

AN OVERVIEW ON SICKLE CELL DISEASE PROFILE

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ABSTRACT

Sickle cell disease (SCD) is a very devastating condition caused by an autosomal recessive inherited haemoglobinopathy. This disease affects millions of peoples globally which results in serious complications due to vasoocclusive phenomenon and haemolysis. This genetic abnormality is due to substitution of amino acid valine for the glutamic acid at the sixth position of beta chain of haemoglobin. This disease was described about one hundred year ago. The haemoglobin S (hbS) produced as result of this defect is poorly soluble and polymerized when deoxygenated. Symptoms of sickle cell disease are due to chronic anaemia, pain full crises, acute chest syndrome, stroke and susceptibility to bacterial infection. In recent years measures like prenatal screening, better medical care, parent education, immunization and penicillin prophylaxis have successfully reduced morbidity and mortality and have increased tremendously life expectancy of affected individuals. Three principal current therapeutics modalities available for childhood SCD are blood transfusion, Hydroxy urea and bone marrow transplantation. Genetic counseling, continued medical education for health professionals about sickle cell disease, its complications and management is necessary. World health organization has actively promoted several national screening programmes with dual goals of informing reproductive choice and thereby reducing the number of severely affected children.

Keywords: Anaemia, Crises, Haemoglobin, Polymerization, Sickle cell anaemia, vaso-occlusive

INTRODUCTION

Sickle cell Disease (SCD), is a group of genetic disorders commonly seen in United States and Third world countries. The term *disease* is applied to this condition because the inherited abnormality causes a pathological condition that can lead to death and severe complications. It is inherited autosomal recessive disorder with presence of HbS in blood. Not all inherited variants of haemoglobin are detrimental, a concept known as genetic polymorphism. This disease has significant morbidity and potentially a fatal disease. Patients undergo painful crises and may have renal failure, heart failure, infections and other complications. In addition to its impact on patient's health it causes huge financial burden, because heavy expenses are required for frequent hospitalization, medication and blood transfusion. Sickle cell has a profound impact, not just on the patient, but on the whole family dynamic. Regular follow up and care may improve patient's ability to lead productive life and reduction in acute care cost. Because of its significant impact on society and the individual, it is important for the medical fraternity to completely understand this disease, it's precipitance and proposed pathophysiology, evaluation and treatment¹.

Categorization of Sickle Cell Disease (SCD)

The sickle cell disease is categorized into three sub-headings :- (a) Sickle Cell Disorder: It includes all states in which a sickle gene is inherited. This group includes all patients with a positive sickle preparation smear. The patient may or may not be symptomatic.(b)Sickle Cell Disease: It is a disorder in which significant morbidity, such as organ failure or vaso-occlusive pain crises (VPC), results from the sickling of red blood cells.(c)*sickle cell*

anemia : It is usually reserved specifically for patients who are homozygous for hemoglobin S (hemoglobin SS).

Historical Background of SCD

Sickle cell disease is caused by one point mutation in beta chain of haemoglobin causing such dreadful disease which created history. Historical aspects of this disorder are described briefly in figure No.1²⁻²³.

Natural History of the Disease

The study of the natural history of this disease is also called as the Cooperative Study of Sickle Cell Disease (CSSCD). It was commissioned in 1978 by the National Heart, Lung, and Blood Institute to characterize prospectively the clinical course of SCD in more than 4,000 patients from 23 centers across the United States²⁴.

It was observed that more than 50% of patients with SCD have at least one crisis per year and the association between multiple pain episodes and early death in young adults²⁵⁻²⁶. Treatment with hydroxyurea also puts light on incidence of complicating condition like allo-immunization²⁷, pregnancy²⁸ and surgery²⁹. It has improved the survival rate of patients with SCD but the survival is associated with a discernible increase in the incidence of chronic organ dysfunction, especially pulmonary hypertension³⁰. The lesson learnt from the study of the natural history of SCD underscored the fact that this disease, which is caused by a single miss-sense mutation in a gene whose expression is restricted to the hematopoietic system, can have wide-ranging manifestations and complications that affect every aspect of the life of afflicted patients.



Figure 1: History of Sickle cell Disease

Genetics of SCD

Sickle cell disease is a hereditary hemoglobinopathy resulting from inheritance of a mutant version of the β -globin gene (β^A) on chromosome 11, this gene codes for assembly of the β -globin chains of the protein hemoglobin A. The mutant β -allele (β^S) codes for the production of the variant hemoglobin, hemoglobin S. The heterozygous carrier state is known as sickle cell trait (SCT) ³¹. The sickle cell gene mutation is a point mutation in the sixth codon of exon 1 in the β^A gene, replacing adenine with thymine (guanine-adenine-guanine \rightarrow guanine-thymine-guanine) ³² as depicted in figure No.2³³.

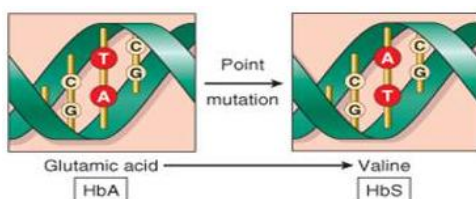


Figure 2: Representing replacing adenine with thymine

Homozygosity for the sickle mutation (i.e., HbSS disease) is responsible for the most common and most severe variant of SCD. Several other genetic variants of SCD result from the interaction of different mutations of the human β -globin genes Table No.1 ³⁴. Sickle-cell disease symbolizes all genotypes containing at least one sickle gene, in which HbS makes up at least half the haemoglobin present. In addition to the homozygotic HbSS disease (sickle-cell anaemia), five other major sickle genotypes are linked to the disease. Production of HbS is a monogenic event, determining the polymerisation of the deoxygenated haemoglobin. The process is an indispensable but insufficient determinant of phenotype. By contrast, the phenotype of sickle-cell anaemia is multigenic ³⁵. Other genes, unlinked to the β -globin locus, contribute in relevant pathological events (e.g., rapid destruction of sickle cells, dense cell formation and adhesion to endothelium) that are controlled by many genes, known as pleiotropic or secondary effector genes³⁶. Severity of sickle cell anaemia varies greatly among individuals, since not all patients have identical pleiotropic genes. Some carriers have mutated genes that can either ameliorate or exacerbate the phenotype.

