Original Article

An Overview On Sickle Cell Anaemia

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Abstract

A condition known as sickle cell anaemia (SCA) is brought on by the creation of aberrant haemoglobin. This faulty haemoglobin links to other defective haemoglobin molecules inside the red blood cell, causing the cell to rigidly deform. This deformity makes it difficult for the cell to move via tiny vascular channels, which may lead to sludging and congestion of the vascular beds and tissue ischemia and infarction. The earliest clinical symptom of SCA, the acute pain crisis, which is assumed to be caused by marrow infarction, is caused by infarction, which is widespread throughout the body in SCA patients. Such injuries eventually lead to epiphyseal osteonecrosis and medullary bone infarcts. White matter and grey matter infarcts are observed in the brain, which lead to cognitive dysfunction and functional neurologic impairments. Common lung complications include infarcts, emboli (from marrow infarcts and fat necrosis), and a significantly higher risk of pneumonia. Infarction can occur in the kidney, liver, and spleen as well. Sequestration syndrome, a rare but potentially fatal consequence of SCA, occurs when a sizable portion of the intravascular volume is concentrated in one organ (often the spleen), leading to vascular collapse.

Key words: sickle cell anemia

INTRODUCTION

Sickle Cell Anaemia

In Sickle Cell Anaemia the word Anaemia refers to “deficiency of blood”. Sickle cell anaemia (SCA) is also be called as sickle cell disease (SCD). SCA is an inherited disorder affecting RBC structure and make it sickle or crescent moons in shape, which is sticky and rigid in nature [(1)]. The normal shape of RBC’s (which is important for oxygen transportation in body) is biconcave i.e., oval round shape but because of mutation in the gene (DNA) some proteins are produced which makes haemoglobin to produce phytoproteins which changes the shape of normal red blood cell to Sickle shape [(2)]. The life span of normal RBC’s is about 120 days but the life span of RBC’S Sickle cell patient is about 10-20 days (on an average 17 days). Shorter life span of RBC’s results in decreasing of healthy RBC’s thus creating Anaemia (deficiency of blood). As there are cell crises (block blood flow which causes pain) which can be fatal resulting in organ damage. It is a genetic disorder and also an Autosomal recessive disorder. Sickle cell anaemia occur due to mutation in the gene (DNA) [(3)].

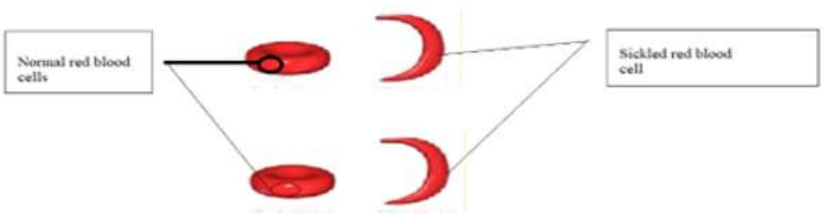

Fig 1. Shape of RBC’s in sickle cell anemia.

The term "sickle cell disease" (SCD) refers to a group of hereditary illnesses in which haemoglobin is physically aberrant, causing periodic sickle-shaped red blood cells (RBCs) to develop with a variety of clinical symptoms. In healthy adult Hb A, two chains of -globin and two chains of -globin combine to form a tetramer that is stabilised by certain intramolecular points of contact but does not interact with other tetramers inside the RBC [(4)]. 4 The molecule changes shape when it absorbs or releases oxygen. Deoxygenation in HbS reveals the aberrant valine residue on the surface of the molecule, which subsequently interacts hydrophobically with surrounding chains. The resultant polymers connect into

bundles, distorting the RBC into a crescent or sickle shape and decreasing flexibility and deformability, which hinders the passage of the cells through small blood arteries. Sickling can be triggered by environmental variables such hypoxia, low pH, cold, and RBC depletion, as well as adhesion molecules and cytokines linked to infections. Vaso-occlusion and hemolysis are two major pathogenic mechanisms that contribute to the clinical symptoms of SCD. Sickle cells form heterocellular aggregates with non-sickled RBCs, leukocytes, and platelets. These aggregates cling to the vascular endothelium and obstruct the lumen of small blood vessels [(1)]. This microcirculatory obstruction causes acute and chronic tissue ischemia and infarction, with multisystem consequences, especially in the bone, lungs, brain, kidneys, and spleen. Many of the long-term problems seen in SCD, including acute painful episodes and crises, are caused by it. Sickled RBCs are more easily destroyed by the reticulo-endothelial system, in part because of their rigidity, which makes them easier to filter in the spleen, and in part because changes in the structure of the lipid bilayer (with the exposure of anionic phosphatidylserine on the RBC surface), which promotes phagocytosis. An estimated 100,000 Americans and millions of others worldwide suffer from the genetic illness known as sickle cell disease (SCD), which is autosomal-recessive.
In accordance with the systematic analysis of the Global Burden of Disease Study, 43 million people have sickle cell trait (i.e., are carriers of the mutation), 3.2 million people have sickle cell disease, and 176,000 people pass away each year as a result of problems associated with SCD. All mutations in the beta-globin gene that result in the same clinical condition are collectively referred to be SCD^3. The outcome is a mutant haemoglobin tetramer HbS in the erythrocytes of people with sickle cell anaemia because it causes a hydrophilic glutamic acid residue to be replaced with a hydrophobic valine residue at the sixth position in the B-globin chain. According to a number of interconnected molecular and cellular pathways, including those detailed in the next sections, other kinds of SCD can result from homozygous inheritance of the s mutation (HbSS) or coinheritance of BS with other mutations like BC, BD, Bo, or BE [(2)].

History of Sickle Cell Anaemia

At order to enrol in the Chicago College of Dental Surgery, Walter Clement Noel set out from Grenada in 1904. A leg ulcer and acute respiratory distress, both of which are today recognised as signs of sickle cell, led to his admission to the Presbyterian Hospital in Chicago a few months later [(6)]. The day's intern doctor, Dr. Earnest E. Irons, was the first to notice these "pear-shaped, elongated" sickled blood cells while doing a regular blood test and urine analysis for Noel. The report detailing these "peculiar elongated and sickle-shaped red blood corpuscles in a case of acute anaemia" wasn't published until 1910 by Dr. James Herrick, the doctor who oversaw Dr. Irons. In terms of Western medicine, this was the first instance of sickle cell ever reported and documented. After returning to Grenada in 1907, Dr. Noel continued to practise dentistry in the nation's capital, St. Georges, where he remained until his death from acute chest syndrome at the age of 32 [(4)]. 1917 Emmel. genetic underpinnings of SCD, Dr. V. In 1915, Cook and Meyer reported on the third instance of sickle cell anaemia in a woman. She was 21 years old. Intriguingly, blood tests from the patient and her father, who had no symptoms, revealed sickling red cell malformation, and three of her brothers had passed away from severe anaemia. Dr. Emmel's discoveries led to a period of misunderstanding on the genetics of the sickness but also suggested a genetic basis for the illness. Sickle Cell Anemia is first described by Dr. V.R. Mason in 1922.
The first person to refer to the condition as "sickle cell anaemia" and to recognise the parallels between the cases was Dr. Mason, who saw the fourth known instance of sickle cell. Inadvertently contributing to the widespread belief that persons with sickle cell anaemia are of African descent, he also noticed that all of these patients were black [(5)].

