REVIEW ARTICLE

# Splenic Changes in Sickle Cell Anaemia

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## ABSTRACT

***Background**: The spleen is one of the most frequently affected organ in Sickle cell anaemia (SCA). This has been attributed to its complex anatomy and prominent reticuloendothelial functions which include clearance of unwanted particulate matter in blood ( culling), defense against infection and reservoir for blood cells. This paper aims to highlight the current information on the changes that occur in the spleen of Sickle Cell Disease patients in this environment*

***Method**: A review of relevant literature on the subject of splenic changes in Sickle Cell Disease sourced by manual library and medline search.*

***Results**: The essential splenic change in SCA is splenomegaly and subsequent shrinkage in size (auto-splenectomy), which may be due to several factors. These include: high levels of irreversible sickle cells, decreased HbF associated with increased intravascular sickling and chronic Malaria infection secondary to hyperplasia of the reticulo-endothelial system and increased antibody production especially IgG and IgM. Finally, the clinical complications of these splenic changes such as increased susceptibility to infection, acute splenic sequestration and hypersplenism are also reviewed in this paper.*

***Conclusion**: In view of the above changes, it is important to ensure regular monitoring and follow-up in order to prevent complications, recurrent crisis and death.*

***KEYWORDS:** Splenic changes; Sickle cell; Anaemia.*

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## INTRODUCTION

The spleen is one of the most frequently affected organs in sickle cell anaemia and this has been attributed to the complex anatomy and the prominent reticuloendothetial role of the spleen[1,2]. In order to appreciate the splenic changes in sickle cell anaemia, a brief anatomy and function of the normal spleen will be discussed.

### Anatomy and Function of the Normal Spleen

The spleen is a large mass of reticuloendothelial tissue located in the left hypochondrium. It lies between the fundus of the stomach and the diaphragm. The average adult spleen weighs about 135g (100-250g) and measures about 12cm x 7cm x 3cm in length, width and thickness respectively[2]. It is encapsulated by a coat of fibromuscular connective tissue. A ridge on the medial splenic surface constitutes the hilus through which blood vessels enter and leave the spleen. The splenic pulp which is the stroma of the spleen is made up of a mesh work of reticular cells and reticular fibres forming the filtration beds that filter the blood. Histologically, the white pulp is composed of the periarteriolar lymphatic sheaths and lymphoid nodules. Each nodule consists of a peripheral or marginal zone of densely packed small lymphocytes, a germinal center containing mainly developing lymphoblasts and an eccentrically placed central artery. The periateriolar lymphatic sheath contains primarily T cells while the lymphatic nodules contain B cells and is the main site of splenic immunologic activity. The red pulp is made up of numerous vascular sinusoids separated by a reticular mesh of splenic cords. The splenic cords are thin aggregates of lymphatic tissue containing small lymphocytes and macrophages, which are loosely connected through dendritic processes to create a physical and functional filtration bed. The marginal zone is also made up of reticular fibre mesh of filtration beds[1,2].

### Blood Supply

The spleen has a complex vascular system made up of the splenic central artery and its branches of trabecular arteries, which extend from the capsule and terminates in the red pulp as arteriolar capillaries. They are surrounded by a sieve loose reticular tissue packed with small lymphocytes, known as the periarterial lymphatic sheaths. Blood entering the spleen through the arterial system runs through the marginal zone and the splenic cords, into the splenic vein and sinuses in the red pulp. In order to be pooled in the vein, blood from the splenic cord passes through the inter endothelial slits of the sinuses to reach the vein (close circuit). To accomplish this process the red cell must be extremely pliable or deformable to pass between the slits[1,2].

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## Functions of the Spleen

**Splenic clearance** One of the major functions of the spleen is the filtration of unwanted particulate matter (defective red cells, antigens, microorganism, cellular debris), from the blood and destroying it by phagocytosis in the splenic cord (culling). In addition the spleen also has the ability to neatly remove particles from intact cells without destroying it (Pitting), thus cellular inclusion bodies (such as Heinz-bodies, Howell Jolly bodies, intracellular organism and malaria parasite) are removed from the red cells[1,2].