Table 1: Depicts genotypes and phenotypes of different sickling disorders.

Genotype	Interacting genes	Typical clinical severity	% of Hb type/total Hb in a typical patientA,B				
			Hb S	Hb A	Hb F	Hb C	Hb A2
HbAA (normal)	b and b	None	-	96%	2%	-	2%
HbSS	b ^s and b ^s	Severe	95%	-	3%	-	2%
HbSC	b ^s and b ^c	Mild	48%	-	3%	47%	2%
HbSb⁰	bS and b ⁰ -thalassemia	Severe	93%	-	2%	-	5%
HbSb+	bS and b+-thalassemia (severe thalassemia mutation)	Moderate	85%	6%	5%	-	4%
HbSb+	bS and b+-thalassemia (mild thalassemia mutation)	Mild	70%	23%	3%	-	4%

“Typical” refers to the most common presentation of a particular sickling genotype. It should be noted that in many patients, the genotype does not accurately predict the clinical phenotype. B Assessed by gel electrophoresis. Hb A2, minor adult hemoglobin.

When the b^s (beta globin S) gene interacts with the b^c (glutamic acid at position 6 is replaced by lysine) gene, the resulting sickling disorder known as HbSC disease is typically very mild³⁷. When a b^s gene interacts with a b-thalassemia gene (a mutant b-globin gene that either fails to produce normal b-globin mRNA or produces it at markedly decreased levels), the severity of the resulting sickling disorder depends on the severity of the co-inherited b-thalassemia mutation. When the co-inherited b-thalassemia gene is completely inactive (i.e., b⁰-thalassemia), the resulting sickling disorder known as Sb⁰-thalassemia tends to be as severe as that of homozygous HbSS disease³⁸. In contrast, when the co-inherited b-thalassemia gene is partially active (i.e., b+-thalassemia), the resulting sickling disorder known as Sb+-thalassemia can have a spectrum of clinical severity. If the b+-thalassemia mutation is mild, as is commonly the case in people of African descent, the resulting Sb+-thalassemia tends to be clinically mild. In contrast, if the b+-thalassemia mutation is severe, as is commonly the case in the Mediterranean populations, the clinical sickling disorder tends to be moderate³⁹.

Surprisingly, the sickle gene frequency has remained relatively stable⁴⁰⁻⁴¹. One theory put forth to explain the evolutionary survival of a gene mutation with such devastating clinical manifestations and early morbidity is called balanced polymorphism. According to this theory, the negative effects of a genetic mutation are balanced by its protective benefits, which aids in natural selection. In this case, the Hb S gene offers some benefit in terms of protection against malaria⁴²⁻⁴³. The greatest prevalence of the Hb S gene exists in the malarial regions of Africa, and children with sickle cell trait (true heterozygotes) are afforded some degree of protection against malaria, particularly the type caused by *Plasmodium falciparum*⁴⁴.

Mode of transmission and inheritance of SCD

Sickle cell anemia is transmitted from one generation to another, due to acquisition of two abnormal genes one from each parent. Sickle cell anemia evolves when a heterozygote (AS) (carrier) marries either a fellow carrier or a homozygote (SS) (sufferer). Various conditions associated with inheritance are as under⁴⁵⁻⁴⁶:-

- 1) The marriage between carriers has been found to have 25% chance of having sickler, 25% normal and 50% carrier (Figure No.3 A)
- 2) Marriage between normal and Carrier there is 50% chance of having normal children and 50% carriers (Figure No. 3B).
- 3) The marriage between normal (AA) and homozygote (SS) has been shown to have 100% chance of having carriers (Figure No.3 C).
- 4) The marriage between heterozygote (AS) and homozygote (SS) has been shown to have 50% chance of having a sickler and 50% carrier (Figure No.3 D).
- 5) The marriage between sicklers is very rare. If it occurs then it has 100% chance of having sicklers.

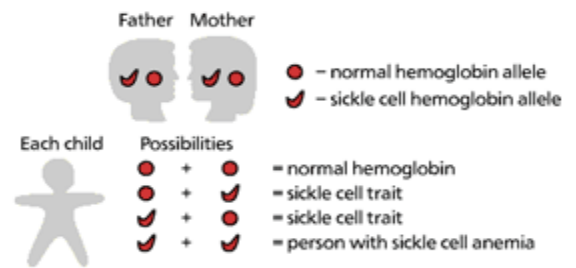


Figure 3A: Two parents carrying the Sickle cell trait.

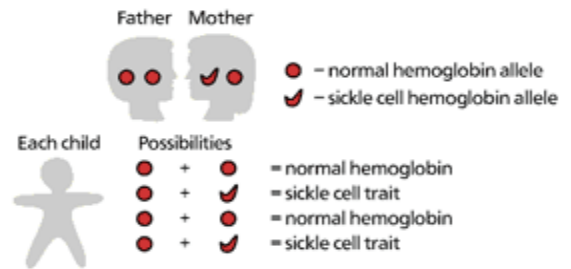


Figure 3B :One parent carrying sickle cell trait and one normal

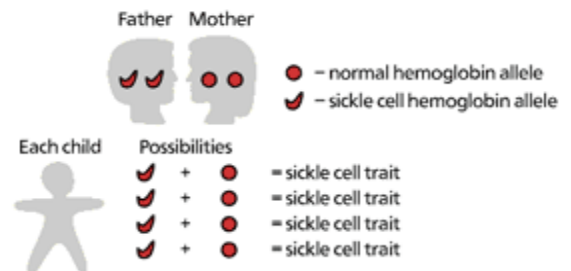


Figure 3C:One parent with sickle cell anaemia and normal.

