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ADVANCES IN THE UNDERSTANDING AND TREATMENT OF SICKLE CELL ANEMIA

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ABSTRACT

Sickle cell anemia (SCA) is a hereditary hemoglobin disorder caused by a point mutation in the *HBB* gene on chromosome 11, resulting in substitution of glutamic acid with valine at the sixth position of the β-globin chain and formation of abnormal hemoglobin S (HbS). Under low oxygen tension, HbS polymerizes, leading to rigid, sickle-shaped red blood cells with a shortened lifespan. These abnormal cells cause vaso-occlusion, chronic hemolytic anemia, tissue ischemia, inflammation, and progressive organ damage. Clinically, SCA presents with recurrent pain crises, anemia, infections, and complications affecting multiple organs including the brain, lungs, kidneys, heart, and eyes. The disease follows an autosomal recessive inheritance pattern, with highest severity in individuals homozygous for HbS (HbSS), while compound heterozygous forms such as HbSC and HbS/β-thalassemia show variable severity.

Diagnosis involves prenatal testing (chorionic villus sampling, amniocentesis, and non-invasive prenatal testing), as well as postnatal and adult evaluation through clinical history, complete blood count, peripheral smear, hemoglobin electrophoresis or HPLC, and genetic testing. Management focuses on symptom control and prevention of complications through pain management, hydration, infection prophylaxis, hydroxyurea therapy to increase fetal hemoglobin, and blood transfusions. Curative approaches include hematopoietic stem cell transplantation and emerging gene therapy strategies, though access and affordability remain significant challenges. Increased awareness, early diagnosis, comprehensive medical care,

and ongoing research are essential to improving quality of life and reducing morbidity and mortality associated with sickle cell anemia.

1. INTRODUCTION

Sickle Cell Anemia is a disease that occurs due to the point mutation that takes place in the B chain of the chromosome number 11. The normal shape of the Hemoglobin that is Biconcave changes into elongated Sickle cell this mutation changes the amino acid residue Glutamate to Valine. It is an autosomal recessive trait that can be transmitted from parents to the offsprings when both the partners are carriers for the gene (heterozygous). Individuals having Hb^S ($Hb^SHb^{S)}$ which shows the diseased phenotype. Under low oxygen tension the cell changes its shape and start polymerization [1]. The average life span of the sickle cell is 10 to 20 days. Due to its shape the sickle cell stars accumulation in the blood vessels which causes the blockage of the blood vessel which slows the blood flow resulting in reduction in the level of oxygen in the body (Hypoxia and Ischemia) which causes excruciating pain in the body or acute pain crisis, loss of tissues and if prolonged episodes take place, then it can also permanently damage organs and ultimately causes death. This is a medical condition that requires consistent medical attention and care of the individual suffering from it Patients of this disease have weak immune systems which makes then vulnerable to other diseases. The Sickel cell Anemia works in two interrelated ways Vaso-occlusion pathway and by activation of Immune System. In Vaso occlusion the cells block the small blood vessel and capillaries which causes prolonged tissue damage and it results in the activation of the immune system which release inflammation causing cytokines which leads to more blockage and worsens pain in the patients [2-4]. There are different types of sickle cell diseases in which the most common type is sickle cell anemia which is caused by inheriting HbS gene from both the parents, this forms hemoglobin known as Hb SS. Hemoglobin SC disease is the second most common type and it occurs when HbC gene from one parent and HbS gene from another parent is inherited. However, this anemia is less severe. Hemoglobin SB+ (beta) thalassemia affects the generation of beta globin gene which causes decrease in the cell size as less beta protein is produced, if inherited with the HbS gene the anemia becomes hemoglobin S beta thalassemia (SBthal). The symptoms of the diseases include Fatigue, shortness of breath, pale skin and fingernails, and causes severe pain. Sickle cell anemia affects various organ and systems which results in the complications like frequent infections, eye problems including blindness and stroke, renal damage, stroke, heart failure and even in some cases death etc [5,6]. This condition requires medical attention and research for new treatments and cures. A

