

Erythropoietin in Sickle Cell Anaemia: A Review

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ABSTRACT

Sickle Cell Anaemia (SCA) is one of the most prevalent monogenic disorders. The formation of polymerized haemoglobin leading to erythrocyte rigidity and appearance of characteristic sickle-shaped Red blood Cells (RBCs) resulting in vascular occlusion and haemolysis is central to the molecular pathogenesis of the disease. Normally, Erythropoietin (EPO) level vary inversely with haematocrit if the kidney is not adversely damaged. Hypoxia stimulates Erythropoietin (EPO) release, which, in turn, stimulates bone marrow erythrocyte production. High blood levels of RBC, hemoglobin, haematocrit, or oxygen suppress the release of (EPO).

INTRODUCTION

Genetics of Sickle Cell Anaemia

Sickle Cell Disease is a haemoglobinopathy in which there is substitution of a single amino acid in the beta chain of adult haemoglobin resulting in haemoglobin S, C, D or E depending on amino acid substitution. Haemoglobin S and C are present in Nigeria while haemoglobin G (HbG), haemoglobin D (HbD) and haemoglobin E (HbE) rarely exist in West Africa (Emechebe *et al.*, 2017). These abnormal haemoglobins are transmitted as autosomal recessive genes. Heterozygous inheritance of an abnormal haemoglobin with a normal one results in a symptomless carrier state or 'trait'. Inheritance of haemoglobin S (HbS) with any other abnormal haemoglobin like beta thalassemia (Bo or B+), HbC, HbS results in SCD. However homozygous inheritance of HbSS is called SCA. In HbS, Valine replaces glutamic acid at position 6 in amino acid sequence of beta chain. In haemoglobin C (HbC) lysine replaces glutamic acid at position 6 in the beta chain. While in haemoglobin D (HbD) glutamine replaces glutamic acid at position 121 in the amino acid sequence. These amino acid substitutions lead to decreased solubility of the haemoglobin molecule in low oxygen tension (Emechebe *et al.*, 2017). The genetic disorder is due to the mutation to a single nucleotide, from a GAG to GTG codon mutation. This is normally a benign mutation, causing no apparent effects on the secondary, tertiary, or quaternary structure of haemoglobin.

What it does allow for, under conditions of low oxygen concentration, is the polymerization of the HbS itself. The deoxy form of haemoglobin exposes a hydrophobic patch on the protein between the E and F helices. The hydrophobic residues of the valine at position 6 of the beta chain in haemoglobin are able to associate with the hydrophobic patch, causing haemoglobin S molecules to aggregate and form fibrous precipitates (Obeagu *et al.*, 2015)

The allele responsible for sickle cell anaemia is autosomal recessive and can be found on the short arm of chromosome II. A person that receives the defective gene from both father and mother develops the disease; a person that receives one defective and one healthy allele remains healthy, but can pass on the disease and is known as a carrier. If two parents who are carriers have a child, there is a 1 - in - 4 chance of their child's developing the disease and a 1 - in - 2 chance of their child's being just a carrier since the gene is incompletely recessive, carriers can produce a few sickled red blood cells, not enough to cause symptoms, but enough to give resistance to malaria. Because of this, heterozygotes have a higher fitness than either of the homozygotes. This is known as heterozygotes advantages (Obeagu *et al.*, 2015).

Clinical Manifestations of Sickle Cell Anaemia

Paleness is a typical condition in principally sick patients and results in a high prerequisite for blood transfusions related with poor results. Anaemia is the primary symptom which is

associated with SCA. The adaptability of the erythrocytes is crumbled, its life expectancy is abbreviated, and the capillaries in the body are most likely going to impede. This implies that there are insufficient solid red platelets to transport oxygen all through the body. When this happens, a person might present with tiredness, pale skin colour, and delayed puberty. Pain is the most widely recognized entanglement of SCD, and typically most common reason that the patients with SCD go through the crisis. In the sequential effect of SCA, RBCs of most of the patient loose affinity for oxygen and the patient suffers with hypoxia. The patient becomes fatigued easily and experiences shortness of breath (Chatterjee *et al.*, 2018).