Origin

It was initially believed that a single mutation occurred in the fertile Arabian Peninsula during the Neolithic period. However, as the region became a desert, people who may have carried the gene migrated to India as a result of the changing climatic conditions. Saudi Arabia moves quicker, and Africa is down so much. Citations provided in support of this claim ethnographic data as well as the distribution of specific agricultural methods.
But it is now abundantly obvious that there were numerous independent events that contributed to the sickle cell mutation [(7)]. The Hb S gene has been found to be linked to a few frequently occurring haplotypes that are typically distinct from those carrying the Hb A gene. Different chromosome structures (haplotypes) are identified using a variety of different restrictions end nucleases.The Hb S gene is linked to at least three distinct haplotypes that are separate mutations in Africa. They are the Benin haplotype, the Senegal haplotype, and the Central African Republic haplotype, also known as the Bantu haplotype, which may be found in central west Africa, the African west coast, and central Africa (African continent where Bantu languages are spoken), respectively [(8)]. The eastern Saudi Arabian province and central India both include the fourth haplotype, known as the Asian haplotype. It appears that the sickle cell mutation has happened at least three times in Africa and at least once in either the Arabian Peninsula or Central India. From these primary sites, the sickle cell mutation has spread to the other areas. This may account for the finding by numerous researchers that the gene cluster haplotypes are widely distributed on the chromosome in the United States as opposed to the homozygous state in Africa, the Arab world, or Asia. The unique gene haplotype prevalent in their region was present in the sickle cell trait slaves who were sold from different parts of Africa to the United States, but following their arrival in the US, Jamaica, and Brazil, there was significant admixture of African ethnicity throughout time. Based on estimations, this gene may have evolved between 3000 and 6000 generations ago, or roughly 70000–150000 years ago. There isn't a clear reason for why the Persian Gulf region and India have the same haplotypes. Indian tribal tribes, who are still largely cut off from the rest of civilization, are the main groups affected by sickle cell disease [(9)]. Rates of heterozygosity that can reach up to 35% in some tribes are not likely to be explained by an outside-Indian infusion of the sickle cell gene. Gene flow from India to

the Persian Gulf region via trade and migration appears to be the more likely scenario, despite the lack of conclusive information at this time [10]. It's interesting to note that modest clusters of sickle genes from African haplotypes can be found along parts of India's western coast. The descendants of African immigrants, who immigrated to India during the mogul era, frequently serving as "praetorian guards" for Indian rulers, are affected by sickle cell disease in this region [6].

Haemoglobin

The primary protein and pigment that convey oxygen in red blood cells. The link between oxygen and haemoglobin is brittle and reversible. Oxygenated haemoglobin (bright red). Low levels of deoxyhaemoglobin (purple-blue). The groups that surround a globin group make up each haemoglobin molecule. Iron-containing heme gives the molecule its red hue. Two pairs of polypeptide chains are joined to form globin [11].

Types of Haemoglobin

- Normal: Hb A, Hb A2, Hb F
- Abnormal: Hb S, Hb C, Hb E

Life Span of Haemoglobin

Life span of normal RBC's is 120 days but the life span of RBCs in Sickle cell patient is about 10-20 days (on an average about 17 day) [12].

Characteristics of RBC and Sickle Cell

RBC: Its life span is 120 days and Haemoglobin has normal oxygen capacity carrying. 12-14g/dl of Hb. Sickle Cell Anaemia: Its life span is about 17 to 20 days and Haemoglobin has decreased oxygen capacity carrying. 6-9g/dl of Hb [11].

Genetics of Sickle Cell Anaemia

Haemoglobin's structure changes, which causes a change in cell structure. Haemoglobin aggregates as a result of a single amino acid alteration [8].

Types of Sickle Cell Anaemia

Different gene mutations are responsible for the four primary forms of sickle cell anaemia.

1. SS illness in haemoglobin

The form of sickle cell disease that is most prevalent is haemoglobin SS illness. It happens when both of your parents give you an extra copy of the haemoglobin S gene. By doing so, Hb SS haemoglobin is created. Individuals with this kind of SCD, which is the most severe, also more frequently exhibit the worst symptoms.

2. The SC illness of haemoglobin

Sickle cell disease of haemoglobin SC is the second most prevalent variety. When you receive the Hb C gene from one parent and the Hb S gene from the other, it is known as haemophilia. Hb SC patients have symptoms that are comparable to those of Hb SS patients. But the anaemia is not as bad.

3. Haemoglobin SB+ (beta) thalassemia is third.

Beta globin gene production is impacted by haemoglobin SB+ (beta) thalassemia. Because less beta protein is produced, the size of the red blood cell shrinks. You will have haemoglobin S beta thalassemia if the Hb S gene is inherited. Less severe symptoms are seen.

4. SB Haemoglobin 0 (Beta-zero) thalassemia

Fourth in a family of sickle cell diseases is sickle beta-zero thalassemia. The beta globin gene is also involved. Symptoms are comparable to those of Hb SS anaemia. The signs of beta zero thalassemia can occasionally be more severe, though.

5. Sickle cell disease

A person is said to have sickle cell trait if they only have one parent who carries the defective gene (haemoglobin S). They could exhibit fewer or no symptoms [13].

Types of Anaemia

Haemorrhagic anaemia: Anemia brought on by bleeding is referred to as haemorrhagic anaemia.

Haemolysis, or the destruction of RBCs, causes haemolytic anaemia. Sickle cell anaemia. Anemia caused by a nutritional deficiency: erythropoiesis requires nutrients such iron, proteins, and vitamins C, B12, and folic acid. Anemia from dietary inadequacy is caused by a lack of these substances.

Aplastic anaemia: Aplastic anaemia is brought on by a red bone marrow abnormality.

Chronic anaemia is characterised by the limited lifespan of red blood cells, which is brought on by an imbalance in iron metabolism [(14)].

Who is impacted by Sickle cell disease?

90,000 to 100,000 Americans, mostly Blacks or African-Americans, are thought to be affected by sickle cell disease. About 1 in 500 Black or African-Americans and 1 in every 36,000 new born in the United States are affected by these diseases [(8)].

