A REVIEW ON SICKLE CELL ANEMIA

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ABSTRACT
Sickle cell disease is a hereditary blood disorder. Characterized by abnormality in the oxygen carrying hemoglobin. It is characterized by various sign and symptoms sickle cell crisis, vaso-occlusive the splenic sequestration crisis . The pathophysiology is related to the actual anemia of the illness is caused by hemolysis. For the diagnosis purpose in Hbss, the complete blood account reveals hemoglobin level in the range of 0.8g/dl. Management are carried out by folic acid and penicillin, hydroxyl urea, transfusion therapy. Further research is needed on the relationship between this condition of sickle cell anemia.

KEYWORDS: Sickle cell, hemoglobin, abnormality.

INTRODUCTION
The first modern report of sickle-cell disease may have been in 1846, where the autopsy of an execute runaway slaves was discussed; the key finding was the absence of spleen. There were report amongst Africanes slaves in the US exhibiting resistance to malaria but being prone to leg ulcers. The abnormal characteristic of red blood cell, which later lent there name of the condition, was first describe by Ernest Edward Irons (1877-1959).

The highest frequency of sickle-cell disease is found in tropical region particulary in sub-saharan Africa, India and middle East. sign and symptoms of sickle cell is characterized by sickle crisis, vaso-occlusive crisis, splenic sequestration crisis, acute chest syndrome. In sickle cell various complication lead like bacterial infection, prevent the oxygen for reaching the brain, cholelithiasis.

The loss of red blood cell elasticity is central to the pathophysiology of sickle cell disease. Diagnosis is related to in Hbss, complete blood count reveals hemoglobin level in the range 6-8gm/dl. In that management is done by doing folic acid and penicillin, malerial chmpophylaxis, transfusion thereby bone marrow transplant. In the research gene thereby is carried out. Further research are needed on the relationship between this condition of sickle cell disease.
HISTORY

The first modern report of sickle-cell disease may have been in 1846, where the autopsy of an executed runaway slave was discussed; the key findings was the absence of the spleen.[76][77] There were also reports amongst African slaves in the United States exhibiting resistance to malaria but being prone to leg ulcers.[77] The abnormal characteristics of the red blood cells, which later lent their name to the condition, was first described by Ernest Edward Irons (1877–1959), intern to the Chicago cardiologist and professor of medicine James B. Herrick (1861–1954), in 1910. Irons saw "peculiar elongated and sickle-shaped" cells in the blood of a man named Walter Clement Noel, a 20-year-old first-year dental student from Grenada. Noel had been admitted to the Chicago Presbyterian Hospital in December 1904 suffering from anaemia.[78][79] Noel was readmitted several times over the next three years for "muscular rheumatism" and "bilious attacks" but completed his studies and returned to the capital of Grenada (St. George's) to practice dentistry. He died of pneumonia in 1916 and is buried in the Catholic cemetery at Sauteurs in the north of Grenada.[79][80] Shortly after the report by Herrick, several other cases appeared in the medical literature. In the description by Verne Mason in 1922, the name "sickle cell anemia" is first used.[80][81] Childhood problems related to sickle cells disease were not reported until the 1930s, despite the fact that this cannot have been uncommon in African-American populations.

The Memphis physician Lemuel Diggs, a prolific researcher into sickle cell disease, first introduced the distinction between sickle cell disease and trait in 1933, although it took until 1949 until the genetic characteristics were elucidated by James V. Neel and E.A. Beet.[80] 1949 was the year when Linus Pauling described the unusual chemical behaviour of haemoglobin S, and attributed this to an abnormality in the molecule itself. The actual molecular change in HbS was described in the late 1950s by Vernon Ingram. The late 1940s and early 1950s saw further understanding in the link between malaria and sickle cell disease. In 1954, the introduction of haemoglobin electrophoresis allowed the discovery of particular subtypes, such as HbSC disease. Large scale natural history studies and further intervention studies were introduced in the 1970s and 1980s, leading to the more widespread use of prophylaxis against pneumococcal infections amongst other interventions. The 1990s saw the development of hydroxycarbamide, and reports of cure through bone marrow transplantation appeared in 2007.
Prognosis

About 90% of patients survive to age 20, and close to 50% survive beyond the fifth decade. [49]

In 2001, according to one study performed in Jamaica, the estimated mean survival for sickle-cell patients was 53 years old for men and 58 years old for women with homozygous SCD. [50]