Acute chest syndrome (ACS), described by fever and new opacification of the lungs on chest radiograph, is the second most common reason for hospitalization in patients with sickle cell ailment and causes 25% of deaths. Rehashed scenes of ACS are related with advancement of incessant lung sickness, with dynamic hypoxemia and diminished survival. About 30% of adult patients with SCA suffer from pulmonary hypertension, and the complication is a strong negative prognostic factor. Recent examinations have uncovered that adenosine concentrations are fundamentally lifted in SCD and add to infection pathology by initiating adenosine receptors on red platelets. Apart from adenosine, hypoxia additionally causes haemoglobin discharge through haemolysis (Chatterjee *et al.*, 2018).

In a severe situation, large number of sickle cells gets trapped in the spleen and makes it enlarged. Symptoms shown by the individual are extreme thirst, left abdominal pain, weakness, pale lips, fast heartbeat and breathing. This event can be life threatening, in most cases. Medically, this discomfort is known as splenic sequestration. In the worst case scenario, major organ failure is the critical situation which arises. Initially, clinically apparent as auto splenectomy, followed by cerebral infarction during childhood and finally in young adulthood as end stage renal failure (glomerulosclerosis), disabling leg ulcers, generalized osteonecrosis, intracranial haemorrhage, retinopathy and sickle chronic lung disease (Chatterjee *et al.*, 2018).

Vaso-occlusion in sickle cell disease is a multiple process that involves initiation, propagation and resolution phase. The two major factors have been widely identified to contribute to red blood entrapment during crises

are reduced deformability of sickle blood cell and adhesion between endothelium and erythrocytes. Episodes of VPC are common and are perhaps the most important feature of SCD. VPC is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts two or more hours. Bone is the usual site of vaso-occlusion during pain crises. Common precipitants of VPC include cold weather, relative high hemoglobin concentration, dehydration, infection, exercise, dampness, poor diet, hypoxia, acidosis, emotional stress, and fatigue (Kaur *et al.*, 2013)

Pathophysiology of Sickle Cell Disease

As a result of the replacement of negatively charged hydrophilic glutamic acid with the non-polar hydrophobic valine at position six on the 146 amino acid β -chain. There is loss of the electrical charge, which results in particular clinical significance. First, the absence of the negative charge significantly destabilizes the structure of oxygenated haemoglobin, causing accelerated denaturation and breakdown. Second, the nonpolar hydrophobic substitute causes considerable decrease in the solubility of deoxygenated haemoglobin (Kaur *et al.*, 2013). The conformational change due to deoxygenation results in formation of hydrophobic bond between the β S-6 valine of one tetramer and the β -85phenylalanine and β -88 leucine of an adjacent tetramer, thus generating a nidus of polymerized haemoglobin S. Further aggregation of deoxygenated haemoglobin tetramers form long helical strands of polymers. Progression of this process generates a critical nucleus to which additional tetramers bind. Polymerization then proceeds in an explosive autocatalytic fashion, causing the haemoglobin to gelate or precipitate out of solution. These two features of haemoglobin S, instability and insolubility, account for the majority of cellular and clinical pathology (Kaur *et al.*, 2013).