Effect of Malaria on Sickle Cell Anaemia Patients

Intriguingly, there is a connection between SCD and malaria. Given that heterozygous sickle trait gives protection against severe and life-threatening malaria, it has been hypothesized that the maintenance of the sickle mutation at such a high frequency in African communities despite the severity of SCD is a result of this (in particular cerebral malaria caused by Plasmodium falciparum)[15]. The presence of HbS is linked to decreased erythrocyte penetration by parasites, impaired multiplication, and quicker splenic clearance of parasites because RBC infection causes intracellular hypoxia, which leads to sickling and splenic filtration of parasitized cells. It may be thought that having homozygous SCD would improve resistance to malaria, but since malaria is the most prevalent initiating factor and co-existence of the two is linked to worse mortality and morbidity, this is not the case[15].

This mostly reflects the broad consequences of systemic infection, which include a significant release of inflammatory cytokines. Hypoxia, acidosis, and consequently sickling are brought on by parasites' metabolic activities within RBCs. Even in healthy people, red blood cells carrying schizonts can clog capillaries by adhering to the endothelium of the lining of the blood vessel. The harmful consequences of this are amplified in SCD patients. The spleen is crucial in the prevention and treatment of malaria by removing damaged and parasitized RBCs from circulation, "pitting" infected cells (removing parasites and returning the cells to circulation intact), and producing particular B and T cell responses[16]. Although P. falciparum splenectomized people had less RBC clearance, it is unknown if they also experience more severe malaria symptoms. Numerous factors, including malaria, can result in anaemia. When merozoites grow and emerge, infected RBCs hemolyze, and non-infected cells can also hemolyze as a result of the development of auto-antibodies against RBC surface chemicals. Virus- and non-virus-infected cells are both phagocytosed by macrophages. Malaria can result in dyserythropoiesis and the sequestration of RBCs in the spleen (for instance, in young children who have not yet undergone autosplenectomy), and repeated hemolysis can result in a folate-deficiency anaemia. It is especially problematic in SCD because anaemia can be very severe in normal persons[17].

Inheritance

1. Usual (AA) and Trait (AS)

None of the children will have sickle cell anaemia if one parent carries the sickle haemoglobin trait (HbAS) while the other does not (HbAA). A child's risk of receiving one copy of the HbAS gene and developing sickle cell trait is one in two (50%) at any given time. Every child has an equal chance of receiving two HbAA genes while remaining unaffected.

2. Trait (AS) and Trait (AS)

There is a one in four (25%) probability that any given kid may be born with sickle cell anaemia if both parents have sickle cell trait (HbAS). Additionally, a child's likelihood of being fully unaffected is one in four. Any given child has a 50% chance of inheriting the sickle cell trait, or one in two.

3. Trait (AS) and Anaemia (SS)

All of the offspring will carry the sickle cell trait if one parent has sickle cell anaemia (HBSS) and the other is unaffected (HbAA). Nobody will be sickle cell negative. Only each of the children born to a parent with sickle cell anaemia (HbSS) can inherit the sickle haemoglobin gene.

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Mechanism

- Sickle haemoglobin (HbS) clumps together when tissues receive oxygen from it.
- Within RBC, lengthy rods develop.
- RBC start to stiffen up and take on a sickle-like form. Blocks small blood arteries instead of being allowed to pass through them. Bodily tissues receiving less oxygen
- HbS-containing RBCs live shorter lives.
- Typically, 20 days.
- Anemia that is persistent[17].

Symptoms

Note: Sickle cell disease (SCD) can be occurred in any part of the body and it usually appears around 6 months of age.

Anaemia: In anaemia the life span of RBC's (10-20 days) is shorter as compared to life span of normal RBC's (120 days). RBCs are necessary for transportation of oxygen in the body (for normal working of the body)[13]. As in anaemia there are shortage of red blood cells which causes fatigue. Because of shorter life span of red blood cells, this results in decreasing of healthy red blood cells thus deficiency of blood (anaemia) occurs in body.

Episodes of pain: It is a type of symptom which causes extreme pain in the body, which is termed as pain crises. This develops when Sickle shaped red blood cells blocks the tiny blood vessels at a particular part of body and thus creating extreme pain or pain in joint areas, chest, abdomen, etc. The pain varies from person to person and the pain may be last for a few hours to few days. Some people have pain only for some times i.e., for a year after that they are not suffering but some people suffer for a long time i.e., for several years[18].

Sickle cell crises (SCC): SCC can be fatal, thus resulting in organ damage, spleen damage, increasing the risk of infections.

Delayed puberty: Due to decrease in healthy red blood cells, the body of infants and children cannot full fill the demands of oxygen and nutrients required by the body. As a result, the growth and development of the body does not occur properly at time which results in delayed puberty[18].

Swelling of hands and feet's: Sickle shaped red blood cells blocks the tiny blood vessels during the flow of blood form one part of the body to another party of the body, thus resulting in swelling of hands and feet's and it further results in difficult walking[17].

One sided paralysis: Seek immediate medical assistance if a child has a temperature higher than 101.5 F because child ren with sickle cell anaemia are more susceptible to infections, which frequently begin with a fever and can be fatal (38.5 C). Seek immediate medical attention if you experience any stroke symptoms, such as one-sided paralysis or weakness in your face, arms, or legs.

Stroke: Sickled cells frequently congregate and find it difficult to pass through blood channels. They may gather and obstruct blood arteries. This may result in the formation of a clot that travels to the brain and causes a stroke. Damage to the blood arteries in the brain brought on by SCD can also result in a stroke[19].

Vision problems: Due to changed structure of red blood cells, tiny blood vessels of eye can be plugged or blocked which creates disruption in the system of retina which further leads to vision problems.

In urinary system:

Protein in the urine – Protein generally does not pass through the kidneys to leave the blood. Protein in the urine in lar ge amounts is a symptom of sickle cell renal disease.

Too much water in the urine – Normal urine contains a certain quantity of waste. An indication of sickle cell kidney disease ma y include urine that is primarily water and contains less waste than usual.

Urine with blood in it — Urine from your child may seem red, brown, or cola- coloured. Alternatively, without a microscope, the blood can be invisible.

Yellow skin and eyes: A prominent indicator and symptom of sickle disease is jaundice. Due to their shorter lifespan than typical red blood cells, sickle cells are degenerating faster than the liver can remove them from the body. These disintegrated cells produce bilirubin, which gives things their yellow hue, which piles up in the body and causes jaundice[19].

