IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Sickle Cell Anemia: A Review On Genetic Basis, Clinical Manifestations, And Management Strategies

Ms. Akanksha Arun Khoje , Dr. Sunil S. Jaybhaye , Ms. Vidya V. Ekhande

Student of Bachelor in Pharmacy, Dr. Babasaheb Ambedkar Technological University, Raigad, Lonere

Department of Pharmacy, Faculty of Pharmacy, Dr. Babasaheb Ambedkar Technological University, Raigad, Lonere

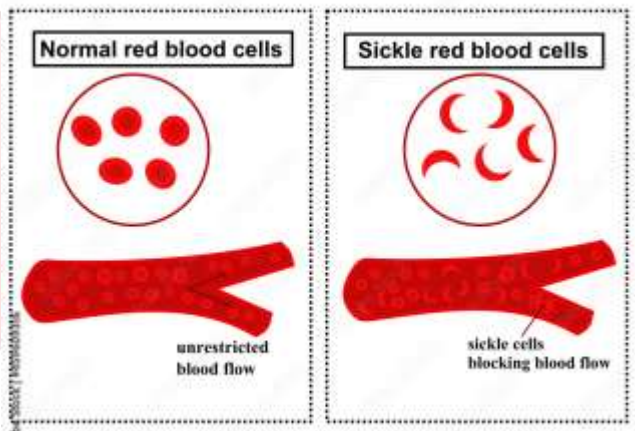
1) ABSTRACT

Sickle cell anemia (SCA) is a hereditary hemoglobinopathy characterized by the presence of abnormal hemoglobin S, leading to chronic hemolysis, vaso-occlusion, and multi-system complications. This review provides a comprehensive evaluation of the clinical manifestations and current management strategies associated with SCA. The disease presents with diverse symptoms, including recurrent painful vaso-occlusive crises, chronic anemia, susceptibility to infections, acute chest syndrome, stroke, and progressive organ dysfunction. Early diagnosis through neonatal screening and laboratory evaluation remains essential for timely intervention. Management approaches have evolved significantly, ranging from conventional therapies such as analgesics, antibiotics, blood transfusions, and hydroxyurea to advanced disease-modifying and curative options including L-glutamine therapy, voxelotor, crizanlizumab, hematopoietic stem cell transplantation, and emerging gene-editing techniques. Comprehensive care also emphasizes patient education, prophylactic vaccinations, and regular monitoring to prevent long-term complications. Overall, advancements in pharmacological and curative therapies, combined with multidisciplinary care, have improved patient outcomes, although access and affordability remain major challenges particularly in resource-limited settings. This review highlights the need for continued research, improved therapeutic accessibility, and strengthened public health initiatives to effectively manage and reduce the global burden of sickle cell anemia

