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Sickle cell anaemia: Historical perspective, Pathophysiology and Clinical manifestations

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Abstract

Sickle cell disease is a group of haemoglobinopathy disorder as result of single mutation in beta globin chain of haemoglobin resulting in sickling of red blood cells under deoxygenated condition. It presents with serious crisis which is challenging both to the parents and the patients. A lot of researches have been going on this direction to discover the cure for sickle cell anaemia but the only cure now is bone marrow transplant at early stage of life. This paper discussed the history, pathophysiology and clinical manifestation of sickle cell anaemia.

Keywords: *Sickle cell anaemia,* historical perspective, pathophysiology and clinical manifestations

Historical perspective

In 1904, Walter Clement Noel travelled from Grenada to the United States to began researching at the Chicago College of Dental Surgery. A few months later he was admitted to the Presbyterian Hospital in Chicago when he discovered serious respiratory distress and leg ulcer, both of which we now regarded as symptoms of sickle cell. Dr Earnest E. Irons. The intern who was on schedule that day, did a routine blood test and a urine analysis for Noel and was the first to notice these “pear shaped, elongated” sickled blood cells. It was not until 1910 that Dr Herrick, the supervisor of Dr Irons, released his article describing these “peculiar elongated and sickle shaped red blood corpuscles in a case of serious anaemia”. This was the first documented and recorded case of sickle cell in Western medicine (Herrick , 1910).

The second case was described in a 25 year old female Negro origin, three months later of the first report, the stated that she complained of breathlessness, weakness, episodes of pains and swelling in the ankles and wrist with leg ulceration and the blood film was similar to that of Herrick case.

The third case of Sickle cell was described in 1915 by Cook and Meyer in 21 year-old woman. Interestingly, blood samples from both the patient and her father, who showed no symptoms, showed the sickling deformity of the red cells and three of her siblings had died from severe anaemia. These observations made by Dr Emmel suggested a genetic basis for the diseases but also led to a period of confusion with the genetics of the disease (Cook and Meyer, 1915).

Dr Mason who recorded the 4th documented case of sickle cell, was also the first to called the diseases “Sickle cell anaemia” and to notice the similarities between the cases. He also reported that all of these patients were black, inadvertently giving rise to the popular misconception that sickle originated from people of African region (Mason, 1922). Hahn and Gillespie were the first to associate the red cell sickling

to low oxygen and acidic conditions. They were able to revert sickled cells back to their normal discoid shape by simply providing the cells with oxygen. Further experiments showed that, apart from oxygen, increased serum acidity also induced sickling of red blood cells (Mason, 1922).

The protective function of foetal haemoglobin HbF was discovered in the 1940s, when Dr. Janet Watson suggested association between HbF levels and the presence of disease symptoms in 1948. She observed that higher HbF levels in newborns kept them asymptomatic. Humans have predominantly HbF in their foetal life but within 12 weeks after birth the production of HbF synthesis is shut off and replaced by the production of adult haemoglobin HbA. It is now known that in some sickle cell patients this switch does not occur as efficiently, resulting in higher than normal HbF levels. These differences in HbF levels mark the differences between symptom manifestations where patients with higher HbF levels have a milder form of the disease. (Watson, 1948 **cited** in A brief history of Sickle cell Disease, 2002).

Sickle cell was the first molecular diseases discovered, in 1940 Irwin Sharman noticed a difference between the way light passed through sickled blood cells compared to normal cells. Dr Castle, a Harvard professor in medicine, understood the implication of this finding: a change in the spatial orientation inside these sickled blood cells. In a chance conversation, Dr Castle mentioned this to Linus Paulinga scientist, who worked extensively on haemoglobin ultimately resulting in the identification of two different forms of haemoglobin present in people with sickle cell. Pauling tested the haemoglobin samples from normal individuals, sickle cell patients and people with sickle trait using a technique called electrophoresis. This was the first reported case where a change in protein structure was shown to be inherited in a mendalian fashion (Pauling *et al*.,1949). Sickle cell disease is a genetic chronic haemolytic anaemia whose clinical manifestation arise from the tendency of the haemoglobin(HbS or sickle haemoglobin) to polymerize and deform red blood cells into the characteristics sickle shape. This property is due to single nucleotide change in the Beta-globin gene leading to substitution of valine for glutamic acid at position 6 of the Beta globin chain ($\beta^{6glu\text{-}val}$). The homozygous (state HbSS or sickle cell anaemia)is the most common form of sickle cell diseases, but interaction of HbS with Thalassemia and certain variants Haemoglobin also leads to sickling. The term sickle cell disease is used to describe all entities associated with sickling of haemoglobin within red cells (Hoffbrand *et al.*, 2005).

