The clinical care of adult patients with sickle cell disease

Sickle cell disease is the most common inherited disease in the UK and is associated with significant morbidity and mortality. All health professionals should be aware of the common acute and chronic complications of sickle cell disease and the basic principles of their management.

Sickle cell disease is the most common inherited blood disorder worldwide, with an estimated yearly birth rate of affected infants of 300 000–500 000 (Weatherall and Clegg, 2001). It is the most common genetic disease in the UK, and an understanding of the management of its acute and chronic complications is therefore essential for all doctors. Historically its distribution across the UK has been very patchy with the majority of cases being found in big cities, such as London, Birmingham and Manchester. With increased migration and ethnic diversity across the UK, sickle cell disease is now becoming more common, even in previous low incidence areas, and it is in these areas that expertise is often lacking.

Sickle cell disease is part of the neonatal screening programme in England and Wales, and all newborn babies are screened for sickle cell disease via the Guthrie test by the 10th day of life, enabling those affected to be enrolled into comprehensive medical services. This simple exercise has the ability to prevent death from acute complications attributable to the condition.

The *Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK* (Sickle Cell Society, 2008) is a comprehensive document, which aims for the first time to outline minimum standards of care in the UK. It reflects concerns of patients and medical professionals that there is an inequity in care provision across the UK, in part as a result of the unique geographical distribution of sickle cell disease. It is recognized that there are many centres in the UK offering excellent care to patients with sickle cell disease while services are non-existent in other areas. Even those which are strong in some aspects of sickle care may need additional support or training in other aspects.

Mechanisms of disease

Sickle cell disease is inherited as an autosomal recessive condition and refers to patients who are homozygous for sickle haemoglobin (HbSS) or who are compound heterozygotes for sickle haemoglobin and another clinically significant abnormal haemoglobin, e.g. haemoglobin C (HbSC) or beta thalassaemia (HbSBthalassaemia).

Central to the pathophysiology of the sickling disorders is the abnormal polymerization of de-oxygenated haemoglobin S, which distorts the red cell shape to form inflexible misshapen red cells leading to occlusion within the microcirculation and deprivation of blood flow to the supplied organ. Abnormal adherence of white cells, young red cells (reticulocytes) and platelets to activated endothelium and coagulation abnormalities all contribute to tissue ischaemia with consequent organ damage.

Acute pain

By far the most common manifestation of tissue ischaemia is the painful vaso-occlusive crisis as a result of infarction within the bone marrow cavity. Vaso-occlusive crisis accounts for 90% of hospital attendances for the management of pain. The intensity of pain is variable within the individual and between individual patients even with the same genetic composition. Mild to moderate pain is managed by paracetamol, non-steroidal anti-inflammatory drugs and weak opioids. Strong opioids are indicated for severe episodes. Pethidine is no longer recommended because of its association with fits in large doses. Morphine and diamorphine are preferred and a good knowledge of their pharmacokinetic and pharmacodynamics is to be encouraged by prescribing physicians. No clinical trials have been conducted to date with the newer opioids such as oxycodone or fentanyl. When opioids are used diligently and appropriately, the risk of addiction is very low.

Sickle-related pain is often badly managed in part as a result of poor knowledge by health-care providers, and service user involvement in drawing up individual pain protocols is key. Various national and local guidelines exist on the medical management of painful crises (Rees et al, 2003). An aggressive, dignifying pain management strategy at the outset leads to early discharge and a satisfied, well-adjusted patient. Patients should receive the first dose of potent analgesia within the first 30 minutes of triage in hospital and the pain should be controlled by 2 hours. Continuous evaluation of vital signs and assess-

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ment of pain must be undertaken regularly by trained staff and recorded. If complications are recognized, early, prompt treatment is needed.

Considerable debate exists over which setting an acute painful episode should be managed in. In a centre that serves a large population, a day hospital may be suitable for management of an uncomplicated painful crisis. Complicated cases (*Table 1*) should be managed within a hospital accident and emergency department where a multidisciplinary approach is accessible. Discharge summaries with medication history should be dispatched to GPs within 10 days of the patient leaving hospital.

Acute complications

Infections are common in patients with sickle cell disease partly as a result of abnormal splenic function. Encapsulated organisms such as pneumococci and meningococci are mainly responsible, but atypical organisms such as chlamydia also cause morbidity.