2) INTRODUCTION

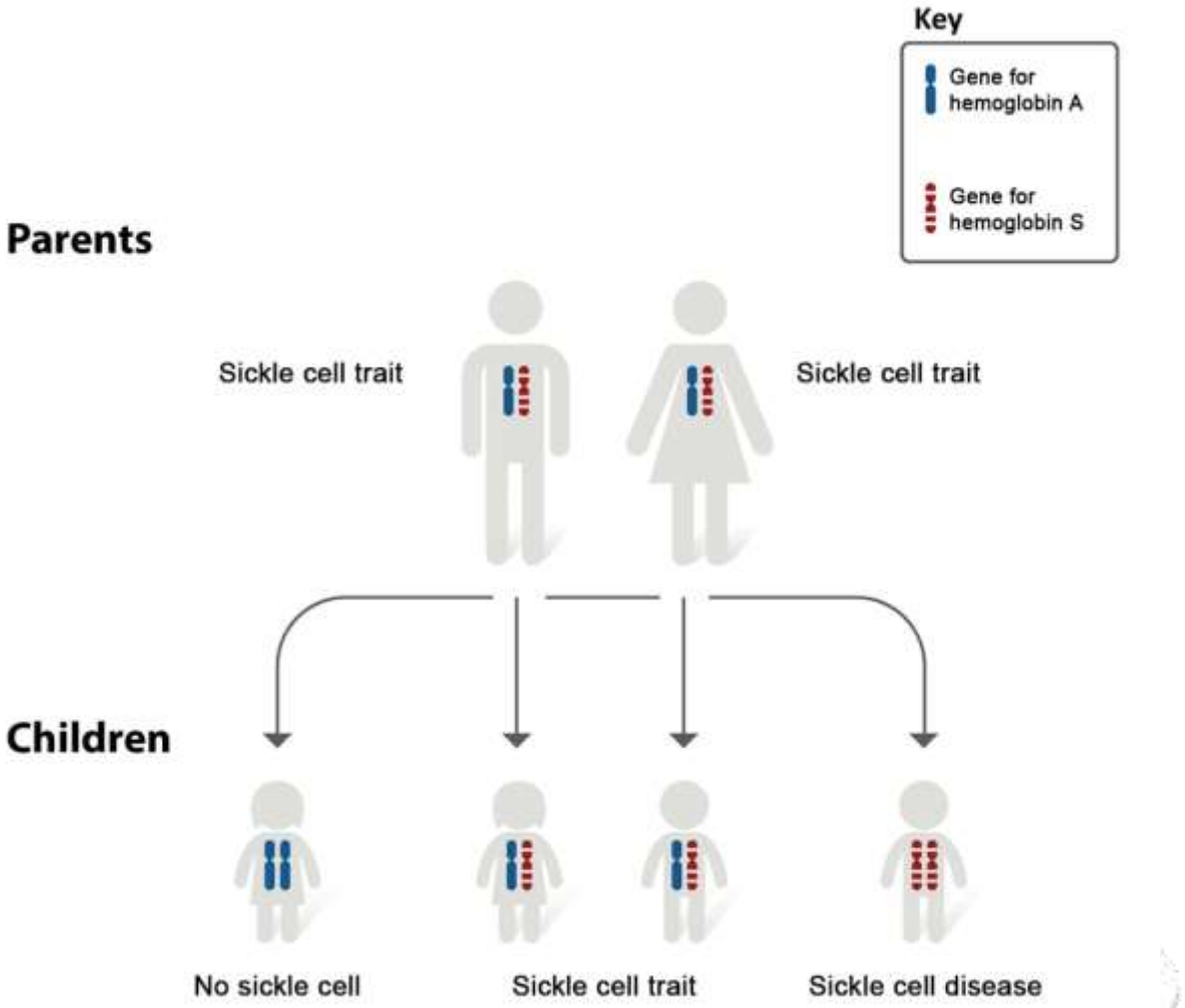
Normal red blood cells are disc-shaped and flexible cells that transport oxygen bound to hemoglobin throughout blood circulatory system. Sickle cell disease (SCD) is an autosomal- recessive genetic condition. Sickle cell hemoglobin occurs when the red blood cell becomes sickle-shaped, giving the disease its name. An individual became a sickle cell trait when they received a single gene mutation of the inherited disease. A person will acquire the disease when they attain two faulty hemoglobin genes, with both hemoglobin S gene inherited from each parent, or inherit one hemoglobin S from one parent, and another faulty hemoglobin gene, such as beta (β) thalassemia, hemoglobin C, hemoglobin D, or hemoglobin E, from the second parent (NHLBI, 2024; Johns Hopkins Medicine, 2024). The likelihood of a child being born with SCD increases significantly if both parents are carriers, with a 25% probability of inheritance per pregnancy.