hallmark for the sickle cell anemia is the pain known as Sickel cell anemia crises which requires immediate medical attention, hydration or hospitalization in some cases. If not treated properly it can also contribute to higher mortality rate. Individuals are prone to various infections like pneumonia, meningitis, UTIs, Sepsis Hepatitis B and C etc. Individuals also face a psychological burden and can develop many psychological disorders like anxiety, PTSD, Depression and feeling of social isolation which requires emotional care and support while treating the disease. Treatments include rehydration with IV fluids to help the blood vessel to return to their normal shape can reduce the rate of dehydration of the cells, Blood transfusions can be done to treat anemic conditions to improve the transfer of oxygen and nutrients, Drugs like antibiotics and vaccines to treat and prevent the infections which can be caused because of the disease, Pain relieving medicines during the crises like NSAIDs, Hydroxyurea, drugs which inhibits the polymerization of the cells and hemolysis to be given to reduce the complication of the sickle cell anemia, Gene therapy and stem cells and bone marrow transplantation are also effective in treating the disease but as of now there is not a permanent cure for this disease. Most of the treatments are not affordable for many people in the world which leads to higher mortality rate and psychological burdens. Enfacement in the awareness, education of the people can help improve the lifestyle of the individuals suffering from the sickle cell diseases and can significantly reduce the mortality rate. Various research and advancement in the field of treatment and management of disease is being done to find a cure for individuals living with sickle cell anemia [7, 8].

2. Causes of Sickle Cell Anemia

A mutation in the HBB gene on chromosome 11, which codes for the β-globin portion of hemoglobin, causes sickle cell anemia, a hereditary condition. Hemoglobin is the oxygen-carrying protein in red blood cells. The disorder arises from a single nucleotide point mutation in which adenine (A) is replaced by thymine (T) in the DNA sequence of the HBB gene. This mutation results in the substitution of valine for glutamic acid at the sixth position of the β-globin chain, leading to the formation of abnormal hemoglobin known as hemoglobin S (HbS). Under conditions of low oxygen tension, HbS molecules undergo polymerization and form rigid, rod-like structures that distort red blood cells into a characteristic sickle shape instead of their normal flexible, biconcave form. These sickle-shaped red blood cells are less deformable and tend to block small blood vessels, impairing blood flow to tissues and organs, which can result in cellular damage and organ dysfunction. Sickle cell anemia is inherited as an autosomal recessive disorder, meaning that the disease occurs only when the mutated gene is inherited from both parents [9, 10]. Individuals who

inherit the mutation from only one parent are carriers and typically do not show symptoms but can pass the gene to their offspring. When both parents are carriers, there is a higher risk of their child developing the disease. Additionally, environmental factors such as infection, dehydration, and high altitude can promote red blood cell sickling by reducing oxygen levels. In summary, sickle cell anemia is caused by a point mutation that alters hemoglobin structure and function, leading to red blood cell sickling, vascular blockage, and the clinical manifestations of the disease [11, 12].

3. Genetic Basis and Molecular Pathophysiology

Sickle cell disease (SCD), also known as sickle cell anemia, is an inherited blood disorder characterized by abnormal red blood cells (RBCs). These abnormal RBCs have a crescent or sickle shape due to a gene mutation that converts normal hemoglobin (HbB) into hemoglobin S (HbS). The abnormal hemoglobin stimulates the cells to become sticky, stiff, and crescent-shaped, homologous to a banana or a "C" shape. These sickle-shaped cells do not flow easily through blood vessels, leading to various complications, including organ damage, reduced blood flow, oxygen shortage, and stroke. Under low oxygen conditions, the abnormal hemoglobin becomes volatile and activates the HbS molecules to stick together, synthesizing long chains of rigid fibers in RBCs. This altered form of hemoglobin results to severe pain episodes known as pain crises or sickle cell crises [13].

There are some steps in which mechanism are performed and caused Sickle cell anemia:- Genetic Mutation, Production of abnormal hemoglobin S (HbS), Polymerization of deoxygenated HbS, Distortion of red blood cells into sikkal shape, Vaso- occlusion and tissue ischemia, Hemolysis and premature destruction of RBC, endothelial dysfunction and inflammation, Chronichemolytic anemia and vaso occlusive crises, Organ damage and increased risk of infection, hemoglobin polymerization and erythrocyte membrane damage, ion channel dysfunction, red blood cell dehydration, increased adhesion of sickle red blood cells, activation of inflammatory pathways, organ dysfunction and failure, pulmonary hypertension, stroke and neurological complications are followed.

a) Genetic Mutation: Sickle cell anemia is caused by a mutation in HBB gene, which provides procedures for making Beta globin, a component of hemoglobin, it is located on chromosome 11, On the distinct mutation displaces, amino acid glutamic Acid with valine at 6th position of beta globin chain. This abnormal hemoglobin result as mutation And has predisposition/tendency of coagulate together under low oxygen level. When HbS molecules coagulate together, they twist the red blood cells into Crescent or sickle shape. Sickle cell are delicate And can block the blood vessels leading the pain membrane damage, organ damage

and other severe diseases. In inheritance of sickle cell anemia they transmitted from carrier parents to their child 2 clones of gene (One from each parent) and cause diseases [14, 15].

