Sickle Cell Disease and Sickle Cell Anaemia

Sickle cell haemoglobin (HbS) results from an autosomal recessively inherited mutation in which the 17th nucleotide of the beta globin gene is changed from thymine to adenine and the amino acid glutamic acid is replaced by valine at position 6 in the beta globin chain. Sickle cells have a reduced deformability and are easily destroyed, causing occlusion of the microcirculation and a chronic haemolytic anaemia with a median haemoglobin concentration level of about 9 g/dL. Sickling disorders include heterozygous (AS) sickle cell trait, homozygous (SS) sickle cell disease, compound heterozygous states for HbS with haemoglobins C, D, E, or other structural variants and the combination of the sickle cell gene with different forms of thalassaemia.

Sickle cell disease refers to the group of disorders that affects haemoglobin to form abnormal haemoglobin molecules (HbS). Sickle cell anaemia is the name of the specific form of sickle cell disease in which there is homozygosity for the mutation that causes HbS (ie HBSS).

Classification

The major sickle genotypes are:[1]

- **HbSS disease or sickle cell anaemia**: homozygote for the beta S globin with usually a severe or moderately severe phenotype.
- **HbS/beta0 thalassaemia**: severe double heterozygote for HbS and beta0 thalassaemia, and almost clinically indistinguishable from sickle cell anaemia.
- **HbSC disease**: double heterozygote for HbS and HbC with intermediate clinical severity.
- **HbS/beta+ thalassaemia**: mild-to-moderate severity, but variable in different ethnic groups.
- **HbS/hereditary persistence of fetal Hb (S/HPHP)**: symptom-free.
- **HbS/HbE syndrome**: very rare and generally very mild clinical course.
- **Rare combinations of HbS with HbD Los Angeles, HbO Arab, G-Philadelphia, among others**.

Clinical severity of sickle cell disease is very variable: a minority have few complications and their disease is clinically unapparent; a majority have intermediate forms, and another minority have severe complications including sepsis, strokes, recurrent painful episodes, acute chest syndrome, pulmonary hypertension and priapism.[3]

Sickle cell trait[4]

- Heterozygotes; there is typically 60% HbA and 40% HbS. Sickle cell trait protects against malaria.
- Sickle cell trait occurs in approximately 300 million people worldwide, with the highest prevalence of approximately 30% to 40% in sub-Saharan Africa.
- People with sickle cell trait are generally asymptomatic and have no abnormal physical findings. However, sickle cell trait is occasionally associated with significant morbidity - eg, haematuria, decreased ability to concentrate urine, renal papillary necrosis, splenic infarction, exertional rhabdomyolysis and exercise-related sudden death. Sickle cell trait is also associated with rare but often fatal renal medullary cancer.
- Despite the associated morbidity, the average lifespan of individuals with sickle cell trait is similar to that of the general population.
- Laboratory tests are normal with no anaemia, no evidence of haemolysis, and no laboratory abnormalities other than the presence of haemoglobin AS on haemoglobin electrophoresis.
- Sudden death may be induced by severe hypoxia (including flying in unpressurised aircraft, visiting very high altitudes or problems during general anaesthesia), severe dehydration and severe physical exertion.[5]
- Adequate hydration, avoidance of excessive fluid loss and avoiding severe heat are very important to help prevent complications such as exertional heat injury, splenic infarction, pain episodes and sudden death.
- Those people with sickle cell trait who participate in sporting activities should be advised to build up slowly in training with paced progressions, allowing longer periods of rest and recovery between repetitions. Pre-season strength and sports-specific conditioning programmes should be encouraged.[5]

Sickle cell disease

- Sickle cell disease is thought to be the most common severe genetic disease in the UK and France, with 10,000-15,000 people affected.[6]
- The prevalence of sickle cell disease is highest in sub-Saharan Africa.[7] The sickle beta globin gene is spread widely throughout Africa, the Middle East, the Mediterranean and India (eg, sickle genes are present in 1 in every 50 Asians and 1 in every 100 Northern Greeks). The gene has spread through population movement to the Caribbean, North America and Northern Europe.
- The frequency of sickle cell carriers is up to 1 in 4 in West Africans and 1 in 10 in Afro-Caribbeans. There is evidence for partial resistance of carriers to all forms of *Plasmodium falciparum* malaria in many populations.[7]

Presentation
The symptoms of sickle cell disease can begin between 3 months and 6 months of age when HbF levels are falling.