Sickle cell disease or sickle cell anemia (or depanocytosis) is a lifelong blood disorder characteristic of red blood cells that believe that a Unusual, hard, sickle shape. Sickling decreases resulting in flexibility of cells and exposure to different type complication the disease causes mutations in the hemoglobin gene. Life expectancy of 42 and 48 years for men and women, respectively [4]. Sickle cells anemia (SCA) is a type of abnormal blood disease commonly called sickle cell disease (SCD) or as common sickle room. In the human body, blood flows through small circular shape that carries oxygen to the organs where sickle cell shape is shaped (sickle) shaped cells as shown in fig.1. The life span of a normal blood cell is approximately 120 days. A new blood cell occurs after 120 days generated [5]. The life span of sickle cells is 10 to 20 days [6]. This cell is an inherited disorder that affects normal hemoglobin present in red color blood cell (RBCs) [5, 7]. Presence of sickle what does the cell make into hemoglobin? Sickle shaped cells that 2are very hard and sticky as shown in fig.2. This types of anemia can be severe pain, necrosis and serious causes complications, in some cases it can be death.



CAUSES OF SICKLE CELL

The cause is inherited (genetic). It‟s a change in a gene that tells the body how to make an important protein. It is called hemoglobin. To get SCD, you need two altered hemoglobin genes, one from each parent if you have only one of these genes, you will have sickle cell trait, which is very mild.The most common types of SCD is where you have two sickle cell genes (sickle cell anemia) medical. The shorthand for this is hemoglobin SS or HbSS other types of SCD involve one sickle cell gene and another. A different type of abnormal hemoglobin genes these include: hemoglobin s/beta thalassemia : hemoglobin S/ lepore, hemoglobin



KEY POINT OF VARICOSE VEIN

1) Sickle Cell Anemia

2) Hemoglobin S

3) Vaso-occlusion

4) Hydroxyurea,

5) Blood transfusion

6) L-glutamin

7) Voxelotor

8) Crizanlizumab

9) Stem cell therapy

10) Gene-editing therapies Hemoglobinopathy

11) Prophylactic

12) vaccination

13) Multidisciplinary care

14) Chronic anemia

Signs and Symptoms

PREGNANCY IN SCD – Pregnancy in sickle cell complaint can be complicated as both prospective mama and bambino are at increased threat of adverse issues. The physiological changes of gestation like increased metabolic demand, increased blood density and hyperactive coagulability gets exacerbated in SCD cases leading to increased prevalence of complications like a vaso- occlusive extremity, acute casket pattern, osteonecrosis, hepatic necrosis, leg ulcers, and thromboembolic events. Vaso- occlusion also occurs in placenta leading to villous fibrosis, necrosis, and infarction, thereby causing disabled uteroplacental rotation, which leads to habitual fetal hypoxia and adverse fetal issues [11,12]. Early reports on the outgrowth of gestation in women with sickle cell anemia, depicted an nearly universal adverse outgrowth for mama and child, but with advancements in medical care, especially 4the preface of prepossession care, the outgrowth has dramatically bettered. This enhancement in fetomaternal outgrowth is inadequately reflected insub-Saharan Africa where the frequence and complications of sickle cell complaint in gestation is loftiest in the world, and a motherly mortality rate of0.38 –1.29/ 100,000 births and perinatal mortality rate of1.21 –2.50/ 100,000 births are still being reported.[13] This has been attributed to modest medical and prenatal care installations, and scarce so, or virtuality of prepossession care installations in utmost communities insub- Saharan Africa

Genetic basis of sickle cell Anemia

Sickle cell anemia is a genetic disorder caused by mutations in the HBB gene (the gene for the beta-globin subunit of hemoglobin), located on chromosome 11. The mutation leads to the production of abnormal hemoglobin, known as hemoglobin S (HbS). Here's a breakdown of the genetic basis of sickle cell anemia

1. Normal Hemoglobin (HbA) vs. Abnormal Hemoglobin (HbS)

Normal Hemoglobin (HbA): The hemoglobin in healthy individuals is composed of two alpha- globin chains and two beta-globin chains.
Abnormal Hemoglobin (HbS): In sickle cell anemia, there is a mutation in the beta- globin gene (HBB) that substitutes the amino acid glutamic acid with valine at position 6 of the beta-globin chain. This is referred to as the HbS mutation.