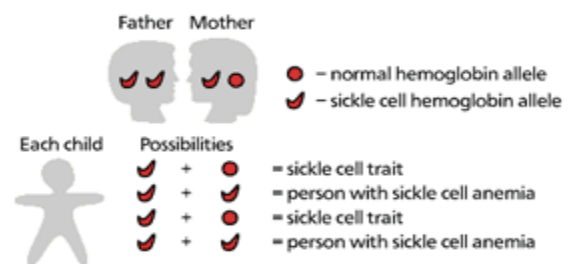


Figure.3 D: One parent with sickle cell anaemia; one parent carrying the trait.

Figure 3 :Represents the inheritance of disease SCD.

Sickle cell hemoglobin has also been inherited in association with other hemoglobin variants such as Hb SC, Hb SD, Hb SE and Hb S alpha or beta thalassemia. These sickle cell traits occur when a gene for sickle cell hemoglobin is inherited from one parent and a gene for either hemoglobin A, C, D, E alpha or beta thalassemia is inherited from the other parent. Although many of the sub-types such as heterozygote hemoglobin HbSD and HbSE are of little clinical significance, a few important sub-types such as Hb SC, HbS beta thalassemia and HbS alpha thalassemia have been isolated these might be present with clinical conditions similar to sickle cell disease. Today sickle cell disease synonymously called sickle cell anemia is the commonest and most severe variant widely distributed throughout the world.

Polymerization of HbS

As a result of the replacement of negatively charged hydrophilic glutamic acid with the non-polar hydrophobic valine at position six on the 146 amino acid β -chain⁴⁷⁻⁴⁸. There is loss of the electrical charge, which results in particular clinical significance. First, the absence of the negative charge significantly destabilizes the structure of oxygenated hemoglobin, causing accelerated denaturation and breakdown⁴⁹⁻⁵⁰.

Second, the nonpolar hydrophobic substitute causes considerable decrease in the solubility of deoxygenated hemoglobin⁵¹. The conformational change due to deoxygenation results in formation of hydrophobic bond between the β^5 -6 valine of one tetramer and the β -85 phenylalanine and β -88 leucine of an adjacent tetramer, thus generating a nidus of polymerized hemoglobin S. Further aggregation of deoxygenated hemoglobin tetramers form long helical strands of polymers. Progression of this process generates a critical nucleus to which additional tetramers bind. Polymerization then proceeds in an explosive autocatalytic fashion, causing the hemoglobin to gelate or precipitate out of solution. These two features of hemoglobin S, instability and insolubility, account for the majority of cellular and clinical pathology⁵² figure No.4 of RBCS polymer formation⁵³.

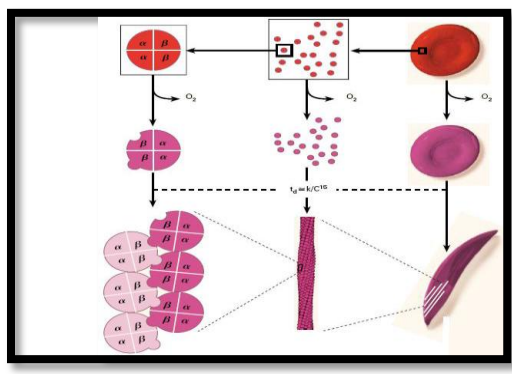


Figure 4: Depicts polymerization of deoxygenated HbS

Histophysiology Associated with HbS

HbS is more unstable than HbA, it exposes the erythrocyte cell membrane to the destructive oxidant potential of free radicals produced due to oxidant potential intracellular iron⁵⁴⁻⁵⁵. Under normal physiological conditions, oxidative damage is limited due to balance between the ROS and the defense system of antioxidant enzymes and antioxidants. Even in healthy individual, ROS such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^\bullet) are produced as a result of intracellular metabolic activity. Oxidative stress is the result of an imbalance between oxidants and antioxidants⁵⁶.

Oxygen is the most important factor responsible for HbS polymerization. Even a minute change in arterial oxygen tension, with oxygen saturation greater than 90%, can result in sickling⁵⁷. Cellular HbS concentration, pH, and temperature are other features that influence polymer formation⁵⁸. Reduction in oxygen availability and drops in pH, in the terminal arteriole and capillary circulation, enhance HbS polymerization.

Obstruction of blood flow is also responsible for complications of sickle cell disease⁵⁹. Rheologic factors include the presence of sickled cells, the vessel diameter, and the hematocrit. Vascular beds with low flow and high oxygen extraction are more prone to sickling and secondary vascular occlusion. Peripheral area of retina and macula are more susceptible to vascular occlusion⁶⁰. The terminal capillary bed in each of these zones borders on a vascular area and thins to a two-dimensional capillary bed⁶¹.

A diminutive change in blood vessel diameter radically affects the blood flow because flow resistance is inversely proportional to the fourth power of the vessel radius⁶². The vascular occlusion of sickle cell retinopathy occurs in the arterioles rather than in the capillaries, perhaps because the sphincters of the pre-capillary arterioles are narrower than the true capillaries⁶³⁻⁶⁴.