Fig .2 Structure of blood vessels

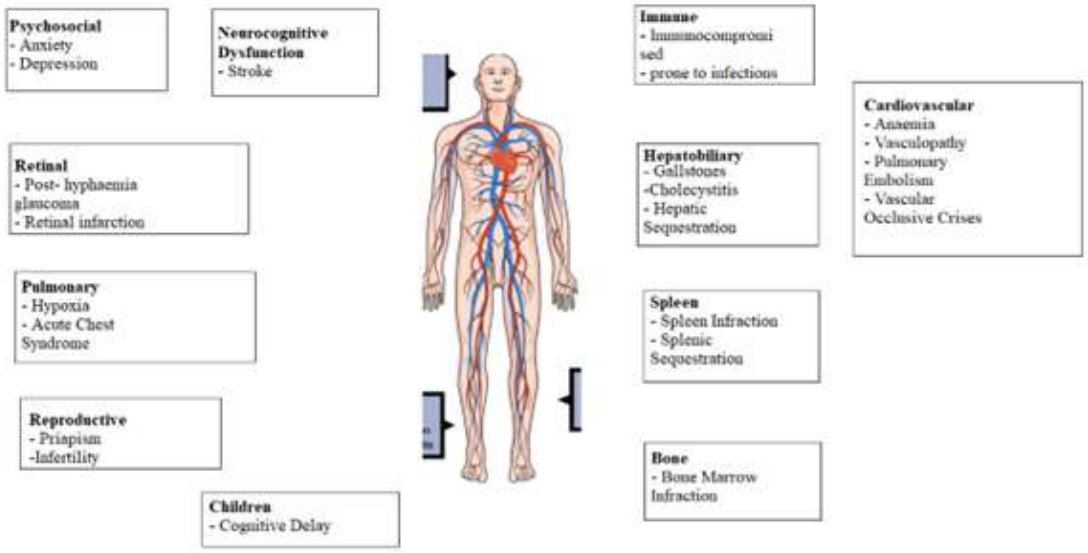

Fig 3. Sickle cell causes abnormalities in the body

Genetic Counselling

Expectant parents can determine whether their child is affected by two tests.

1. Usually performed between 14 and 16 weeks of pregnancy, amniocentesis examines a sample of the foetus' amniotic fluid for signs of genetic abnormalities (the fluid and the foetus have the same DNA). A little needle is placed into the woman's womb through her belly while she is under local anaesthetic. A sample of about 20 millilitres (or four tablespoons) of fluid is taken and sent to a lab for analysis. Usually, test results come back in 1-2 weeks[20].
2. During the early stages of pregnancy, a very small sample of the placenta is taken and tested using a procedure called chorionic villus sampling, or CVS. The sample is taken out using a catheter, a fine needle inserted through the cervix, or a fine needle inserted through the abdomen. The sample contains the same DNA as the developing foetus. The tissue is examined for genetic alterations found in a family member who has been affected. Typically, results are ready in two weeks[21].

Medication

Antibiotics: Penicillin is an antibiotic that can be given to children with sickle cell anaemia as early as 2 months old and should be continued until they are at least 5 years old.

Infections like pneumonia, which can be fatal to a baby or young child with sickle cell anaemia, are prevented as a result of doing this.

If you had your spleen removed as an adult or have pneumonia, you might need to take penicillin for the rest of your life.

Medicine for reducing pain. to alleviate discomfort during a sickle cell crisis. Hydroxyurea (Droxia, Hydrea): Daily hydroxyurea use decreases the number of uncomfortable crises and may lessen the need for blood transfusions and hospital stays. It appears that hydroxyurea works by igniting[20].

Causes

The Sickle cell anaemia is caused due to gene mutation (beta chain of haemoglobin). Gene is responsible to make haemoglobin which is further allows red blood cells to carry oxygen throughout the body. So, the haemoglobin associated with the Sickle cell Anaemia causes red blood cells to become rigid, sticky, and misshaped[22].

From parents to off spring: Either parent must have Sickle cell trait. They are carrier of the disease, but they generally do not have symptoms.

Through blood transfusion: If the blood of an infected person transfers into the body of healthy person[22].

Factors affecting

Genetic Factor

Despite having the same underlying genetic defect, the severity of SCD's phenotypic varies dramatically; with some patients incapacitated by chronic problems and recurrent crises while others lead essentially normal lives. Additionally, various people have varying predispositions to specific pathological illness presentations. Given that numerous unrelated genes are involved in the pathogenic processes underlying SCD (such as the death of sickled cells or endothelial adhesion), this suggests that the trait is multigenic and that variation in alleles at various loci may affect outcome. Increased vulnerability to infection in SCD has been linked to polymorphisms in a number of immune response-related genes, according to certain theories[23].

Mechanical Factor

SCD's pathogenic effects have the potential to foster an inflammatory environment. Osteomyelitis is more likely to affect children with SCD. Oxygen demand is high and the bone marrow space is enlarged to support the increased hematopoiesis required to counteract chronic hemolysis. Circulation is also sluggish at this time. These elements work together to make bone prone to infarction and vaso-occlusive events. The infection spreads by hematogenous dissemination and establishes foci in areas of necrotic bone. 30 Staphylococcus aureus is the main pathogen in osteomyelitis in children who do not have SCD.S. aureus, Gram-negative enteric bacteria, and Salmonella are the most frequent causes of SCD, respectively. Salmonella caused 57% of instances of acute osteomyelitis and 41.7% of cases, respectively, in long-term retrospective investigations from the USA32 and Saudi Arabia[24]. Over a 15-year period, Salmonella was found to be the cause of 52.3% of all bacteremia in SCD patients in London, as opposed to 0.4% in non-SCD patients. One-third of these infections led to osteomyelitis, which was primarily caused by Salmonella typhimurium, a typical food-borne pathogen. Possible explanation: Microvascular occlusion-induced patchy ischemia and infarction of the bowel allows gut bacteria to breach the intestinal wall and enter the bloodstream. However, there does not appear to be any proof that asymptomatic SCD patients have higher gastrointestinal Salmonella carriage[23].

Another enterobacterium associated with SCD has been observed to occur more frequently: Edwardsiella tarda. This relationship is most likely caused by SCD's increased biliary sludging and intestinal permeability[25].

Complication

Brain Stroke: signs of stroke include seizures, weakness, or numbness of arms and legs, sudden speech difficulties, and loss of consciousness.

Acute chest syndrome: An infection in lungs due to SC, results in chest pain, fever, breathing problems and may be life threatening.

Organ damage: Due to shorting of oxygen level in SC, organ can't get oxygen resulting in nerve and organs damage like kidney, liver, spleen, which is also fatal[16].

Blindness: Due to changed structure of red blood cells, tiny blood vessels of eye can be plugged or blocked which creates disruption in the system of retina which further leads to vision problems and for a very long period of time, and this can lead to blindness.

