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Sickle Cell Disease (SCD)

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Abstract

Sickle cell anemia (SCA) is a disease that is caused by the formation of an abnormal hemoglobin type, which can bind with other abnormal hemoglobin molecules within the red blood cells (RBCs) to cause rigid distortion of the cell. This distortion prevents the cell from passing through small blood vessels; leading to occlusion of vascular beds, followed by tissue ischemia and infarction. Infarction is frequent all over the body in patients with SCA, leading to the acute pain crisis. Over time, such insults result in medullary bone infarcts and epiphyseal osteonecrosis. In the brain, cognitive impairment and functional neurologic deficits may occur due to white matter and gray matter infarcts. Infarction may also affect the lungs increasing susceptibility to pneumonia. The liver, spleen, and kidney may show infarction as well. Sequestration crisis is an unusual life-threatening complication of SCA, in which a significant amount of blood is sequestered in an organ (usually the spleen), leading to collapse. Lastly, since the RBCs are abnormal, they are destroyed, resulting in a hemolytic anemia. However, the ischemic complications in patients with SCA disease far exceed the anemia in clinical significance.

Keywords: Sickle, update, hydroxyuria

1. Introduction

1.1. Hemoglobinopathies

Hemoglobin is needed for transfer of oxygen to different body organs. The shape of the red blood cell can be affected by the type of the hemoglobin. Hemoglobinopathies are hemoglobin abnormalities that influence its formation. The severity of these disorders varies widely and can lead to death. Hemolytic anemia is a common presentation for hemoglobinopathies. Sickle cell anemia is one of these hemoglobinopathies.

1.2. Definition of sickle cell anemia

Sickle cell anemia is an inherited disease characterized by the presence of an abnormal hemoglobin called hemoglobin S (HbS). During deoxygenation, the red blood cell (RBC) shape changes from the biconcave shape to the sickle shape due to the abnormal hemoglobin. The shape of the RBC changes back to the biconcave shape after reoxygenation. However, the frequent sickling and unsickling leads to hemolysis and anemia. [1]

1.3. Inheritance of hemoglobinopathies

There are three types of normal hemoglobin: hemoglobin A (HbA), hemoglobin F (HbF), and hemoglobin A_2 (HbA$_2$). Each hemoglobin molecule contains four polypeptide chains that differ from one type to another. Hemoglobin A contains 2 alpha globin chains and two beta globin chains and comprises 95–97% of the normal hemoglobin. Hemoglobin A_2 contains 2 alpha globin chains and two gamma globin chains and comprises 2.5–3.5% of the normal hemoglobin. Hemoglobin F contains 2 alpha globin chains and two delta globin chains and comprises <1% of the normal hemoglobin. The gene coding for the α globin chain is sited on chromosome 16, however, the non-α globin gene cluster is located on chromosome 11. [2,3]

There is a transversion mutation at the sixth codon of the β globin gene from A to T which produces HbS, with a substitution at the 6th amino acid position in the β globin polypeptide chain to be valine instead of glutamic acid. Patients with sickle cell anemia (homozygous to HbS gene) have HbS instead of HbA associated with formation of HbF and HbA$_2$. Some patients with sickle cell disease (double heterozygous) have got HbS together with other types of abnormal hemoglobin or even they are sickle-thalassemia. However, thalassemias on their own occur more frequently giving rise to homozygous disease conditions.[4]Abnormal hemoglobin is responsible for hemolysis and vaso-occlusion that can lead to tissue infarction. [5,6]

1.4. Pattern of inheritance of hemoglobinopathies

Hemoglobin abnormalities and the thalassemias are inherited as autosomal recessive (AR) disorders, where carrier parents transmit the disease to their offspring. If both parents are heterozygotes for HbS, there is a 25 per cent chance of having a homozygous HbSS (Sickle cell anemia, SCA) child. A double heterozygote state occurs when one parent is a heterozygote for HbS and the other is heterozygote for one of the abnormal HbS or thalassemias. Heterozygotes are asymptomatic carriers (traits), while the SCD is presented in the homozygotes and the double heterozygotes for two abnormal hemoglobin genes or HbS and the thalassemias.[6]