Patients, their carers and admitting staff should be taught how to recognize acute chest syndrome which is the leading cause of death in adult cases and may occur around an admission for painful crisis. It is characterized by fever, difficulty with breathing, chest pain, cough and an abnormal chest X-ray. Antibiotics, oxygen therapy and timely exchange transfusion may be life saving. Any patient suspected of having acute chest syndrome should be discussed with a senior haematologist as a matter of urgency.

Most individuals with sickle cell disease have a well-compensated lifelong steady state anaemia, which does not require blood transfusion. Significant lowering of haemoglobin with absent reticulocytes may occur as a result of parvovirus B19 infection causing transient red cell aplasia. Although systemic symptoms may accompany the aplasia, the complication is self limiting and blood transfusion is indicated for severe anaemia to maintain circulatory volume and oxygen carriage.

Drugs that cause renal toxicity should be avoided and prolonged administration of non-steroidal analgesia for pain is not recommended. The risks of priapism (persistent, painful erection) should be discussed with young men as they enter puberty, and on transition to adult services, so that they recognize stuttering priapism, a prelude to impotence, as pathological and seek urgent medical attention. Acute priapism (<4 hours onset is critical) should be managed by intracorporeal penile aspiration and instillation of α-adrenergic agents by competent urologists. This procedure can be carried out repeatedly while maintaining potency in young men (Mantadakis et al, 2000).

Table 1. Episodes to be managed in a hospital setting

Chest pain and/or breathing difficulties
Signs of dehydration
Atypical pain unlike previous episodes
Significant pyrexia or focus of infection
Associated priapism
Neurological deficit
Repeat painful episodes within 48 hours (revolving door pain)

Chronic complications

Sickle cell disease is associated with many chronic complications, which are becoming increasingly evident as the survival of people with sickle cell disease improves (*Table 2*). Regular outpatient appointment follow up in a specialist haemoglobinopathy or sickle cell clinic should be offered to all adult patients and at these appointments patients should be screened for the development of complications and treatment offered as necessary. Screening should include history and examination, oxygen saturation, blood pressure, urine dipstick testing and echocardiography. Joint clinical management between the haematology team and the relevant specialist team should be instituted if appropriate.

Neurology

Stroke is a common complication of sickle cell disease both in adults and in children. Acute stroke should be treated with urgent exchange transfusion, computed tomography (CT) and/or magnetic resonance imaging (MRI) scan and senior haematology and neurology input. These patients have a 50–92% risk of recurrent stroke (Pegelow et al, 1995) and should be offered long-term regular blood transfusion for secondary stroke prevention. Primary stroke prevention is recommended in the paediatric population, and children who have transcranial Doppler velocities of over 200 cm/second should be offered long-term blood transfusion therapy, which should continue indefinitely (Adams et al, 1998; Adams and Brambilla, 2005). Iron overload is a complication of frequent blood transfusion and should be avoided by serial serum ferritin estimation. Raised transcranial

Table 2. Chronic complications of sickle cell disease

Organ system	Description
Musculoskeletal	Chronic sickle pain, avascular necrosis of the long bones
Genitourinary	Haematuria, priapism, erectile dysfunction
Skin and integuments	Chronic leg ulcers
Ophthalmology	Sickle eye disease
Respiratory	Pulmonary hypertension and heart failure
Cardiology	Cardiac disease and heart failure
Neurology	Adult stroke
Renal	Chronic renal failure

From Weatherall and Clegg (2001)

Doppler velocities have not been demonstrated in adults, and there is no current indication for routine transcranial Doppler screening in adults.

Pulmonary and cardiac disease

Pulmonary hypertension has been described in 5–30% of people with sickle cell disease and is associated with a high mortality (Gladwin et al, 2004). Pulmonary hypertension is diagnosed by the presence of a raised mean pulmonary artery pressure of over 25 mmHg at cardiac catheterization. Doppler echocardiography has been shown to be of value as a non-invasive screening test, with a raised tricuspid regurgitant jet velocity of >2.5 ms correlating with a raised mean pulmonary artery pressure on catheterization. Pulmonary hypertension is often asymptomatic, and treatment may be difficult once symptoms appear so echocardiography screening on an annual or biannual basis is recommended.

