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Madhuri D Shende
Adv. VR Manohar Institute of Diploma in Pharmacy, Wanadongri, Nagpur, Maharashtra, India

Corresponding Author:
Madhuri D. Shende
Adv. V.R. Manohar Institute of Diploma in Pharmacy, Wanadongri, Nagpur, Maharashtra, India

Sickle cell disease: A review

Madhuri D Shende

Abstract
Sickle cell disease (SCD) is a genetic disorder that affects erythrocytes (RBCs) causing them to become sickle or crescent shaped. The effects of this condition due to an abnormality of the hemoglobin molecules found in erythrocytes. The substitution of one amino acid in the hemoglobin molecule results in sickle hemoglobin. As a result RBCs sickle in low oxygen states causing occlusion of blood vessels, increased viscosity and inflammation. These RBCs are prematurely removed from the circulation, resulting in a chronic hemolytic anemia. With new born screening and early treatment, the death rate among children with SCD has declined. In addition, a variety of treatments are being introduced to help manage the various manifestations of disease. Transfusion, simple or exchange, is a mainstay of therapy, since it reduces the amount of Hgb S in circulation and suppresses erythropoiesis. Transfusion is indicated for symptomatic anemia and specifically to prevent stroke (first or recurrent), during acute stroke, and for acute chest syndrome. Unfortunately, transfusion carries risks for infectious disease transmission, as well as immunologic and inflammatory sequelae. For patients with SCD who may be chronically transfused, iron overload occurs frequently. In addition, due to differences in RBC antigens between donors and recipients, these patients are at increased risk for development of RBC alloantibodies, which can complicate further transfusion. It is, therefore, important to prevent all immunization by transfusing leukoreduced RBCs that match the patient for the C, E, and K1 antigens. Human progenitor cell (from bone marrow, peripheral blood stem cells, or umbilical blood) transplant can cure the disease for whom conventional therapy may not be effective. The care of people with sickle cell disease may include infection prevention with vaccination and antibiotics, high fluid intake, folic acid supplementation, and pain medication. Other measures may include blood transfusion and the medication hydroxycarbamide (hydroxyurea). A small percentage of people can be cured by a transplant of bone marrow cells.

Keywords: Sickle cell disease, Red blood cells, haemoglobin, anemia

Introduction
Sickle cell disease (SCD) is a collective term for a number of genetic disorders in which hemoglobin is structurally abnormal, resulting in the episodic formation of sickle-shaped red blood cells (RBCs) and a wide range of clinical manifestations. It affects some 12500 people in the UK and million worldwide [1], particularly those of black African and Afro-Caribbean descent, and also those from the Mediterranean, Middle East, and parts of India [2]. The underlying abnormality is a single nucleotide substitution (GTG for GAG) in the gene for β-globin on chromosome 11, resulting in the replacement of a glutamic acid residue with valine on the surface of the protein (termed HbS) [3]. In normal adult HbA, two chains of α-globin and two of of β-globin form a tetramer within the RBC [4]. When the molecule binds or releases oxygen, it undergoes a conformational change. In HbS, deoxygenating exposes the abnormal valine residue on the surface of the molecule, which then forms hydrophobic interactions with adjacent chains. The resulting polymers align into bundles, causing distortion of the RBC into a crescent or sickle shape and reducing flexibility and deformability, which impairs passage of the cells through narrow blood vessels [3]. Sickling can be precipitated by environmental factors such as hypoxia, low pH, cold, and dehydration of the RBC, as well as adhesion molecules and cytokines associated with infections.
Homozygous SS (sickle cell anemia) is generally considered the most severe form of SCD. Compound heterozygotes, in whom HbS is combined with a different mutation in the second β-globin gene, such as HbC, D, O^{Arab} or β-thalassemia (where β-globin syntheses is reduced) can also be affected, with variable phenotypes. The carrier state (HbAS) does not cause clinically significant disease (though sickling may occur under extreme conditions), so carriers are most often unaware of their genotype or their sickle gene status, and the frequency of the gene in some populations is very high: one in four Nigerians [5].