2. The Mutation and Its Effects

The mutation changes the structure of hemoglobin, making it less soluble under low- oxygen conditions. This causes the hemoglobin molecules to stick together and form long, rigid rods inside the red blood

cells.These rigid rods distort the shape of the red blood cells, causing them to become sickle-shaped instead of the normal biconcave shape.

These sickle-shaped cells are less flexible and can block blood flow in small blood vessels, leading to pain, tissue damage, and other complications like stroke, organ damage, and anemia.

3. Inheritance Pattern: Autosomal Recessive

Sickle cell anemia follows an autosomal recessive inheritance pattern. This means that a person must inherit two copies of the mutated gene (one from each parent) to develop the disease. Homozygous HbS (HbSS): Individuals with two copies of the mutated gene (one from each parent) have sickle cell anemia Heterozygous HbA/HbS (Carrier or Sickle Cell Trait):
Individuals with one normal allele (HbA) and one mutated allele (HbS) are carriers and typically disease, but they can pass the gene to their offspring. These individuals usually don't exhibit symptoms or have only mild symptoms.

Etiology

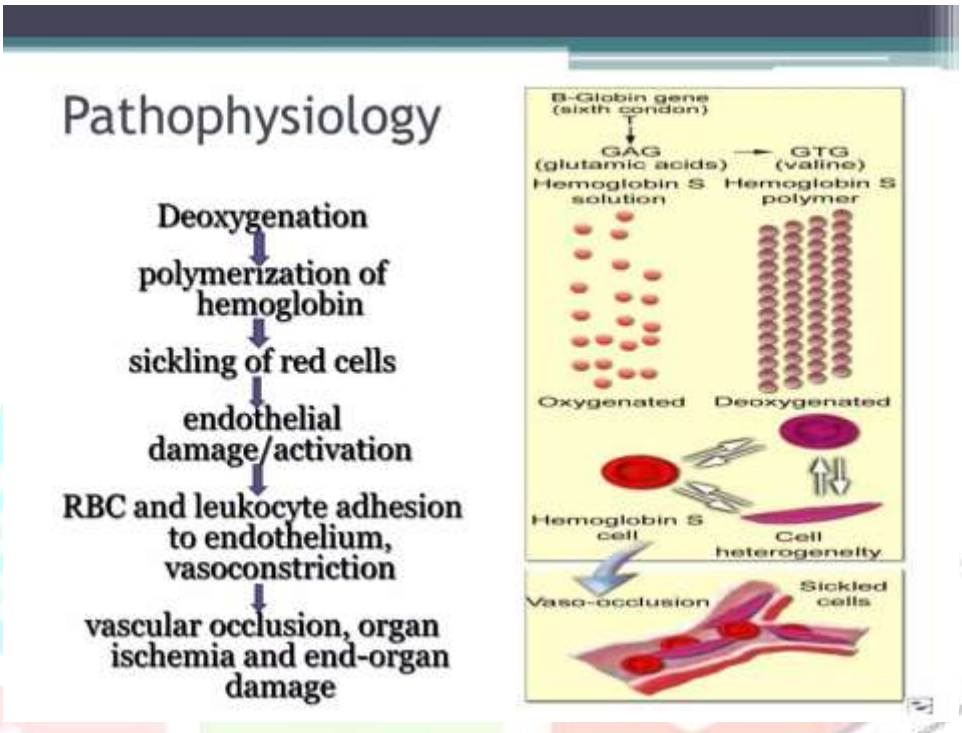
Hemoglobin (Hb) is a significant protein within the red blood cell (RBC). It comprises four globin chains, two derived from alpha-globin (locus on chromosome 16) and two from beta-globin (locus on chromosome 11). There are many subtypes of Hb. The most common ones that are found in adults without hemoglobinopathies are listed here: HbA1- comprises two chains of the alpha- globin and two chains of the beta-globin (a2b2) - This constitutes 95% of the adult hemoglobin.
HbA2- comprises two chains of the alpha-globin and two chains of the delta-globin (a2d2) - This constitutes less than 4% of the adult hemoglobin.