## Defence against infection

The spleen is a major secondary organ of the immune system and antibodies are produced by lymphoid tissues in response to antigenic stimulation. The spleen is also involved in the synthesis of opsonins such as tuftsin and properdin which enhance phagocytosis. In addition, macrophages exhibit non phagocytic function such as the secretion of "Cytokines Interleukins and enzymes[1,2].

## Splenic Reservoir

The spleen, as a result of its rich vascularization, acts as a reservoir for red cells, leucocytes and platelets. The average adult spleen harbours about 30- 40 mls of erythrocyte and approximately 30 -40% of the total body platelets, which may increase to up 80 -90% in splenomegaly. The enlarged spleen may also sequester sufficient amount of blood to induce anaemia, thrombocytopenia and leucopenia[1].

The spleen is not only a source of lymphoreticular cells but sometimes of haemopoietic cells. Normally, splenic haemopiesis ceases before birth, however, in severe anaemia, extramedulary splenic haemopoiesis may be reactivated[1-3].

### THE EFFECT OF SICKLE CELL ANAEMIA ON THE SPLEEN.

The spleen in sickle cell anaemia (SCA) is usually normal in size and functionally competent at birth, but undergoes a sequence of changes with age. The progressive replacement of foetal haemoglobin (HbF) with mainly haemoglobin S (HbS) heralds the onset of haemolysis with resultant increase in splenic size and activity. [1, 4, 5]. Consequently, the spleen becomes palpably enlarged by the fifth month of life and in some children as early as one month[1]. Rogers et al[5] in a representative sample of patients followed from birth, observed splenomegaly in 37% by six months, 65% by twelve months and 77% by twenty-four months. The development of splenomegaly is mainly due to the complex structure of the spleen which encourages stasis, anoxia, and the entrapment of sickle erythrocytes within the splenic pulp and sinuses. The erythrostasis leads to marked congestion of the red pulp and sequestration of blood[6]. However, with recurrent vaso-occulusion and multiple infarctions and fibrosis the spleen begins to regress in size and is later reduced to a siderofibrotic mass consequently, the spleen is no longer palpable[1]. This process is designated auto-splenectomy and it occurs between the ages of 6-8 years [1,7]. Most SCA patients do not have palpable spleen beyond the 8th year of life.[1,7] However, in some patients, especially those living in the tropics, splenomegaly persists up to adolescence and even adulthood [1,7,8]. In Nigeria, Adekile *et al*[7] found splenomegaly in 33.8% of SCA patients between the ages of 10 to 16 years, and Esan[8] reported 15% in adults while Konotey-Ahulu[9] in his Ghanaian series observed splenomegaly in 15% of SCA patients above 10 years. Serjeant [10] also found an incidence of 9% amongst his Jamaican SCA patients above 10 years. He attributed the persistence of splenomegaly to low levels of irreversible sickle cell (ISC) and high levels of HbF which are associated with less intravascular sickling and relatively normal splenic perfusion with less vaso-occlusive lesions. However, in West Africa, because of malaria endemicity, the persistence of splenomegaly in SCA has been linked to chronic malaria infection[7,9]. The pathogenesis of which has been likened to that of tropical splenomegaly syndrome [6,7]. Malaria exerts an intense pressure on the host immune system and the acquired immunity by residents of malaria endemic areas, thus the immune system does not completely eliminate the parasite which is then allowed to persist at low density over a period of time. This results in the hyperplasia of the reticuloendothelial cells of the spleen by the chronic antigenic stimulation by the malaria parasite (antigen)[11]. Consequently, the incidence of splenomegaly in the population within the endemic area varies from 0% at birth to 70% in children less than ten years declining to 20% in adulthood[9,11], this closely parallels the crude parasite rate. Malaria has also been associated with increased synthesis and high levels of IgG and IgM immunoglobulins[9,11]. Adekile in a more recent study was able to establish significantly high levels of IgG specific malaria antibodies in patients with persistent splenomegaly[12]. The co-inheritance of alpha-thalassaenia by SCA patients is also known to cause the persistence of splenomegaly and this has been attributed to reduction in HbS molecule within the erythrocyte[13].