Sickle cell conditions have an autosomal recessive pattern of inheritance from parents [6]. The types of haemoglobin a person makes in the red blood cells depend on what haemoglobin genes are inherited from her or his parents. If one parent has sickle cell anaemia and the other has sickle cell trait, then the child has a 50% chance of having sickle cell disease and a 50% chance of having sickle cell trait. When both parents have sickle cell trait, a child has a 25% chance of sickle cell disease; 25% do not carry any sickle cell alleles, and 50% have the heterozygous condition [7]. In people heterozygous for HbS (carriers of sickling hemoglobin), the polymerization problems are minor because the normal allele is able to produce half of the hemoglobin. In people homozygous for HbS, the presence of long-chain polymers of HbS distort the shape of the red blood cell from a smooth, doughnut-like shape to ragged and full of spikes, making it fragile and susceptible to breaking within capillaries. Carriers have symptoms only if they are deprived of oxygen (for example, while climbing a mountain) or while severely dehydrated. The allele responsible for sickle cell anemia can be found on the short arm of chromosome 11, more specifically 11p15.5. A person who receives the defective gene from both father and mother develops the disease; a person who receives one defective and one healthy allele remains healthy, but can pass on the disease and is known as a carrier or heterozygote. Heterozygotes are still able to contract malaria, but their symptoms are generally less severe [8].

Symptoms of SCD

The clinical manifestations of SCD result from two key pathological processes: vaso-occlusion and hemolysis. Sickle cells, along with non-sickled RBCs, leukocytes, and platelets, form heterocellular aggregates, which adhere to the vascular endothelium, causing obstruction of the lumen of small blood vessels. This microcirculatory occlusion leads to acute and chronic tissue ischemia and infarction, with multisystem effects, particularly in bone, lungs, brain, kidneys, and spleen. It is responsible for acute painful episodes and crises and many of the long-term complications seen in SCD. Sickled RBCs are more readily destroyed by the reticulo-endothelial system, partly as their rigidity makes them more easily filtered in the spleen and partly due to changes in the structure of the lipid bilayer (with exposure of anionic phosphatidylserine on the RBC surface), which promotes phagocytosis [9] With sickle cell anemia (HbSS), this causes a chronic anemia (a steady state Hb of 6–8 g/dl) [6] with a resultant increase in cardiac output and workload, which produces cardiomegaly and reduced exercise tolerance. The increased energy demands due to this and the chronically elevated rate of hematopoiesis contribute towards poor growth in children, and individuals are susceptible to any factor exacerbating the anemia, which can precipitate circulatory failure [7]. Intravascular hemolysis also leads to release of free hemoglobin–an important scavenger of nitric oxide (NO). Reduced levels of this potent vasodilator and the hyper dynamic circulation contribute further to vascular damage and occlusion, including within larger vessels [10]. Despite progress in therapy, SCD remains a cause of significant morbidity and mortality. Life expectancy in HbSS from a multicenter study in the USA in 1994 was estimated at 42 for men and 48 for women [11] and 95% of children survive to adulthood [12]. Virtually all of the major symptoms of sickle cell anemia are the direct result of the abnormally shaped, sickled red blood cells blocking the flow of blood that circulates through the tissues of the body. The tissues with impaired circulation suffer damage from lack of oxygen. Damage to tissues and organs of the body can cause severe disability in patients with sickle cell anemia. The patients endure episodes of intermittent "crises" of variable frequency and severity, depending on the degree of organ involvement.

The major features and symptoms of sickle cell anemia include

1. Fatigue and anemia
2. Pain crises
3. Dactylitis (swelling and inflammation of the hands and/or feet) and arthritis
4. Bacterial infections
5. Sudden pooling of blood in the spleen and liver congestion
6. Lung and heart injury
7. Leg ulcers
8. Aseptic necrosis and bone infarcts (death of portions of bone)
9. Eye damage

Some features of sickle cell anemia that can occur at any age include

1. Fatigue
2. Anemia
3. Pain crises
4. Bone infarcts

Many features typically occur in certain age groups.

Infants with sickle cell anemia do not develop symptoms in the first few months of life because the hemoglobin produced by the developing fetus (fetal hemoglobin) protects the red blood cells from sickling. This fetal hemoglobin is absent in the red blood cells that are produced after birth so that by 5 months of age, the sickling of the red blood cells is prominent and symptoms begin.

Infants and younger children can suffer signs and symptoms of

1. fever,
2. abdominal pain,
3. pneumococcal bacterial infections,
4. painful swellings of the hands and feet (ductility's), and
5. splenic sequestration.

Adolescents (preteens and teens) and young adults more commonly develop

1. Leg ulcers
2. Aseptic necrosis
3. Eye damage

Symptoms in adult typically are intermittent pain episodes due to injury of bone, muscle, or internal organs.