Patients with a high risk of pulmonary hypertension on echocardiography (tricuspid regurgitant jet >3 ms) or who have an intermediate risk of pulmonary hypertension (tricuspid regurgitant jet 2.5–3.0 ms) and are symptomatic should be referred to the local pulmonary hypertension specialist service for further investigation and management. Cardiac catheterization is mandatory before treatment as echocardiography has a high false positive rate.

For chronic sickle lung disease, which causes considerable morbidity, patients should be screened with regular oxygen saturations and further investigation with respiratory function tests, overnight oximetry and CT chest scans may be necessary. All patients should be offered advice on smoking cessation, vaccinations and obtaining rapid treatment for chest infections.

Renal disease

End-stage renal disease is one of the most devastating complications of sickle cell disease and while not common is associated with a high mortality and morbidity. Proteinuria is easy to monitor in the outpatient setting, using a urinary dipstick test and if abnormal confirmatory testing with a 24-hour urinary protein estimation or the equivalent (e.g. protein:creatinine ratio or albumin: creatinine ratio) should be performed. Angiotensin-converting enzyme inhibitors or the equivalent should be considered in patients with persistent proteinuria as they have been shown to decrease the progression of proteinuria in sickle cell disease. Blood pressure and creatinine should also be measured regularly, and strict blood pressure control is important, aiming for a blood pressure of 140/90 mmHg or of 130/80 mmHg in patients with proteinuria.

Other chronic complications

Many of the other chronic complications can be identified through good history taking and examination in the context of the specialist clinic. Patients should have rapid access pathways in place for presentations suggestive of chronic complications. This should be reinforced by the use of patient education leaflets, such as risk of retinal haemorrhaging if visual symptoms develop as an emergency.

Maternity services

Partner screening is recommended pre-conceptually to allow a couple at high risk of having a baby with a major haemoglobinopathy to be counselled before or at an early stage of pregnancy. Pregnancy in women with sickle cell disease has been associated with a significant maternal and fetal morbidity and mortality. Women should be referred for early booking to an obstetrician with an interest in sickle cell disease, if possible. Women will need increased monitoring throughout pregnancy for poor fetal growth and maternal signs of pre-eclampsia, both of which are more common in sickle pregnancies.

Hydroxycarbamide therapy

Hydroxycarbamide (hydroxyurea) has been shown to reduce the frequency of painful episodes, incidence of acute chest syndrome and transfusion requirements in patients with sickle cell disease (Charache et al, 1995). It is indicated in patients with moderate to severe sickle cell disease (more than three painful vaso-occlusive crises a year) but should only be instigated by a haematologist with expertise in this field. Hydroxycarbamide can cause myelosuppression, and regular blood monitoring is essential for all patients taking this drug.

Perioperative care

Patients with sickle cell disease are at increased risk of complications in the perioperative and postoperative periods, so it is vital that patients with sickle cell disease are identified before surgery, ideally before the pre-assessment visit. Key issues are the maintenance of hydration, keeping the patient warm in theatre, careful monitoring of oxygen saturations and adequate postoperative analgesia. Blood transfusion is not necessarily indicated in patients with few sickle complications undergoing low or moderate risk surgery, but individual cases should be discussed with a haematologist.

Conclusions

The UK is ethnically diverse and disorders that were once thought to be rare are now seen increasingly in hospitals throughout the country. These have a significant impact on the health-care system. The improvement in the life expectancy of patients with sickle cell disease from just over a decade in the 1970s to adulthood now has been brought about mainly by improvements in basic care as opposed to ground-breaking science. Newborn screening, vaccination strategies and penicillin prophylaxis, prompt treatment of infections with newer antibiotics, better use of blood transfusion, hydroxycar-

bamide therapy, screening for organ-related damage and disability management where appropriate have all helped to ensure a sizeable patient population. The adult standards represent another significant milestone towards the improved longevity and equity of care in the lives of affected individuals. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The *Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK* were published in 2008 and outline minimum standards of care for patients with sickle cell disease.
- Acute pain is the most common manifestation of sickle cell disease and every hospital should be able to provide prompt and effective pain assessment and pain relief.
- Regular outpatient appointments in a specialist sickle cell or haemoglobinopathy clinic should be available for all patients with sickle cell disease to offer them regular screening for and treatment of the chronic complications of sickle cell disease.
- The management of pregnancy and perioperative care requires close liaison between haematologists and obstetricians, surgeons and anaesthetists.