**HAEMATOLOGY 10
SICKLE CELL DISEASE**

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*Lecture notes prepared by Dr Nina Salooja and Prof Barbara Bain*

**LEARNING OBJECTIVES**

The student should be able to

1. Describe the inheritance of clinical and haematological features of sickle cell anaemia (SS)
2. Outline principles of management
3. Explain the inheritance, clinical significance and diagnosis of sickle cell trait

Sickle cell anaemia results from a single amino acid change in the haemoglobin molecule. The blood disorder that results has long been a source of major interest to doctors and scientists. In 1949 Pauling and associates deduced that this disease was a result of a change in a protein by an allelic change in a single gene. As such, this was the first demonstration of a molecular disease. Although genetically simple, sickle cell anaemia is clinically complex and relating a single amino acid change in a single protein in a single cell type to the variable clinical manifestations represents a scientific challenge. In recent years considerable efforts have been made towards ameliorating the clinical picture which, as you will see, can be severe.

Sickle haemoglobin (HbS) differs from HbA by a single amino acid. The defect is in the β globin chain and results in replacement of glutamic acid at position 6 of the β chain by valine. 3-D models of the deoxyhaemoglobin indicate that the residue at position 6 sits on the surface of the protein. Although glutamate is a highly polar amino acid, the side chain of valine is distinctly nonpolar and this alteration markedly reduces the solubility of deoxyhaemoglobin. These molecules can then polymerise within the red cell, which distorts and undergoes a characteristic shape change: the sickled cell. These cells have a marked decrease in deformability. In addition, the formation of intracellular polymers is associated with red cell membrane changes, which make the red cells particularly “sticky” to vascular endothelium.

Sickle cell anaemia refers to a condition in which there are two βS genes and no normal β genes so that the individual cannot produce any normal β chain and therefore cannot produce any haemoglobin A (see Table). The term sickle cell disease is a more general one that covers also other conditions that lead to formation of sickled red cells such as co-inheritance of haemoglobin S and either haemoglobin C (another β chain variant) or β thalassaemia trait.

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| **Condition** | **β genes** | **Haemoglobins present (in addition to A2 and F)** |
| Sickle cell disease | Sickle cell anaemia | βSβS | S |
| Sickle cell/haemoglobin C disease | βSβC | S and C |
| Sickle cell trait | βSβA | A and S |
| Normal | ΒAβA | A |

The sickle β globin gene (βS) is spread widely throughout Africa, the Middle East, Mediterranean countries and India. The frequency of sickle cell carriers is up to 1 in 4 in West Africans and I in 10 in Afro-Caribbeans, and has reached high levels in these populations because the carrier state protects against malaria. Currently there are more than 10 000 patients with sickle cell disease in Britain.

Only adult Hb is affected because HbF does not have any beta chains. The problems therefore start at 4-6 months or older, after the HbF level decreases and the adult Hb level increases. As sickled red cells become trapped in the small blood vessels, circulation is impaired and there is damage to multiple organs. In children, infarcts of the small bones of the hands of feet may occur and lead to a painful dactylitis called the “hand-foot“ syndrome and, as a later result, shortening of the digits. In adults, generalised pains are more typical and result from oxygen deprivation of tissues and avascular necrosis of the bone marrow. The effects of sickling in various organs are listed next:

Bones dactylitis / osteomyelitis/ avascular necrosis of the hip

Kidneys haematuria and failure to concentrate urine, papillary necrosis

Brain stroke

Lungs “chest crisis”

Spleen splenic sequestration/ hyposplenism

Skin skin ulcers

**Terminology**

***Infarct*** death of tissue due to loss of blood supply

***Dactylitis*** inflammation of a digit (in this case resulting from infarction of bone)

***Avascular necrosis*** death of tissue as a result of loss of its blood supply

***Osteomyelitis*** infection of bone (dead tissue is susceptible to bacterial infection)

***Splenic sequestration*** pooling of large numbers of red cells in the spleen (see below)

***Hyposplenism*** reduced function of the spleen (in this case, as a result of recurrent interruption of the blood supply leading to death of splenic tissue)

