Management of sickle cell disease

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About 250 000 children are born with sickle cell disease every year. Although most people with the disease live in Africa, where the sickle mutation appeared several thousand years ago,[1] sickle cell disease has become common in the United States and Europe since the migration of African people. About 60 000 people in the United States and 10 000 in the United Kingdom have the disease.[2] In our increasingly multiethnic world, a patient with sickle cell disease can present to almost any doctor. As well as specialist services, these patients need help from their general practitioners to cope with everyday life.

Clinical severity of the disease has extreme phenotypic variability across patients: 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. Interaction of environmental factors with genetic polymorphisms is the most likely explanation of this variability.[3] Sickle cell disease can undermine the quality of life of both patients and carers.[4,5] Improvements in the management of the disease have greatly reduced mortality in affected children followed up since neonatal screening.

What is sickle cell disease and how does it manifest?

Sickle cell disease is a genetic disorder of haemoglobin that is transmitted on an autosomal recessive basis. Homozygosity for the HbS allele (homozygous sickle disease (haemoglobin SS disease)) is the most common finding, but some patients are heterozygous for HbS and for another haemoglobin mutation such as HbC (haemoglobin SC disease) or β thalassaemia ($S\beta^0$ and $S\beta^+$ diseases), with the exact proportion of these genotypes varying across countries. SS disease and $S\beta^0$ disease are more severe than SC disease and $S\beta^+$ disease.[6]

The abnormal haemoglobin (haemoglobin S), polymerises when deoxygenated, which distorts the red cells into a sickle shape. The blood film may show sickled red cells. Haemoglobin electrophoresis identifies variant haemoglobins, possibly combined.

Sickle cells have a reduced deformability and are easily destroyed. Chronic haemolytic anaemia is a prominent manifestation of sickle cell disease. The median haemoglobin concentration level was 9.1 (SD 1.8 g/dl (18 g/l) in the cohort of 3380 patients enrolled in the cooperative study of sickle cell disease.[3] The intensity of haemolysis is greater in the SS and $S\beta^0$ genotypes.[6] In addition to HbS polymerisation, key pathophysiological features of the disease include adhesion of young red cells to the venular endothelium; chronic inflammation; ischaemia reperfusion injury, leading to endothelial damage; and dysregulated nitric oxide homoeostasis.[6] Blood vessel occlusion reduces the delivery of oxygen to tissues. Clinical expression of sickle cell disease is highly heterogeneous, ranging from a mild phenotype with survival into the 60s and 70s to a severe disease with substantial organ damage and early death.[7] The table presents the frequency of severe complications.[8]

Pain from vaso-occlusive crises

Pain is the hallmark of sickle cell disease. Dactylitis is a common early manifestation that may occur before age 6 months, and acute painful episodes account for more than 90% of hospital admissions among adults with sickle cell disease.[9] The frequency and severity of painful episodes vary widely both across patients and over time in each patient. Exposure to cold, fever, and dehydration shortens the time needed for haemoglobin S to polymerise and increases the risk of vaso-occlusive episodes.

Infection

Patients with sickle cell disease are particularly susceptible to infections by encapsulated bacteria such as pneumococcus, in part because recurrent splenic infarction decreases the ability of the spleen to clear circulating antigens. The risk of overwhelming infection is highest before age 3 years.[2]

Acute chest syndrome

Acute chest syndrome has been 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, infarcts in adults. Pulmonary fat embolism could be associated in some cases.[10]

Management of acute pain in patients with sickle cell disease

- Assess pain intensity
- Always look for a cause—for example, infection
- Choose the analgesic, dosage, and route of administration
- Admit patients with any of the following: pain that does not subside promptly; a need for opioid treatment; fever, pallor, or signs of respiratory compromise; a low likelihood of receiving appropriate care at home
- Be empathetic, reassuring, and supportive. Benzodiazepines may be helpful to reduce anxiety
- Re-examine the patient often to ensure adequate pain relief, to assess sedation and respiratory rate (to avoid opioid overdose), and to search for evidence of any complications such as acute chest syndrome or anaemia

Anaemia

The most common causes of anaemia are acute splenic sequestration, transient red cell aplasia, and hyperhaemolysis in patients with severe infection.[8]

Stroke

Clinical evidence of stroke occurs by age 20 years in 11% of patients with sickle cell disease, and the incidence of stroke is 1.02% a year between age 2 and 5 years.[11]

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.[6]

Pulmonary hypertension

Pulmonary hypertension occurs in about 30% of adults with sickle cell disease and strongly predicts near-term death (rate ratio, 10.1; 95% confidence interval 2.2 to 47.0; $P<0.001$).[12] Pulmonary hypertension is associated with a haemolytic phenotype (low haemoglobin and raised lactate dehydrogenase levels) and high rates of leg ulcer, priapism, and renal dysfunction.[6]

Chronic organ damage

Vaso-occlusion, hyperhaemolysis, and increased blood viscosity are major determinants of chronic organ damage (osteonecrosis, renal failure, leg ulcer, retinopathy), which varies widely in severity among patients.[6]

How is sickle cell disease diagnosed?