1.5. Pathophysiology of sickle cell anemia

Sickle cell anemia is a single gene disorder which is produced by a point mutation in the beta globin gene which is found on chromosome 11. This leads to replacement of glutamic acid (a hydrophilic amino acid) in the sixth position with valine (a hydrophobic amino acid). [7] Hemoglobin S is formed from the association of two α-globin subunits with two mutant β-globin subunits. On exposure to hypoxic conditions, the absence of a polar amino acid at position six of the β-globin chain encourages the non-covalent polymerization (aggregation)

of hemoglobin, which changes the shape and elasticity of RBCs.In low oxygen media, the cells attain an abnormal shape which is not elastic. When normal oxygen tension is regained, the cells fail to return to their normal shape. Therefore, these distorted RBCs cannot pass through narrow capillaries, leading to occlusion of blood vessels. Vaso-occlusion results in hand-foot syndrome in children. Furthermore, infections, stroke, and acute chest pain are some of the major complications. Most of these complications start in early life, but become clearer with advancing age. Infections, dehydration, cold weather, and stress are considered as precipitating factors for these complications. Treatments of SCD are mostly directed toward prevention of or decreasing sickling and thus reducing the incidence of vascular occlusion. [5-10]

The abnormal shape of the RBCs leads to their destruction by hemolysis. A compensatory bone marrow hyperplasia is not able to match the rate of RBC destruction.[8] Sickle cells only survive 10–20 days in comparison to normal RBCs which typically live 90–120 days.[9]

2. Epidemiology of sickle cell gene

Sickle cell anemia is most common among people from Africa, India, the Caribbean, the Middle East, and the Mediterranean. In the Middle East, the first report of HbS and thalassemias came from Egypt. [11,12] The presence of HbS in Eastern Saudi Arabia was reported by Lehmann. [13] Many studies on hemoglobinopathies have been documented from most countries of the Middle East. Table (1) presents a brief history for identification of abnormal hemoglobins in the Middle East. HbS is the major variant identified in all areas. [14]

Discovery country	Year
First case of SCD in Egypt	1951
HbS in Middle East	1959
HbO-Arab in Egyptian family	1960
HbS in Saudi Arabia	1963
HbS and HbO-Arab in Sudan	1966
HbC in Egyptians	1967
Mild SCD in Saudi Arabia	1969
SCD in Kuwait	1969
HbH disease in Kuwait	1969
HbS in Egyptian western desert	1974
HbC in Libya	1975
HbS in Abu Dhabi	1980
HbC in Saudi Arabia	1979
HbE and HbD in Abu Dhabi	1979
HbO-Arab in Saudi Arabia	1980
HbS. α- and β-thal in several regions of Saudi Arabia	1967–1982