Main factors responsible for Reactive oxygen Species (ROS) generation in SCD

Cell free haemoglobin

Under normal physiological conditions iron homeostasis is tightly regulated by complex mechanisms which avoid cellular injury⁶⁵⁻⁶⁶. It is done by the structure of hemoglobin. Iron-containing heme is placed in hydrophobic globin pocket that limits the reactivity of iron by shielding the heme from most of external solutes. Therefore heme tends to bind reversibly with oxygen in the ferrous (Fe^{2+}) state rather than the ferric (Fe^{3+}) state. Also, the heme is separated by a globin coat that keeps apart iron from potential targets of oxidant damage in the cytosol or membrane⁶⁷. Due to continuous intravascular hemolysis, sickle cell patients have highly increased plasma levels of cell-free hemoglobin⁶⁸⁻⁶⁹. These defense mechanisms which keep check on the reactivity with oxygen and the separation of heme from targets of oxidant damage are disrupted by the instability of hemoglobin S⁷⁰. Structural instability of hemoglobin increases the rate of globin denaturation and deterioration of the protective hydrophobic shield. Oxidation of heme to methemoglobin also increases the ferric state of heme⁷¹. The hydrophobic heme also rapidly intercalates into the plasma membrane of endothelial cells where iron is released from it⁷². This provokes endothelial cell activation and damage by catalyzing non-enzymatic generation of ROS⁷³. Due to increase in cell membrane iron the trans-membrane ion transport pathways is interrupted, leading to pathologic cell dehydration. Cellular dehydration is essential for the deformation or sickling of the deoxygenated erythrocyte⁷⁴⁻⁷⁵. Sickling is caused by widespread polymerization and gelation of hemoglobin S after de-oxygenation.

Xanthine Oxidase Results from Ischemia-Reperfusion

Restoration of oxygen-rich blood flow after ischemic event adds significantly to tissue damage⁷⁶. Out-come of hypoxia and /re-oxygenation is generation of hypoxanthine and xanthine oxidase from adenosine triphosphate and xanthine dehydrogenase⁷⁷⁻⁷⁸. After restoration of oxygen rich blood flow, xanthine oxidase generates superoxide while catalyzing the conversion of xanthine or hypoxanthine to uric acid⁷⁹. As it is catalyzed by iron, the superoxide radical is ultimately converted to the extremely powerful and damaging hydroxyl radical that is reactive with almost all biological substances⁸⁰.

NADPH Oxidase

Leucocytosis which occurs in SCD produce fluxes of superoxide which is an important source of ROS in this disease⁸¹. NADPH oxidase is major superoxide producing enzyme in leucocytes⁸².

Other Sources of ROS

Homocysteine, mitochondria and other sources may also contribute to increased ROS production in SCD. Hyper-homocysteinaemia, which occurs in SCD, appears to enhance the production of ROS⁸³⁻⁸⁴. Mitochondrial membrane leakiness, dispersion of the proton motive force and electron transport chain (ETC) uncoupling could underlie a contribution of mitochondria to enhanced production of superoxide in SCD⁸⁵.

CONSEQUENCES OF SICKLE CELL DISEASE

The SCD is having multi-systemic complications, starting with mutation in one base pair of DNA which involves almost every system of human body which ultimately leads to premature death of affected individual. The various consequences are represented in figure No.5.⁹⁶ . The clinical manifestations of sickle cell disease are due to the poor solubility and intra-erythrocytic polymerization of deoxygenated sickle haemoglobin⁸⁷⁻⁸⁸. The clinical picture appears during the first year of life as foetal Hb concentrations decreases. Foetal Hb inhibits deoxy-Hb S polymerization in the red blood cell. The signs and symptoms of sickle cell vary. Some people have mild symptoms while others have severe symptoms and are to be

hospitalized for treatment. Frequent symptoms in infants are fever, swelling of the hands and feet, pain in the chest, abdomen, limbs and joints, nose bleeds and frequent upper respiratory infections. Pain is the most common complaint in children. It can be severe, acute or chronic, usually from orthopaedic problems in the legs and low back. Other symptoms include: fatigue, dyspnoea, irritability and jaundice. In adolescence or adulthood, symptoms of childhood continue along with new symptoms like delayed puberty, severe joint pain, progressive anaemia, leg sores⁸⁹, gum disease and vision problems. The pathophysiologic processes that lead to sickle cell disease related complications result from a combination of hemolysis and vaso-occlusion.

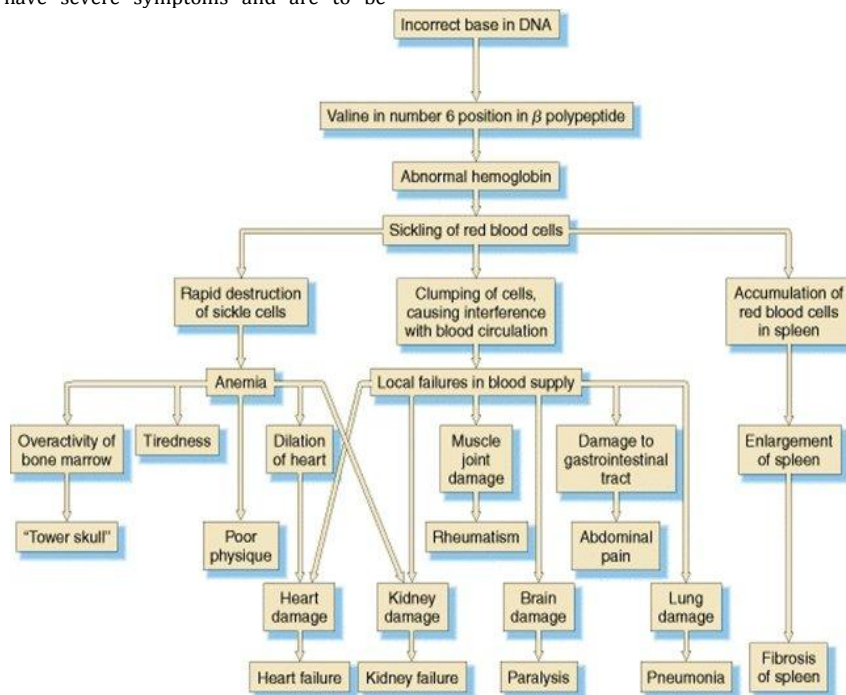


Figure 5: Represents consequences of Sickle Cell Disease

1. Sickle cell crises

The term "sickle cell crises" is used to describe several independent acute conditions occurring in patients with sickle cell disease. Sickle cell disease results in anaemia and crises that could be of many types including the vaso-occlusive crises, aplastic crises, sequestration crises, hyper haemolytic crises and others. Most episodes of sickle cell crises last between five and seven days and patients have to be hospitalized⁹⁰.

