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REVIEW ARTICLE

A Review on Sickle Cells Disease

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ABSTRACT

Sickle cells disease (SCD) is homozygous inherited disorder lead to form hemoglobin called HbS with genotype (HbSS) when each parents carried this type of disorder gene. In which caused by point mutation in the gene that form β -globin chain found on the short arm of chromosome 11 by replacement amino acid glutamine by valine at 6 position. This disorder can be affects millions peoples in the world and showed severe complications due to hemolysis RBCs and vaso-occlusive phenomenon. Low oxygen condition causes accelerated hemoglobin polymerization and form sickle shape of RBC then damage to it cell membrane and decreases elasticity. Many symptoms of SCD due to chronic hemolytic anemia such as episodes of painful crisis, stroke, acute chest syndrome and infection. In recent year's best care of sickle cells disease patients like blood transfusion, bone marrow transplantation, Hydroxyurea and immunization to modifies pathogenesis by reduced mortality and morbidity with increased life of affected individuals.

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INTRODUCTION

Sickle cell disorders: are inherited disorders characterize by presence defect hemoglobin called hemoglobin S (HbSS) in which (RBC) become sickle shaped that lead to low oxygen carrying capacity finally leads to hemolysis of RBC and anemia ¹.

What is Sickle Cells Disease (SCD), Sickle Cells Anemia (SCA) and Sickle Cells Trait (SCT)?

These disorders include the following conditions:

1. **Sickle cell diseases (SCD):** its classified into following categories:
 - A. **Sickle cells anemia:** it is the homogenous formal of hemoglobin S (HbSS) that formed when each parent have β S gene then children have genotype $\beta^S\beta^S$.
 - B. **Sickle cell β thalassaemia**
 - C. **Combination of haemoglobin S (HbS) with other structural haemoglobin**

Sickle cell trait (SCT): That mean carry gene of sickle cell but it does not appear signs of illness ².

History of Sickle Cell Anemia

This disorder still unknown until first described 1904 by **James Herrick** cardiologist doctor and a professor of medicine university in Chicago, when admitted first year dental student a 20 year old to the Chicago Hospital with sign of sever from of anemia, when he was found sickle shaped cells of his blood . In 1922, Vernon Mason that was the first called this type of anemia by (Sickle cells anemia). In 1949, Linus found that Sickle Cell Anemia is genetic disorder resulted from mutation in specific protein and this result was available in their paper "sickle cell Anemia, a molecular Disease" ³.

Pathophysiology and mechanism of Sickle Cells Anemia

Point mutation in specific gene that form β - globin chain of hemoglobin lead to hydrophilic amino acid called glutamic acid replacement by hydrophobic amino acid called valine at sixth position from short arm of chromosome 11 under low oxygen conditions two mutant β -globin association that form hemoglobin S (HbS) ⁴.

HbS Polymerization: HbS molecules Polymerization in side red blood cells are responsible for sickle cells shapes occur by formed bundles of fibres aligned along with axis. Each fiber consists of 14 filaments arranged in pairs. HbS are less flexible and harder in contrast to normal red blood cells in which are quite elastic and easily pass through blood capillaries ^{5, 6}. This Polymerization form abnormal membranes of RBC lead to shortness in lifespan 10-20 days instead of 120 days , causes stuck in small blood vessels and lead to vaso-occlusion, moreover this known as sickle cell crisis ⁷.

Genotypes of Sickle Cell Disease (SCD)

Mutation in Sickle cell gene for single amino acid causes fibers hemoglobin, found normal allele lead to decrease polymerization defect in people with heterozygous because it is able to produce more than 50% of normal hemoglobin. This is the heterozygous carrier state for Hb S (Hb AS) resulted from HbA gene inherited from one parent and HbS inherited from the other that mean carry a sickle gene but didn't showed illness. The genotype is $\beta^S\beta$. While in homozygous people form abnormal hemoglobin, called (HbS) that make sickle RBC The genotype is $\beta^S\beta^S$, Sickle cells β thalassemia: define as two heterozygous state in which β thalassemia gene inherited from one parent and sickle cells gene inherited from the other, it can be divided in to two categories:

1. Sickle cell β^0 thalassemia with genotype $\beta^S\beta^0$ that mean normal β -globin chain synthesis is completely absent and the other is HS gene.
2. Sickle cell β^+ thalassemia with genotype β^S/β^+ that mean normal β -globin chain synthesis is partially deficient.

Combination of hemoglobin S with variants types of hemoglobin can products different heterozygous types of hemoglobin such as Hb SC disease, Hb SD disease, Hb SE disease, Hb SO- Arab disease, etc. ⁸.

