

Review on Sickle cell anemia

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Submitted: 20-11-2023

Accepted: 30-11-2023

ABSTRACT:-

Sickle cell disease (SCD) is a group of inherited diseases caused by mutations in the HBB gene, which encodes the β subunit of hemoglobin. It is estimated that between 300,000 and 400,000 newborns worldwide develop the disease each year, most of them in sub-Saharan Africa. Hemoglobin molecules containing mutant sickle cell β -globin subunits can polymerize; Erythrocytes, which contain primarily hemoglobin polymers, become sickle-shaped and susceptible to hemolysis. Additional pathophysiological mechanisms contributing to the SCD phenotype include vascular occlusion and immune system activation. SCD is characterized by exceptional phenotypic complexity. The most common acute complications include acute pain, acute chest syndrome and stroke. Chronic complications (including chronic kidney disease) can damage all organs. Hydroxycarbamide, blood transfusions and hematopoietic stem cell transplantation can reduce the severity of the disease. Early diagnosis is essential to improve survival. Therefore, some countries have implemented universal newborn screening programs, but these remain challenging in low-income, high-burden areas.

Keywords: Anemia-sickle cell, genetic therapy, hydroxyurea, oxidative stress, poloxamer, stem cell transplantation

I. INTRODUCTION:-

Sickle cell disease (SCD) is a group of hemoglobinopathies in which mutations occur in the gene that codes for the beta subunit of hemoglobin. The first description of an "ACS-like" disorder was made by Dr. Africanus Horton in his book Tropical Climate Disease and Their Treatment (1872). However, it took until 1910 for Dr. James B. Herrick and Dr. Ernest Irons reported that he noticed "crescent-shaped" red blood cells in a dental student (Walter Clement Noel from Grenada).[1] In 1949, independent reports were published by Dr. James V. Neel and Colonel

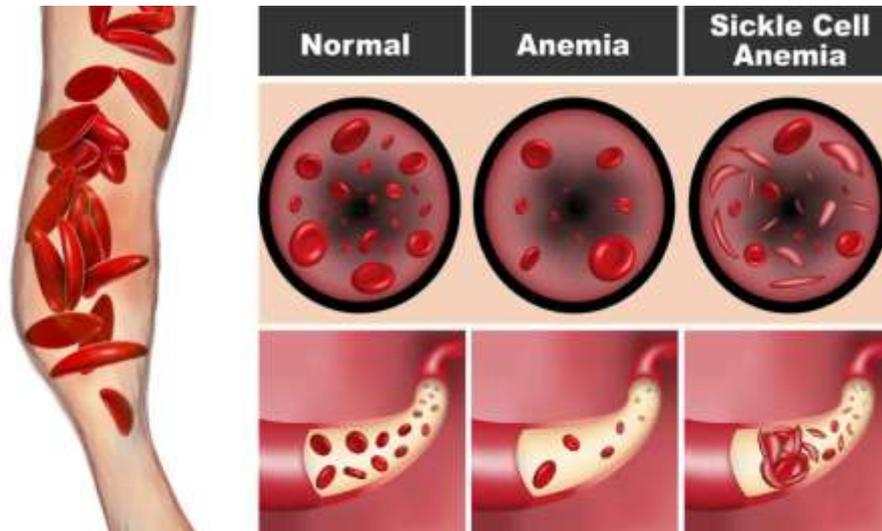
E.A.Burak described transmission patterns in SCD patients. In the same year, Dr. Linus Pauling the molecular nature of sickle cell hemoglobin (HbS) in his paper entitled "Hemoglobin in Sickle Cell Anemia". Ingram Vernon used a fingerprint technique in 1956 to describe the replacement of negatively charged glutamine with neutral valine, confirming Linus Pauling's results.[2]. Since irregular sickle red blood cells were first described more than 100 years ago, our knowledge of this disease has made enormous progress. Recent advances in this field, particularly in the last three decades, have improved the symptoms of countless patients, particularly in high-income countries. In 1984, Platt et al. were the first to report the use of hydroxyurea to increase HbF levels.[3] Since then, the treatment of sickle cell anemia has reached new levels with the introduction of numerous new drugs (voxelotor, crinzalimumab, L-glutamine) and, more recently, gene therapy. Sickle cell anemia or sickle cell anemia (or sickle cell anemia) is a lifelong blood disorder characterized by red blood cells taking on an abnormal, rigid crescent shape. Sickle cell reduces the elasticity of cell number and is associated with the risk of various complications. Sickle cell anemia is caused by a mutation in the hemoglobin gene. The life expectancy of men and women is 42 and 48 years, respectively [4]. Sickle cell anemia, which usually occurs in childhood, is more common in tropical and subtropical regions where malaria is prevalent because invasion of malaria plasmodium is stopped by the lateral movement of infected cells. According to the National Institutes of Health, the incidence of the disease in the United States is about 1 in 5,000 and primarily affects African Americans.