Vaso-occlusive Pain Crises (VPC)

Vaso-occlusion in sickle cell disease is a multiple process that involves initiation, propagation and resolution phase. The two major factors have been widely identified to contribute to red blood cell entrapment during crises are reduced deformability of sickle blood cell and adhesion between endothelium and erythrocytes.

Episodes of VPC are common and are perhaps the most important feature of SCD. VPC is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts two or more hours²¹. Bone is the usual site of vaso-occlusion during pain crises⁹¹. Common precipitants of VPC include cold weather, relative high hemoglobin concentration, dehydration, infection, exercise, dampness, poor diet, hypoxia, acidosis, emotional stress, and fatigue⁹¹. The phases of VPC are as under:-

a. Prodromal phase: of extremity numbness, aches, and paresthesias is described by 58% of patients 1 day before pain onset⁹². During this phase, increased numbers of irreversibly sickled cells (ISCs) and dense cells, and decreased erythrocyte deformability (relative to the individual's steady state values) have been reported⁹².

- b. Initial phase:** (also called first, evolving, or infarctive phase) is characterized by the onset of pain with fever, anorexia, and anxiety. There is relative increase in dense cells, ISCs, and erythrocyte distribution width and a decrease in platelet count.
- c. Established phase:** (second, inflammatory, or post-infarctive phase) lasts for about four to five days in adults. This phase is characterized by severe, persistent pain. Inflammatory signs and symptoms may be prominent, including fever, leukocytosis, swelling, arthralgias, and joint effusions. Bone infarction typically occurs during the established phase. Laboratory evaluation yields an increased C-reactive protein and lactate dehydrogenase along with reticulocytosis and a low concentration of hemoglobin compared with steady state values.
- d. Resolving phase:** (last, healing, recovery, or post-crisis phase) pain gradually decreases over one or two days and the number of dense cells, ISCs, and the degree of erythrocyte deformability return to steady state values.

Recurrent Crises

A subsequent rebound increase in reticulocytes, viscosity, fibrinogen, platelets, and vascular cells adhesion molecule 1 (VCAM-1) may be the cause of the 20% rate of recurrent crises that occur within 1 week of the resolving crises⁹³.

Aplastic Crises

In chronic haemolytic anaemia, temporary cessation of erythropoiesis leads to severe anaemia known as aplastic crises. Although most individuals spontaneously recover in a few days, the

anaemia can be so severe that it causes cardiac decompensation, with rare deaths³⁶.

Splenic Sequestration

Hyposplenism and autoinfarction in HbSS disease occurs during the first two years of life, with slowed onset in HbSC disease⁹⁴. Splenic sequestration thus occurs in HbSS disease, usually within five years of age. The gamut of severity is wide, with rare instances of acute splenic enlargement accompanied by circulatory collapse and death from anaemia and hypovolaemic shock.

2. Bacteremia / sepsis

One of the clearest precipitants of pain episodes and mortality among sickle patients is bacterial infection⁹⁵⁻⁹⁸. Children with sickle cell disease are at potential risk for bacteremia that can result in sepsis and death. The most common organisms involved include *Streptococcus pneumoniae*, *Salmonella species*, and *Haemophilus influenzae*⁹⁹⁻¹⁰⁰.

3. Acute Chest Syndrome

Acute chest syndrome is accompanied by chest pain, fever, coughing, and increased respiration¹⁰¹. Common causes of acute chest syndrome include infection, vasoocclusion, fat embolism, and thrombosis. The fatality rate is lower in children (1.1-1.5%) than adults (4.3-9%), but it has significant proportion of mortality in both groups¹⁰²⁻¹⁰⁵. The common causes ACS is due to pneumonia caused by *Streptococcus pneumoniae* and *Chlamydia pneumoniae* as well as atypical pathogens such as mycoplasma¹⁰³.

4. Pulmonary Hypertension

The prevalence of pulmonary hypertension in adults with sickle cell disease is 25-32% in both the United States and Africa¹⁰⁶⁻¹⁰⁷.

5. Retinopathy

Retinopathy in sickle cell disease occurs due to arteriolar occlusion and ischemia of the peripheral retinal vasculature¹⁰⁸⁻¹⁰⁹. Permanent vision loss is rare.

6. Priapism

It is painful involuntary erection of the penis, occurs in up to half of men with sickle cell anemia¹¹⁰

7. Central Nervous System Disease

Central nervous system disease is common in sickle cell disease and usually manifests as stroke and/or vasculopathy in those with the disease. Overt stroke occurs in up to 10% of children with the disease and usually involves large cerebral vessels that affect large regions of the brain¹¹¹.

8. Renal Effects

Microalbuminuria and albuminuria are common in the more severe genotypes of sickle cell disease and can occur in up to 80% of patients resulting in a glomerulopathy¹¹²⁻¹¹³. Approximately 15% of patients will advance to end stage renal disease by their third decade of life. About 25% of patients with hemoglobin SS disease have renal insufficiency defined as a reduced creatinine clearance of < 90 ml/min¹¹⁴.

9. Avascular Necrosis

Avascular necrosis is one of the few complications that is more common with HbSC than HbSS and its prevalence has been reported

to be as high as 41% of adults with sickle cell disease. With the advent of newer imaging such as magnetic resonance imaging, however, true prevalence remains unknown¹¹⁵. Surgical treatment with coring and osteotomy and joint replacement have both been used for severe disease¹¹⁶⁻¹¹⁷.

10. Hyposthenuria

Hyposthenuria, the relative loss of the concentrating ability of the kidney, occurs as a result of repetitive microinfarctions in the renal medulla and changes in the renal blood flow. Hyposthenuria is progressive with age and is less severe in those with coexisting thalassemia¹¹⁸. Hyposthenuria results in obligatory loss of free water. When not compensated with adequate fluid intake, hyposthenuria would increase the osmolality of the blood. Hyposthenuria contributes to the exertional heat illness and exercise-related death of young persons with sickle cell trait¹¹⁹.

