Haemoglobinopathy and sickle cell disease

Key points

Sickle cell disease (SCD) is a congenital haemoglobinopathy characterized by a mutation on chromosome 11, resulting in the production of the unstable and relatively insoluble haemoglobin S.

Vaso-occlusion and haemolysis are the hallmarks of SCD, resulting in recurrent painful episodes and organ dysfunction.

The sickledex test is an easily performed bedside test which reveals the presence of HbS, but does not differentiate between the heterozygous (sickle cell trait) and the homozygous state.

Progressive inflammatory vascular endothelial damage may play a role in the pathophysiology.

Careful, well-balanced anaesthesia, with attention to oxygenation, analgesia, temperature control, and hydration remains the mainstay of intraoperative management.

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Sickle cell disease (SCD), first described in the early twentieth century, is an inherited haemoglobinopathy resulting from a mutation on chromosome 11.[1] The mutation causes an amino acid substitution on the β-globin subunit of normal adult haemoglobin A, resulting in the formation of haemoglobin S. Haemoglobin S is biochemically unstable and can precipitate out of solution when in the deoxygenated state, forming the pointed, slightly curved 'sickle cells' (Fig. 1).

The greater the proportion of haemoglobin S in the cell, the greater is the propensity to sickle. The heterozygous carrier state or sickle cell trait results in the production of both haemoglobin A and S (usually 30–40% HbS), which has a predominantly benign clinical picture as the cells only sickle under extraordinary physiological conditions. Sickle cell trait provides some protection against the consequences of *Plasmodium falciparum* malaria.[2] The homozygous state (with near 100% HbS) results in SCD. This is a debilitating disease characterized by chronic haemolytic anaemia, recurrent intermittent vaso-occlusion and severe pain, and progressive organ damage and early death. Survival is rare beyond the fifth decade. The HbS gene is found primarily in Africa and south-west Asia, but in light of population migration, is becoming a worldwide phenomenon.

The thalassaemias are a group of hereditary anaemias caused by defective synthesis of the alpha chain (alpha thalassaemias) or the beta chain (beta thalassaemias) of haemoglobin. Heterozygotes have mild anaemia, whereas homozygotes have severe anaemia. Unbalanced synthesis of the alpha and beta chains leads to unstable haemoglobin and early red cell death, usually in the marrow. There may be a compensatory extramedullary haematopoiesis.

Haemoglobin

Normal adult haemoglobin or HbA consists of 2α and 2β subunits or chains. The α subunits are coded on chromosome 16, the β, or non-α subunits are coded on chromosome 11. These are not always β, but could be ε (embryonic), δ (normal minor Hb A_2), or γ (fetal). Normal adult red blood cells have three different types of haemoglobin: HbA ($α_2β_2$) ∼95%; HbA_2 ($α_2δ_2$) ∼2.5%; and HbF ($α_2γ_2$) 2.5%. The spatial arrangement of these subunits determines oxygen affinity, solubility, and stability. At birth, red cells contain 70–90% HbF until about 2–4 months of age. Beta chain production begins just after birth and gamma chain production begins to decline, resulting in an adult profile by age 4 months. Thus, beta chain abnormalities do not manifest in the first few months of life. Haemoglobinopathies result from either the production of an abnormal haemoglobin chain, such as when there is a single substitution of one amino acid as seen with sickling disorders, or the underproduction of a given chain resulting in the thalassaemias (Table 1).

Sickle cell disease

Desaturation of HbS results in the polymerization of haemoglobin, forming large aggregates called tactoids, which deform the red cells into the typical sickle shape. Homozygous (SS) cells begin to sickle at a much higher oxygen saturation, typically 85% (Pa_{O_2} 5.2–6.5 kPa) than heterozygous (AS) cells, which usually do so well below the saturation of venous blood 40% (Pa_{O_2} 3.2–4.0 kPa). Sickling with sickle cell trait is therefore rarely a problem without concomitant stasis.

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The pathophysiological consequences of sickling are two-fold: small vessel obstruction by sickle cells (vaso-occlusive events which can be extremely painful) and haemolytic anaemia due to the greatly reduced half-life of SS cells when compared with normal red blood cells (12 *vs* 120 days).[3] The presence of fetal haemoglobin confers protection against sickling and some adults may be prescribed hydroxyurea to elevate HbF levels. In addition to hypoxia, sickling is also exacerbated by cold, stasis, dehydration, and infection.