Table 1. Hemoglobinopathies in the Middle East Arab countries

3. Clinical manifestations of sickle cell anemia

Sickle cell anemia presents with severe hemolytic anemia interrupted by crises. Symptoms of anemia in SCD are often mild in relation to the severity of the anemia because HbS gives up oxygen (O_2) to tissues relatively easily compared with HbA, its O_2 dissociation curve is shifted to the right (see Figure 1). [15]
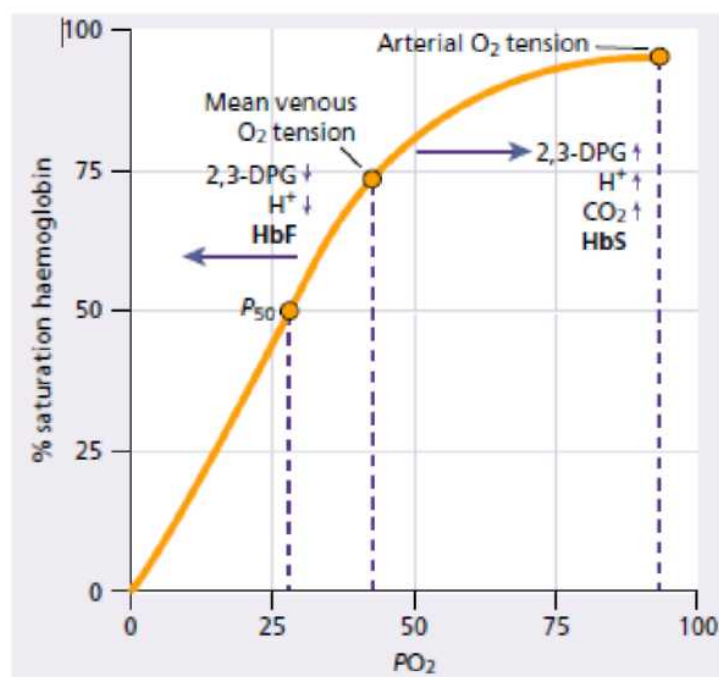

Figure 1. The hemoglobin oxygen dissociation curve. 2,3-DPG, 2,3-diphosphoglycerate.

The clinical presentation of SCD is variable, with some patients having a normal life; however, some patients show increased morbidity and mortality due to severe thrombotic, aplastic, and sequestration crises. [15]

3.1. Vaso-occlusive crises

The vaso-occlusive crises are the commonest. Their etiology is usually attributed to low oxygen tension as in high altitude, water loss, and infection. Vaso-occlusion leads to severe pain especially in bones (hips, shoulders, and vertebrae) (Figures 2–4). [15] Infarcts of the small bones lead to painful dactylitis (hand-foot syndrome). It is usually the first presentation of the disease and may lead to digits of varying lengths (Figure 4). [15] Soft tissues affected include the lungs and the spleen. The most serious vaso-occlusive crisis is of the brain (a stroke occurs in 7% of all patients) or spinal cord.

Transcranial Doppler ultrasonography detects abnormal blood flow indicative of arterial stenosis. This can predict the occurrence of strokes in children.[15]

Figure 2. Radiograph of the pelvis of a young man of West Indian origin, which shows avascular necrosis with flattening of the femoral heads, more marked on the right hip, coarsening of the bone architecture, and cystic areas in the right femoral neck caused by previous infarcts.
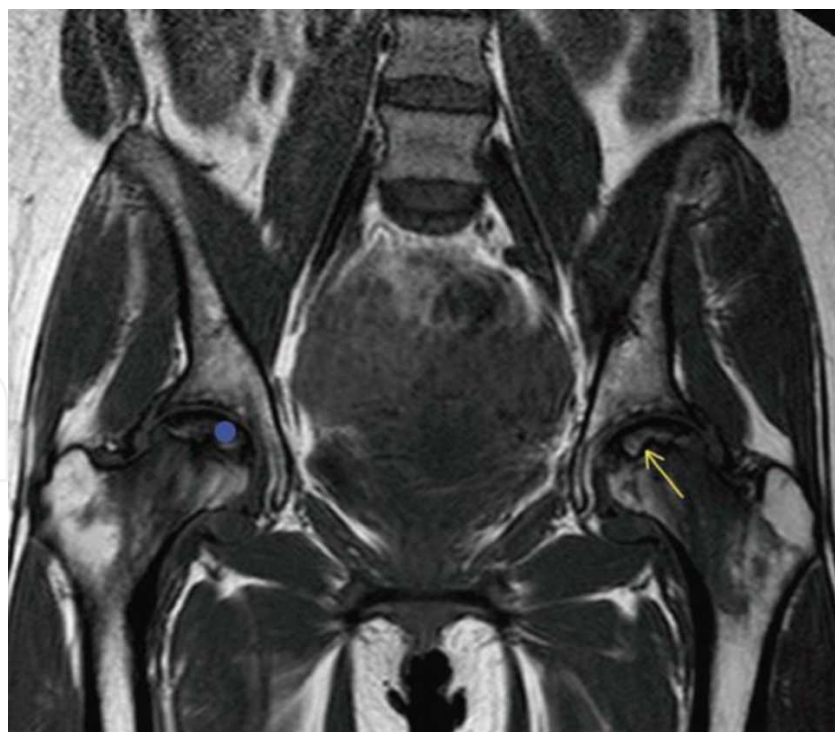