- Anaemia, jaundice, pallor, lethargy, growth restriction and general weakness; the most common causes of anaemia are acute splenic sequestration, transient red cell aplasia, and hyperhaemolysis in patients with severe infection.[3]
- Increased susceptibility to infections by encapsulated bacteria such as pneumococcus; the risk of overwhelming infection is highest before the age of 3 years.[3]
- Splenomegaly may be present in infancy and childhood but recurrent splenic infarcts then cause autosplenectomy.
- Delayed puberty.

Sickle cell crises[7]

- Vaso-occlusive crises (obstruction of the microcirculation by sickled red blood cells, causing ischaemia):[6]
  - This is the most common type of crisis. It may be precipitated by cold, infection, dehydration, exertion or ischaemia. Often no specific cause can be found.
  - Occlusion of small vessels by sickled erythrocytes causes pain which is variable from mild to severe. May present with swollen painful joints, tachypnoea or other signs of lung involvement, neurological signs, acute abdominal distension and pain (mesenteric sickling and bowel ischaemia), loin pain (renal papillary necrosis may cause renal colic or severe haematuria), priapism, hyphaema and retinal occlusion.
  - Large vessels may also be involved, causing thrombotic strokes, acute sickle chest syndrome and placental infarction.
  - Stroke:
    - Variable presentation, including fits and focal neurological signs.
    - Cerebral infarction is more common in children.
    - Haemorrhage from microaneurysms which develop around infarctions (*moyamoya*) is more common in adults.

- Aplastic crisis (temporary cessation of erythropoiesis, causing severe anaemia):
  - Usually precipitated by infection with parvovirus B19.
  - There is usually a drop in haemoglobin over about one week.
  - Recovery may be spontaneous but a transfusion is usually required.
  - With the severe anaemia associated with an aplastic crisis, patients may present with high-output congestive heart failure.

- Sequestration crisis (sudden enlargement of the spleen, causing a decrease in haemoglobin concentration, circulatory collapse and hypovolaemic shock):
  - Occurs mainly in babies and young children. The severity is variable but can present with shock and anaemia.
  - Acute splenic sequestration has been defined as an acute fall of haemoglobin and markedly elevated reticulocyte count, together with an acute increase in spleen size.
  - If unrecognised, sequestration causes significant mortality. Mortality rates can be reduced substantially by parental education, regular palpation of the abdomen at home to detect early signs of splenic enlargement, and prompt transfusion.
  - Recurrent splenic sequestration is an indication for splenectomy.

- Acute chest syndrome (vaso-occlusive crisis affecting the lungs):
  - Defined as a new pulmonary infiltrate on the chest radiograph combined with one or more manifestations such as fever, cough, sputum production, tachypnoea, dyspnoea, or new-onset hypoxia.
  - Lung infections tend to predominate in children, and infarcts predominate in adults.

- Hyperhaemolytic crisis (excessive haemolysis): uncommon; during painful crises there may be a marked increase in the rate of haemolysis with a fall in the haemoglobin level.

Differential diagnosis

- Other causes of haemolytic anaemia.
- Acute pain: assess all patients with sickle cell disease who present with acute pain to determine whether their pain is being caused by an acute painful sickle cell episode or whether an alternative diagnosis is possible, particularly if pain is reported as atypical.[8]

Investigations

- FBC and blood film: the haemoglobin level is in the range 6-8 g/dL with a high reticulocyte count of 10-20%; the blood films may show sickled erythrocytes and features of hyposplenism.
- Sickness of red cells on a blood film with 2% sodium metabisulphite.
- Sickle solubility test: a mixture of HbS in a reducing solution such as sodium dithionite gives a turbid appearance because of precipitation of HbS, whereas normal haemoglobin gives a clear solution.
- Haemoglobin analysis (eg, by electrophoresis) is always needed to confirm the diagnosis. There is no HbA, 80-95% HbSS, and 2-20% HbF.
- Sickle cell trait is diagnosed by the finding of a positive sickling test together with haemoglobins A and S on electrophoresis.
Other investigations such as renal function tests, LFTs and lung function tests should also be performed at diagnosis (baseline) and routine monitoring. Other investigations will depend on any complications - eg, infection screen, abdominal ultrasound, CT scan of the head (eg, if a subarachnoid haemorrhage is suspected).