Diagnosis

The definitive test is haemoglobin electrophoresis, but in emergency cases, a rapid screening test, the 'sickledex test' will detect levels of HbS of >10%; however, it is unable to distinguish SCD from sickle cell trait. Screening should be performed on all patients who originate from endemic SCD countries.
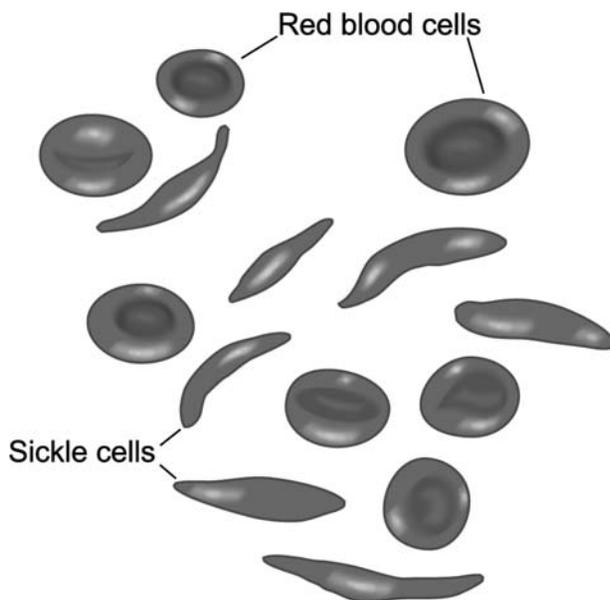

Fig 1 Sickle cells.

Examination of the peripheral blood film may reveal sickle forms or an elevated reticulocyte count relative to the haemoglobin level, but these may not be present in sickle cell trait where the red cell morphology may be essentially normal.[4]

Clinical picture

Patients with sickle cell trait are invariably healthy. However, patients with SCD will usually demonstrate multiple organ damage as a consequence of repeated vascular occlusion superimposed on a background or poor development and failure to thrive. Many patients will have frequent hospital admissions for exacerbations of their disease.[5]

Cardiovascular

Cardiomegaly is usually due to anaemia, but may be due to congestive cardiac failure. Pulmonary artery hypertension secondary to recurrent pulmonary infarction increases the risk of death.

Respiratory

Dyspnoea, cough, haemoptysis, and pleuritic chest pain caused by recurrent pulmonary infarctions are classical features of the 'acute chest syndrome'. Repeated episodes can compromise lung function and lead to respiratory failure.

Head/neck/airway

Marrow hyperplasia may lead to frontal bossing and a prominent maxilla. Eye changes, similar to those seen in diabetes, can include microvascular retinopathy, vitreous haemorrhage, and retinal detachment. Functional asplenism is associated with hypertrophy of other lymphoid tissue, including the tonsils and adenoids and patients may have a history of obstructive sleep apnoea.

Genitourinary

Renal impairment begins in childhood and is common by adulthood. Painful priapism may be seen.

Table 1 Haemoglobin mutations and associated syndromes

Hb	Related condition	Molecular structure	Chromosome mutation
A	Normal adult	$\alpha_2\beta_2$	Nil
A$_2$	Normal minor adult (usually <3%), elevated in β thalassaemia	$\alpha_2\delta_2$	
A	α thalasssaemia, asymptomatic or fatal	Decreased/absent synthesis of α chain	16
A	β thalassaemia, wide spectrum of disease	Decreased/absent synthesis of β chain	11
F	Fetal (<6 months old)	$\alpha_2\gamma_2$	Nil
S	Sickle cell disease/trait	Valine substituted for glutamate at position 6 of β chain	11
H	Formed in severe α thalasssaemia	β_4	16
C	Decreased red cell survival, mild anaemia, vaso-occlusive disease rare	Lysine substituted for glutamate at position 6 of β chain	11
SC	HbS from one parent, HbC from other, intermediate symptoms	See above	11
D	Asymptomatic, unless inherited with HbS	Glutamate substituted at position 121 of the β chain	11
E	Microcytosis, anaemia is rare	Lysine substitution in position 26 of the β chain	11

Gastrointestinal

In time, there is complete autoinfarction of the spleen, with immune incompetence. However, before this the spleen may suddenly enlarge, trapping red blood cells, and platelets. This splenic sequestration, with an associated acute decrease in haematocrit may be life threatening. Pigment gallstones are common and cholecystectomy is frequently required. Intrahepatic sickling may cause painful hepatic enlargement, but liver function is usually spared with only a slight increase in transaminases.