Figure 3. Sickle cell anemia. Coronal hip MRI image revealing established osteonecrosis of femoral heads bilaterally (yellow arrow) with crescentric sclerotic margin (blue dot) as a consequence of sickle cell disease (Courtesy of Dr A. Malhotra).

Figure 4. Sickle cell anemia: **(a)** painful swollen fingers (dactylitis) in a child; and **(b)** the hand of an 18-year-old Nigerian boy with the ' hand - foot ' syndrome. There is marked shortening of the right middle finger because of dactylitis in childhood affecting the growth of the epiphysis..

3.2. Sequestration crises

These crises are caused by pooling of blood, with severe exacerbation of anemia. The acute sickle chest syndrome is the most common cause of death after puberty. The patients present with dyspnea, arterial hypoxia, chest pain, and lung infiltrates on chest X-ray. Treatment includes analgesics, oxygen, exchange transfusion, and ventilator support if needed. Hepatic and splenic sequestration may lead to severe disease necessitating exchange transfusion. The splenic sequestration is characteristically found in infants and clinically presents with an enlarging spleen, decreased hemoglobin, and abdominal pain. The patients are treated mainly with blood transfusion, and they must be monitored frequently as rapid progression may occur. The crises are usually recurrent and the patient is usually in need of splenectomy. [15]

3.2.1. Aplastic crises

Aplastic crises are due to parvovirus infection and are characterized by a sudden fall in hemoglobin, usually requiring transfusion. The patient shows anemia together with reticulocytopenia. [15]

3.2.2. Hemolytic crises

In these crises, the patients show a higher rate of hemolysis with a decline in hemoglobin level associated with reticulocytosis. Hemolytic crises usually accompany vaso-occlusive crises.

3.2.3. Other clinical features

Chronic hemolytic anemia is the main clinical presentation of SCD with recurrent attacks of acute painful vaso-occlusive crises. SCD is also associated with multi-organ acute and chronic complications. The clinical features of SCD are summarized in Table (2). The size of the spleen is increased during infancy and early childhood but later is usually decreased due to infarction

(autosplenectomy). Pulmonary hypertension and tricuspid regurgitation may occur and increases the risk of mortality. Retinopathy and priapism may also complicate the course of patients with SCD. Chronic liver damage may occur due to microinfarction associated with gall bladder stones. Renal medullary infarction with papillary necrosis may be present in the course of sickle cell anemia. The ability of the kidney to concentrate urine may be lost leading to dehydration and vaso- occlusive crises, and nocturnal enuresis is common. [15]

Although the genetic aberration in SCD is precisely well understood, there is a clear variability in the clinical severity of the disease among patients. Some patients lead a normal life, free of problems; others may show severe crises or have fatal complications. The life expectancy of patients with SCD is decreased but is increasing due to the improvement in supportive therapies, especially prophylactic antibiotics, stroke screening in early childhood, increased administration of hydroxycarbamide or transfusion, and improved care. Intensive care is needed for patients complicated by acute chest syndrome (ACS), acute stroke, or acute renal injury.[16]