Epidemiology

The highest frequency of sickle cell disease is found in tropical regions, particularly sub-Saharan Africa, India and the Middle-East. [51] Migration of substantial populations from these high prevalence areas to low prevalence countries in Europe has dramatically increased in recent decades and in some European countries sickle-cell disease has now overtaken more familiar genetic conditions such as haemophilia and cystic fibrosis. [52] In 2010, there were about 29,000 deaths attributed to sickle-cell disease globally. [53]

Sickle-cell disease occurs more commonly among people whose ancestors lived in tropical and sub-tropical sub-Saharan regions where malaria is or was common. Where malaria is common, carrying a single sickle-cell allele (trait) confers a selective advantage—in other words, being a heterozygote is advantageous. Specifically, humans with one of the two alleles of sickle-cell disease show less severe symptoms when infected with malaria. [54]

Signs and symptoms
Sickle-cell disease may lead to various acute and chronic complications, several of which have a high mortality rate.[1]

**Sickle-cell crisis**

The terms "sickle-cell crisis" or "sickling crisis" may be used to describe several independent acute conditions occurring in patients with SCD. SCD results in anemia and crises that could be of many types including the vaso-occlusive crisis, aplastic crisis, sequestration crisis, haemolytic crisis, and others. Most episodes of sickle-cell crises last between five and seven days.[2] "Although infection, dehydration, and acidosis (all of which favor sickling) can act as triggers, in most instances, no predisposing cause is identified."[3]

**Vaso-occlusive crisis**
The vaso-occlusive crisis is caused by sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ resulting in ischaemia, pain, necrosis, and often organ damage. The frequency, severity, and duration of these crises vary considerably. Painful crises are treated with hydration, analgesics, and blood transfusion; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manage on NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia devices are commonly used in this setting. Vaso-occlusive crisis involving organs such as the penis [4] or lungs are considered an emergency and treated with red-blood cell transfusions. Incentive spirometry, a technique to encourage deep breathing to minimise the development of atelectasis, is recommended.[5]

Splenic sequestration crisis
Because of its narrow vessels and function in clearing defective red blood cells, the spleen is frequently affected.[6] It is usually infarcted before the end of childhood in individuals suffering from sickle-cell anemia. This autosplenectomy increases the risk of infection from encapsulated organisms;[7][8] preventive antibiotics and vaccinations are recommended for those with such asplenia.

Splenic sequestration crises are acute, painful enlargements of the spleen, caused by intrasplenic trapping of red cells and resulting in a precipitous fall in hemoglobin levels with the potential for hypovolemic shock. Sequestration crises are considered an emergency. If not treated, patients may die within 1–2 hours due to circulatory failure. Management is supportive, sometimes with blood transfusion. These crises are transient, they continue for 3–4 hours and may last for one day.[9]

Acute chest syndrome
Acute chest syndrome (ACS) is defined by new pulmonary infiltrate with a manifestation of pulmonary symptoms such as tachypnea and dyspnea.[10] It is the second-most common complication and it accounts for about 25% of deaths in patients with SCD, majority of cases present with vaso-occlusive crises then they develop ACS.[10][11] Nevertheless, about 80% of patients have vaso-occlusive crises during ACS.

Aplastic crisis
Aplastic crises are acute worsenings of the patient's baseline anaemia, producing pallor, tachycardia, and fatigue. This crisis is normally triggered by parvovirus B19, which directly affects production of red blood cells by invading the red cell precursors and multiplying in and
destroying them.[12] Parvovirus infection nearly completely prevents red blood cell production for two to three days. In normal individuals, this is of little consequence, but the shortened red cell life of SCD patients results in an abrupt, life-threatening situation. Reticulocyte counts drop dramatically during the disease (causing reticulocytopenia), and the rapid turnover of red cells leads to the drop in haemoglobin. This crisis takes 4 days to one week to disappear. Most patients can be managed supportively; some need blood transfusion.[13]

**Haemolytic crisis**

Haemolytic crises are acute accelerated drops in haemoglobin level. The red blood cells break down at a faster rate. This is particularly common in patients with coexistent G6PD deficiency.[14] Management is supportive, sometimes with blood transfusions.[5]

**Other**

One of the earliest clinical manifestations is dactylitis, presenting as early as six months of age, and may occur in children with sickle-cell trait.[15] The crisis can last up to a month.[16] Another recognised type of sickle crisis, acute chest syndrome, is characterised by fever, chest pain, difficulty breathing, and pulmonary infiltrate on a chest X-ray. Given that pneumonia and sickling in the lung can both produce these symptoms, the patient is treated for both conditions.[17] It can be triggered by painful crisis, respiratory infection, bone-marrow embolisation, or possibly by atelectasis, opiate administration, or surgery.