Skeletal/skin

Deformities may arise from marrow hyperplasia or repeated microvascular occlusion and infarction. Aseptic necrosis and leg ulcers are common.

Neurological

There is an increased incidence of transient ischaemic attacks (TIA), thrombotic stroke, and haemorrhagic events.

Haematological

Acute decreases in haemoglobin may be caused by infection-induced myelosuppression (e.g. parvovirus-induced hypoplastic crisis) or by splenic sequestration syndrome. Blood transfusion may be required. Bone marrow failure (aplastic crisis) may also occur and is associated with a high mortality.

Treatment

Treatment in the symptom-free period involves patient education to prevent dehydration, including advice concerning hydration during exercise or hot weather and the avoidance of excess alcohol. Patients with evidence of splenic involvement should be vaccinated against *Pneumococcus, Haemophilus influenzae B*, and *Neisseria meningitidis*. Folic acid prescription prevents deficiency as a result of chronically elevated erythropoiesis within the bone marrow. Hydroxyurea has been shown to reduce the frequency and severity of symptoms and of vaso-occlusive crises and has also been shown to reduce transfusion needs. It increases the formation of HbF, which confers some protection against sickling.[6] Its use is recommended before elective surgery if time permits. The only curative therapy is bone marrow transplantation, but pre-existing organ damage and the limited availability of compatible donors and also the 10% mortality have limited its use to symptomatic children <16 yr old.

Management of the acute crisis involves symptom control with analgesia and rehydration. This may be performed at home with simple analgesics and fluids, but pain may require hospitalization for more potent analgesia. Blood transfusion is often required. Any suspicion of infection should be treated using broad-spectrum antibiotics after culture of blood, sputum, and urine.

Anaesthesia and surgery

Preoperative assessment

Historically, perioperative mortality was as high as 10–50%, but more recent studies have reported mortality of around 1%. Wide-spread organ damage prevents a standard perioperative pathway being applied to all patients. A careful history and examination is required to assess disease severity (e.g. hospital admissions, number and timing of crises) and identify triggers. It should be noted that sickle cell crises may mimic acute surgical conditions, for example, an acute abdomen, and the need for surgery must be considered carefully. The patient should be assessed for signs of fever, dehydration, and vaso-occlusion. Minimization of the fasting period combined with preoperative hydration may help prevent sickling. Thus, patients are often admitted at least 1 day before surgery.

Signs of organ dysfunction should be sought and preoperative investigations should include chest X-ray, electrocardiogram, full blood count, urea and electrolytes, liver function tests, and oxygen saturation.[7] An arterial blood gas sample will be useful, as there is often a higher level of methaemoglobin in these patients causing the pulse oximeter to underestimate saturations. Pulmonary function tests should be performed before major elective surgery. Chest physiotherapy is an important part of both pre- and postoperative care.

The ideal haematocrit and the role of preoperative transfusion remains contentious as the incidence of complications related to transfusion are higher in this group and are not insignificant. Traditionally, an aggressive transfusion policy targeting an HbS concentration of <30% was suggested. Most authors would now suggest a simple transfusion policy to a haemoglobin of 10 g dl^{-1} in all but the lowest risk procedures, where transfusion is not indicated. In very high-risk cases, a more aggressive approach may be required, but this must be discussed in advance with a haematologist, as the risk of transfusion-related complications such as iron overload, alloimmunization, transfusion-related acute lung injury, and allergic reactions are all increased.