Leg ulcer: Sickle cell anaemia cause painful open sores on the leg

Splenic sequestration: Enlargement of spleen due to trapping of large number of Sickle cell (SC) in the spleen leading to belly pain[18].

Gall stones: Due to breakdown of red blood cells bilirubin is produces inside the body which causes increased level of bilirubin which further leads to gallstones.

Priapism: In this condition patient with Sickle cell Anaemia can have painful, long-lasting erections. Sickle cell can block the blood vessels in the penis, which can lead to impotence over time.

Deep vein thrombosis: Sickle cell Anaemia can cause blood clots, increasing the risk of clot loading in a deep vein (deep vein thrombosis) or a lung (pulmonary embolism).

Pregnancy complication: Can increase the risk of high B.P and blood clots at the time of pregnancy. Risk of miscarriage, premature birth, having low birth weight babies[25].

Prevention

- Getting vaccine (penicillin) between the ages of about 2 months to 5 years. Helps in preventing infections, such as pneumonia.
- All the recommended childhood vaccination, as well as vaccines against pneumonia, meningitis, hepatitis B and an annual flu shot.
- Adults who are having Sickle cell disease might need to take penicillin throughout their lives if they have pneumonia or surgery to remove the spleen[23].
- Drink plenty of water: Dehydration can increase risk of sickle cell crisis. Increase the amount of water in summer season or when you perform any kind of exercise either low or high intensity form of exercise.
- Avoid temperature extremes: Exposure to extreme heat or cold can increase the risk of a sickle cell crisis[24].

Diagnosis

Prenatal testing: There is prenatal testing to detect if a new born screening fetus carriers Sickle cell alleles.

New born screening: There are new born screening to see if a new born infant is carrying a mutated allele for Sickle cell disease[24].

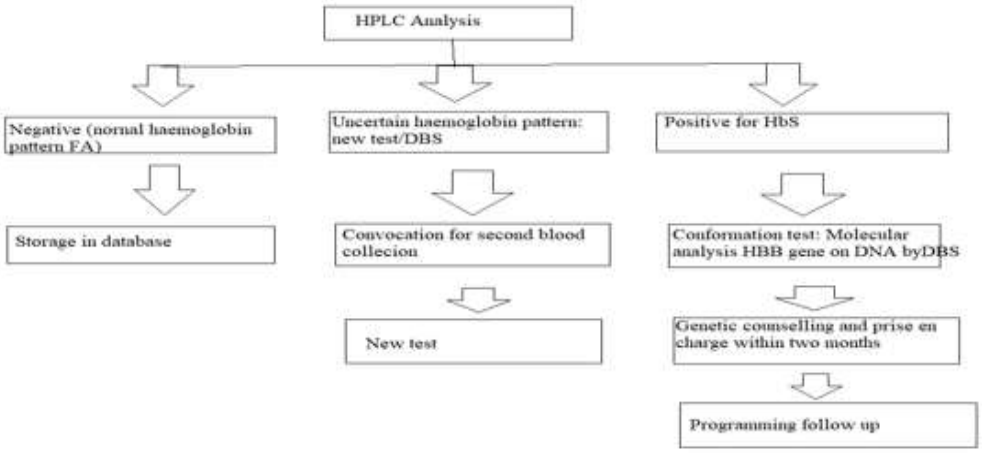

Fig 4. New born screening diagnosis

HPLC (High Performance Liquid Chromatography): HPLC can be performed to assess and also haemoglobin electrophoresis can be used to diagnose Sickle cell disease and usually it is either with a cellulose acetate or citrate agar gel and if there is more than 30% haemoglobin S in patient then the patient has Sickle cell disease[25].

Treatment

Hydroxyurea (Droxia, Hydrea, Siklos): Hydroxyurea can reduce episode of acute pain or the frequency of painful crisis and it can also reduce the need of blood transfusion and hospitalization rates and can also prolong survival of patients with Sickle cell disease. Pregnant woman should avoid this drug. L- glutamine oral powder (Endari)[26].

Hematopoietic cell transplantation: In this we dick cell transplantation which is usually thought to be the only cure for Sickle cell disease and it is usually performed only in individuals less than 16 years old and blood transfusion can be performed in patients with Sickle cell disease because especially in patients with severe anaemia if they have low haemoglobin[25].

Blood transfusion: To prevent complications such as stroke etc. Stem cell transplant: It is the only known cure for sickle cell anaemia. Clinical trials are ongoing to address stem cell transplantation in adults and gene therapies. Take folic acid supplements daily which is very much necessary for bone marrow to make new RBS and have healthy diet which includes vegetables, fruits, whole grains, lentils, etc. Use pain medication such as ibuprofen (Advil, Motrin LB, Children's Motrin, others) or naproxen sodium (Alove). Consult with the doctor before taking any kind of non-prescription drugs[19].

Bone Marrow Transplant: The only option for treating sickle cell anaemia is bone marrow transplantation, often known as stem cell transplantation. Finding a donor is challenging, and the procedure carries significant risks, including death, for those over the age of 16. As a result, it is typically reserved for those under the age of 16.

During a bone marrow transplant, healthy bone marrow from a donor is substituted for sickle cell anaemia-affected bone marrow in the patient. A sibling or other compatible donor who does not have sickle cell anaemia is typically used in the surgery. Many people lack access to donors. However, umbilical cord blood stem cells may be a possibility.

A bone marrow transplant is only advised for patients, mainly youngsters, who have severe symptoms and complications from sickle cell anaemia due to the dangers involved in the treatment[26].

The patient with sickle cell anaemia receives radiation or chemotherapy to eliminate or diminish his or her bone marrow stem cells if a donor is located. Healthy stem cells from the donor are administered intravenously to the sickle cell anaemia patient, where they go to the bone marrow and start producing new blood cells.

A lengthy hospital stay is necessary for the surgery. You will be given medication following the transplant to help prevent the donated stem cells from being rejected. Nevertheless, your body could reject the transplant, creating potentially fatal problems[25].