**Screening**

Neonatal screening programmes that can identify children with sickle cell disease before they present with potentially fatal sepsis. Heel prick blood spots are usually collected 3 to 10 days after birth and haemoglobin analysed. This reliably identifies affected babies and allows penicillin to be started by 3 months of age.\[6\]

- Preconceptual testing for haemoglobinopathies is recommended in at-risk groups.\[9\]
- Policies for antenatal and neonatal screening vary throughout the UK.\[10\]
- Pre-operative screening for sickle cell disease should be carried out in patients from ethnic groups in which there is a significant prevalence of the condition. Emergency screening with sickle solubility tests must always be followed by definitive analysis.\[9\]
- Prenatal diagnosis: sickle cell disease can also be diagnosed in a fetus through prenatal diagnosis (following genetic counselling) from amniocentesis, chorionic villus sampling and fetal blood sampling.\[3, 11\]
Indications for urgent referral to hospital in sickle cell disease

- Severe pain not controlled by simple analgesia or low-dose opioids.
- Dehydration caused by severe vomiting or diarrhoea.
- Severe sepsis: temperature >38.5°C or >38°C if under 2 years old, temperature <36°C, or hypotension.
- Symptoms or signs of acute chest syndrome including tachypnoea, oxygen saturation more than 5% below steady state, signs of lung consolidation.
- New neurological symptoms or signs.
- Symptoms or signs of acute fall in haemoglobin.
- Acute enlargement of spleen or liver over 24 hours, particularly in young children.
- Marked increase in jaundice.
- Haematuria.
- Fulminant priapism lasting more than two hours or worsening of recurrent episodes.

Management

National haemoglobinopathy cards are available for affected, carrier and normal individuals following haemoglobinopathy screening. It is considered good practice to issue haemoglobinopathy cards to those with a major haemoglobinopathy and also to carriers where a definitive diagnosis can be made.

It is very important that people with sickle cell disease should be reviewed regularly at a specialist centre; non-specialist hospitals should contact the nearest specialist centre when treating patients with sickle cell disease. Patients should be monitored regularly in specialist clinics for their growth, development and organ function so that active management may be considered before organ failure develops. Referral for specialist assessment should be made if puberty is delayed beyond 14 years in girls or 14.5 years in boys.

- Parental and patient education:
  - Avoiding situations that can precipitate crises (e.g., cold, dehydration, and exhaustion) and early recognition and treatment of infection.
  - Palpation for splenic size to ensure early presentation of splenic sequestration can significantly reduce deaths.
  - All patients should be advised to avoid alcohol because of its dehydrating effects and smoking because it may cause the acute sickle chest syndrome.

Folic acid supplementation may be required. Zinc supplementation should also be considered if growth is restricted. Vitamin D deficiency is very prevalent in non-white children in the UK and may co-exist with sickle cell disease, so advice should be given regarding vitamin supplementation.

- Psychological:
  - Good support of patients, families and other carers is essential.
  - Cognitive behavioural therapy may be indicated.

- Infection:
  - Oral penicillin prophylaxis is started at diagnosis. The risk of pneumococcal infection remains high but decreases with age. There is a steady rise in prevalence of penicillin-resistant pneumococci.
  - Penicillin prophylaxis is continued throughout life in some countries but is stopped at age 5 years in other countries.
  - Routine childhood vaccinations include protection against *Haemophilus influenzae* type B and conjugated vaccines against *Streptococcus pneumoniae* in most high-income countries.
  - Children should also receive unconjugated pneumococcal vaccine from 2 years of age, repeated every three to five years, and immunisation against meningococcus, influenza, and hepatitis B.
  - Because malaria is a significant cause of morbidity and mortality in patients with sickle cell disease, malaria chemoprophylaxis is often recommended.