HbF- comprises two chains of the alpha-globin and two chains of the gamma-globin (a2g2) - This Hb is more prevalent in the fetus (due to the high oxygen binding affinity that helps extract oxygen from maternal circulation). The sickle cell mutation occurs when negatively charged glutamate is replaced by a neutral valine at the sixth position of the beta-globin chain. The mutation is transmitted via Mendelian genetics and is inherited in an autosomal codominant fashion.[5] A homozygous mutation leads to the severest form of SCD, ie, SCA- also called HBSS disease. The coinheritance of beta-naught thalassemia and sickle cell mutation leads to HBS-Beta-0 disease, which phenotypically behaves like HBSS disease. A heterozygous inheritance leads to HbAS. Patients with HbAS are not considered within the spectrum of SCD as most of them never present with typical symptoms of SCA

They might only be detected during childbirth, blood donation, or screening procedures. Several other compound heterozygotes exist where a single copy of the mutated beta-globin gene is coinherited with a single copy of another mutated gene. The second most common variant of SCD is the HbSC disease, where the sickle cell gene is coinherited with a single copy of the mutated hemoglobin C gene. HbC is formed when lysine replaces glutamine at the sixth position on the beta-globin chain. HbSC disease accounts for 30% of patients in the United States.

Pathophysiology

Sickle cell anemia is characterized by two major components: Hemolysis and vaso- occlusive crises (VOC). The defect in the beta-globin gene makes the sickle hemoglobin (HbS) molecule susceptible to converting into rigid, elongated polymers in a deoxygenated state. The sickling process is cyclical initially, where sickle erythrocytes oscillate between the normal biconcave shape and the abnormal crescent shape (acquired under low oxygen pressure). However, there comes a time when the change becomes irreversible, and the sickle erythrocytes develop a permanent sickle shape, increasing the risk for hemolysis and VOC. All variants of SCD share the same pathophysiology leading to polymerization of the HbS component.[3]



Multiple factors inherent to sickle erythrocytes, like the low affinity of HbS for oxygen, physiologically high 2,3-diphosphoglycerate, and increased sphingokinase- 1 activity, lead to deoxygenation, which promotes the polymerization of HbS. In addition to this, a high concentration of HbS, abnormal activity of the Gados channel leading to dehydration, and repeated damage to the red blood cell (RBC) membrane also increase the risk of polymerization of HbS.

Oxidative stress contributes to hemolysis by auto-oxidation of HbS, leading to erythrocyte cell membrane damage. The increased expression of xanthine dehydrogenase, xanthine oxidase, and decreased expression of NADPH oxidase increase the oxidative stress within sickle RBC. A hemolyzed cell releases free hemoglobin (scavenges nitrous oxide) and arginase 1 (competes for L- arginine) that prevent the action and formation of nitrous oxide and contribute to oxidative stress and vascular remodeling (arginase-1 converts arginine to ornithine).[3] Besides the polymerization of the HbS and intravascular hemolysis, several other factors also contribute to vaso-occlusion. For example, the sickle RBC (expresses several adhesion molecules on the surface), free heme and Hb, reactive oxygen species, and endothelium interact with each other and with neutrophils and platelets to promote vaso-occlusion and thrombosis. Besides the polymerization of the HbS and intravascular hemolysis, several other factors also contribute to vaso-occlusion. For example, the sickle RBC (expresses several adhesion molecules on the surface), free heme and Hb, reactive oxygen species, and endothelium interact with each other and with neutrophils and platelets to promote vaso-occlusion and thrombosis.