Pathophysiology

Sickle-cell anaemia is as a result by a point mutation in the β-globin chain of haemoglobin, causing the hydrophilic amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the sixth position. The β-globin gene is found on chromosome 11(Obeagu *et al.,* 2015).The association of two wild-type α-globin subunits with two mutant β-globin subunits forms haemoglobin S (HbS). Under low-oxygen conditions (being at high altitude, for example), the absence of a polar amino acid at position six of the β-globin chain promotes the non-covalent polymerisation (aggregation) of haemoglobin, which alters erythrocytes into a sickle shape and decreases their elasticity (Obeagu, 2018).

The loss of erythrocytes elasticity is central to the pathophysiology of sickle-cell disease. Normal erythrocytes are quite elastic, which allows the cells to deform to pass through capillaries. In sickle-cell disease, low-oxygen tension enhances erythrocyte sickling and repeated episodes of sickling damage the cell membrane and reduces 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 (Swem *et al.,* 2018).

The actual anaemia of the illness is caused by haemolysis, the destruction of the red cells, because of their misshape. Although the bone marrow attempts to compensate by creating new red cells, it does not match the rate of destruction. Healthy erythrocytes typically live for 120 days, but sickle cells only survive 10–20 days.

Clinical manifestation

Clinical features of sickle cell could be divided into acute and crisis phase then chronic and unmerited phase. The clinical consequence are more of rheologic than anaemia itself, sickling results in elevated in viscosity of blood leading to reduced circulation and deoxygenation (Ham and castle 1940 cited by Serjeant (2001).This viscosity is due to several inter-related factors which are membrane rigidity haemoglobin polymerization increased intracellular haemoglobin concentration (Steinberg, 2001).

Common Symptoms in infancy and childhood are fever, pain and swelling of the limbs and abdomen. Poor appetite, vomiting and diarrhoea. These are frequently, confused with rheumatism, Dactylitis and hard foot syndrome. Most children are asymptomatic until 3-6 months, this is because of HbF generally suppresses sickling although infection, haemolyses and jaundice even in newborn have been described.

Symptoms vary often between patients with SCD for several reasons. The disease is more serious in patients with HbSS or HbS 0-thalassaemia than in those with HbS-thalassaemia or HbSC disease. The Arab–Indian haplotypeproduces a less serious disease than the African haplotypes. The co-inheritance of one or two gene deletions also modifies the clinical picture. The high HbF level observed in hereditary persistence of foetal haemoglobin (HPFH) is linked with very mild disease. However, for poorly recognized reasons, the disease severity varies enormously even within the subgroup of patients with HbSS.

In countries with inadequate healthcare, Sickle cell disease is linked high mortality in the first 3 years of life as a result of sepsis and splenic sequestration. In the developed world, the typical patient with Sickle cell disease has moderately severe anaemia, leads to relatively normal life interrupted by 'crises' as a result of vaso occlusion has a life expectancy of 45 years (Hoffbrand *et al.*, 2005).

Conclusion

Sickle cell disease is a group of haemoglobinopathy disorder as result of single mutation in beta globin chain of haemoglobin resulting in sickling of red blood cells under deoxygenated condition. It presents with serious crisis which is challenging both to the parents and the patients. There should be more concerned researches to discover cure for sickle cell anaemia to enhance the lifespan and wellbeing of the patients. More resourses should be made available by organizations and individuals for research in this direction. Life is precious and should be wisely and carefully handled by everybody.

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