Complication	Clinical presentation
Painful crisis	These crises occur in most of patients with SCD; they are variable in frequency and severity
	May lead to a chronic pain syndrome
Neurological	Microvascular occlusion may be seen on MRI. May lead to cognitive disability.
	Stroke affects 10% of children; it is a leading cause of morbidity and mortality. Can be prevented by regular blood transfusion
Pulmonary	Acute chest syndrome
	Asthma, fibrotic lung disease
	The main cause of death in adults, high risk of acute respiratory failure There is an increased association with airway hyperactivity.
Gastrointestinal	Most patients have gall bladder stones due to hemolysis
Cholelithiasis Hepatopathy	Decompensated liver disease may be present in some patients
Renal, Urological	Chronic renal failure occurs in 20% of patients
	Priapism may be present leading to sexual dysfunction
Ophthalmology	Proliferative retinopathy is common in patients with HbSC disease
Orthopedic	Common complication of hip and shoulders, requiring replacement
Avascular necrosis	Salmonella is the most common organism
Osteomyelitis	
Hematological	Chronic hemolysis, usual Hb 6–9 g/dL, higher in HbSC
Hemolytic anemia	Parvovirus B19 infection may trigger red cell aplasia.
Aplastic crisis	The combination of red cell aplasia and hemolysis can be fatal
Splenic sequestration	Typically seen in infants with a rapidly enlarging spleen

Table 2. Clinical presentation of sickle cell disease (SCD)

3.3. Diagnosis

In HbSS, the complete blood count shows hemoglobin levels in the range of 6-8 g/dL with reticulocytosis (due to compensatory bone marrow hyperplasia). In other forms of sickle-cell disease, Hb levels tend to be higher. A blood film may reveal sickle shaped cells and features of hyposplenism (target cells and Howell-Jolly bodies) (Figure 5). [15]
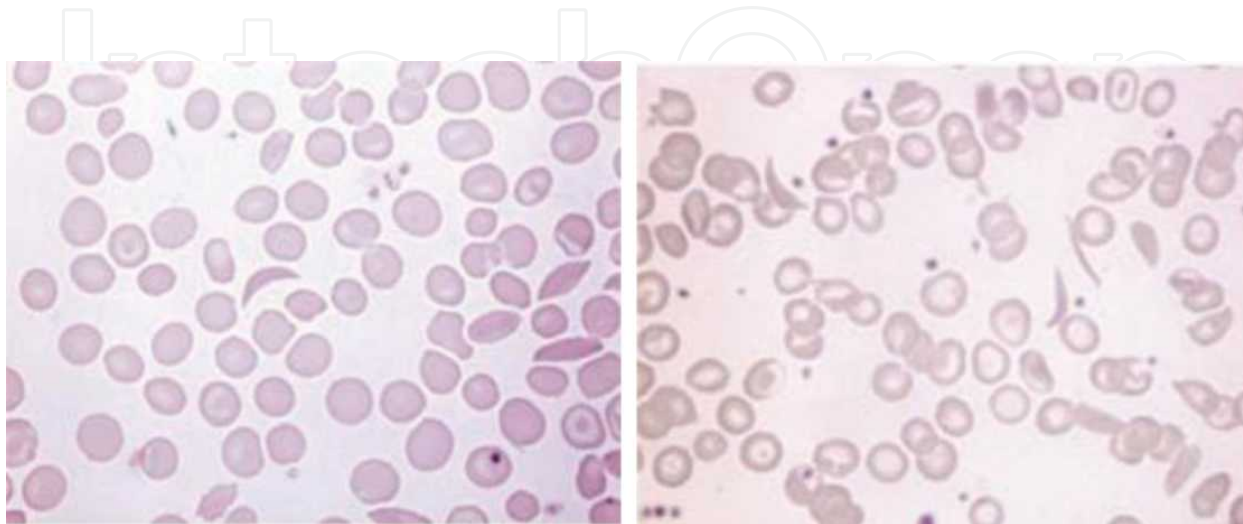

Figure 5. Sickle cell anemia: peripheral blood films showing deeply staining sickle cells, target cells and polychromasia.