## CLINICAL CONSEQUENCES OF SPLENIC CHANGES IN SICKLE CELL DISEASE

Acute splenic sequestration (ASS), hypersplenism and increased susceptibility to infection are some of the

clinical complications associated with these changes.

**Acute Splenic Sequestration** (ASS)

This is a clinical syndrome characterized by a sudden splenic enlargement, increased intrasplenic pooling of blood and a precipitous fall in haemoglobin level. In addition to hypercellular marrow and increased reticulocyte count. ASS may result in sudden life threatening fall in haemoglobin with death from circulatory failure. It is an important cause of mortality in children[1]. However, ASS can also occur in young adults and in pregnancy. The natural history of ASS indicates a tendency to recurrence. However this can be prevented by education of parents, chronic blood transfusion programme and prophylactic splenectomy [1,14].

**Hypersplenism**

Is another syndrome associated with persistent splenomegaly. It is characterized by a chronically enlarged spleen, excessive destruction of red cells, leucocytes, platelets and raised reticuocyte counts. The excessive destruction of red cell leads to gross bone marrow hyperplasia with increased demands for haematinics such as folate, as well as growth impairment from high energy demands[1]. Hypersplenism may occur insidiously or follow ASS, and is mostly managed conservatively by chronic blood transfusion and in more serious cases, by surgical splenectomy[1].

**Infection**

One of the most important clinical consequences of the structural changes in the spleen is the loss of reticuoendothelial function and as a result, the sickle cell patient is seriously immuno-compromised. The onset of splenomegaly at the age of 5 months in sickle cell anaemia paradoxically is associated with a decline in immune function of the spleen[1, 15, 16]. This disparity between splenic size and splenic function is termed functional hyposplenia, a concept originated by Pearson et al[16]. Functional hyposplenia is characherised by few Howel Jolly bodies in the circulating red cells while 99 TC scan shows little or no uptake of radio-colloids by the spleen [16]. Splenic hypofunction can be rapidly restored at this stage by the transfusion of normal (HbAA) red cells[16] the splenic function however, continues to decline as the damage to the spleen progresses until the period of autosplenesomy when anatomic asplenia occur by the age of 6-8 years[15,16]. Anatomic asplenia signifies a total absence of splenic function characterised by the presence of more Howel Jolly bodies and increased pitted red cells in the peripheral blood while the 99 TC scan shows no splenic uptake of radio-colloids[16]. In addition, blood transfusions are ineffective in restoring normal splenic function at this stage.Common defensive and immunological functions lost in sickle cell anaemia include: loss of humoral and cell mediated immunity[15], defective Opsonisation and alternate complement pathway [1,15] and impaired leucocyte function[15]. Sickle cell patients, consequently are highly susceptible to infections and [15] mortality rate as high 25-35% in sickle cell children has been attributed to infection. Akinyanju also reported infections to be a leading cause of death amongst SCA Children in Nigeria[17]. The common infections encountered include pneumococcal, meningococcal, *H. influenza* and malaria[15,18]. It is estimated that SCA Children are about 300 times more likely to develop severe pneumococcal and meningococcal septicaemia than children with normal haemoglobin in the same environment [13,15]. Malaria is a common precipitating factor of crisis and a major cause of death among sickle cell patients in the tropics[18,19].

## CONCLUSION

In view of the serious nature of the splenic changes in sickle cell Anaemia: hypersplenism, acute splenic sequestration and repeated infections due to auto splenectomy plus hyposplemism, it is important to ensure regular monitoring and follow-up of these patients in order to prevent complications, recurrent crisis and death.

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