L- glutamine

Because the body normally produces enough glutamine, it is a conditionally essential amino acid. During times of stress, however, the body's need for glutamine increases, and it must rely on dietary glutamine to meet this demand. In July 2017, the American Food and Drug Administration (FDA) authorized the use of pharmaceutical-grade L-glutamine for sickle cell patients who were five years of age or older[27]. The prevalence of acute complications of SCD was dramatically decreased, according to formal clinical trials, by this purified form of glutamine. There do not seem to be any significant side effects and no lab testing is necessary. Based on the findings of two double-blind, randomised, placebo-controlled trials, the FDA approved the use of L-glutamine to treat adults and children over five years old with HbSS or Hb S/Bo thalassemia. In a phase III double-blind, placebo-controlled trial, 230 patients between the ages of 5 and 58 were randomised in a 2:1 ratio to receive either placebo or 0.3 g/kg oral L-glutamine twice daily, rounded to 5 g doses with a maximum of 30 g, or a placebo. The high dropout rate of the study, with 97 (63.8%) participants in the intervention group and 59 (75.6%) in the placebo group finishing the eleven-month study, raises questions about the study's findings. The L-

glutamine group experienced 17.9% fewer sickle crises on average (3.2 against 3.9 in the L-glutamine and placebo groups, respectively; p = 0.0152) and considerably fewer pain crises (median 3.0 in the L-glutamine group versus 4.0 in the placebo group; p = 0.005). Hospitalizations were significantly lower in the L-glutamine group (median 2.0 versus 3.0 in the placebo group, p = 0.005) [69]. Additionally, there were notable decreases in the frequency of acute chest crises (8.6% on the L-glutamine group against 23.1% in the placebo group, p = 0.003) and the length of hospital stays (median 6.5 on the L-glutamine group versus 11 in the placebo group, p = 0.02)[28]. Lack of long-term follow-up evidence, higher costs relative to hydroxycarbamide, and theoretical worries about patients seeking more naturalistic treatments diminishing treatment concordance with hydroxycarbamide therapy are a few potential issues with utilisation[27].

Hydroxycarbamide

The use of hydroxycarbamide is now generally approved around the world. Increasing total haemoglobin concentration and Hb F synthesis is the primary way that hydroxycarbamide acts in SCD, despite the fact that it was initially utilised as a cytoreductive drug by blocking ribonucleotide reductase. Additionally, hydroxycarbamide lowers the quantity of leucocytes in the blood as well as the expression of surface adhesion molecules on neutrophils, red blood cells, and vascular endothelium[28]. This improves blood flow and lowers vaso-occlusion.Long-term hydroxycarbamide treatment has demonstrated positive results in a number of studies involving both adults and children, including a decrease in the severity and frequency of crises in kids with SCD. According to the Multi-Centre Study of Hydroxycarbamide (MSH), adults taking hydroxycarbamide had significantly fewer painful crises over a two-year follow-up period than those taking a placebo (median 2.5 versus 4.5, respectively, p = 0.001), as well as fewer cases of acute chest syndrome (25 versus 51, p = 0.001) and fewer blood transfusions (48 patients versus 73, p = 0.001). Those using hydroxycarbamide had a 40% lower mortality rate, according to a subsequent observational research that tracked MSH trial participants over the course of nine years.SCD patients with higher HbF levels have less pain and live longer. In a meta-analysis conducted in 2007, researchers examined the effectiveness, efficacy, and toxicity of hydroxycarbamide in children with SCD[29]. They discovered that HbF levels increased by about 10% and that there was a significant increase in haemoglobin concentration by about 1%. Additionally, they discovered that there was an average 71% decrease in hospitalisation rates and a decrease in the frequency of pain crises. The use of hydroxycarbamide depends on the patient's phenotype, age, and practice. According on the phenotype, age, and specific practise, different hydroxycarbamide indications are used. Despite the fact that actual practise differs greatly between continents, the British Society of Haematology and the US National Institutes of Health (NIH) both recommend giving hydroxycarbamide to all children with the HbSS and HbS/B0 thalassaemia genotypes starting at the age of one year.

Indications for hydroxycarbamide in adults could include:

1. Chronic, incapacitating pain that is not controlled by standard protocols or frequent painful episodes (more than three per year).
2. Stroke history, high risk of stroke, or other severe vaso-occlusive events
3. Extremely noticeable anaemia.
4. Acute chest syndrome past.

Patients using hydroxycarbamide are routinely checked for the emergence of leucopenia and/or thrombocytopenia. Although hydroxycarbamide has not yet been connected to human birth problems, it has been shown to induce birth malformations in animal models, which is why using it while pregnant is advised. Only mild side effects have been observed in short-term studies, and taking hydroxycarbamide provides long-term advantages that outweigh any short-term drawbacks[25].

Gene Therapy

Early research is being done on gene therapy as a potential treatment for sickle cell anaemia. The strategy is based on stem cells and gene therapy; rather of employing embryonic stem cells, host stem cells are created by reprogramming and manipulating cells from the patient's own blood cells, [and] genetic engineering is then utilised to fix the inborn genetic defect. There is no need to identify a stem cell donor because the patient's own cells can be used, and there shouldn't be any GVHD danger as the patient is the source of the cells[18]. The goal is to replace the damaged gene by converting a patient's blood cells into pluripotent stem cells.

Following that, these cells will be encouraged to develop into hematopoietic cells, which can precisely regenerate the full spectrum of red blood cells. In three clinical studies of gene therapy using various lentiviral vectors, a small number of patients with SCD appear to have been treated as of the time of this writing. The promise of combination therapy is no longer a distant dream thanks to a variety of novel sickle cell treatment alternatives that are in the works[19]. This necessitates an immediate discussion on the ideal patient profile, appropriate drug combinations, and accessibility for the vast majority of patients. Therefore, it is appropriate to commission such a review on newborn sickle cell screening for all nations, not only those in Europe, which naturally face the burden of immigration[19].

Experimental Treatments

Gene therapy is one of the novel treatments for sickle cell anaemia that researchers are looking at. Researchers are investigating if a normal gene might restore normal haemoglobin in sickle cell anaemia patients' bone marrow.

The potential of deactivating the problematic gene while activating a different gene in charge of creating foetal haemoglobin, a type of haemoglobin seen in new-borns that prevents the formation of sickle cells, is also being investigated by scientists. Gene therapy treatments are still decades away, though.
It is wise to be aware of the obstacles that still stand in the way of SCD gene therapy, even though some of the first obstacles seem to have been removed[28].
Lentiviral vectors have improved the efficiency of HSC transduction, however producing high-titer viruses with strong transduction remains difficult due to the complex design of numerous globin vectors. A difficult difficulty in scaling up operations to many patients. Only thorough clinical trials with lengthy patient follow-up can confirm a product's safety and effectiveness. As gene engineering techniques advance quickly, "second-generation" gene therapy strategies might be easier to design in the years to come. Options for gene therapy for SCD patients are now available after many years of preclinical laboratory research[30].