What is sickle cell anemia?

Sickle cell anemia is a form of hereditary blood disease, sickle cell anemia. Sickle cell anemia affects red blood cells, transforming them from round, flexible disks into stiff, sticky, sickle-shaped cells. Sickle cell anemia prevents red blood cells from doing their job of transporting oxygen

throughout the body. Additionally, sickle cell patients do not live as long as normal red blood cells. As a result, you don't have enough healthy

red blood cells and develop anemia, a condition called sickle cell anemia.[5]



Types of sickle cell disease:-

There are several types of sickle cell disease. The different types depend on the genes a person inherits from their parents.

Hemoglobin SS (HbSS)

HbSS is a serious form that affects 65% of people with sickle cell disease. People with this form inherit a gene encoding hemoglobin S from each parent. Most or all of the hemoglobin is abnormal, causing chronic anemia.

Hemoglobin SC (HbSC)

HbSC is a mild to moderate form that affects around 25% of sufferers. People with this form inherit the hemoglobin S gene from one of their parents. They inherited a different abnormal type, hemoglobin C, from the other parent

Hemoglobin (HbS) beta thalassemia

People with this form inherit the hemoglobin S gene from one of their parents. They inherited an abnormal form called beta thalassemia from the other parent. There are two subtypes:

- **“Plus” (HbS beta +):-** This subtype affects about 8% of people with sickle cell anemia and is usually milder.
- **“Zero” (HbS beta 0):-** Its subtype affects about 2% of people with sickle cell anemia and is more severe, similar to hemoglobin SS disease.

There are other, rarer forms, including hemoglobin SD (HbSD), hemoglobin SE (HbSE), and hemoglobin SO (HbSO). People with one of these forms have inherited a hemoglobin S gene and a gene that codes for another abnormal gene (D, E, or O).

Etiology :-

Hemoglobin (Hb) is an essential protein of red blood cells (RBCs). It contains four globin chains, two of which come from alpha globin (locus on chromosome 16) and two from beta globin (locus on chromosome 11). There are many subtypes of Hb. The most common in adults without hemoglobinopathy are listed below: ,
HbA1 - consisting of two alpha globin chains and two beta globin chains (α₂β₂) - makes up 95% of adult hemoglobin.

HbA2 - Consists of two chains of alpha globin and two chains of delta globin (α₂δ₂) - Makes up less than 4% of adult hemoglobin.

HbF - consists of two chains of alpha globins and two chains of gamma globins (α₂γ₂) - Hb is more common in the fetus (due to its strong binding affinity for oxygen, which helps extract oxygen from the maternal circulation).[6]

The autosomal recessive disease that results from the mutation of the gene is sickle cell anemia. A nucleotide mutation on chromosome 11 causes glutamic acid to be replaced by valine at the sixth th position of the beta-globin unit. This changes the physical properties of the globin chain.

Factors that cause this change in red blood cells include dehydration, hypoxia, stress, infections and colds. There are many other compound heterozygotes in which a single copy of the mutated beta-globin gene is inherited along with a single copy of another mutated gene. The second most common variant of SCD is HbSC disease, in which the sickle cell anemia gene is inherited along with a single copy of the mutated hemoglobin C gene. HbC is formed when lysine replaces glutamine at the sixth position in the beta-globin chain. HbSC disease occurs in 30% of patients in the United States.[7]

History And Physical :-

Most patients with the HbSS phenotype do not present with classic sickle cell crises shortly after the birth. HbF is still present in the blood and helps maintain tissue oxygenation. It takes 6 to 9 months to clear completely. Not all SCAs have the same phenotype. Many phenotypes can coexist or appear as a disease spectrum.