b) Production of abnormal hemoglobin HbS:-The single amino acid mutation results to the abnormal hemoglobin S production. This Sickle shape hemoglobin are less flexible so they can stuck in the blood vessels, Blocking blood flow and can pain crisis and organ damage due to rigid shape. Other hbb gene mutants can lead varied types of pathological hemoglobins such as HbC and HbE this mutant can also cause sickle cell disease or other hemoglobinopathies disorders when combined with HbS or other beta globin chain with abnormal hemoglobin [16, 17].

c) Polymerization of deoxygenated HbS:- HbS polymerization forming long, rigid chain , The shape and membrane integrity of red blood cells are disrupted, this process is reversible at first time but becomes irreversible over time with repeated Sickling episodes. There are main condition of favouring HbS polymerization are deoxygenation in which decreases oxygen tension and increases polymer synthesization. In low pH (acidic), promotes deoxygenated HbS, in high HbS concentration it increases polymer density and speed [18, 19].

d) Distortion of Red blood Cell into Sickle shape:- Polymerization of HbS etiologies RBCs to become rigid & distorted . Its leads to characteristics of sickle shape. This shape has changed due to long, rigid fibres that push against cell membranes & caused it into Sickle shape [20].

e) Vaso occlusion and tissue ischemia:- It is a complication due to sickle cell anemia. Mostly in adolescents and adults. It can be caused by rigid Sickle shape & it can blocked blood vessels by sucking RBCs. It may be triggered (e.g. by stress, illness, temperature changes and dehydration. It is acute and severe pain is starts happening. It can lead to tissue ischemia and pain in our body as well as the blood viscosity is also increased [21, 22].

f) Hemolysis, Endothelial dysfunction and inflammation:- Red blood Cells life span is 120 days after completing its cycle those RBCs breaks in the liver and another RBCs replaces it, also sickle RBCs have a shortened lifespan due to their increased fragility and sensitivity to Hemolysis. Also repeated vaso occlusion and Hemolysis, the endothelial dysfunction or damage and inflammation are leading. The endothelial lining of blood vessels is activated, leading to production of pro-inflammatory cytokines and retrieval of WBCs [23, 24].

g) Chronic hemolytic anemia & organ damage: - The premature destruction of RBCs leading to decrease in their lifespan and resulting in anemia. Also increased of rapid breakdown of RBCs, Surpassing our body’s replacement capacity, mostly kidney, lungs and

liver are affected. Sickle cell anemia patients are more susceptible to infections due to spleen damage and impaired immune functions [25, 26].

h) Ion channel dysfunction: - Revise ion channel function contributes to RBCs dehydration and increased Sickling. The Gardos channel, a calcium- potassium channel is activated in Sickle Red blood Cells, leads to potassium efflux and dehydration, because of the RBCs dehydration are also increased the concentration of HbS making it more polymerize and cause Sickling. The dehydration is caused due to loss of potassium ions and water in our body [27, 28].

4. Diagnosis of sickle cell anemia

Diagnosis of a disease is the process of dictating if the disease or disorder is present or not .or we can say identification and confirmation of a disease or disorder is called diagnosis. Diagnosis of sickle cell anemia can be done by following methods:

A. Diagnosis in fetus: The Diagnosis of SCD in fetus is very important when the both parents are carrier (both have sickle cell trait or family history). There are three major steps of diagnosis of SCD in fetus

I. Chorionic villus sampling-10-13 weeks of gestation period in this process cell of placental tissue (chorionic villi) are taken through cervix or abdomen and it is tasted. The DNA analysis of HBB gene to identify it.

II. Amniocentesis- 15-20 weeks of gestation. In this process amniotic fluid is tested to identify the disorder. This method is ban due to its misuse by people to identify the gender of the fetus.

III. Non invasive parental testing (NIPT): In this method testing of fetal DNA fragment in Mother's blood is done. It is not risky for the fetus but may not be definitive as other two methods.

These are the methods used for the detection of SCD in fetus. The Diagnosis is important as the early we diagnose we can be able to provide the treatment and risks can be managed. These methods have some risks minor chances of miscarriage [29].

B. Diagnosis in adults- Adults with sickle cell disease (SCD) are diagnosed using a combination of laboratory testing and clinical assessment. While neonatal screening programs diagnose the majority of SCD patients during infancy, adult diagnoses may emerge in undiagnosed individuals or in areas with limited screening [30].

