Sickle cell disease

Key facts

- Sickle cell disease (SCD) is an autosomal recessive genetic condition that describes a group of haemoglobin disorders caused by genetic variants in the *HBB* gene, resulting in the production of sickle haemoglobin (HbS) rather than normal haemoglobin A (HbA).
- Sickle cell anaemia (SCA) is the most common, and often the most severe, of the sickle cell diseases and occurs when both copies of the *HBB* gene have a sickle cell variant, with a variant inherited from each parent.
- SCA is characterised by episodes of pain, chronic haemolytic anaemia and severe infections, usually beginning in early childhood.
- Other forms of SCD occur where there is inheritance of sickle cell variant from one parent and another *HBB* gene variant from the other parent.
- Individuals with one normal *HBB* gene and one haemoglobin gene with a sickle variant are healthy 'carriers', (sometimes referred to as having 'sickle cell trait'). These individuals do not manifest symptoms of sickle cell disease.
- Sickle cell disease is common in people of African, Mediterranean, Middle Eastern, and Asian ancestry, and in people from the Caribbean and parts of Central and South America. The highest incidence worldwide is in West Africa, where 25% (one-in-four) of the population are carriers of the sickle gene variant.
- Being a carrier of the sickle gene variant grants some protection against falciparum malaria and, as such, there is an increased prevalence of people with sickle cell trait where falciparum malaria is endemic.

Clinical features

- SCD is characterised by episodes of pain due to venous occlusion by sickled red blood cells, termed a sickle cell crisis. These pain episodes can be mild, moderate or severe. Other complications exist due to chronic haemolytic anaemia, the susceptibility to severe infections, and both short and long term damage to tissues and organs.
- Red blood cells that contain large quantities of sickle haemoglobin cause the haemoglobin molecules to aggregate and form long stiff rods when deoxygenated. The cells assume a crescent shape when deoxygenated, become dehydrated, lose vital chemicals and become rigid and brittle; their shape makes it difficult for them to manoeuvre through narrow blood vessels causing them to periodically obstruct blood flow - this is known as a vaso-occlusive crisis, or a sickle cell crisis.
- Unlike healthy red blood cells which live for 120 days, the red blood cells of those with SCA live for between approximately 10 and 20 days - this is the main cause of the haemolytic anaemia associated with this condition. The red blood cells of those with other forms of SCD can live longer, and typically cause less episodes of vaso occlusion and other possible complications.
- Due to damage to the spleen from early childhood, those with SCD are immunosuppressed making them prone to frequent infections, which can be fatal, especially in childhood.
- Those with SCD are asymptomatic at birth due to high levels of fetal haemoglobin (HbF) which reduces gradually in the first year of life; symptoms usually begin after HbF levels have diminished and increasing levels of HbS are synthesised. Symptoms occur commonly from about six months of age in those with SCA,

although symptoms can present later in those with other forms of SCD.

- Sickle cell crisis can occur in any part of the body, but occurs most commonly in the bones, joints and abdomen. It can also cause complications in any organ, including the brain, which can cause a stroke, especially in children.
- Clinical manifestations are extremely variable depending on the severity of the condition inherited; other inherited factors may ameliorate or increase the severity of the disease.
- Clinical manifestations and complications of SCD are often unpredictable and can prove fatal, especially if there is no access to expert medical management or healthcare.
- SCD can be fatal at any stage throughout life, including in childhood.

Diagnosis

- The SCD diagnosis is established by demonstrating the presence of significant quantities of HbS by haemoglobin electrophoresis and other laboratory techniques.
- Antenatal screening is available throughout the UK, and screening for the sickle gene variant is part of the national antenatal and newborn screening programme.
- National newborn screening in the UK is comprehensive, and all newborn babies are offered testing for sickle cell disease as part of the 'heel prick' newborn blood spot screening programme.
- If a child has not been tested at birth, the condition is suspected with the presentation of features such as: painful swelling of the hands, feet or digits, pallor, jaundice, pneumococcal sepsis or meningitis, severe anaemia with splenic enlargement and/or pain in any part of the body without evidence of physical trauma.

Genetic basis

- SCD is an autosomal recessive condition, which means that the affected individual has two altered copies of the *HBB* gene. In the majority of cases, both of their parents have one altered copy of the *HBB* gene and one normal copy. These individuals are said to be carriers (this is sometimes referred to as having 'sickle cell trait'). If a couple are both carriers of the sickle variant, each time they are expecting a child there is a 25% (one-in-four) chance that their child will inherit sickle cell anaemia.
- Individuals with a sickle cell variant in one copy of the *HBB* gene and a different *HBB* gene variant in the other copy also have a form of sickle cell disease. These forms are often less clinically severe, but in some cases can be as severe as SCA with a high risk of fatality.
- Examples of other forms of SCD include haemoglobin C disease (when a haemoglobin C variant is inherited with a sickle cell variant), and sickle beta thalassaemia disease (when a beta-thalassaemia variant is inherited with a sickle variant).

Genetic testing

- Genetic testing can be used to offer prenatal and pre-implantation genetic diagnosis:
  - » Prenatal diagnosis is usually possible by chorionic villus sampling (CVS) or amniocentesis. If a couple are considering prenatal diagnosis, referral should be made to the local clinical genetic or specialist haemoglobinopathy service, ideally prior to conception or as early as possible in pregnancy. This ensures that appropriate advice and investigations are undertaken to confirm whether an individual or couple are at risk of having a child with a clinically significant disease state.
  - » All couples considering pre-implantation genetic diagnosis must be referred to their local clinical genetics service.

- Genetic testing is available across the UK and referral can be arranged by the GP, specialist haemoglobinopathy centre or via regional genetic centres.

Clinical management

- Early diagnosis, parental education and commencement of prophylactic treatment is key for effective management of SCD.
- In accordance with national newborn sickle cell standards, when a child is diagnosed with SCD in the national newborn screening programme:
  - the child's parents must be notified of the result by four weeks of child's age;
  - the child must commence prophylactic penicillin by 12 weeks of age;
  - the child must be referred to a paediatrician for care by eight weeks of age; and
  - the child must be seen in an outpatient clinic by 12 weeks of age.
- Multidisciplinary management should aim to prevent and treat infections and any presenting symptoms, including adequate and effective pain relief (NICE guidelines state that pain relief should be given within 30 minutes of presentation).
- The mainstay of primary prevention is to avoid dehydration, infection, extremes of temperature, overt physical exertion, environments with low oxygen tension and acidosis.
- Regular monitoring in an outpatient clinic will ensure early identification of possible complications and the opportunity for prevention or treatment, to minimise the long term effects of any identified complication.
- Management must include social- and psycho-educational support, as these aspects can have as much impact on the affected individual and their family as the physical aspects of living with the disease.

Direction to further reading, guidelines and patient groups

For detailed and comprehensive guidance in management of sickle cell disease, see:

- Sickle cell disease in childhood: standards and recommendations for clinical care (2019)
- Standards for the clinical care of adults with sickle cell disease in the UK (2018)
- Information on screening programmes
- **Sickle Cell Society**
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  Harlesden
  London NW10 4UA
  Tel: 020 8961 7795
  Email: info@sicklecellsociety.org
  Website: www.sicklecellsociety.org
- **United Kingdom Thalassaemia Society**
  19 The Broadway
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This information is intended for educational use and was current in March 2020. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and Brent Sickle Cell & Thalassaemia Centre, London North West University Healthcare NHS Trust.