***‘Chest crisis’*** hypoxia resulting from death of lung tissue

Sickled cells are fragile and have a shortened life span (***haemolysis***), which results in anaemia. The affinity of HbS is lower than that of HbA so it gives up oxygen more readily to tissues and anaemia is often well tolerated. In an attempt to compensate for the shortened red cell life span there is an increased turnover of red cells and the body’s supply of folic acid can become low. The shortened life span of the red cells makes patients with sickle cell disease particularly susceptible to the effects of parvovirus B19 infection. This virus infects red blood cell precursors and stops red cell production for up to a week. In the setting of a short red cell life span, if red blood cell production stops for even short period of time the Hb level can fall dramatically; this is called an aplastic crisis. Children are also at risk of another sort of crisis called a splenic sequestration crisis. Abdominal pain, pallor and shock together with a large spleen and low haemoglobin are indicative. The reticulocyte count is raised in a sequestration crisis but in an aplastic crisis it is much lower than normal.

In one large survey the median life expectancy for men and women with homozygous sickle cell anaemia was 42 and 48 years respectively and the causes of death were:

21% associated with a painful crisis

14% associated with a chest syndrome

9% associated with renal failure

7% associated with infection

6% perioperative

**Note**: you do NOT have to memorise these figures – they are just to give you an idea of the long term clinical features of this disease

# Laboratory features and diagnosis

1. The **blood count** shows a low Hb *e.g.* 6-9 g/dl and raised reticulocyte count
2. **Blood film** shows sickled cells. Also it may show signs of hyposplenism, namely the presence of Howell-Jolly bodies (which are nuclear remnants usually removed in the spleen) and target cells.
3. Simple screening tests.

These tests depend on the decreased solubility of haemoglobin S when the oxygen tension is low. One such test is a **sickle solubility test** in which a reducing agent is added to diluted blood and leads to formation of many sickle cells (in sickle cell trait as well as in sickle cell anaemia). This makes the blood turbid. A positive result must be confirmed by Hb electrophoresis.

1. Definitive diagnosis requires **haemoglobin electrophoresis** (or an equivalent test)as well as a sickle solubility test. Electrophoresis separates proteins according to their charge; this varies according to the pH at which electrophoresis is carried out. So, at alkaline pH, HbS separates readily from Hb A and F. However, there are some non-sickling haemoglobins (called HbD and HbG) that run with HbS – this is why a sickle solubility test is also needed. In sickle cell anaemia no HbA is detected and there is a variable (5-15%) amount of HbF and a small amount of HBA2. Patients with sickle trait have Hbs A and S (plus small amounts of HbA2 and HbF).

# Management

1. **Painful crisis**

Factors known to precipitate a crisis should be avoided. Fast, adequate pain relief with strong analgesics should be given and precipitating factors should be reduced by rehydration, warmth and additional oxygen as necessary. Infection should be excluded by chest X-ray and appropriate cultures, *e.g*. of urine and blood. If infection is present, antibiotics are needed.

1. **Folic acid 5mg /day**
2. **Vaccination to protect against pneumococcal infection**
3. **Prophylactic penicillin** to prevent some of the infections caused by hyposplenism
4. **Blood transfusion**

a) top up blood transfusion e.g. if aplastic or sequestration crises

b) exchange blood transfusion if life threatening/severe disease such as a stroke, or chest crisis. An exchange transfusion aims to reduce the HbS to less than 20%

**NOTE:** top-up blood transfusion is NOT a treatment for painful crisis; it will increase blood viscosity and may make the painful crisis worse

1. **Stem cell transplantation**

Consider in children with severe disease. Currently survival is 90-95%.

# Sickle cell trait

This is the carrier state for sickle cell disease. This does not affect life expectancy, and is often clinically silent. However it needs to be identified because certain situations can provoke sickling e.g. anaesthesia, high altitude, air travel in unpressurised planes. All patients from ethnic groups in whom βS occurs should be screened prior to surgery. Sickle trait must also be identified in pregnant women so that their partners can be tested and appropriate counselling given and action taken if necessary.



A sickle solubility test (from Bain BJ, Interactive Haematology Imagebank, Blackwell Publishing, Oxford, 1999 — available on Intranet)

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