Intraoperative management

No particular anaesthetic technique has been shown to be more or less advantageous for patients with SCD. Debate continues over whether regional techniques are safer than general anaesthesia. Although regional techniques have been argued for on the basis of improved peripheral blood flow, improved analgesia and the avoidance of intubation where anatomical abnormalities may make this difficult, equally strong arguments have been made against these due to associated hypotension, hypoperfusion and the need for vasoconstrictors. The use of epinephrine with local anaesthetic solutions must, however, be avoided. It should be noted that epidural analgesia has been successfully used to treat painful vaso-occlusive crises. The technique used is likely to be much less important than

the meticulous attention to detail with regard to perfusion, temperature control, and oxygenation.[8]

Where general anaesthesia is used, preoxygenation is recommended and hypotension should be avoided by careful titration of induction agents. Except for the shortest procedures, controlled ventilation is recommended to ensure good oxygenation and normocarbia. Fluid losses should be replaced promptly, and this may be facilitated by measuring urine output and central venous pressure in longer cases. Temperature should be monitored and a warm ambient theatre temperature, pre-warmed fluids, and warming blankets are essential.

Venous stasis should be minimized by careful positioning, avoidance of caval compression, and avoidance of high-risk positions such as the prone position or the supine pregnant patient. The use of tourniquets remains extremely controversial as reduction of blood flow, hypothermia, acidosis, and hypoxia of the exsanguinated limb has been thought to cause sickling in the reperfusion period. A number of small retrospective reports have shown no evidence of sickling with the use of tourniquets when a bloodless field is highly desirable. If a tourniquet is used then careful exsanguination before inflation is to be recommended.

The use of cell salvage is not recommended by the machine manufacturers, but they have been successfully used on a number of occasions.[9]

Analgesia remains an important component of any well-balanced anaesthetic technique. This is no different for patients with SCD, but it should be noted that such patients may have been, or continue to be taking opioids before operation and higher doses may be required. Mutimodal analgesia with the concomitant use of acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and local anaesthetics may reduce opioid requirements. NSAIDs should be avoided if there is evidence of renal dysfunction.

Postoperative management

Most of the serious complications of SCD such as painful vaso-occlusive crises, acute chest syndrome, and stroke can occur in the postoperative period. Particular attention to oxygen supplementation, hydration, and analgesia is required and an extended period of monitoring in the postoperative period may be advisable thus making day surgery inadvisable in these patients.

Sickle HbC disease

Patients with both HbS and HbC (HbSC or S–C disease) have less frequent and less severe vaso-occlusive episodes. These patients are usually only mildly anaemic and may not need preoperative transfusion for more minor procedures. However, transfusion has been shown to be of benefit in more major abdominal procedures. There remains significant clinical variability and potential complications of SC disease including all those seen with SS disease. Similar perioperative precautions are recommended.

Thalassaemias

Beta thalassaemias

The heterozygous state is known as thalassaemia minor and results in a mild hypochromic, microcytic anaemia with haemoglobin levels $2-3$ g dl^{-1} below normal for age. The homozygous disease is known as thalassaemia major or Cooley Anaemia, and results in profound anaemia requiring repeated blood transfusions.

Alpha thalassaemias

These are prevalent in south-east Asia. Haemoglobin synthesis proceeds at a normal pace in the marrow, but there is a decreased red blood cell life span because of increased splenic uptake.

A combination of the genes for SCD and thalassaemia results in a disease more severe than either alone, known as haemoglobin S-thalassaemia. There is a moderately severe microcytic haemolytic anaemia in addition to vaso-occlusive crises.

Anaesthetic considerations

The haematocrit must be evaluated before operation. Nucleated red blood cells may appear to artificially elevate the white blood cell count if automated methods are used. This is usually only a problem if point of care analysers are used because most labs correct for this before issuing results. Splenomegaly may result in thrombocytopaenia. Thorough preoperative cardiac evaluation is recommended as haemosiderosis, secondary to chronic haemolysis or repeated transfusions, may adversely affect cardiac function.

Facial changes from marrow hyperplasia may cause difficulties with laryngoscopy.

Those patients who have had a splenectomy will be at risk of postoperative infection which can precipitate haemolysis. It should also be noted that oxidant drugs such as prilocaine, nitroprusside, vitamin K, aspirin, and penicillin may also precipitate haemolysis.

Summary

The perioperative morbidity and mortality of patients with haemoglobinopathies has been greatly reduced in recent years. This is partly due to improvements in anaesthetic standards of care and by a greater understanding of the underlying disease processes. Although the knowledge of the pathophysiology of these diseases continues to increase our understanding and suggest new treatments, in the absence of definitive outcome data, the anaesthetic management of these patients must continue to include meticulous attention to hydration, oxygenation analgesia, and temperature control.

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Please see multiple choice questions 19–21