Epidemiology of Sickle Cell Disease

Sickle cell disease is one of the most common inherited life-threatening disorders in human, it predominantly affects people of African, Indiana and Arab ancestry. It is estimated that over 80% of over 300,000 annual births occur in sub-Saharan Africa (SSA), the largest burden from Nigeria and Democratic Republic of Congo (Baba *et al.*, 2019). The gene frequency is highest in West African countries with 1 in 4 to 3 (25–30%) being carriers of HbS compared to 1/400 African Americans and is variable in

European populations. The prevalence of SCD in developed countries is increasing partly due to migration from high prevalent countries. It is estimated that over 14,000 people live with sickle cell disease (SCD) in the UK, similar to France, while countries like Italy, Germany have seen increasing numbers from Africa (Baba *et al.*, 2019). With increasing survival, the age distribution of SCD is changing from a childhood disorder pattern that patients now survive into adulthood and old age. It is now reported that over 94% of those born with SCD now survive into adulthood in the US, France and UK in contrast to the high mortality in SSA where 50–90% may die in the first five years of life. In low resource settings and countries where newborn screening is not yet standard care, patients may die young even before diagnosis is confirmed. Among the common causes of death in the absence of early diagnosis followed by education and preventive therapies such as penicillin prophylaxis and regular surveillance include infections, severe anaemia (acute splenic sequestration, aplastic anaemia) and multi-organ failure. It is essential therefore that Newborn and Early Infant diagnosis is given the priority it deserves by those countries where SCD is a public health problem. The implementation of early infant diagnosis remains out of reach for the majority of countries in SSA despite multiple declarations by international organizations and public statements by politicians to honour such commitments. The benefits for screening can only become meaningful when such practice is embraced by policy-makers across the continent and India where the majority of SCD is born and live. Comprehensive care includes penicillin V prophylaxis, Hydroxycarbamide therapy and preventive therapies such as anti malarial and health promotion where relevant will improve outcomes and health related quality of life (Baba *et al.*, 2019).

Diagnosis of Sickle Cell Disease

The prenatal diagnosis (PND) for the disease has opened a window of opportunity for expectant couples to have information about the haemoglobin (Hb) genotype of their unborn child. This gives them the option of termination of the pregnancy in case of positive result and to prepare them psychologically, financially and medically for the arrival of the new child when abortion is not an option. Prenatal diagnosis is usually carried out using either chorionic villus sampling (CVS) or amniocentesis and the samples taken have DNA analysis done on

them. Both procedures are invasive with CVS being done between the 10th and 12th week of pregnancy while amniocentesis is usually carried out later (between the 14th and 20th week). Sickle cell disease can be diagnosed in newborns, as well as older persons, by hemoglobin electrophoresis, isoelectric focusing, high performance liquid chromatography or DNA analysis (Kaur *et al.*, 2013).

For young individuals displaying symptoms of SCA, blood smear is observed under microscope to check the abnormal sickle-shaped cells. Smearing of blood using a special low oxygen preparation is done for testing and this is referred to as sickle prep. Other prep tests can likewise be utilized to distinguish the strange HbS. Preparatory tests also include dissolvability tests performed on the blood samples. The infection can be affirmed by particularly evaluating the kinds of haemoglobin, utilizing a haemoglobin electrophoresis test (Chatterjee *et al.*, 2018). This electrophoresis test recognizes the haemoglobin in the blood by isolating them. The partition of the diverse hemoglobin's is conceivable due to the unique electrical charges they have on their protein surfaces, causing them each to move distinctively in an electric field.

Red Blood Cell Effects on Erythropoietin

The principal physiological function of erythropoietin is red blood cell production, which results from a tightly controlled proliferation and differentiation pathway, early haematopoietic progenitor cells differentiate into burst-forming unit Erythroid cells (BFU-Es). Continuous stimulation with erythropoietin triggers the differentiation of CFU-Es into erythroblasts, which lose their nuclei to form reticulocytes. After a few days, reticulocytes lose reticulium and become erythrocytes (red blood cells). Reticulocytes and erythrocytes stop expressing EPOR and cease being responsive to erythropoietin (Obeagu *et al.*, 2015). Erythropoietin has been shown to exert its effects by binding to the erythropoietin receptor (EPOR) (Chatterjee *et al.*, 2018).