Clinical Manifestations

Sickle cell anemia is a genetic blood disorder caused by mutations in the hemoglobin gene, which results in the production of abnormal hemoglobin (hemoglobin S). The sickled shape of red blood cells leads to various clinical manifestations due to poor oxygen delivery, blockages in blood flow, and hemolysis (destruction of red blood cells). The severity and types of manifestations can vary based on the individual and whether they have sickle cell trait or sickle cell disease.

Common Clinical Manifestations of Sickle Cell Anemia:

1. Pain Crises (Vaso-occlusive Crises)

Description: One of the hallmark features of sickle cell anemia. It occurs when sickled red blood cells obstruct blood flow, causing tissue ischemia and pain. Location: Can affect any part of the body, but common sites include the bones (especially long bones like the femur and humerus), chest, abdomen, and joints. Duration: Episodes can last from hours to days. Triggering Factors: Infection, dehydration, extreme temperatures, or stress.

2. Anemia

Description: Chronic hemolysis (destruction of red blood cells) leads to a decrease in the number of red blood cells, causing anemia.
Symptoms: Fatigue, weakness, pallor, dizziness, and shortness of breath.

3. Jaundice

Cause: Due to the breakdown of hemoglobin from destroyed red blood cells, bilirubin is released into the bloodstream, leading to jaundice (yellowing of the skin and eyes). Symptoms: Yellowish tint to the skin or eyes, especially during pain crises.

4. Splenomegaly and Auto splenectomy

Splenomegaly (enlarged spleen): Often occurs in early childhood due to splenic congestion and sequestration of sickled cells.Auto splenectomy: Over time, recurrent splenic infarctions (damage due to poor blood flow) can lead to shrinkage or complete loss of spleen function, typically by adolescence.

5. Acute Chest Syndrome (ACS)

Cause: A serious complication, often triggered by infection or embolism, where sickled cells block blood flow in the lungs.
Symptoms: Chest pain, cough, difficulty breathing, fever, and hypoxia (low oxygen levels).

6. Stroke

Cause: Vaso-occlusion in the brain can lead to stroke, which is a significant risk in sickle cell anemia.
Symptoms: Sudden weakness or numbness, difficulty speaking, loss of coordination, and altered consciousness.

7. Leg Ulcers

Cause: Chronic poor circulation due to sickled red blood cells, healing leading to non- sores, usually on the lower legs.
Symptoms: Painful, slow-healing ulcers on the legs, typically in adults with sickle cell disease.

8. Chronic Organ Damage

Description: Long-term damage to organs such as the kidneys (leading to kidney failure), liver, and heart due to ongoing vaso-occlusion and hemolysis. Symptoms: Progressive organ dysfunction may not have immediate symptoms but can result in complications like renal failure or heart failure.

9. Increased Risk of Infections

Cause: Due to spleen dysfunction (especially in autosplenectomy), individuals with sickle cell anemia are more vulnerable to infections caused by encapsulated bacteria such as Streptococcus pneumoniae and Haemophilus influenzae. Symptoms: Fever, chills, and general malaise.

10. Delayed Growth and Puberty

Cause: Chronic anemia and poor oxygenation can interfere with normal growth and development in children.
Symptoms: Slower-than-normal physical growth, delayed puberty.

11. Priapism

Cause: A prolonged and painful erection caused by blood trapped in the penis due to sickling of red blood cells.
Symptoms: Painful, persistent erection that may require medical intervention.

12. Acute and Chronic Pain
Cause: The sickled red blood cells can cause pain by blocking blood flow in various organs, leading to ischemia and tissue damage. Symptoms: Episodes of severe pain that can occur in the chest, abdomen, back, or
Joints.