Sickle Cell Disease	Genotype	Clinical Manifestations	Hb electrophoresis
Sickle cell anemia	β^S/β^S	Moderate to severe, No anemia; crises	HbS predominant
Sickle cell β^0 thalassemia	β^S/β^0	Moderate anaemia; splenomegaly persists in adults	HbS predominant; No HbA; HbA2 increased
Sickle cell trait	β^S/β	No anemia	HbA >HbS
Sickle cell β^+ thalassemia	β^S/β^+	Mild anemia	HbS>HbA; HbA2 increased

Signs and symptoms of Sickle Cell Disease (SCD)

1. **Vaso-occlusive Pain crisis (VPC) or pain crisis:** these symptoms are most common in kids and adults, it is occur when small blood vessels in bones obstruction by sickle cells causes pain in joints and bones this pain occur suddenly and variety from mild to severe ⁹.
2. **Acute chest syndrome (ACS):** can be define as pulmonary infiltrate accompanied by coughing, chest pain, fever, fibrotic lung disease and Asthma, its common in pregnant women, (ACS) consider important cause of death in adults than children ⁷.
3. **Infections:** Children with SCD have increased risk for bacterial infection that may be lead to sepsis and death form certain types of bacteria such as *meningitis, pneumonia, septicaemia, Salmonella* and *Haemophilus* these symptoms includes feeling generally ill, ever and pain in the affected part of the body ¹⁰.
4. **Anemia crisis:** in sickle cell anemia, patients increase RBC hemolysis with decrease level of hemoglobin associated with reticulocytosis ¹¹.
5. **Central Nervous System Disease (CNSD):** it most common in children with SCD in which may causes stroke and/or vasculopath, Stroke affects 10% of children, lead to increase mortality and morbidity Micro-vascular obstruction seen by MRI ⁷.
6. **Priapism: it occur in more than** half of men with SCA by painful involuntary erection of the penis, probability of **Priapism** episode is 89% of 20 year ages ^{12, 13}.

Diagnostic of Sickle Cell Disease (SCD)

1. **Complete blood counts:** showed anemia in normocytic and normochromic with hemoglobin levels 6-8g/dl, increase reticulocyte count while during vaso-occlusive Crisis Thrombocytopenia occurs.
2. **Blood smear:** Irreversibly sickle cells form about 5-10% of total RBCs from blood smear, and this percentage usually parallels to the degree of hemolysis, frequent Target cells and Howell-Jolly bodies are especially t in sickle cell β thalassemia. Mild polymorph nuclear leukocytosis found.

3. **Sickle solubility test:** this abnormal hemoglobin can be detected by slide solubility test using 2% sodium Metabisulfite of hemoglobin (HbS) in a showed unclear appearance, while normal hemoglobin show clear solution.
4. **Alkali denaturation test (estimated amount of HbF):** that important to determine persistence of fetal hemoglobin (HPFH) and related to severity of sickle cell anemia.
5. **Estimation of HbA2:** is required for the diagnosis of sickle cell β thalassemia.
6. **Gel Electrophoresis diagnostic:** abnormal types of hemoglobin can be detected by Varity move speed especially two types of Hemoglobin that most common in sickle cell disease HbS and HSC.
7. **High performance liquid chromatography (HPLC)** ^{8,9,11}.

Treatment of Sickle Cell Disease (SCD)

1. **Measures to prevent crises:** avoid exposure to extreme cold, hypoxia, stress, dehydration, fever and Hard exercise.
2. **Immunizations:** all infections should be early detection and treatment and recommended vaccinations to the both childhood and adults suffer from SCD such as hepatitis B, meningitis, Pneumococcal and influenza vaccine once a year.
3. **Oxygen:** Patients with Acute chest syndrome have low oxygen saturation level in blood arteries and oxygen recommended for treated this acute complications.
4. **Antibiotic:** it usually recommended if the patients have infection (erythromycin or penicillin) especially in children under 5 years.
5. **Analgesics:** Relief of pain is an important aspect for treatment of vaso-occlusive episode various types of Analgesics can be recommended Depending on the amount of pain, mild to Moderate pain used (ibuprofen, paracetamol and codeine) in severe pain (morphine) used in hospital in which keeping patient warm, improves oxygenation, decrease percentage of sickled cells and reduce organ damage during episode.
6. **Therapy by Blood transfusions:** this type of treatment used in some case such as severe anemia or acute chest syndrome by add normal RBC to the blood to prevent the irreversible organ damage but at the same time ⁷. Blood transfusions have many side effect such as increase in blood viscosity, increase iron overload and transferred infection then it given for specific need.
7. **An experimental form of therapy (hydroxyurea):** it is tried by increases HbF production, reduced polymerization of HbS, other benefit effects for Hydroxyurea are reduction in WBC count, reduce expression adhesion of molecules on red cells, reduce the number of painful crises and increase of red cell hydration.
8. **Stem cells Transplantation of Hematopoietic tissues:** only type of therapy can cure this type of anemia since it is associated with significant morbidity and mortality, this method established its activity in children ^{7, 8, 9, 11, 14}.

CONCLUSIONS

Sickle cells disease is inherited disorder of hemoglobin result from point mutation by replacement glutamine by valine at 6 position of β -globin chain lead to hemolytic anemia. Acute case found in homozygous mutation form genotypes β^S/β^S with abnormal hemoglobin called HbS (HbSS) this promote polymerization of hemoglobin which causes decreases elasticity and inflexible red blood cells then difficult to pass through narrow blood capillaries, leading to vessel occlusion, ischemic with pain. Occlusive can treated by Analgesics treatment. Hydroxyurea drug reported used to decrease number of painful crises. New treatments for SCD needed and modifying agents.

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