Hemoglobin electrophoresis is used to diagnose the presence of abnormal hemoglobin types. Hemoglobin S and hemoglobin SC are the two most common forms detected in sickle cell-diseased patients. High-performance liquid chromatography (HPLC) is used to confirm the diagnosis. Genetic study is not frequently done as electrophoresis and HPLC are accurate in detecting HbS and HbC.[17]

Infection may precipitate the acute sickle-cell crisis. Therefore, a urinalysis to detect an occult urinary tract infection, and chest X-ray to look for occult pneumonia should be performed.[18]

Genetic counseling is usually needed for carriers of SCD before they have a child. Fetal blood sampling or amniocentesis can be done to see if the fetus has the disease. Miscarriage is more common with fetal blood sampling than with amniocentesis.

4. General principles of management of SCD

Crises management is usually supportive unless blood transfusion is indicated. The aim of treatment is to prevent the sickling of RBCs, dehydration, hypoxia, and acidosis that can induce sickling. Painful attack is the main presentation. Subcutaneous morphine or another strong opiate is frequently required for management of severe attacks of pain. Pethidine can precipitate Grand mal seizures; therefore, it is preferable to be avoided. Satisfactory fluid intake is mandatory.

4.1. Folic acid and penicillin

Children born with sickle-cell disease will take folic acid (1 mg dose) daily for life. In addition, Patients from birth to five years of age have to take penicillin daily due to susceptibility to pneumococcal infection.

4.2. Acute chest syndrome

Acute chest syndrome is an acute illness with fever and/or respiratory symptoms associated with a new lung infiltrate. It is the main cause of mortality in adults with SCD and the most common cause of intensive care unit admission. The patient who needs mechanical ventilation is reported to have a mortality rate of 5%.[16] Symptoms include cough, wheeze, dyspnea, and chest pain, which may be pleuritic or affect the ribs and sternum. The acute chest syndrome is unique to SCD and is associated with a more severe course and worse outcome than pneumonia.

Blood transfusion is used to treat patients with acute chest syndrome and will improve the oxygenation. Blood transfusion is useful in less severe cases with a low Hb (<7 g/dL); however, exchange transfusion is needed in severe cases, in patients with high Hb levels, or those with severe hypoxia. The target is a final Hb level of 9–10 g/dL. Severe hypoxia, dyspnea and respiratory acidosis are indications for initiating advanced respiratory support.[19]

4.3. Stroke

Patients with SCD are commonly associated with ischemic and hemorrhagic strokes, with a prevalence rate of more than 5%. Incidence of stroke is greatly reduced after the introduction of transcranial Doppler screening and primary stroke prevention with transfusion. A stroke may be precipitated by dehydration or a coincident illness.

Early imaging is essential to confirm the diagnosis and exclude hemorrhage. MRI is the imaging of choice with high sensitivity and specificity. If the MRI confirms a stroke, immediate exchange transfusion should be done to achieve an HbS less than 30%. Ischemic stroke prevention can be done by long-term exchange transfusion, however the efficacy of anti-platelet therapy in primary or secondary stroke prevention in SCD is not proved.[20]

4.4. Sepsis

Patients with sickle cell anemia have functional hyposplenism. This makes them more susceptible to infection by capsulated organisms. Sepsis caused by gram-negative organisms is common together with osteomyelitis. Children with sickle cell anemia have to be vaccinated against pneumococcal, meningococcal, and *Hemophilus influenza* infection. Oral penicillin could be given on daily basis after the time of diagnosis to guard against pneumococcal infection. [21]

4.5. Other complications of SCD

Patients with SCD have low renal concentrating ability and are therefore susceptible to dehydration. Over time, the patients may show proteinuria and chronic renal impairment as

a result of glomerular damage. This leaves patients liable to acute kidney injury during a crisis. Chronic lung disease is common and manifests as either a restrictive lung defect or an overnight hypoxia and sleep apnea. Pulmonary hypertension is more common in SCD and can lead to marked hypoxia.[16]