Diagnosis

Diagnosis is a key phase for parents of a child having a chronic illness¹²⁰. Early diagnosis improves the scenario for adequate care, adjustment and coping with disease state¹²¹⁻¹²². The anticipation of diagnosis is a period of anguish and uncertainty¹²³. The actual diagnosis may induce feeling of guilt, frustration, anxiety, helplessness and resentment¹²⁴, particularly since parents usually expect a 'healthy' child¹²⁵. The diagnosis for SCD is usually considered for these target populations: pre-conception, prenatal, infant and adults of reproductive age as depicted in figure No. 6. Newborns with sickle cell disease benefit from early detection through early institution of penicillin prophylaxis to prevent pneumococcal sepsis¹²⁶.



Figure 6 :Represents the Diagnosis of SCD in target population

The prenatal diagnosis (PND) for the disease has opened a window of opportunity for expectant couples to have information about the haemoglobin (Hb) genotype of their unborn child. This gives them the option of termination of the pregnancy in case of positive result and to prepare them psychologically, financially and medically for the arrival of the new child when abortion is not an option. Prenatal diagnosis is usually carried out using either chorionic villus sampling (CVS) or amniocentesis and the samples taken have DNA analysis done on them. Both procedures are invasive with CVS being done between the 10th and 12th week of pregnancy while amniocentesis is usually carried out later (between the 14th and 20th week)¹²⁷.

Sickle cell disease can be diagnosed in newborns, as well as older persons, by hemoglobin electrophoresis, isoelectric focusing, high-performance liquid chromatography or DNA analysis described in Table No. 2¹²⁸ and Figure No.7. In general, these tests have comparable accuracy. The testing method should be selected on the basis of local availability and cost.

Table 2: Sickle Hemoglobinopathies: Diagnostic Test Results*

Sickle cell variants	Hemoglobin electrophoresis (< 2 months of age)†	Serial complete blood count, reticulocyte count	Hematologic studies (9 months of age)			Parents' usual phenotypes		
			MCV‡	Hemoglobin A2 (%)§	Hemoglobin F (%)§	DNA dot blot	One parent	Other parent
Homozygous sickle cell	FS	Hemolysis and anemia usually	Normal or increased	<3.6	< 25	βS	AS	AS

disease, or hemoglobin SS disease		by 6 to 12 months of age						
Sickle β ⁰ -thalassemia	FS	Hemolysis and anemia usually by 6 to 12 months of age	Decreased	>3.6	< 25	βAβS	AS	A on routine electrophoresis A2 > 3.6 on quantitative electrophoresis F increased on quantitative electrophoresis MCV decreased on hemogram
Sickle β ⁺ -thalassemia	FSA	Mild anemia or no anemia by 2 years of age	Normal or decreased	>3.6	<25	βAβS	AS	A on routine electrophoresis A2 > 3.6 on quantitative electrophoresis MCV decreased on hemogram
Hemoglobin SC disease	FSC	Mild anemia or no anemia by 2 years of age	Normal or decreased	Not applicable	<15	βSβC	AS	AC

MCV = mean corpuscular volume; F = fetal hemoglobin; S = sickle hemoglobin; A = normal hemoglobin; C = hemoglobin C.

*—This table shows typical results; exceptions occur.

†—Hemoglobins are reported in order of quantity (e.g., FSA = F > S > A). Fetal hemoglobin is significantly reduced by 6 months of age.

‡—Normal mean corpuscular volume is ≥ 70 per μm³ (70 fL) at 6 to 12 months of age, and a normal MCV is ≥ 72 per μm³ (72 fL) at 1 to 2 years of age.

§—Obtained by quantitative hemoglobin electrophoresis.

||—This table assumes that both parents are heterozygous.