Epidemiology

The majority of those affected by SCD are of African, Indian, and Arab ancestry. It is one of the most prevalent inherited, life-threatening disorders in humans. It is estimated that more than 80% of the more than 300,000 births each year take place in sub-Saharan Africa (SSA), with Nigeria and the Democratic Republic of the Congo bearing the heaviest burden. In West African nations, the gene frequency is highest, with 1 in 4 to 3 (25–30%) people carrying the HbS gene, compared to 1 in 300 African Americans, and it varies in European cultures. SCD prevalence in industrialised nations is rising in part as a result of immigration from nations with a high frequency[31]. Similar to France, it is estimated that over 14,000 people in the UK have SCD, and numbers from Africa are also rising in countries like Italy and Germany. The age distribution of SCD is shifting away from a pattern associated with childhood disorders as more patients are living into maturity and old age. In the US, France, and the UK, it is now estimated that over 94% of people born with SCD survive into adulthood, in contrast to the high mortality in SSA, where 50–90% of people may pass away during the first five years of life[32]. Patients may pass away young even before a diagnosis is certain in low resource settings and nations where newborn screening is not yet considered conventional medical treatment. Infections, severe anaemia (acute splenic sequestration, aplastic anaemia), and multiple organ failure are among the prevalent causes of death in the absence of early diagnosis, education, and preventative medicines such penicillin prophylaxis and routine surveillance. In nations where SCD is a public health issue, it is crucial that newborn and early infant diagnosis receive the attention it needs. Despite several promises made by international organisations and in-public pledges made by politicians to uphold such commitments, the majority of SSA nations are still unable to execute early newborn diagnosis. When policymakers across the continent and in India, where the majority of people with SCD are born and live, adopt this strategy, only then will the benefits of screening become substantial. When appropriate, comprehensive care will improve outcomes and health-related quality of life by using penicillin V prophylaxis, hydroxycarbamide therapy, and preventive medications such antimalarials[33].

Pathophysiology

The pathophysiology of sickle cell anaemia (disease) deals with the haemoglobin beta globin chain. Beta globin chain of haemoglobin is affected and this beta globin chain is encoded on chromosome 11 and in Sickle cell disease it is actually all due to an amino acid substitution at position 6 on the beta globin chain and all it is a substitution from glutamic acid to valine. There is only a single point mutation changing glutamic acid to valine at position 6 on the beta globin chain and this causes deformed red blood cell shape[33]. The problems in Sickle cell anaemia are all due to single point mutation. When beta globin chain is mutated (haemoglobin S) and haemoglobin S is less soluble than deoxygenated haemoglobin A (the normal haemoglobin)[4].
Deoxygenated haemoglobin S can lead to RBC sickling and RBC sickling occur during conditions of stress and when red blood cells do undergo sickling they can lead to haemolysis and they can lead to vasculature in individual and if the Sickle cell shape are traveling they may get clogged and may get stuck in certain areas in the vasculature (capillary) and this is called micro vascular trapping and this leads to haemo phagocytosis and the life span of Sickle cell red blood cells is about 17 days (10 to 20 days)[23].

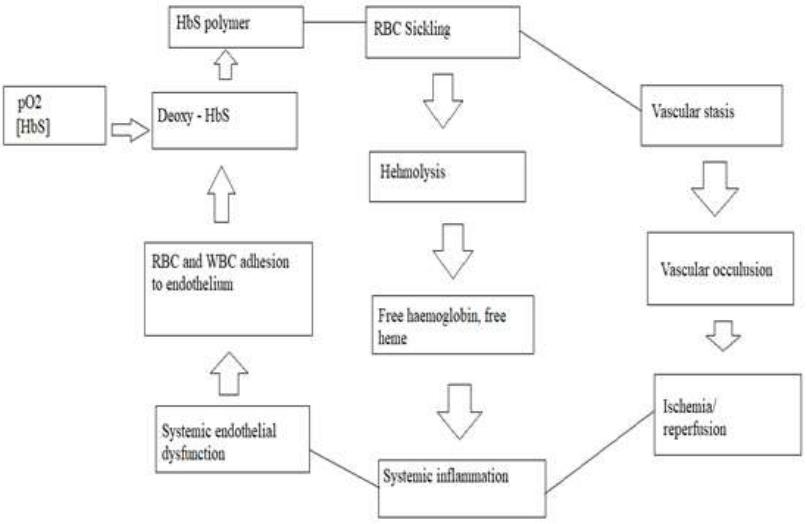

Fig 5. Flow chart of Pathophysiology

CONCLUSION

Sickle cell anaemia (SCA) is a condition characterised by the creation of defective haemoglobin, which combines with other aberrant haemoglobin molecules inside the red blood cell, causing the cell to deform rigidly. This distortion limits the cell's capacity to travel through narrow vascular channels, resulting in sludging and congestion of arterial beds, followed by tissue ischemia and infarction. Infarction occurs often throughout the body in SCA patients, and it is responsible for the initial clinical symptom, the acute pain crisis, which is assumed to be caused by marrow infarction. Such assaults cause medullary bone infarctions and epiphyseal osteonecrosis over time. White matter and grey matter infarcts are detected in the brain, producing cognitive impairment and functional neurologic impairments.

Many SCA consequences are infarctive in nature, such as osteonecrosis, ACS, stroke, and renal papillary necrosis. Children with SCA are more vulnerable to bacteremia and infection. With advancements in preventive antibiotic medication, transfusion therapy, Hb F induction, and bone marrow and stem cell transplantation, control of these feared consequences is increasing. The prospect of curative marrow replacement gives SCA patients hope. Stem cell treatment and bone marrow transplantation advancements appear to be heralding a cure for this dreadful lifelong condition.

SCD gene therapy has great promise as a potential curative treatment, however safety issues with random genomic insertion must first be addressed. There are several other potential for therapeutic treatments given the extensive variety of problems brought on by the sickle cell mutation. After reading this article, the readers can conclude that SCA is a haemolytic anaemia characterized by the production abnormal haemoglobin chains that tend to polymerize when deoxygenated. Many of the complications of SCA are infective, including osteonecrosis, ACS, stroke, and renal necrosis. The promise of curative marrow replacement gives hope to SCA patients.