13. Gallstones
Cause: Increased breakdown of red blood cells leads to an excess of bilirubin, which can form gallstones.
Symptoms: Abdominal pain, nausea, vomiting, and jaundice (in severe cases). Complications in Sickle Cell Anemia: Painful episodes (vaso-occlusive crises) Stroke and neurological deficits Acute chest syndrome Organ damage (kidney, liver, heart, lungs) Increased risk of infection, particularly due to splenic dysfunction Chronic fatigue and poor quality of life Possible infertility due to chronic health issues or organ damage

Diagnosis

A blood test can check for the 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 get the test too. In adults, a blood sample is taken from a vein in the arm. In young children and babies, the blood sample is

usually collected from a finger or heel. The sample then goes to a laboratory to be screened for the sickle cell form of hemoglobin.

If you or your child has sickle cell anemia, your healthcare professional might suggest other tests to check for possible complications of the disease. If you or your child carries the sickle cell gene, you'll likely be referred to a genetic counselor.

Assessing stroke risk

A special ultrasound machine can reveal stroke risk in children. The test uses sound waves to measure blood flow to the brain. This painless test can be used in children as young as 2 years old. Regular blood transfusions can decrease stroke risk.

Tests to detect sickle cell genes before birth

Sickle cell disease can be diagnosed in an unborn baby by sampling some of the amniotic fluid surrounding the baby in the womb. If you or your partner has sickle cell anemia or the sickle cell trait, ask your healthcare team about this screening.

Management strategies

Management of sickle cell anemia (SCA) focuses on both preventing complications and treating symptoms. This requires a comprehensive, multidisciplinary approach. The key strategies typically include medical treatment, lifestyle adjustments, and patient education. Below are the main management strategies for sickle cell anemia:

1. Pain Management

Pain crises, or sickle cell pain episodes, are one of the most common complications of SCA. They occur when sickled red blood cells block blood flow in small blood vessels. Acute Pain Management: Hydration: Ensuring proper fluid intake is crucial to reduce blood viscosity and prevent clotting.

Analgesics: Mild to moderate pain can be managed with over-the-counter pain relievers like acetaminophen or ibuprofen. Severe pain may require opioids (e.g., morphine) for short periods. NSAIDs: Nonsteroidal anti-inflammatory drugs can help reduce inflammation and pain.

Chronic Pain Management:

NSAIDs for ongoing pain. Hydroxyurea (see below) can reduce the frequency of pain episodes. Transfusion Therapy may help in some cases of chronic pain. Physical therapy and cognitive- behavioral therapy may also help manage chronic pain and its impact on quality of life.

2. Hydroxyurea Therapy

Hydroxyurea is a chemotherapy drug used to reduce the frequency of pain crises and improve overall quality of life in patients with sickle cell anemia. It works by increasing the production of fetal hemoglobin (HbF), which reduces the sickling of red blood cells. Hydroxyurea has been shown to: Reduce pain crises. Reduce hospitalizations. Improve oxygen delivery and blood flowr Lower the risk of stroke. Patients on

hydroxyurea require regular monitoring (e.g., blood tests) to check forside effects such as bone marrow suppression and liver toxicity.

3. Blood Transfusions

Blood transfusions can be used to: Treat or prevent stroke in children or adults with a history of transient ischemic attacks or strokes. Help in managing severe anemia and prevent complications like organ damage. Exchange transfusions, where sickle cells are removed and replaced with normal red blood cells, may be used for severe complications like acute chest syndrome or organ failure.

4. Bone Marrow or Stem Cell Transplant

The only curative treatment for sickle cell anemia is a hematopoietic stem cell transplant (HSCT) or bone marrow transplant. This procedure involves replacing the patient's bone marrow with healthy stem cells, usually from a matched sibling donor. While it can cure sickle cell anemia, it comes with significant risks, including graft- versus-host disease (GVHD) and complications related to the transplant itself. This option is generally considered for younger patients with severe disease.