- Blood transfusions:
  - Transfusion therapy is a key intervention in decreasing morbidity and mortality in patients with sickle cell disease.
  - Transfusion may be required for severe anaemia or to reduce the proportion of HbS if there are lung or central nervous system complications.
  - Partial exchange transfusion (rather than top-up transfusion) is indicated when it is necessary to reduce the percentage of haemoglobin S quickly in acute life-threatening complications, such as severe acute chest syndrome, acute stroke, multi-organ failure or urgent preparation for major surgery.
  - Iron overload is a possible complication of regular transfusions and iron chelation should be started in all children receiving regular blood transfusions.
- **Hydroxycarbamide (hydroxyurea):**
  - Many cytotoxic drugs increase fetal haemoglobin concentrations, which is potentially beneficial for patients with sickle cell disease. Benefits include increasing haemoglobin concentrations, and decreasing platelet and white cell counts. \[^{1}\]
  - Concerns remain about its myelosuppressive and teratogenic effects and its possible long-term toxicity. Hydroxycarbamide (hydroxyurea) should be stopped at least three months before conception. \[^{14}\]
  - Hydroxyurea can reduce:
    - The frequency of crises in sickle cell disease.
    - The episodes of acute chest syndrome. \[^{7}\]
    - The need for blood transfusions. It is not yet licensed for use in sickle cell disease.

  It should still be used only on a named patient basis with close haematological supervision.

- **Bone marrow transplantation:** \[^{6}\]
  - Haematopoietic stem cell transplantation is potentially curative but is currently used only in patients with a severe clinical course and a matched sibling donor.
  - Its use is limited by the toxicity and the availability of suitable donors.

- **Stroke:** \[^{3}\]
  - Stroke prevention: it is recommended that transcranial Doppler ultrasonography be performed annually in children aged 2-16 years with sickle cell disease and that regular blood transfusions should be considered in those with abnormal findings on transcranial Doppler ultrasonography.
  - Assessment and prevention of nocturnal hypoxia (obstructive sleep apnoea) when relevant may be important in preventing strokes.
  - Exchange transfusion should be performed when a stroke occurs. Stroke is considered an indication for bone marrow transplantation in children and adolescents who have siblings with identical HLA.

- **Treatment of acute chest syndrome:** \[^{5}\]
  - Treatment includes inspired oxygen, incentive spirometry (also used for pain crises with back or chest pain), continuous positive airways pressure and exchange transfusion. Occasionally ventilation may be necessary.
  - Antibiotics are given using a combination of a macrolide with intravenous Doppler ultrasonography.
  - Transfusion or exchange transfusion produced improvements in several uncontrolled studies.
  - Hydroxycarbamide decreased the episodes of acute chest syndrome in one multicentre study.
  - Periodic transfusion is also effective in preventing recurrences.

- **Treatment of priapism:** \[^{7}\]
  - Priapism is an emergency requiring hydration and analgesia.
  - In minor episodes, bladder emptying, exercise such as jogging, warm baths and analgesia may help abort an attack.
  - Oral etilefrine may reduce the frequency of stuttering priapism.
  - In a prolonged episode, aspiration and irrigation of the corpora cavernosa with adrenaline (epinephrine) or etilefrine is now the treatment of choice.
  - Children and their carers should be advised to seek treatment early and should attend hospital as an emergency if priapism persists for more than two hours.

- **Contraception:**
  - Hormone and barrier methods are all acceptable choices but intrauterine devices are not recommended, as they may be associated with uterine bleeding and infection.
  - Depot contraceptive (Depo-Provera®) is safe and has been found to improve the blood picture and reduce pain crises. \[^{15}\]

**Painful crises**

Many episodes of uncomplicated acute pain can be managed at home with simple analgesia and community support. \[^{6}\]

- Pain experienced in a vaso-occlusive crisis results from oxygen deprivation of tissues and avascular necrosis of the bone marrow.
- Dactylitis is a common early manifestation that may occur before the age of 6 months. It is uncommon after 2 years of age. \[^{8}\]
- The risk of vaso-occlusive episodes is increased by exposure to cold, fever, and dehydration.
- Over 90% of hospital admissions for patients with sickle cell disease are for painful crises, but nearly all sickle pain is coped with in the community.
- Pain has been reported to occur on up to 30% of days with a loss of 10% of schooldays in children.
- Hydroxycarbamide can reduce the frequency of painful crises in sickle cell disease (unlicensed indication in the UK). \[^{16}\]

**Management:**

- Avoid exposure to cold, fever, dehydration and stress.
- Most episodes coped with at home respond to simple oral analgesia, increased fluid intake, warmth and rest.
- A simple analgesic ladder is appropriate, starting with paracetamol and/or ibuprofen. \[^{7}\]
- If necessary, use weak opioids (eg, codeine or dextropropoxyphene) for patients with mild pain. \[^{3}\]
- Always look for a cause - eg, infection. \[^{3}\]
- Admit patients if pain does not subside promptly, if there is a need for strong opioid treatment, or if fever, pallor or signs of respiratory compromise are noted. \[^{5}\]
- Benzodiazepines may be helpful to reduce anxiety. \[^{3}\]
Pregnancy

Pregnant women with sickle cell disease must be monitored by an obstetrician and a specialist in the disease working closely together. Fetuses are at increased risk of prematurity, low birth weight and death.