Diagnosis of SCD: A blood test can check for the defective form of hemoglobin that underlies sickle cell anemia. In the United States, this blood test is part of routine newborn screening. But older children and adults can be tested, too. In adults, a blood sample is drawn from a vein in the arm. Sickle cell disease can be identified by the following tests

- review of newborn screening results
- hemoglobin electrophoresis

- complete family history
- additional blood tests

Management and treatment of sickle cell disease

Sickle cell disease usually requires lifelong treatment. Children and adults with sickle cell disease are supported by a team of different healthcare professionals working together at a specialist sickle cell centre. People with sickle cell disease (SCD) start to have signs of the disease during the first year of life, usually around 5 months of age. Symptoms and complications of SCD are different for each person and can range from mild to severe. Treatment involves a number of measures. While it has been historically recommended that people with sickle cell disease avoid exercise, regular exercise may benefit people [13]. Dehydration should be avoided [14]. A diet high in calcium is recommended15 but the effectiveness of vitamin D supplementation remains uncertain [16]. L-glutamine use was supported by the FDA starting at the age of five, as it decreases complications [17].

Hydroxyurea is the Gold- Standard Treatment for Sickle Cell Disease

Hydroxyurea or hydroxycarbamide (HU) is the key therapeutic tool for SCD approved by Food and Drug Administration (FDA) and European Medical Agency (EMEA). US and European guidelines highlighted that HU should be available for all SCD patients from pediatric to adult populations [18, 19].

Studies in SCD show a multimodal action of HU, which (i) increases HbF production, resulting in delayed HbS polymerization; (ii) reduces hemolysis and increase NO availability targeting cGMP production; (iii) modulates endothelial activation and reduces neutrophil counts, contributing to the reduction of chronic inflammation [20-24]. Long-term use of HU has been shown to be safe and well-tolerated in large cohorts of children and adults with SCD, reducing mortality and morbidity of both children and adult patients [18, 25–28]. Indeed, HU reduces (i) the frequency of VOC and the rate of hospitalization; (ii) the incidence of ACS; (iii) the transfusion requirements; and (iv) the severity of dactilitis in SCD pediatric population [21, 32–36].

The mainstay of treatment of patients with sickle cell disease (SCD) remains blood transfusion or hydroxyurea therapy.

Blood transfusion

Transfusions can be administered as a simple transfusion or as an exchange transfusion. The aims of transfusion in SCD are both to increase oxygen-carrying capacity and to decrease the proportion of sickle hemoglobin (HbS) relative to hemoglobin A (HbA) to prevent or reverse the complications of vaso-occlusion. In the acute situation, simple transfusion will increase oxygen-carrying capacity but with a risk of hyper viscosity if the Hb is increased to significantly over the patient's baseline. Therefore, the target Hb should be 10 g/dL in patients with homozygous HbS (HbSS) [29]. Exchange transfusion has the advantage of both increasing oxygen-carrying capacity and reducing HbS%. In patients on long-term transfusion, both repeated simple and exchange transfusion can maintain a low HbS%, and if HbS% is maintained below 30% to 40%, Hb can safely be maintained at a higher level with less risk of hyper viscosity. Simple transfusion is the most common method of transfusion used in chronic transfusion programs, particularly in children, but at the cost of high rates of iron loading. Most patients on long-term simple transfusion will need iron chelation therapy after approximately 1 year of transfusion, and lack of adherence to iron chelation will result in iron overload.

Stem cell transplantation

The only cure available to patients with sickle cell disease is stem cell transplantation. However, the selection of patients who should benefit from this treatment modality is controversial. Transplant has been performed, for the most part, in patients who have suffered a stroke, have had multiple episodes of acute chest syndrome, or have had recurrent vaso-occlusive crises (≥3 episodes requiring hospitalization per year), ie, patients considered to have the worst disease severity [30]. Controversies have arisen not only about whom to transplant but also about the optimal age to transplant, source of donor cells, and type of conditioning regimen.[31-35] Most stem cell transplants thus far have relied upon myeloablative conditioning regimens and have been bone marrow–derived with human leukocyte antigen (HLA)-matched sibling donors as the source of stem cells [36, 37]. But the probability of an individual having a matched sibling donor is only 16%-20% among minorities if an 8 of 8 allele match is sought [31, 38]. The effort to expand the availability of transplant for most patients with sickle cell disease has led to consideration of alternative donor sources, such as cord blood, matched unrelated, and haploidentical cells.