1. Vascular occlusive subphenotype – characterized by a higher hematocrit (Hct) than other ACS. A higher Hct value leads to increased viscosity, which promotes frequent vascular crises and acute chest syndromes.
2. Hemolysis and vascular subphenotype: Hct lower than others AUC, higher lactate dehydrogenase (LDH), serum bilirubin - means higher degree of hemolysis and severe anemia.
 - Higher risk of gallstones, pulmonary hypertension, ischemic stroke, priapism and nephropathy.
 - Severe anemia increases strain on the heart and blood flow to organs, making them vulnerable to damage.
 - Higher levels of free heme and Hb in blood vessels cause oxidative damage.
3. Elevated Hb-F-A subtype An HbF value of 10-15% relieves the symptoms of sudden cardiac arrest. However, the distribution of HbF in the body is not uniform.
4. Pain sensitive subphenotype. Altered neurophysiology leads to pain sensitivity in different people. Some people with ACS are more sensitive to pain than others.
 - Key Points from the ACS Patient Story:-
 - All ACS patients suffer from VOCs during their lifetime. The first manifestation is dactylitis in children aged six months.
 - VOCs can grow in any organ of the body (head, eyes, etc.), but the limbs and chest are most commonly affected. If the pain caused by

VOCs seems unusual, a history should be taken to rule out other causes.

- A thorough history of pain management should determine the best analgesics for the patient.
- A history of drug abuse, mental disorders, and psychotropic drug use should be obtained.
- History of blood transfusions and blood exchange - helps assess the risk of iron overload, the presence of alloantibodies (repeated transfusions in the past can lead to the development of alloantibodies, which can help assess the risk of post-fusion reactions) and after previous blood transfusions -fusion reactions.
- Have you ever had other diseases that could be related to ACS: stroke, thrombosis, priapism, etc.?
- It is also advisable to contact the primary hematologist treating the patient: this is useful to help understand the patient's normal physiology. .
- History of previous operations.
- History of life-threatening seizures: If present, notify your doctor to ensure that a similar event does not occur again. For example, fat embolism may occur more frequently in patients with ACS.[8]

Epidemiology:-

Epidemiological data on sickle cell anemia are rare. SCD and HbAS are known to occur more frequently in sub-Saharan Africa, where HbAS carriers have natural protection against severe malaria caused by *Plasmodium falciparum*. In 2010, an estimated 230,000 children with sudden cardiac arrest and more than 3.5 million newborns with HbAS were born in sub-Saharan Africa. An estimated 75% of births related to sickle cell anemia occur in sub-Saharan Africa. West Africa is home to the largest population of people with HbSC.[3] Despite numerous declarations by international organizations and public declarations by politicians to fulfill these commitments, the implementation of early childhood diagnosis remains out of reach for most countries in sub-Saharan Africa. The benefits of screening will only become clear when the practice is adopted by policymakers across the continent and in India, where most SCD are born and live. Comprehensive care that includes penicillin V prophylaxis, hydroxycarbamide treatment, and preventative therapies such as antimalarial drugs, as well as health promotion as

appropriate, will improve outcomes and health-related quality of life.[9]

Clinical Features :-

Sickle cell anemia is characterized by a variety of symptoms ranging from acute widespread pain to early stroke, leg ulcers and risk of premature death due to multi-organ failure . Due to the action of HbF, clinical symptoms do not appear until the middle or second half of the first year of life after birth, when hemoglobin changes, especially in adults.[10,11]

Diagnosis :-

Overall, mutations in the globin gene that affect hemoglobin are common, affecting 7% of the entire global population. There are over 1,000 types of hemoglobin. However, only a few varieties are clinically important.