- Worsening anaemia, vaso-occlusive crises, and acute chest syndrome may occur during pregnancy. women with sickle cell disease should be considered for low-dose aspirin - 75 mg once daily - from 12 weeks of gestation in an effort to reduce the risk of developing pre-eclampsia.
- Women with sickle cell disease should be advised to receive prophylactic low molecular weight heparin during antenatal hospital admissions.
- Routine prophylactic transfusion is not recommended during pregnancy for women with sickle cell disease. If an acute exchange transfusion is required for the treatment of a sickle complication, it may be appropriate to continue the transfusion regimen for the remainder of the pregnancy.

General anaesthesia

- Patients with sickle cell disease are at high risk of perioperative complications, especially acute chest syndrome and pain.
- Pre-operative transfusion may decrease the risk of postoperative complications.

Travel advice

- Increased fluid intake, abstinence from alcohol, and physical movement during travel, including flights, are helpful.
- Appropriate antimalarial prophylaxis is essential for patients travelling to areas at risk of malaria.
- Emphasis on a bacteriologically clean drinking water supply. Patients should increase their oral fluid intake above the standard 3 L/day for adults when they are in hot climates, to compensate for the increased insensible losses.

Sickle cell disease is a good candidate for gene therapy because a normal phenotype can be restored in diseased cells with only a single normal copy of the mutant gene. However, there is currently no research evidence on which to make any practice recommendations on gene therapy for sickle cell disease.

Complications

- Sickle cell disease is very variable in its manifestations. The pattern of organ involvement alters with age.
- Chronic pain.
- Nocturnal enuresis.
- Infection: patients are prone to infection, especially pneumococcus, typhoid osteomyelitis and haemophilus because of hyposplenism resulting from sickling and consequent autosplenectomy.
- Stroke: clinical evidence of stroke occurs by age 20 years in 11% of patients with sickle cell disease.
- Priapism: males with sickle cell disease may experience painful erections, which may be brief but recurrent or may last six hours or more and can lead to impotence.
- Cardiac failure: left-sided heart disease occurs in about 13% of adults with sickle cell disease and is mainly caused by diastolic dysfunction, which is an independent risk factor for mortality.
- Chronic pulmonary disease usually develops in patients older than 30 years. Cor pulmonale may develop. Pulmonary hypertension occurs in about 30% of adults with sickle cell disease and is associated with high rates of leg ulcer, priapism, and renal dysfunction.
- Gallstones caused by chronic haemolytic anaemia.
- Eye: retinopathy, retinal infarcts, retinal haemorrhage and retinal detachment.
- Transfusion complications: alloimmunisation, exposure to possible infections, risk of iron overload and consequent organ damage.
- Chronic leg ulcers may become infected.
- Avascular necrosis is a frequent and severe complication of sickle cell disease. It often affects the femoral head and humeral head.
- Chronic organ damage: vaso-occlusion, hyperhaemolysis, and increased blood viscosity are major causes of chronic organ damage (osteonecrosis, liver failure, renal failure, leg ulcer, retinopathy), which is very variable in severity.
- Chronic kidney disease: causes a worsening anaemia and may require treatment with high doses of erythropoietin.
- Learning difficulties: Subtle, but important and widespread, neuropsychological defects result from sickle cell disease and may be present even in the absence of overt neurological complications.
- This damage is probably responsible for the decreased intellectual ability of about five points in IQ in patients with sickle cell disease compared with controls.
- This reduction indicates an increased risk for significant learning difficulties and the need for remedial education compared with their peers.

Prognosis

- Clinical severity and prognosis are very variable, ranging from survival into the 60s and 70s to a severe disease with substantial organ damage and early death.
- Median life expectancy is currently 40-60 years in high-income countries but much less in low-income areas.
- The most common cause of death in the first two years of life is infection, with or without splenic sequestration.
- In adults, common causes of death are cerebrovascular accidents, sepsis, acute chest syndrome and pulmonary hypertension.

Further reading & references
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