Avascular necrosis

When treating avascular necrosis of the bone with sickle cell disease, the aim of treatment is to reduce or stop the pain and maintain joint mobility [39]. Current treatment options include rest the joint, physical therapy, pain-relief medicine, joint replacement surgery, or bone grafting [39]. High quality, randomized, controlled trials are needed to assess the most effective treatment option and determine if a combination of physical therapy and surgery is more effective than physical therapy alone [39].

Malaria

The relationship between malaria and SCD is an intriguing one. The persistence of the sickle mutation at such high frequency in African populations in spite of the severity of SCD has been attributed to the fact that heterozygous sickle trait confers protection against severe and life-threatening malaria (in particular cerebral malaria caused by *Plasmodium* falciparum). The presence of HbS is associated with reduced parasitic invasion of erythrocytes, impaired multiplication, and accelerated clearance of parasites by the spleen, as RBC infection produces intracellular hypoxia, provoking sickling and hence splenic filtration of parasitized cells [40]. It might be assumed that homozygous SCD would confer greater resistance to malaria, however co-existence of the two is associated with increased mortality and morbidity, and malaria is the most common precipitating cause of crisis in endemic countries [41].

Folic acid and penicillin

From birth to five years of age, penicillin daily, due to the immature immune system that makes them more prone to early childhood illnesses, is recommended.[42] Dietary supplementation of folic acid had been previously recommended by the WHO [43]. A 2016 Cochrane review of its use found "the effect of supplementation on anemia and any symptoms of anemia remains unclear" due to a lack of

medical evidence [44].

Treating other problems: Sickle cell disease can also cause a number of other problems that may be treated [45].

For example

- A short course of hormonal medicine may be prescribed to trigger puberty in children with delayed puberty.
- gallstones may be treated with gall bladder removal surgery.
- Bone and joint pain can be treated with painkillers, although more severe cases may require surgery.
- persistent and painful erections (priapism) may require medication to stimulate blood flow or using a needle to drain blood from the penis.
- Leg ulcers can be treated by cleaning the ulcer and dressing it with a bandage.
- people at increased risk of having a stroke, or those who have had a stroke, may need regular blood transfusions or treatment with hydroxycarbamide
- Acute chest syndrome, a serious lung condition, usually requires emergency treatment with antibiotics, blood transfusions, oxygen and fluids given into a vein – hydroxycarbamide may be needed to prevent further episodes.
- People who need a lot of blood transfusions may also need to take medicine called chelation therapy. This reduces the amount of iron in their blood to safe levels.

Prognosis in SCD

When talking about the prognosis for people with SCA, experts tend to look at mortality rates [46].

The mortality rate of SCA for children has dropped dramatically over the last few decades. A 2010 review references a 1975 study indicating a mortality rate of 9.3 percent for people with SCA under the age of 23. But by 1989, the mortality rate for people with SCA under the age of 20 dropped to 2.6 percent.

Prevention of SCD

SCD is an inherited condition, therefore you cannot prevent it. However, it is possible to be tested for sickle cell trait. If you are pregnant, you can have chorionic villus sampling (CVS) or amniocentesis (amnio) to test for SCT or SCD. A genetic counsellor can help you navigate both your blood test results and the questions that come up afterward. Looking at the test results from both you and your partner, they can give you more specific information about the chances of your child having either SCT or SCD. Finding out that any future children with your partner could have SCA can also be difficult to process. Genetic counselors can help you navigate these emotions and consider all of the options available to you.

Conclusion

Sickle cell disease (SCD) is a potentially devastating condition that is caused by an autosomal recessive inherited haemoglobinopathy which results in the vaso-occlusive phenomena and haemolysis. Sickle cell is a hereditary chronic condition that can manifest symptoms in a patient as early as 5-6 months. This means that the treatment is for life. This condition can affect practically every system in the body and put the patient in risk of infections, stroke and other conditions. Sickle cell patient require extensive psychological support. There have been significant advances in the management of sickle cell disease leading to increased survival and a decrease in complications. Transfusions play a major role in preventing complications and end-organ dysfunction. Hydroxyurea is very useful in these patients, but its role may be limited in certain circumstances. Early diagnosis, prompt treatment and extended screening programme are necessary to reduce morbidity and mortality.

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