**Complications**

Sickle-cell anaemia can lead to various complications, including:

- Increased risk of severe bacterial infections due to loss of functioning spleen tissue (and comparable to the risk of infections after having the spleen removed surgically). These infections are typically caused by encapsulated organisms such as Streptococcus pneumoniae and Haemophilus influenzae. Daily penicillin prophylaxis is the most commonly used treatment during childhood, with some haematologists continuing treatment indefinitely. Patients benefit today from routine vaccination for S. pneumoniae.[18]

- Stroke, which can result from a progressive narrowing of blood vessels, prevents oxygen from reaching the brain. Cerebral infarction occurs in children and cerebral haemorrhage in adults.

- Silent stroke causes no immediate symptoms, but is associated with damage to the brain. Silent stroke is probably five times as common as symptomatic stroke. About 10–15% of
children with SCD suffer strokes, with silent strokes predominating in the younger patients.[19][20]

- Cholelithiasis (gallstones) and cholecystitis may result from excessive bilirubin production and precipitation due to prolonged haemolysis.
- Avascular necrosis (aseptic bone necrosis) of the hip and other major joints may occur as a result of ischaemia.[21]
- Decreased immune reactions due to hyposplenism (malfuctioning of the spleen)[22]
- Priapism and infarction of the penis[23]
- Osteomyelitis (bacterial bone infection), the most common cause of osteomyelitis in SCD is Salmonella (especially the atypical serotypes Salmonella typhimurium, Salmonella enteritidis, Salmonella choleraesuis and Salmonella paratyphi B), followed by Staphylococcus aureus and Gram-negative enteric bacilli perhaps because intravascular sickling of the bowel leads to patchy ischaemic infarction.[24]
- Opioid tolerance can occur as a normal, physiologic response to the therapeutic use of opiates. Addiction to opiates occurs no more commonly among individuals with sickle-cell disease than among other individuals treated with opiates for other reasons.
- Acute papillary necrosis in the kidneys
- Leg ulcers[25]
- In eyes, background retinopathy, proliferative retinopathy, vitreous haemorrhages, and retinal detachments can result in blindness.[26] Regular annual eye checks are recommended.
- During pregnancy, intrauterine growth retardation, spontaneous abortion, and pre-eclampsia
- Chronic pain: Even in the absence of acute vaso-occlusive pain, many patients have unreported chronic pain.[27]
- Pulmonary hypertension (increased pressure on the pulmonary artery) can lead to strain on the right ventricle and a risk of heart failure; typical symptoms are shortness of breath, decreased exercise tolerance, and episodes of syncope.[28]
- Chronic renal failure due to sickle-cell nephropathy manifests itself with hypertension, protein loss in the urine, loss of red blood cells in urine and worsened anaemia. If it progresses to end-stage renal failure, it carries a poor prognosis.[29]

Pathophysiology
Scanning electron micrograph showing a mixture of red blood cells, some with round normal morphology, some with mild sickling showing elongation and bending

The loss of red blood cell elasticity is central to the pathophysiology of sickle-cell disease. Normal red blood cells are quite elastic, which allows the cells to deform to pass through capillaries. In sickle-cell disease, low-oxygen tension promotes red blood cell sickling and repeated episodes of sickling damage the cell membrane and decrease the cell's elasticity. These cells fail to return to normal shape when normal oxygen tension is restored. As a consequence, these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischaemia.

The actual anaemia of the illness is caused by haemolysis, the destruction of the red cells, because of their shape. Although the bone marrow attempts to compensate by creating new red cells, it does not match the rate of destruction.[35] Healthy red blood cells typically function for 90–120 days, but sickled cells only last 10–20 days.[36]

**Diagnosis**

In HbSS, the complete blood count reveals haemoglobin levels in the range of 6–8 g/dl with a high reticulocyte count (as the bone marrow compensates for the destruction of sickled cells by producing more red blood cells). In other forms of sickle-cell disease, Hb levels tend to be higher. A blood film may show features of hyposplenism (target cells and Howell-Jolly bodies). Sickling of the red blood cells, on a blood film, can be induced by the addition of sodium metabisulfite. The presence of sickle haemoglobin can also be demonstrated with the "sickle solubility test". A mixture of haemoglobin S (Hb S) in a reducing solution (such as sodium dithionite) gives a turbid appearance, whereas normal Hb gives a clear solution.
Abnormal haemoglobin forms can be detected on haemoglobin electrophoresis, a form of gel electrophoresis on which the various types of haemoglobin move at varying speeds. Sickle-cell haemoglobin (HgbS) and haemoglobin C with sickling (HgbSC)—the two most common forms—can be identified from there. The diagnosis can be confirmed with high-performance liquid chromatography. Genetic testing is rarely performed, as other investigations are highly specific for HbS and HbC.[37]

