about in every 500 African American births. Hispanic American are also affected, the condition occurs in 1 out of every 1000 to 1400 Hispanic American births. About 2 millions American have sickle cell trait. About in 12 African, American has sickle cell trait.

**Signs and symptoms of Sickle cell Anemia –** the signs and symptoms of sickle cell anemia are different in each person. Some people have mild symptoms others have very severe symptoms and are often hospitalized for treatment. Although sickle cell anemia is present at birth many infants don't show any sign until after 4 months of age.

The most sign and symptoms are linked to anemia and pain. Sudden episodes of pain throughout the body are common symptoms of sickle cell anemia and are often referred to as sickle cell crises. Occurs when the Red blood cells sickle and stick together in clumps. The clumps blocked the flow of blood through the small blood vessels in limbs and organs. Sickle crises can cause acute and chronic pain the pain usually (in acute) from hours to a few days' chronic pains for weeks to months. Many factors can contribute to a sickle cell crises often more than one factor is involved and the exact cause can't be identified. The most common site affected by sickle cell crises are bones, lungs, abdomen and joints. The blocked blood flow can cause pain and organ damage.[4]

When sickle cell blocked the small blood vessels in hand or feet pain and swelling along with fever can occur swelling usually occurs on the back of the hand and feet and moves in to fingers and toes this may be first sign of sickle cell anemia in infants.

Splenic (Sequestration) Crisis - The spleen is an organ in the abdomen that filters out abnormal red blood cells and helps fight infection. Sometimes, the spleen traps many cells that should be in the bloodstream and it grows large. This causes anemia. Blood transfusions may be needed until the body can make more cells and recover. If the spleen becomes too clogged with sickle cells, it can't work normally. It begins to shrink and stop working.

**Infections -** Both children and adults with sickle cell anemia have a hard time fighting infections. Sickle cell anemia can damage the spleen. Infants and young children with a damaged spleen are more likely to get infections that can kill them within hours or days. Pneumonia is the most common cause of death in young children who have sickle cell anemia. Meningitis, influenza, and hepatitis are other infections that are common in people with sickle cell anemia.

**Acute Chest Syndrome -** Acute chest syndrome is a life-threatening condition linked to sickle cell anemia. It's similar to pneumonia and is caused by an infection or by sickle cells trapped in the lungs. People with this condition usually have chest pain, fever, and an abnormal chest x ray. Over time, lung damage may lead to pulmonary arterial hypertension

- **Delayed Growth and Puberty in Children -** Children with sickle cell anemia often grow more slowly and reach puberty later than other children. A shortage of red blood cells (anemia) causes the slow growth rate. Adults with sickle cell anemia often are slender or small in size.[5]
- **Stroke -** Sickle-shaped red blood cells may stick to the walls of the tiny blood vessels in the brain. This can cause a stroke. This type of stroke occurs mainly in children. The stroke can cause learning disabilities or more severe problems.
- **Eye Problems -**The retina, a thin layer of tissue at the back of the eye, takes the images you see and sends them to your brain. When the retina doesn't get enough blood, it can weaken. A weak retina can cause serious problems, including blindness.
- **Priapism** - Males with sickle cell anemia may have painful and unwanted erections called Priapism (PRI-a-pizm). This happens because the sickle cells stop blood flow out of an erect penis. Over time, Priapism can damage the penis and lead to impotence.[6]
- **Gallstones -** When red blood cells die, they release their hemoglobin, which the body breaks down into a compound called bilirubin. When there is too much bilirubin in the body, stones can form in the gallbladder. Gallstones can cause steady pain that lasts for 30 minutes or more in the upper right side of the belly, under the right shoulder, or between the shoulder blades. The pain may happen after eating fatty meals. People with gallstones may have nausea, vomiting, fever, sweating, chills, clay-colored stool, or jaundice (yellowish color of the skin or whites of the eyes).
- **Ulcers on the Legs -** Sickle cell ulcers (sores) usually begin as small, raised, crusted sores on the lower third of the leg. Leg sores occur more often in males than in females and usually appear between the ages of 10 and 50. The cause of leg ulcers is not clear. The number of ulcers can vary from one to many. Some heal rapidly, but others persist for years or come back after healing.
- **Pulmonary Arterial Hypertension (High Blood Pressure) -** Damage to the small blood vessels in the lungs makes it hard for the heart to pump blood through the lungs. This causes blood pressure in the

lungs to increase. This condition is called pulmonary arterial hypertension. Excessive shortness of breath is an important symptom linked to Paste.