5. Prevention and Management of Complications

Sickle cell anemia can lead to various complications, including stroke, organ damage, acute chest syndrome, and infection. Strategies include: Stroke Prevention: Children with sickle cell disease are at higher risk for stroke. Regular screening with transcranial Doppler (TCD) ultrasonography can identify children at higher risk, allowing for early intervention with blood transfusions or hydroxyurea. Acute Chest Syndrome: This is a potentially life-threatening condition characterized by chest pain, fever, and difficulty breathing. It is often treated with oxygen therapy, antibiotics, and blood transfusions. Infection Prevention: Children with sickle cell disease are more vulnerable to infections, particularly bacterial infections like pneumococcus. Preventative measures include: Vaccination (e.g., pneumococcal vaccine, meningococcal vaccine, and Haemophilus influenzae type b vaccine). Regular penicillin prophylaxis in children under 5 years of age. Prompt treatment with antibiotics for infections.

6. Folic Acid Supplementation

People with sickle cell anemia are often given folic acid supplements to help produce new red blood cells, as the sickle cells are destroyed more quickly than normal red blood cells.

7. Lifestyle Adjustments

Avoiding Extreme Temperatures: Sickle cell patients are advised to avoid sudden temperature changes, as extreme heat or cold can precipitate a sickle cell crisis. Regular Exercise: Moderate exercise is encouraged but should be done with caution.

Excessive physical exertion in extreme conditions can trigger pain episodes. Hydration: Sickle cell anemia can cause dehydration, which may lead to increased sickling of cells, so it is important to maintain proper fluid intake.

8. Psychosocial Support

Living with sickle cell anemia can lead to mental health challenges such as chronic pain, depression, and anxiety. Therefore, addressing the psychosocial needs of the patient is crucial. Interventions include: Counseling or psychotherapy for coping with chronic illness. Support groups for patients and families to share experiences and coping strategies. Encouragement of emotional and psychological well-being through education and resources.

9. Gene Therapy (Emerging Treatment)

Gene therapy is an emerging treatment for sickle cell anemia, and although still in the experimental stage, it shows promise. This involves editing the patient's DNA to either correct the sickle cell gene or introduce a form of the gene that produces fetal hemoglobin, similar to what hydroxyurea does. Several clinical trials are ongoing, and while gene therapy has shown potential to cure sickle cell anemia, it's not yet widely available.

10. Patient Education

Health education on the importance of early intervention for complications like stroke or infection.

Pain management education to help patients manage crises at home and recognize when to seek urgent medical attention.

Prenatal Counseling: For families with sickle cell anemia, counseling about genetics and inheritance patterns (sickle cell trait vs. sickle cell disease) is important.

11. Monitoring and Regular Follow-Up

Patients with sickle cell anemia require regular visits to healthcare providers for: Routine blood tests to monitor hemoglobin levels, organ function, and complications. Regular imaging studies (e.g., echocardiograms or Doppler ultrasonography) for heart and blood flow assessments. Early screening for organ damage (kidneys, lungs, liver) and stroke.

Conclusion

Sickle cell anemia is a genetic blood disorder characterized by the production of abnormal hemoglobin, known as hemoglobin S. This condition causes red blood cells to take on a rigid, sickle-like shape, leading to blockages in blood flow, tissue damage, and a variety of complications, including pain crises, anemia, increased risk of infections, and organ damage.

The disorder is inherited in an autosomal recessive pattern, meaning both parents must carry the sickle cell trait for a child to be affected. While sickle cell anemia primarily affects individuals of African, Mediterranean, Middle Eastern, and Indian descent, its global impact is significant. Advances in medical research and treatments, such as blood transfusions, pain management, and newer therapies like hydroxyurea, have improved quality of life and extended life expectancy for many individuals with the condition. Additionally, gene therapy and bone marrow transplants offer potential curative options, though they remain limited by cost, accessibility, and risk.

Despite these advancements, sickle cell anemia remains a major public health issue, particularly in resource-limited regions. There is a need for greater awareness, early diagnosis, and improved access to care to better manage the disease. Further research is crucial to develop more effective treatments and,

ideally, a cure for those affected by this debilitating disorder. The ongoing commitment to scientific progress and global health initiatives will be key to alleviating the burden of sickle cell anemia worldwide.

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