I. Clinical Evaluation

- Clinical history- clinical history of the patient is taken.

To diagnose SCD, a thorough clinical history is necessary. Patients frequently exhibit symptoms like weariness, shortness of breath, jaundice, repeated episodes of discomfort, and delayed growth or development. Because the condition is inherited, a complete family history is especially crucial. Carriers and impacted individuals can be identified by evaluating inheritance patterns using surveys or family tree research.

- Past Medical History

Previous episodes of anemia, splenic sequestration, infections, or cerebrovascular events like stroke may be revealed by the patient's medical history. These results corroborate the SCD clinical suspicion.

II. Laboratory diagnosis

- CBC or complete blood count: Reduced hemoglobin levels and an increased reticulocyte count are common signs of chronic hemolytic anemia on a complete blood count.
- Smear of Peripheral Blood: Sickle-shaped red blood cells, target cells, and Howell-Jolly bodies all signs of splenic dysfunction may be seen under a microscope when the peripheral blood smear is examined.
- Tests for Confirmation: High-performance liquid chromatography (HPLC) or hemoglobin electrophoresis is used to confirm a definitive diagnosis. These tests provide precise SCD genotype categorization by identifying and measuring various hemoglobin variations, such as HbS, HbA, HbF, and HbC.3. Genetic testing-DNA analysis of HBB gene mutation.
- Sickling Test: The sickling test is a screening method based on red blood cell sickling under deoxygenated conditions. Although less commonly used today, it may still serve as an initial screening tool in resource-limited settings.

C. Additional workup

I. Renal function test: Check of proteinuria or hematuria

II. Liver function test: Asses hemolysis and iron overload.

III. Pulmonary emulation: Pulmonary related test like pulmonary function test [31, 32].

5. TREATMENT OF SICKLE CELL ANAEMIA

Sickle cell anaemia is a chronic inherited blood disorder caused by a mutation in the gene that produces haemoglobin. RBC is a biconcave and flexible so permit easily through blood vessel but in independent Sickle cell disease the RBC becomes inflexible and take a crescent shape. This uncommon shaped cell plunge in small blood vessel leading to obstruction that cause pain and injury and harm and other complication, although there is no universal cure

but various treatments are available to manage symptoms and prevent complication. The sickle cell anaemia management and treatments strategies include medication and therapy and other treatments. One of the most common symptoms of SCA is intense pain called as sickle cell crisis. These pain can be managed with pain- relieving medication such as penicillin codeine NSAID's and severe cases like morphine [33].

Hydroxyurea- Hydroxyurea is considered a very effective and reliable drug in the treatment of SCA. This drug helps in increasing the amount of fetal hemoglobin (HbF) in the body. This drug helps to reduce the pain attacks in the patient and reduce the need of blood transfusion and also decrease the risk of sudden serious complication of acute chest syndromes. Patients are also advised to take a folic acid supplement. It is helpful for production of new RBC, which is destroyed due to the Sickle cell disease and health check - ups are also essential parts of supportive care [34].

Blood Transfusions- Blood transfusion is play a crucial role in the management of sickle cell anaemia (SCA) they helps increase the number of healthy red blood cell and increase the delivery of oxygen to tissues and organ and also reduces the risk of stroke in children and the blood transfusion must be matched carefully ensure compatibility between the donor's blood type and the recipients. Cross matching is performed to reduce the risk of adverse reaction. And the frequent blood transfusion that caused the amount of iron will increase in your body. Patients may require iron chelation therapy to manage excess iron [35].

Bone Marrow transplantation- Bone marrow transplantation also known as hematopoietic stem cell transplantation. And it is a permanent cure for especially in children with severe disease. This procedure that involves replacing the patient's faulty bone marrow with healthy donor marrow. The primary mechanism of action in bone marrow transplantation for SCA are as follows, in sickle cell anemia the bone marrow produces faulty RBC due to the gene mutation. A successful bone marrow transplant introduces healthy hematopoietic stem cells that produce normal hemoglobin thereby preventing the production of sickle shape red blood cell. This not only alleviates the symptoms of SCA but can potentially cure the disease as it corrects the genetic defect responsible for the disease and bone marrow transplantation can prevent organ damage, including damage to the lungs, kidney, heart which can occur in untreated SCA. Patient undergo successful transplantation can experience an improvement in their health [36].