- **Multiple Organ Failure -** Multiple organ failure is rare, but serious. It happens when a person has a sickle cell crisis that causes two out of three major organs (lungs, liver, or kidney) to fail. Symptoms linked to this complication are a fever and changes in mental status such as sudden tiredness and loss of interest in your surroundings.
- **Premature death -** Homozygous individual of sickle cell anemia die before they rich adulthood (< 20years).[3]
- **Infection -**Salmonella infection is found more in this disease.[6]

Let us see the block blood vessels due to Sickle shaped Red Blood Cells.

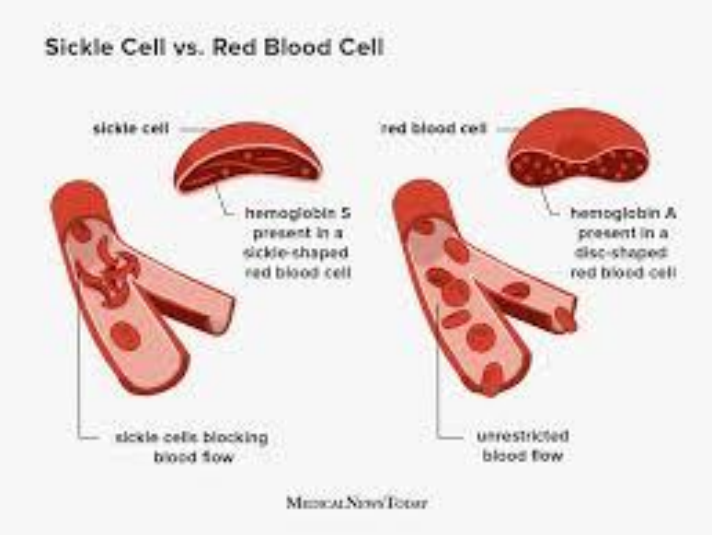


**Fig. 4: Difference between Normal RBCs and Sickle Cell RBCs.**

**Figure A** shows normal red blood cells flowing freely in a blood vessel. The inset image shows a cross-section of a normal red blood cell with normal hemoglobin.

**Figure B** shows abnormal, sickled red blood cells clumping and blocking the blood flow in a blood vessel. The inset image shows a cross-section of a sickled red blood cell with abnormal strands of hemoglobin

- **Diagnosis of Scikle cell anemia** - Early diagnosis of sickle cell anemia is very important

So that children who have the condition can get proper treatment. In the United States, 44 States, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands now test all newborns for sickle cell anemia. In the other six States, you can request a sickle cell test. The test uses blood from the same blood samples used for other routine newborn screening tests. It can show whether the newborn infant has sickle cell anemia or sickle cell trait. If the first test shows some sickle hemoglobin, a second blood test is done to confirm the diagnosis. The second blood test looks at how hemoglobin moves in an electric field, a process called electrophoresis (ee-LEK-tro-for-EE-sis). Sickle hemoglobin moves differently than normal hemoglobin. Electrophoresis is usually used to diagnose older children and adults. It's also possible to identify sickle cell anemia before birth. This is done using a sample of amniotic fluid or tissue taken from the placenta. (Amniotic fluid is the fluid in the sac surrounding a growing embryo. The placenta is the organ that attaches the umbilical cord to the mother's womb.) This test can be done as early as the first few months of pregnancy. It identifies the sickle gene, rather than the hemoglobin it makes.[7]

**1. Sickle test –** this is a simple microscopic examination of blood smear prepared by adding reducing agents such as sodium dithionite sickle erythrocytes can be detected under the microscope.

**2. Electrophoresis –** When subjected to electrophoresis in alkaline medium (pH – 8.6) sickle cell hemoglobin moves slowly towards anode than does adult hemoglobin. The slow mobility of Hbs is due to less negative charge, caused by the absence of glutamate residues that carry negative charge. In case of sickle cell trait, the fast moving HbA and slow moving Hbs are observed. The electrophoresis of hemoglobin obtained from lysed erythrocytes can be routinely used for the diagnosis of sickle cell anemia and sickle cell trait.