REFERENCE

1. Lonergan GJ, Cline DB, Abbondanzo SL. Sickle cell anemia. Radiographics. 2001 Jul;21(4):971-94.
2. Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia, a molecular disease. Science. 1949 Nov 25;110(2865):543-8.
3. Mason VR. Sickle cell anemia. Journal of the American Medical Association. 1922 Oct 14;79(16):1318-20.
4. JV. The inheritance of sickle cell anemia. Science. 1949 Jul 15;110(2846):64-6.
5. Platt OS. Sickle cell anemia as an inflammatory disease. The Journal of clinical investigation. 2000 Aug 1;106(3):337-8.
6. Mason VR. Sickle cell anemia. Journal of the American Medical Association. 1922 Oct 14;79(16):1318-20.
7. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine. 2005 Nov 1;84(6):363-76.
8. Henderson AB. Sickle cell anemia: clinical study of fifty-four cases. The American journal of medicine. 1950 Dec 1;9(6):757-65.
9. Diggs LW. The Crisis in Sickle Cell Anemia. Hématologie Studies. American journal of clinical pathology. 1956;26(10):1109-8.
10. BRODY JI, GOLDSMITH MH, PARK SK, SOLTYS HD. Symptomatic crises of sickle cell anemia treated by limited exchange transfusion. Annals of Internal Medicine. 1970 Mar 1;72(3):327-30.
11. Singer K, Robin S, King JC, Jefferson RN. The life span of the sickle cell and the pathogenesis of sickle cell anemia. The Journal of laboratory and clinical medicine. 1948 Aug 1;33(8):975-84.
12. Andrews CH, England Jr MC, Kemp WB. Sickle cell anemia: an etiological factor in pulpal necrosis. Journal of Endodontics. 1983 Jun 1;9(6):249-52.
13. Steinberg MH. Sickle cell anemia, the first molecular disease: overview of molecular etiology, pathophysiology, and therapeutic approaches. The Scientific World Journal. 2008 Dec 25; 8:1295-324.
14. Ballas SK. Complications of sickle cell anemia in adults: guidelines for effective management. Cleveland Clinic Journal of Medicine. 1999 Jan 1;66(1):48-58.
15. Steinberg MH, Adewoye AH. Modifier genes and sickle cell anemia. Current opinion in hematology. 2006 May 1;13(3):131-6.
16. Bookchin RM, Lew VL. Pathophysiology of sickle cell anemia. Hematology/oncology clinics of North America. 1996 Dec 1;10(6):1241-53.
17. Adams RJ, McKie VC, Brambilla D, Carl E, Gallagher D, Nichols FT, Roach S, Abboud M, Berman B, Driscoll C, Files B. Stroke prevention trial in sickle cell anemia. Controlled clinical trials. 1998 Feb 1;19(1):110-29.

18. Platt OS. Preventing stroke in sickle cell anemia. New England Journal of Medicine. 2005 Dec 29;353(26):2743-5.
19. McGann PT, Nero AC, Ware RE. Current management of sickle cell anemia. Cold Spring Harbor Perspectives in Medicine. 2013 Aug 1;3(8):a011817.
20. Saiki RK, Chang CA, Levenson CH, Warren TC, Boehm CD, Kazazian Jr HH, Erlich HA. Diagnosis of sickle cell anemia and β-thalassemia with enzymatically amplified DNA and nonradioactive allele-specific oligonucleotide probes. New England Journal of Medicine. 1988 Sep 1;319(9):537-41.
21. Steinberg MH. Overview of sickle cell anemia pathophysiology. InSickle cell anemia 2016 (pp. 49-73). Springer, Cham.
22. Alavi JB. Sickle cell anemia: Pathophysiology and treatment. Medical Clinics of North America. 1984 May 1;68(3):545-56.
23. Steinberg MH. 6 Pathophysiology of sickle cell disease. Baillière's clinical haematology. 1998 Mar 1;11(1):163-84.
24. Platt OS. Hydroxyurea for the treatment of sickle cell anemia. New England Journal of Medicine. 2008 Mar 27;358(13):1362-9.
25. Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, Cassady JP, Beard C, Brambrink T, Wu LC, Townes TM, Jaenisch R. Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. Science. 2007 Dec 21;318(5858):1920-3.
26. Goldberg MA, Brugnara C, Dover GJ, Schapira L, Charache S, Bunn HF. Treatment of sickle cell anemia with hydroxyurea and erythropoietin. New England Journal of Medicine. 1990 Aug 9;323(6):366-72.
27. Broderick GA. Priapism and sickle-cell anemia: Diagnosis and nonsurgical therapy. The journal of sexual medicine. 2012 Jan 1;9(1):88-103.
28. Vichinsky E, Hurst D, Earles A, Kleman K, Lubin B. Newborn screening for sickle cell disease: effect on mortality. Pediatrics. 1988 Jun;81(6):749-55.
29. Goossens M, Dumez Y, Kaplan L, Lupker M, Chabret C, Henrion R, Rosa J. Prenatal diagnosis of sickle-cell anemia in the first trimester of pregnancy. New England Journal of Medicine. 1983 Oct 6;309(14):831-3.
30. Platt OS. Prevention and management of stroke in sickle cell anemia. ASH Education Program Book. 2006;2006(1):54-7.
31. Charache S, Scott JC, Charache P. 'Acute Chest Syndrome'in Adults With Sickle Cell Anemia: Microbiology, Treatment, and Prevention. Archives of Internal Medicine. 1979 Jan 1;139(1):67-9.
32. Wood DH. Cerebrovascular complications of sickle cell anemia. Stroke. 1978 Jan;9(1):73-5.
33. Pareek A, Khandekar A, Acharya S, Tidake P, Shukla S. Correlation between nephropathy and ophthalmic complications in cases of sickle cell anemia: an entangled association. Indian Journal of Medical Specialities. 2019 Apr 1;10(2):72.
34. Page C, Gardner K, Height S, Rees DC, Hampton T, Lay Thein S. Nontraumatic extradural hematoma in sickle cell anemia: a rare neurological complication not to be missed. American Journal of hematology. 2014 Feb;89(2):225-7.
35. Galloway SJ, Harwood-Nuss AL. Sickle-cell anemia—a review. The Journal of emergency medicine. 1988 May 1;6(3):213-26.
36. Hoppe CC, Walters MC. Bone marrow transplantation in sickle cell anemia. Current opinion in oncology. 2001 Mar 1;13(2):85-90.
37. Fryer RH, Anderson RC, Chiriboga CA, Feldstein NA. Sickle cell anemia with moyamoya disease: outcomes after EDAS procedure. Pediatric neurology. 2003 Aug 1;29(2):124-30.
38. Gladwin MT, Kato GJ. Cardiopulmonary complications of sickle cell disease: role of nitric oxide and hemolytic anemia. ASH Education Program Book. 2005;2005(1):51-7.
39. Jenkins TL. Sickle cell anemia in the pediatric intensive care unit: novel approaches for managing life-threatening complications. AACN Advanced Critical Care. 2002 May;13(2):154-68.
40. Miller ST, Macklin EA, Pegelow CH, Kinney TR, Sleeper LA, Bello JA, DeWitt LD, Gallagher DM, Guarini L, Moser FG, Ohene-Frempong K. Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the Cooperative Study of Sickle Cell Disease. The Journal of pediatrics. 2001 Sep 1;139(3):385-90.
41. Adekile AD (2011) Limitations of Hb F as a phenotypic modifier in sickle cell disease: study of Kuwaiti Arab patients. Hemoglobin 35(5–6):607–617