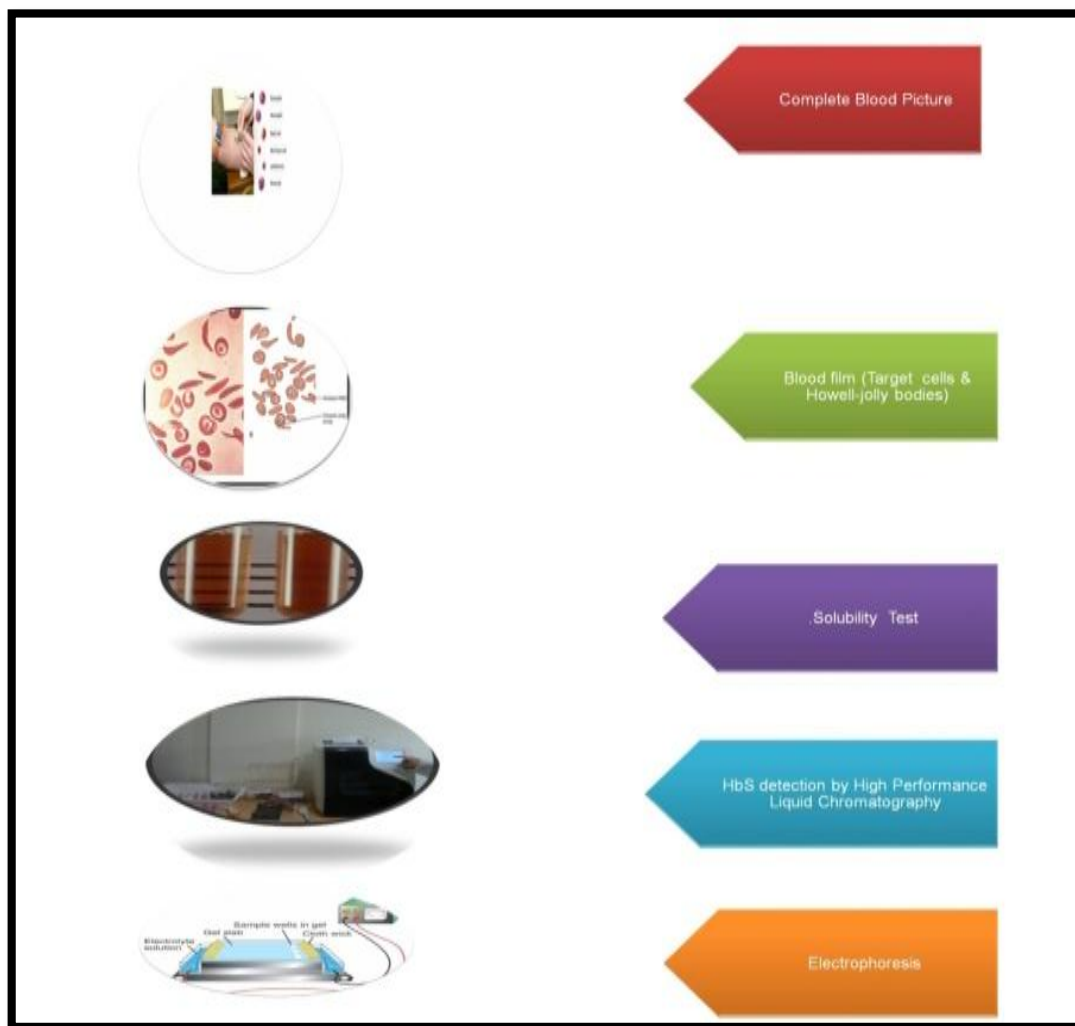


Figure.7: Diagrammatic representation various test used for diagnosis of SCD

Management of Sickle Disease

Management of SCD includes complete follow up of the patient from birth or in case of adult when patient is established as a case of SCD. The main aim of management is to prevent complications and treat

diseases symptomatically. Follow up includes health maintenance having measures to prevent specific disease complications or at least to facilitate their diagnosis and ameliorate their impact Table No.3¹²⁸.

Table 3 :Guide to Outpatient Follow-up of Children and Adolescents with Sickle Cell Disease*

Age	Routine visits	Laboratory tests	Immunizations	Medications	Screening procedures	Referrals	Anticipatory guidance
Prenatal or preconception visit		CBC with MCV and hemoglobin electrophoresis			Amniocentesis if needed	Geneticist High-risk obstetrics if needed	Genetic counselling
Birth to 6 months	Every 2 months	CBC every visit	Heptavalent conjugated pneumococcal vaccine at 2, 4 and 6 months	Penicillin V, 125 mg twice daily, initiated at 2 to 3 months of age	Hearing, vision, PPD as per standard practice		Genetic counselling of parents Review diagnosis and signs of illness.
6 months to 2 years	Every 3 months	UA annually every 3 to 6 months Ferritin or serum iron and TIBC once at 1 to 2 years of age BUN, creatinine and LFTs once at 1 to 2 years of age	Heptavalent conjugated pneumococcal vaccine booster at 15 months Influenza vaccine	Continue penicillin V. Start folic acid daily at 1 year of age.	Hearing, vision, PPD as per standard practice	Consultation with sickle cell program or pediatric hematologist	Review signs of illness. Teach spleen palpation. Discuss cold avoidance and maintenance of hydration as preventive measures.
2 to 5 years	Every 6 months	CBC and UA at least yearly BUN, creatinine and LFTs every 1 to 2 years	23-valent pneumococcal vaccine at 2 years of age; booster at 5 years of age Influenza vaccine yearly	Increase penicillin to 250 mg twice daily from 3 years of age.	Hearing, vision, PPD as per standard practice	Dentist	Review all previous instructions. Medical identification bracelet Give written baseline laboratory values to parent.
> 5 years	Every 6 to 12 months	CBC and UA at least yearly BUN, creatinine and LFTs every 2 to 3 years	Influenza vaccine yearly	Continue folic acid. Option to stop penicillin V	Hearing, vision, PPD as per standard practice	Yearly retinal examination by ophthalmologist, beginning at 10 years of age	Review all previous instructions as needed.
Adolescence	Yearly	CBC and UA yearly BUN, creatinine and LFTs every 2 to 3 years Ferritin or serum iron and TIBC at least once	Influenza vaccine yearly	Medications as needed for chronic problems (e.g., hydroxyurea [Hydrea] for pain and to prevent or lower incidence of acute chest syndrome)	Hearing, vision, PPD as per standard practice	Annual Papanicolaou's smear for sexually active girls Yearly retinal examination by ophthalmologist	Discuss sports participation, prompt care of leg abrasions and cuts, sexuality, pregnancy risk and contraception and genetic counseling.

CBC = complete blood count; MCV = mean corpuscular volume; PPD = purified protein derivative (tuberculin skin test); UA = urinalysis; TIBC = total iron-binding capacity; BUN = blood urea nitrogen; LFTs = liver function tests.

Symptomatic Treatment

- Folic acid and penicillin:** Children having SCD should be kept under close observation of the paediatrician and to be managed by a haematologist to keep them healthy. These patients will take a 1 mg dose of folic acid daily and upto five years of age penicillin daily because of poor immune system, they are more prone to early childhood illnesses¹²⁹⁻¹³⁰.
- Painful (vaso-occlusive) crises:** Most people with sickle-cell disease get extremely painful episodes called vaso-occlusive crises. The rate, severity, and duration of these crises vary tremendously. These situation are managed by antibiotics, blood transfusion (normal or exchange transfusion), oxygen, pain control with paracetamol-codeine, ibuprofen or morphine analogues. Usually hyperbaric oxygen therapy ("caisson") is not available. Sufficient fluid should be administered because the kidneys suffer from hyposthenuria. Frequently 3 to 4 litres a day are given (adults), if possible orally, otherwise IV. Severe

acidosis is best corrected by bicarbonate, although no definite results can be expected. Wound healing, surgery in the case of osteomyelitis and a need for convalescence after CVA depend on the clinical profile of the patient. Incentive spirometry is important in acute chest syndrome. In the case of rib or tissue infarctions, and also in chest disorders, it is important that the patient is urged to breathe deeply (10 maximum inspirations) at regular intervals, e.g. every two hours. It prevents atelectasis. Corticoids reduce inflammation of the pleura (area lying against rib infarction). Haematuria caused by a sickle cell crises can be improved by the diuretic furosemide (Lasix®). The administration of hypotonic fluids improves osmolarity of blood as a result of which sickling occurs less quickly. The polymerising of Hb S is promoted strongly by dehydration. Due to higher concentration of salt in the blood, RBC'S sickle quickly. Desmopressin (DDAVP) lowers the salt content in the blood (hyponatraemia). As a result of osmosis the red blood cells swell some what and the concentration of deoxy-Hb S falls.