4.5.1. Admission to critical care unit

Patients with sickle cell anemia may need admission to the intensive care unit either due to liver cell failure, sepsis, or multi-organ damage. This acute deterioration may necessitate urgent blood transfusion aiming for an Hb of 9–10 g/dL and HbS% of less than 30%. This will improve tissue oxygenation and perfusion, whatever the underlying etiology.[22]

4.5.2. Transfusion in SCD patients

Regular blood transfusion is needed to prevent brain strokes. Special situations such as circulatory disturbances, sequestration crises and priapism may need blood transfusion to optimize oxygen transport. [23]

Partial exchange transfusion is usually preferred to simple transfusion if routine or multiple transfusions are necessary. It decreases the iron overload and prevents increased blood viscosity.

5. Health maintenance

There are some lines of treatment that decreases the morbidity and mortality in children with sickle cell anemia, including:

1. Vaccination against capsulated organisms (e.g. Hib, Pneumococci, and meningococci).

2. Hydroxyurea and folic acid supplementation.

3. Oral penicillin prophylaxis in children less than 6 years.

4. Early detection and management of severe bacterial infections.

Hydroxyurea, by increasing HbF and thereby reducing sickling, decreases painful crises (by 50%) and decreases acute chest syndrome and transfusion requirements. The dose of hydroxyurea is variable and is adjusted to increase HbF.

Hydroxyurea is more effective in some patients if given with erythropoietin (40,000-60,000 units/week). However, hydroxyurea can cause neutropenia and thrombocytopenia. Hydroxyurea is also a teratogen and should not be given to females in the child-bearing period.

The screening for stroke in children with SCD is recommended to be done from age 2 to 16 years using transcranial Doppler flow studies. Risky children can get benefit from prophylactic, chronic partial exchange transfusions keeping HbS at < 30% of total Hb.

Erythropoietin use in patients with anemia not related to chemotherapy is associated with high incidence of venous thromboembolism and cardiopulmonary complications (as myocardial infarction); it is not useful in patients with sickle cell disease except possibly if given in combination with hydroxyurea.[23]

6. Novel medications

6.1.1. Omega-3 fatty acids

Omega-3 fatty acids are significantly reduced in SCD patients. In a single-center study conducted in Sudan, there was a randomized, placebo-controlled, double-blind design for studying the effect of omega-3 treatment on sickle cell anemia patients. One hundred and forty patients were monitored for 1 year, and it was found that omega-3 treatment leads to a decline in occlusive crises and blood transfusion. Treatment with omega-3 was well tolerated by the patients and needs further study. [24]

6.1. Prasugrel

It is a new thienopyridine P2Y12 ADP receptor antagonist, which inhibits ADP-mediated platelet activation and aggregation. Phase 2 randomized, double-blind, placebo controlled studies to examine safety were completed in adults. There were no hemorrhagic events requiring medical intervention in either study arm. Mean pain rates (percentage of days with pain) and intensity in the prasugrel arm were decreased compared with placebo. But, these results were not statistically significant. It was well tolerated and a phase 3 trial in children is registered. [25]

7. Prognosis

The life span of homozygous patients with SCD has gradually increased to > 50 years. Common causes of death are acute chest syndrome, recurrent infections, pulmonary embolism, infarction of a vital organ, and renal failure. [23]

8. Summary

Sickle cell disease is an inherited hemoglobinopathy affecting mainly the black races and leading to chronic hemolysis. The abnormal HbS found in homozygous patients changes the shape of RBCs to become sickle-shaped. These cells can occlude small blood vessels leading to ischemia and pain. The patients may be complicated by acute chest syndrome, sepsis, sequestration, and aplastic crises. Sickle cell disease is characterized by anemia and can be diagnosed by Hb electrophoresis. Blood transfusion may be needed for these patients.

Occlusive crises are treated mainly by pain killers. Hydroxyurea may decrease the frequency of these crises. Early management of bacterial infections and vaccination against capsulated organisms can prevent sepsis.

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