- Typical variants of SCA or HbSS disease
- Hemoglobin thalassemia S-beta-0 (behaves clinically exactly like HbSS disease)
- Hemoglobin SC (a milder variant of SCD) - may show a phenotypic pattern of sickle cell anemia
- Hemoglobin S-beta+ thalassemia (a milder variant of SCD)
- There are many other hemoglobin variants that can mimic SCA when inherited with HbS.
- Jamaica Plain hemoglobin (Beta-68 [E12] Leu -> Phe)
- Quebec Chori hemoglobin (Beta-87 [F3] Thr > Ile)
- D-Punjab hemoglobin (Beta globin, codon 121, glutamic acid). Acid)
- Hemoglobin O-Arabic Hemoglobin E
- A blood test can check the form of hemoglobin that causes sickle cell anemia. In the United States, this blood test is part of routine newborn screening. But older children and adults can also be tested.
- In adults, blood is taken from a vein in the arm. For small children and infants, a blood sample is usually taken from the finger or heel. The sample is then sent to a laboratory where it is tested for the sickle cell form of hemoglobin.
- If you or your child has sickle cell disease, your doctor may recommend other tests to check for possible complications of the disease.

- If you or your child is a carrier of the sickle cell disease gene, you will likely be referred to a genetic counselor.[12]

Complication :-

Treatment and management :-

SCD causes a range of acute and long-term complications that require a multidisciplinary approach involving various specialists. In the UK, comprehensive care for sickle cell anemia is coordinated by specialist haemoglobinopathy teams

- Patients with SCA present with acute and chronic complications

Management of Acute Complications

Pain management is a key component of ACS. Accurately assessing the condition of patients is a challenge for doctors. needs, especially when encountering them for the first time. SCA patients often suffer from the stigma of having to take high doses of opioids for pain relief, leading to them being labeled as “opioid addicts.” “Manipulators,” “Drug seekers.”

1. Administration of analgesics begins concurrently with cause identification, preferably within 30 minutes of triage and 60 minutes of registration.
2. Develop individual pain management plans: These should be made available to the emergency department and implemented whenever a patient experiences VOCs and pain.
3. NSAIDs are used in patients with mild to moderate pain who report previous episodes of relief from NSAIDs
4. Opioids
 - Pain should be assessed every 15 to 30 minutes and opioids re-administered if necessary. The opioid dose increase occurs in 25% increments.
 - Patient-controlled analgesia (PCA) is preferable. If an on-demand setting is used in PCA, long-acting analgesia should be continued.
5. Meperidine is not used to treat pain caused by VOCs unless it is the only medication used to control pain.
6. Antihistamines only help control opioid-induced itching. Use only oral preparations if necessary - re-administer every 4-6 hours if necessary.

• **Management of Chronic Complication**

1. Avascular necrosis: Approximately 40-80% of hip AVN cases are bilateral; Therefore, both joints should be examined at the same time. Pain treatment and physiotherapy should be started as soon as possible. In advanced cases, a hip replacement may be necessary.
2. Leg ulcer: Conservative measures include wound care, wet or dry dressings, and pain control. Hydroxyurea should be avoided in patients with open leg ulcers because it may prevent healing. The degree of healing or the absence of infection and osteomyelitis should be assessed regularly. For infected ulcers, local and systemic antibiotics are used.
3. Ophthalmological complications: Refer patients with ACS for regular ophthalmological examination, especially if they complain of slow changes in vision. Direct and indirect ophthalmoscopy, slit lamp biomicroscopy, and fluorescein angiography are used to evaluate patients with ACS. Laser photocoagulation therapy is used to treat sickle cell proliferative retinopathy. In rare cases of vitreous hemorrhage or retinal detachment, a vitrectomy or retinal repair may be necessary.
4. Blood transfusion: Blood transfusions are an essential part of treating cardiac arrest. The aim of the transfusion is to increase the blood's ability to carry oxygen and reduce the HbS content. In order to keep the HbS value below 30%, blood (normal or replacement blood) is transfused (studies STOP 1 and 2).[14] For patients receiving regular exchange transfusions (history of stroke, intolerance or contraindication to hydroxyurea), a more practical HbS target is 25% to prevent HbS from exceeding 30%.