Erythropoietin is highly glycosylated (40% of total molecular weight), with half-life in blood around five hours. Erythropoietin's half-life may vary between endogenous and various recombinant versions. Additional glycosylation or other alterations of erythropoietin via recombinant technology have led to the increase of erythropoietin's stability in blood (thus

requiring less frequent injections). Erythropoietin binds to the erythropoietin receptor on the red cell progenitor surface and activates a JAK2 signaling cascade. Erythropoietin receptor expression is found in a number of tissues, such as bone marrow and peripheral/central nervous tissue. In the bloodstream, red cells themselves do not express erythropoietin receptor, so cannot respond to erythropoietin. However, indirect dependence of red cell longevity in the blood on plasma erythropoietin levels has been reported, a process termed neoc (Obeagu *et al.*, 2015). Erythropoietin levels in blood are quite low in the absence of anaemia, at around 10 mU/ml. However, in hypoxic stress, erythropoietin production may increase 1000fold, reaching 10,000 mU/ml of blood. Erythropoietin is produced mainly by peritubular capillary lining cells of the renal cortex, which are highly specialized, epithelial-like cells. Regulation is believed to rely on a feedback mechanism measuring blood oxygenation it is believed to be synthesized by renal peritubular cells in adults, with a small amount being produced in the liver (Obeagu *et al.*, 2015).

Erythropoietin Levels in Sickle Cell Anaemia

In sickle cell anaemia, increased serum hepcidin seems to limit enteral iron absorption and release of iron from the hepatic tissue; and reticuloendothelial system to normalize serum iron levels. Some studies have given credence to the work in which the level of hepcidin was remarkably increased which in other words; suggest strongly that increased hepcidin play a major role in sickle cell anaemia (Johnkenedy *et al.*, 2015). On the other hand, the level of erythropoietin was significantly decreased in sickle cell anaemia, erythropoietin has been report to exert its effects by binding to the erythropoietin receptor. It is associated with neuronal protection during induced cerebral hypoxia in rats pretreated with it. Several studies have indicated that erythropoietin could improve memory. This particular effect does not depend on its effect on haematocrit. However, it is linked with an increase in hippocampal response and effects on synaptic connectivity, neuronal plasticity and memory linked neural networks. The erythropoietin is primarily involved in the red cell production (Johnkenedy *et al.*, 2015). Hence, the low level of erythropoietin in sickle cell disease could be associated with decreased red blood cell production. Indeed, the low level of erythropoietin could be attributed to impaired

iron utilization suppression of erythroid progenitor cell differentiation and inadequate erythropoietin production. In addition, there could be a reduced red blood cell life span that cannot be compensated for because of erythropoietin lack. Sickle cell anaemic patients are mostly immunosuppressed and at risk for infections which could attack erythroid progenitor cells and block erythropoiesis. Erythropoietin is elevated in Sickle Cell Disease due to anaemia- and micro vascular occlusion-associated hypoxia and hydroxyurea treatment in SCA increases the production of foetal haemoglobin or haemoglobin F, which interferes with haemoglobin S polymerization and ameliorates clinical complications. A number of researchers have observed paradoxically higher serum erythropoietin (EPO) levels with hydroxyurea treatment in SCD despite higher haemoglobin concentrations (Xu *et al.*, 2016).

Erythropoietins available for use as therapeutic agents are produced by recombinant DNA technology in cell culture, and include Epogen/Procrit (epoietinalfa) and Aranesp (darbepoietinalfa); they are used in treating anaemia resulting from chronic kidney disease, inflammatory bowel disease (Crohn's disease and ulcer colitis) and myelodysplasia from the treatment of cancer (chemotherapy and radiation), but include boxed warnings of increased risk of death, myocardial infarction, stroke, venous thromboembolism, tumor recurrence, and other severe off-target effects (Obeagu *et al.*, 2015).