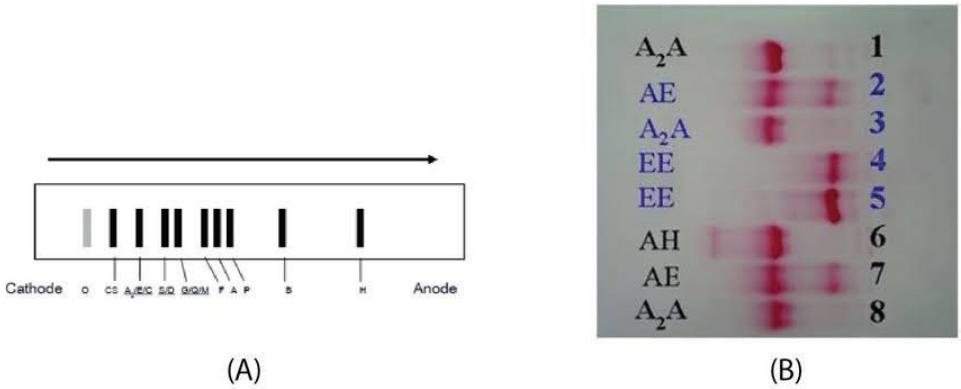


**Fig. 5: Electrophoresis of hemoglobin's at pH 8.6.**

HbA – Normal adult Hemoglobin; HbS – Sickle cell Hemoglobin.[3]

- **Treatment –** There is no specific therapy avoid fatigue, exposure to cold, stress infection, of fever, dehydration. Folic acid is recommended to counteract the secondary folate deficiency that develops due to rapid red cells turn over. Various methods have been suggested form time to time for the painful crises. Crises are due sludging and vascular occlusion with or without myleo suppressive effects.

It is most unusual for the new born to get crises. This is explained on the basis of high fetal hemoglobin level and low level of HbS. Carbonic anhydrous inhibitors, alkalization with sodium bicarbonate administration conversion of a portion of Hb to oxy Hb. By oxygen administration or by carbon monoxide to carboxy hemoglobin or mat hemoglobin. Has been no benefit. Though this form do not Sickle. Magnesium salts therapeutic defibrination, anti coagulant, expansions of blood volume with low molecular weight. Dextrans have been suggested but are still under investigation. The best is to provide supportive and symptomatic therapy. Splenectomy is of moderate benefit in those subjects where there is a excessive blood destruction. Red Cell survival increases after Splenectomy and the frequency of blood transfusion is decreased. Heme turnover is increased during urea therapy due to increased hemolysis of red cell. Which are prevented from aggregating in the microcirculation.

Recent suggestion is administration of oral or intravenous injections of 10 % sodium citrate, 6G in 400ml. Of water every two hours for 2 days. For 24 hour followed by the same every 2 hours for 2 days and then every 6 hours. Codeine is helpful. Sodium citrate may be given in I.V. 200ml. Of M/6 sodium lactate in 3 hours. Hyper transfusion is also used. Corticosteroids have been beneficial, phenothiazine and oral contraceptive are of no value. Analgesic and antipyretic drugs must be used for comfort of the patient. Intravenous distilled water may interfere with sickling. Antibiotics should be used if infection is present. Blood transfusion is necessary for aplastic crises and in pregnancy. Packed Red Cells are preferable. Transfusion decreases.

Viscosity and is helpful. Repeated transfusion would lead to hemosiderosis and iron over load. According to modified muryamma hypothesis for the molecular mechanism of sickling. Which implicates intertertrameric hydrophobic bond on the basis of this hypothesis intravenous urea in sugar solution is used as an effective chemical agent for desickling. This solution reverses and blocks sickling without hemolysis. A high blood nitrogen gradient of 150 to 200mg. Per 100ml./ is achieved rapidly and maintained until the vascular occlusion is reversed. The relief of pain signals this and the urea is discontinued. The maintenance of hydration is critically important and is achieved by the adertically importance and is achieved by the administration of ringers lactate solution by a central; venous catheter to prevent the complication occasionally caused by 30% urea solution prepared by taking 0.05 to .10M. urea (300 to 600mg./100ml.) in sugar solution in a peripheral vein.[8]

- **Side effects –** sedation that is desirable and diuresis. Oral prophylactic urea reduces the number of crises. 160gm of urea per day divided into four doses are given individualization is necessary. Bon should be maintaining at 40 to 50mg/100ml.

Since cyanate (NCO) is present in urea, it can react with N-terminal residues of protein to form carbimilate derivative. This reaction is essentially irreversible.

Low concentration of cyclamate inhibit Sickling the amount bound cyanate per moil is in range of 0.1 to 1per mole of hemoglobin this not only prevents sickling but also blocks the gelling of hemoglobin no side effect were observed.

Partial exchange perfusion is used for prophylaxis and treatment two units of buffu coat free packed sales in two units of whole blood every 6 to 8 weeks for 1.5 to 6 years. This maintenance from 15 to 40% normal circulating RBCs. There is a melioration of crises in 24 hours. And complete relief in 48 hours.