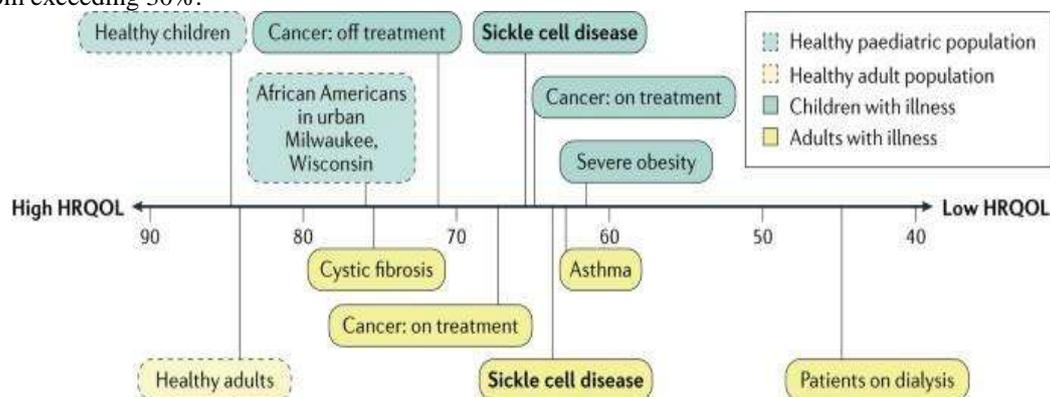
What types of blood transfusions are used for cardiac arrest?

- Simple transfusion: Transfusion of a pair of packed red blood cells (PRBCs).
- Exchange transfusion: Transfusion of PRBCs with simultaneous blood collection from the patient.[13]

Quality of Life :-

Generic health-related quality of life (HRQOL) instruments (e.g., the 36-item Short Form Health Survey (SF-36) for adults and the Pediatric Quality of Life Inventory (PedsQL) for children) measure physical, emotional and social states Work and enable comparisons between people with sickle cell anemia and healthy people.[14] Disease-specific measures, such as the PedsQL Sickle Cell Module for children with sickle cell disease, have greater specificity in detecting differences in the sickle cell disease population and are intended to detect changes in HRQOL over time[15].

In adults and children with sickle cell disease, baseline quality of life is significantly impaired (Figure 7).[16] Compared to healthy individuals, people with sickle cell disease have impaired quality of life in almost all areas, particularly pain, fatigue, and physical function. Adolescents and adults report poor sleep quality, moderate fatigue, and that sleep quality plays a mediating role in the association between pain and fatigue[17]. The HRQOL baseline range of physical functioning in many people with SCD is worse or comparable to that of people with other chronic diseases such as cancer, cystic fibrosis or obesity.[18]



Physical functioning outcomes were measured using the 36-item Short Form Health Survey (SF-36) and the Pediatric Quality of Life Inventory (PedsQL) General Core Scale in healthy individuals and those with chronic illnesses 237, 272. Scores range from 100, which represents the highest health-related quality of life (HRQOL) with 0. Specific domains represented in the physical function scores include the ability to perform all types of physical activity, such as running, short walking distances, lifting weights, and lifting weights, heavy objects, and bathing without assistance.[19]

Outlook:-

A widespread introduction of cost-effective interventions, including neonatal diagnosis, penicillin prophylaxis and vaccination (which have led to significant reductions in mortality among children with sudden cardiac arrest under 5 years of age in high-income countries), could extend the lives of approximately 5 million newborns with SCA. SCA to 2050. (Ref. 17). Likewise, large-scale screening and treatment programs could save the lives of 10 million newborns with sudden cardiac arrest worldwide, primarily in sub-Saharan African countries.[20]

Screening:-

Screening for sickle cell anemia and related diseases is essential in Africa, where the incidence of the disease is highest. However, implementing universal newborn screening programs remains a major economic and public health challenge. African communities and governments should also develop culturally acceptable adult family planning screening programs. The development of new rapid, accurate and affordable diagnostic tests would provide low- and middle-income countries with a long-awaited point-of-care testing option. Clinical validation of these tests has shown that they can reliably detect β S and β C alleles with high specificity and sensitivity[24]. These tests can be used as a first step in large-scale screening before confirming the diagnosis by HPLC or isoelectric focusing. This is necessary to identify people who also have thalassemia or other Hb variants.[21,22]

II. CONCLUSION :-

These examples of new approaches to treating patients with sickle cell anemia illustrate some of the current attempts to alleviate or cure the disease. Interest in sickle cell research has grown

and can now provide hope to many people suffering from this disease around the world. It is necessary to launch many more clinical trials and subject them to more in-depth research and analysis than before. Efforts must be made to bring these therapies to the least developed countries, where the majority of people with sickle cell anemia live. These initiatives seem more possible than ever.

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