Laboratory Diagnosis of Erythropoietin

In vivo bioassays for Erythropoietin are commonly performed in rodents by measurements of reticulocytes or incorporation of radioactive iron (^{59}Fe) in blood. One international Erythropoietin unit (IU) produces the same erythropoietic response in the animals as 5micromol cobalt (Co^{2+}) chloride. The specific in vivo activity of epoetin 9 (about 200,000 IU/mg peptide) is higher than that of purified human urinary Erythropoietin (70,000 IU/mg peptide). In vitro bioassays for Erythropoietin can be performed in Erythropoietin-responsive cell cultures by measurements of enzyme activities, or of haeme or DNA synthesis. In clinical routine, enzyme-linked immuno-sorbent assays (ELISAs) for Erythropoietin are commonly used to measure Erythropoietinimmunoreactivity units (U). The normal concentration of Erythropoietin in

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human plasma amounts to about 15 U/l (~5 pmol/l). The *in vivo* bioassay is required to calibrate rhErythropoietin for therapeutic purposes because immunoassays provide no clear information on ESA activity in the organism (Wolfgang, 2013)

COMPLICATIONS ASSOCIATED WITH SICKLE CELL DISEASE

Chronic Anaemia

Chronic haemolytic anaemia is a hallmark of sickle cell disease. Sickled erythrocytes are destroyed randomly with a mean life span of 17 days. In addition erythropoietin levels are inappropriately low, suggesting the presence of subclinical renal disease. Haemolytic anaemia may be exacerbated by any of several events: aplastic crisis, and acute splenic sequestration or, less commonly, sequestration in other organs, chronic renal disease, and bone marrow necrosis, deficiency of folic acid or iron and hyperhaemolysis (Obeagu *et al.*, 2015)

Acute Painful Episode

An episode of acute pain was originally called a "Sickle cell crisis" by Diggs, who used the expression "crisis" to refer to any new rapidly developing syndrome in the life of a patient with sickle cell disease. In modern parlance, the term acute painful episode is favored over crisis.

Acute pain is the first symptom of the disease in more than one - fourth of patients, the most frequent symptom after age 2 years, and the complication for which patients with sickle cell disease most commonly seek medical attention (Obeagu *et al.*, 2015). The frequency of pain peaks between the age of 19 and 39 years. After the age of 19, more frequent is associated with higher mortality rate.

Bone Complications

Chronic tower skull, bossing of the forehead and fish mouth deformity of vertebrae are the result of extended hematopoietic marrow causing widening of the medullary space, thinning of the trabeculae and cortices, and osteoporosis (Obeagu *et al.*, 2015). The excruciating pain of bone infarction in the "hand- foot syndrome" that occurs around the age of 12 years is often the first symptom of sickle cell disease. This dactylitis resolves spontaneously and is treated with hydration and analgesic. Necrosis occurs with equal frequency in the femoral and humeral heads, but the femoral heads more commonly undergo progressive joint destruction, as a result of chronic weight bearing. Arthritic pain,

swelling, and effusion may be related to periarticular infarction or to gouty arthritis. Bone marrow infarction causes reticulocytopenia, exacerbation of anaemia, a leukoerythroblastic picture, and sometimes pancytopenia (Obeagu *et al.*, 2015).

Pain may be precipitated by events such as cold, dehydration, infection, stress, menses, and alcohol consumption, but most painful episodes have no identifiable cause. It can affect any area of the body, may vary from trivial to excruciating, and is usually endured at home without a visit to the emergency department. Painful episodes are bio psychosocial events caused by vaso - occlusion in an area of the body having nociceptors and nerves (Emechebe *et al.*, 2017).