Frequency of crises is not affected the hospital stay is reduce.

## MATERIALS AND METHODS

- **Study Design and Population**

A cross-sectional study was conducted to evaluate hematological parameters and genetic markers associated with Sickle Cell Anaemia (SCA). A total of 100 individuals were enrolled, including 50 diagnosed SCA patients (HbSS) and 50 healthy controls (HbAA). Participants were recruited from the hematology unit of a tertiary care hospital following ethical approval and informed consent.[9]

- **Sample Collection**

Venous blood samples (5 mL) were collected from each participant using sterile EDTA vacutainers. Samples were kept at 4°C and analyzed within 4 hours of collection.

- **Hematological Analysis**

Complete blood count (CBC) was performed using an automated hematology analyzer (Sysmex XN-1000, Kobe, Japan). Parameters measured included hemoglobin concentration, hematocrit, red blood cell count, mean corpuscular volume (MCV), and white blood cell count.

- **Hemoglobin Electrophoresis**

Hemoglobin variants were identified using cellulose acetate electrophoresis at pH 8.6. This allowed differentiation of normal (HbA) and abnormal hemoglobins (HbS, HbC, etc.). Electrophoresis patterns were interpreted following standard protocols (Bain, 2010).

- **DNA Extraction and PCR**

Genomic DNA was extracted from peripheral blood leukocytes using the Qiagen DNA Blood Mini Kit (Qiagen, Germany) as per the manufacturer's instructions. Polymerase Chain Reaction (PCR) followed by Restriction Fragment Length Polymorphism (RFLP) analysis was used to detect the presence of the sickle cell mutation in the β-globin gene (HBB). The DdeI restriction enzyme was used to digest the amplified fragments, and products were visualized on 2% agarose gels stained with ethidium bromide.[10]

- **Statistical Analysis**

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY). Independent t-tests and chi-square tests were employed to assess differences between groups. A p-value of less than 0.05 was considered statistically significant.

## RESULTS AND DISCUSSION

### Hemoglobin Electrophoresis

The study revealed significant differences in hematological parameters between individuals with Sickle Cell Anaemia (HbSS) and healthy controls (HbAA). The HbSS group exhibited markedly reduced hemoglobin levels (mean: 7.8 ± 1.1 g/dL) compared to controls (13.5 ± 0.8 g/dL), consistent with chronic hemolytic anemia. Hematocrit and red blood cell counts were also significantly lower in the HbSS group. In contrast, white blood cell counts were elevated, indicating a state of chronic inflammation and potential infection risk.

These findings are in agreement with those reported by Akinbami et al. (2012), who observed significantly lower hemoglobin and higher leukocyte counts in SCA patients due to chronic hemolysis and inflammation.

### Hemoglobin Electrophoresis

Hemoglobin electrophoresis identified HbSS as the dominant hemoglobin in the test group, confirming the diagnosis of Sickle Cell Anaemia. Controls showed normal HbA bands. The electrophoresis method remains a primary tool for the differentiation of hemoglobinopathies, especially in resource-limited settings (Bain, 2010).

### Molecular Confirmation

PCR followed by RFLP confirmed the presence of homozygous sickle mutation (β^S/β^S) in all HbSS individuals. The mutation is a result of a single nucleotide substitution (GAG → GTG) in the β-globin gene (HBB), leading to the formation of valine instead of glutamic acid at the sixth position (Ingram, 1957)

The molecular approach confirmed the electrophoresis results and offered a reliable method for prenatal or[12] neonatal screening and genetic counseling, as recommended by WHO guidelines (WHO, 2006).

### Clinical Implications

The lower hemoglobin and red cell indices in HbSS patients reflect ongoing hemolysis, which contributes to fatigue, pallor, and delayed growth in affected children. Elevated WBC counts are a predictor of disease severity and risk of vaso-occlusive crises.

The importance of early detection through hemoglobin electrophoresis and molecular diagnosis cannot be overstated. Effective management strategies such as hydroxyurea therapy, regular monitoring, and patient education can significantly reduce complications and improve quality of life.

## CONCLUSION AND RESULT

Sickle cell anemia is serious condition and not have any permanently treatment Effective treatments are available to help relieve the symptoms and complications of sickle cell anemia, but in most cases there's no cure[1] but according to reference. Remove the effects and you remove the disease.[5] the homoeopathy medicinal system is also a subject to treat patient those are suffering from sickle cell anemia.

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