Gene Therapy- Gene therapy is a modern treatment of SCA. This treatment tries to change and correct the faulty gene in the body. Gene therapy delivers functional copies of the beta globin gene into the patient's hematopoietic stem cell. the introduction of corrected genes

leads to increased production of normal hemoglobin (hemoglobin A) and a corresponding decrease in the proportion of abnormal hemoglobin (hemoglobin S) .As result ,the patient's RBC are less inclined to sickling. Gene therapy holds the potential to provide a permanent or sustained cure for SCA and gene therapy can prevent organ damage, such as damage to heart, kidney, lungs which can occur untreated SCA. Patients who undergo successful gene therapy can experience a significant improvement in their overall quality of life and they are no longer load by chronic pain, anemia and further hospitalization [37].

Treatment of acute complication- In SCA acute complication is arise due to the crescent shaped red blood cells blocking blood vessels leading to the organ damage and reduce oxygen supply .managing these acute complication involve addressing symptoms promptly to prevent further complication and improve the patient outcomes pain crises can be managed with the help of analgesic medication as it helps in relieving the pain. Opioids, Non-steroidal anti-inflammatory drugs (NSAIDs) and other pain medication are used to control pain severity. Adequate hydration is essential to prevent red blood cell shrinkage. intravenous fluid are administered to maintain the hydration and improve the blood flow in the body and providing oxygen therapy helps increase the oxygen level in the blood , reducing the severity of the pain and tissue damage Similar to pain episodes , supplemental oxygen is provided to maintain sufficient oxygen levels and ease respiratory discomfort . Broad-range antibiotics are commonly used to treat infraction that may contribute to acute chest condition in critical cases, blood transfusion may be necessary to enhance oxygen supply and replace injured red blood cells. in situation of serious splenic pooling .sudden accumulation of blood in the spleen ,urgent blood transfusion are often required to stabilize the patient and avoid further complication [38, 39].

Chronic transfusion- Long term transfusion area treatment option used in individuals with serious SCA to manage issues and lower the risk of certain problem associated with the disease. This treatment involves routinely planned blood transfusion to help prevent or relieve complications related to sickle cell disease. Long-term transfusion are generally considered for individuals with SCA who have experienced complication such as frequents strokes, severe blood deficiency, acute chest disorder or other serious issues .also, children found to be at high risk for stroke through TCD (transcranial doppler) test may be chosen for happening. The main aim of regulation transfusions in SCA is to lower the amount of sickle hemoglobin (HbS) in the blood and increase the level of healthy red blood cells. By raising the number of normal red blood cells, regular blood transfusion can help stop the making of sickle -shaped cells, reduce the chance of problems like stoke, and improve overall health.

Also, infection reactions from transfusion and other side effects are possible risks linked with regular transfusion treatment .people getting regular transfusion need to be carefully watched by doctor's routine blood tests, like checking iron levels and how well organs are working, are done to understand the effect of the treatment and to handle any possible problems. For some patients, other treatments like hydroxyurea or stem cell transplant may be used as other options or additional treatment along with regular transfusion therapy [40-42].

6. CONCLUSION

A single point mutation in the HBB gene causes sickle cell anemia, a severe hereditary hemoglobin disease that significantly impairs red blood cell structure and function. Red blood cell sickling, chronic hemolysis, vaso-occlusion, inflammation, and progressive multi-organ damage are all consequences of aberrant hemoglobin S synthesis. Numerous clinical manifestations, such as recurring pain crises, anemia, increased susceptibility to infections, and potentially fatal consequences like stroke, acute chest syndrome, and organ failure, are caused by these pathophysiological pathways.

Effective illness care and the avoidance of sequelae depend on early and precise diagnosis through prenatal screening, neonatal programs, and confirmation laboratory testing in adults. Significant advancements in treatment options, such as hydroxyurea therapy, blood transfusion programs, bone marrow transplantation, and emerging gene therapy, have significantly improved survival rates and quality of life for affected individuals, even though there is currently no universally accessible permanent cure. However, there are still significant obstacles due to the high cost, scarcity of cutting-edge treatments, and lack of awareness in many areas.

Therefore, boosting patient education, expanding access to affordable healthcare, encouraging genetic counseling, and bolstering public health programs are crucial elements in lowering the burden of disease. Ongoing research and advancements in healing therapies offer potential for the future, providing optimism for a conclusive cure and improved results for those affected by sickle cell anemia.

AUTHOR CONTRIBUTIONS

Ocean Suryawanshi, Atharv Tripathi, Deepika Vishwakarma, Khushi Kinkar, Ashutosh Nagar, Ashish Kumar, conceptualized and drafted the manuscript, while Dr. Swati Rathore supervised the work and performed the statistical analysis. All authors reviewed and approved the final version of the manuscript.

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The authors affirm that none of their interest's conflict.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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