Vaso Occlusive Crises

Vaso occlusive crises is also called pain or thrombotic crises due to vascular occlusion by sickled cells and can affect any part of the body but is more common over the long bones, abdomen, chest, and the back. Central nervous system involvement leads to cerebrovascular accident (Emechebe *et al.*, 2017). Precipitating factors include physical exertion, exposure to extremes of weather, fever, dehydration, acidosis, infection, emotional disturbance and sometimes the cause is not known. Hepatic crisis which is also called right upper quadrant syndrome and consists of right upper quadrant pain, fever, jaundice, elevated transaminases and hepatic enlargement, occurs in about 10% of patients with vaso occlusive crisis. The rapid decrease in transaminases during the recovering phase differentiates this condition from slower decline characteristic of acute viral hepatitis. Acute viral hepatitis has the same clinical course in these patients as in the general population but with higher peak bilirubin level because of additional haemolysis from haemoglobinopathy. Another manifestation of vaso-occlusive crisis in the chest is known as acute chest syndrome, young children will present with chest pain, fever, cough, tachypnoea, leukocytosis, and pulmonary infiltrates in the upper lobes, often difficult to differentiate from pneumonias; adults are usually afebrile, dyspneic with severe chest pain, with multilobar/lower lobe disease. Pulmonary hypertension is increasingly being recognized as a serious complication of SCD (Emechebe *et al.*, 2017).

Anaemic crisis can be caused by hyperhaemolysis, aplastic crisis and acute sequestration crisis (Emechebe *et al.*, 2017).

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1. Hyperhaemolysis is precipitated by infections, glucose-6-phosphate dehydrogenase (G6PD) deficiency, acidosis and dehydration. There is increased pallor, jaundice and hepatosplenomegaly
2. Aplastic crisis is characterized by an acute failure of erythropoiesis often following viral infections especially parvovirus B19. The patient will present with weakness, progressive pallor and pancytopenia. During this crisis the patient may have associated bone and joint pain. Blood transfusions are often necessary in order to preserve the patient's life.
3. Acute sequestration is caused by pooling of blood in the spleen and the liver characterized by sudden onset of progressive anaemia, splenic enlargement, abdominal pain and shock. Various crisis and increased susceptibility to infections are responsible for recurrent illness in patients with sickle cell disease (Emechebe *et al.*, 2017).

Other Complications

The complications listed above are highlighted as those affecting babies and young children, because these are immediately relevant after newborn screening. Older children, adolescents, and young adults develop many chronic complications: stroke, cognitive dysfunction, priapism, leg ulcers, avascular necrosis (of the femoral head or humeral head), chronic pain, retinopathy, pulmonary hypertension, acute kidney injury, chronic kidney disease, thromboembolic events, and hepatic sequestration (Baba *et al.*, 2019), cholelithiasis (gallstones) and cholecystitis as a result of excessive production and precipitation of bilirubin due to haemolysis. SCD also increases susceptibility to complications in pregnancy (Baba *et al.*, 2019).

Management of Sickle Cell Disease

Many of the manifestations of sickle cell disease can be better managed if the diagnosis is made early and regular prospective follow up instituted. The management of sickle cell anaemia is in two phases' quiescent stage and crisis stage. (Obeagu *et al.*, 2015)

Quiescent stage management may include (Obeagu *et al.*, 2015)

- Nutrition
- Prophylaxis against infections
- Therapy of infections
- Avoidance of adverse climatic conditions

- Hydration
- Education

Crisis stage management may include (Obeagu *et al.*, 2015)

- Blood transfusion
- Use of cyanate food derivatives
- Analgesics
- Steroids drugs and hormones
- Bone marrow transplants

CONCLUSION

Sickle cell disease (SCD) and thalassemia are haemoglobinopathies affecting the production of haemoglobins. Generally, the production of variant haemoglobins in sickle-cell disease make cells to undergo the process of becoming sickle-shaped, and with this format, they tend to block blood flow, causing anemia, pain and damage to several organs. One of the main complications of sickle-cell disease is renal impairment, a condition that worsens anemia. The treatment of serious anemia in patients with sickle-cell disease currently has two approaches as options: hydroxyurea which is not always effective for anemia and regular transfusion which may lead to alloimmunization iron overload and hyper-haemolysis in pregnant women. Erythropoietin, a hormone released by kidneys for the purpose of regulating red blood cell production and consequently, keeping haemoglobin (Hb) concentration constant, could be an option for the treatment of anemia, mainly in patients not tolerating high hydroxyurea doses.

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