It is given as nasal spray/drops (0.1 –0.4 ml per day) or can be given IM or IV (1 to 4 µg per day; 1 ampoule = 1 ml = 4 µg). The price is very high for developing countries to bear. Its therapeutic role is controversial.

Acute chest crises: Management is similar to vaso-occlusive crises, with the addition of antibiotics (usually a quinolone or macrolide, since wall-deficient ["atypical"] bacteria are thought to contribute to the syndrome)¹³¹, oxygen supplementation for hypoxia, and close observation. Should the pulmonary infiltrate worsen or the oxygen requirements increase, simple blood transfusion or exchange transfusion is indicated. The latter involves the exchange of a significant portion of the patient's red cell mass for normal red cells, which decreases the percent of haemoglobin S in the patient's blood.

- 3. Hydroxyurea:** The first approved drug for the causative treatment of sickle-cell anaemia, hydroxyurea, was shown to decrease the number and severity of attacks in a study in¹³² and shown to possibly increase survival time in a study in 2003¹³³. This is achieved, in part, by reactivating fetal haemoglobin production in place of the haemoglobin S that causes sickle-cell anaemia. Hydroxyurea had previously been used as a chemotherapy agent, and there is some concern that long-term use may be harmful, but this risk has been shown to be either absent or very small and it is likely that the benefits outweigh the risks¹³⁴.
- 4. Bone marrow transplants:** Bone marrow transplants have proven to be effective in children¹³⁵. At present it is only available curative therapy for sickle cell anemia. While the survival rate from this procedure is roughly 91% and the cure rate is 82%¹³⁶. This option is currently limited primarily to children under 16 years of age with severe, pre-existing complications. There is difficulty in finding suitable donor for the vast majority of patients; it is estimated that only 14% of patients have a human leukocyte antigen (HLA)-matched sibling donor¹³⁶. There are so many short and long-term complications after transplantation including intracerebral hemorrhage, graft-versus-host disease (GVHD), seizure, and gonadal dysfunction¹³⁶⁻¹³⁷.
- 5. Blood Transfusion:** Blood transfusion is widely used in the treatment of sickle cell anemia. It is estimated that 50% of all patients receive a red cell transfusion at some point in their lives and that 5% receive chronic transfusions¹³⁸. Serious complications associated with this therapy include iron overload, allo-immunization, and risk of transmitted infection¹³⁷.

Management of sickle-cell disease at different levels of the health-care system should emphasize programmes that use simple, affordable technology and are accessible to a large proportion of the community.

Prevention

The management of SCD has remained a matter of concern in both developed and developing countries, A greater awareness and understanding of the communities and health care personnels about SCD and its detection has been found to be beneficial in the management of the disease¹³⁹⁻¹⁴⁰. Several studies have clearly shown that genetic counseling is considered as one of the best ways of controlling the disease¹⁴¹.

The preventive measures include:- (a) Continued community education programmes for areas with high prevalence of the disease by creating and strengthening the national sickle-cell disease control programmes. (b) Setting up sickle-cell screening and genetic counselling programmes. The disease should be identified during the prenatal period or at birth as part of a routine screening programme. (c) Use of prophylactic drugs namely chloroquine and penicillin. (d) Ongoing basic and clinical research. (e) Provision of primary health care (access of sickle cell children to health centers). (f) Improved standard of living and better feeding for patients with SCD.

Future Therapies

Even though their significant collective amount of knowledge of sickle cell disease treatment option are few, owing to complex pathology of the condition. Future treatments are directed at ameliorating the secondary events related to sickling as well as finding new foetal Hb-modulating agents. Clinical trials are in progress to moderate red blood cell dehydration by blocking the Gardos channel¹⁴².

Clotrimazole inhibits the Gardos channel and magnesium retards potassium efflux, preventing erythrocyte dehydration and thereby reducing sickling⁵³. Clotrimazole is administered via tablets given orally at 10 mg/kg body weight per day, which is increased to 20 mg/kg body weight per day on day 7 of therapy. Clotrimazole's major side effects are dysuria and elevated transaminases, which usually occur at higher doses¹⁴³. Sodium cromoglycate has also been noted to have some anti-sickling properties¹⁴⁴.

To evaluate the new compounds that can increase nitric oxide bioavailability, and augment foetal haemoglobin production. Recently research has begun to focus on therapies which prevent the red blood cells deforming by reducing the loss of water and ions from the cells¹⁴⁵. It was reported that treatment of SCD with senicapoc, a Gardos channel inhibitor. It reduces number of dehydrated cells, increases haemoglobin level and diminishes hydrolysis¹⁴⁶.

CONCLUSION

Sickle cell disease is a chronic, debilitating disorder with a myriad of symptoms that make disease treatment challenging. While there is a need for new treatment for sickle cell disease, especially for disease modifying agents, there is also a need to explore new approaches for improving treatment with existing modalities. Preventive measures particularly in disease endemic area must be taken such as pre-marital genetic counseling and screening. Future research must be focused on decreasing the number of crises and blood transfusion through new remedies having easy availability, less cost and minimum side effects.

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