An acute sickle-cell crisis is often precipitated by infection. Therefore, a urinalysis to detect an occult urinary tract infection, and chest X-ray to look for occult pneumonia, should be routinely performed.[38]

People who are known carriers of the disease often undergo genetic counseling before they have a child. A test to see if an unborn child has the disease takes either a blood sample from the fetus or a sample of amniotic fluid. Since taking a blood sample from a fetus has greater risks, the latter test is usually used. Neonatal screening provides not only a method of early detection for individuals with sickle-cell disease, but also allows for identification of the groups of people that carry the sickle cell trait.[39]

Management

Folic acid and penicillin

Children born with sickle-cell disease will undergo close observation by the pediatrician and will require management by a haematologist to assure they remain healthy. These patients will take a 1 mg dose of folic acid daily for life. From birth to five years of age, they will also have to take penicillin daily due to the immature immune system that makes them more prone to early childhood illnesses.

Malaria chemoprophylaxis

The protective effect of sickle-cell trait does not apply to people with sickle cell disease; in fact, they are more vulnerable to malaria, since the most common cause of painful crises in malarial countries is infection with malaria. It has therefore been recommended that people with sickle-cell disease living in malarial countries should receive anti-malarial chemoprophylaxis for life.[40]

Vaso-occlusive crisis

Most people with sickle-cell disease have intensely painful episodes called vaso-occlusive crises. The frequency, severity, and duration of these crises, however, vary tremendously. Painful crises are treated symptomatically with analgesics; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manage on
NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia (PCA) devices are commonly used in this setting. Diphenhydramine is also an effective agent that is frequently prescribed by doctors in order to help control any itching associated with the use of opioids.

**Acute chest crisis**

Management is similar to vaso-occlusive crisis, with the addition of antibiotics (usually a quinolone or macrolide, since cell wall-deficient ["atypical"] bacteria are thought to contribute to the syndrome),[41] oxygen supplementation for hypoxia, and close observation. Should the pulmonary infiltrate worsen or the oxygen requirements increase, simple blood transfusion or exchange transfusion is indicated. The latter involves the exchange of a significant portion of the patient's red cell mass for normal red cells, which decreases the percent of haemoglobin S in the patient's blood.

**Hydroxyurea**

The first approved drug for the causative treatment of sickle-cell anaemia, hydroxyurea, was shown to decrease the number and severity of attacks in a study in 1995 (Charache et al.)[42] and shown to possibly increase survival time in a study in 2003 (Steinberg et al.).[43] This is achieved, in part, by reactivating fetal haemoglobin production in place of the haemoglobin S that causes sickle-cell anaemia. Hydroxyurea had previously been used as a chemotherapy agent, and there is some concern that long-term use may be harmful, but this risk has been shown to be either absent or very small and it is likely that the benefits outweigh the risks.[44]

**Transfusion therapy**

Blood transfusions are often used in the management of sickle-cell disease in acute cases and to prevent complications by decreasing the number of red blood cells (RBC) that can sickle by adding normal red blood cells.[45] In children prophylactic chronic red blood cell (RBC) transfusion therapy has been shown to be efficacious to a certain extent in reducing the risk of first stroke or silent stroke when transcranial Doppler (TCD) ultrasonography shows abnormal increased cerebral blood flow velocities. In those who have sustained a prior stroke event it also reduces the risk of recurrent stroke and additional silent strokes.[46][47]

**Bone marrow transplants**

Bone marrow transplants have proven to be effective in children. Bone marrow transplants are the only known cure for SCD. However, bone marrow transplants are difficult to obtain because of the specific HLA typing necessary. Ideally, a twin family member (syngeneic) or close relative (allogeneic) would donate the bone marrow necessary for transplantation.
Gene therapy

In 2001 it was reported that sickle-cell disease had been successfully treated in mice using gene therapy. The mice – which have essentially the same defect that causes sickle cell disease in humans – through the use a viral vector, were made to express the production of fetal hemoglobin (HbF), which normally ceases to be produced by an individual shortly after birth. In humans, the use of hydroxyurea to stimulate the production of HbF has been known to temporarily alleviate the symptoms of sickle cell disease. The researchers demonstrated this method of gene therapy to be a more permanent means to increase the production of the therapeutic HbF.

Phase 1 clinical trials of gene therapy for sickle cell disease in humans were started in 2014 although one review failed to find.

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