In western Europe and the United States, sickle cell disease is diagnosed by neonatal screening. Screening using cord blood or the heel prick test is universal at birth in Brussels, the United Kingdom, and the United States, and in France it is targeted at babies originating from populations with a high frequency of the mutated gene. In Africa, although several countries are developing neonatal screening, the disease is usually diagnosed if a complication arises (chiefly vaso-occlusive crisis, infection, and acute anaemia).

The results of positive neonatal screening tests should be explained to the parents by doctors who have experience with sickle cell disease, and families should be referred to multidisciplinary sickle cell disease clinics.[13]

Sickle cell disease can also be diagnosed in a fetus through prenatal diagnosis following genetic counselling. Prenatal diagnosis may be offered to at-risk couples.

How does screening improve outcomes?

Neonatal screening enables parents to be educated about preventing complications and recognising the early signs of life threatening events such as fulminant infection and acute splenic sequestration. Parents are taught to recognise fever and pallor and, if possible, to feel the spleen for evidence of sudden enlargement indicating splenic sequestration and consequently a need for immediate hospital attendance for blood transfusion. Screening allows for starting prophylactic antibiotic treatment early. Observational studies have established that neonatal screening leads to major decreases in morbidity and mortality.[14,15] Randomised trials would therefore be unethical.[14]

How can complications be prevented and treated?

Prevention of overwhelming infections

A randomised trial established that routine daily penicillin prophylaxis in children younger than 5 years significantly decreased the risk of pneumococcal disease (odds ratio 0.37; 95% confidence interval 0.16 to 0.86) and adverse drug effects were uncommon and minor.[2] Penicillin is therefore recommended twice daily starting at 2 months of age, but further research is needed to determine the age at which penicillin prophylaxis can be stopped safely.[2]

Given the risk of poor adherence to daily prophylaxis and the development of penicillin resistant *Streptococcus pneumoniae* strains, pneumococcal immunisation as well as prophylactic penicillin is recommended.[16] In observational studies, rates of invasive pneumococcal disease declined among patients younger than 18 years given the 23-valent polysaccharide vaccine.[17] In non-controlled studies, the 7-valent conjugate vaccine decreased the rate of pneumococcal infections in patients younger than 5 years[18] or 10 years.[19] The recommended immunisation schedule for previously unvaccinated children with sickle cell disease consists of three doses of conjugated vaccine six to eight weeks apart, followed by a booster dose one year later, then by a

Frequency of complications in patients with sickle cell disease[8]

Complication	Prevalence (%)
Meningitis-septicaemia	11.4
Osteomyelitis	12
Acute chest syndrome	44.8
Stroke	6.7
Repeated (>1) vaso-occlusive crises	58
Acute aplastic anaemia	46
Acute splenic sequestration	26

METHODS BOX

I searched the Cochrane Database of Systematic Reviews for "sickle cell disease". I reviewed the publication by the National Institutes of Health about the management of sickle cell disease. Finally, I also used my personal reference library, giving preference to randomised trials.

polysaccharide vaccine after age 2 years, with additional doses every three to five years. Experts agree that regular immunisation with the 23-valent vaccine is appropriate in adults, but large, well conducted studies are needed to determine the optimal schedule for administering polysaccharide and conjugate vaccine. Given the risk of pulmonary complications, yearly influenza vaccination is recommended.

Stroke prevention

Primary stroke prevention in children

Children with a cerebral blood flow rate of 200 cm per second or more on transcranial Doppler ultrasonography have a 40% risk of stroke within three years.[20] A randomised trial (STOP 1) compared regular blood transfusions with standard care in 130 children with abnormal results for transcranial Doppler ultrasonography; the study was stopped prematurely, however, when an interim analysis showed a 92% reduction in the incidence of stroke in the transfused group.[21] A subsequent randomised trial (STOP 2) was conducted in children receiving transfusions for a high risk of stroke for 30 months or longer, during which time the results on transcranial Doppler ultrasonography became normal. The transfusions were continued in one arm and stopped in the other. Stopping the transfusions was followed by a high rate of stroke or reversion to abnormal velocities of cerebral blood flow.[22] These well designed studies led to the recommendation that transcranial Doppler ultrasonography be performed annually in children aged 2-16 years with sickle cell disease and that regular blood transfusions should be strongly considered in those with abnormal findings on transcranial Doppler ultrasonography.[23]

Secondary stroke prevention

Experts agree that exchange transfusion should be performed when a stroke occurs. More than half of patients with a first stroke have another. Long term observational studies showed that monthly blood transfusions decreased the risk of recurrent stroke, although transient neurological events were not completely stopped.[24] The target percentage of haemoglobin S in patients receiving regular blood transfusions varied across studies from 30% to 50%, and the optimal target remains to be determined. Stroke is considered an indication for bone marrow transplantation in children and adolescents who have siblings with identical HLA.[23]

TIPS FOR NON-SPECIALISTS

- Expression of sickle cell disease is highly variable, ranging from mild phenotype and clinically unapparent disease (mostly in SC and $S\beta^+$ genotypes) to severe disease (mostly in SS and $S\beta^0$ genotypes)
- Enrolment of patients in comprehensive care programmes has greatly improved the prognosis of sickle cell disease
- Acute pain, fever, and acute anaemia may be life threatening, and any of these requires an immediate visit to an emergency department
- Specific situations such as general anaesthesia and pregnancy often require blood transfusions

Painful crises

Pain management

Effective treatment of acute pain is one of the most common and challenging problems raised by the management of sickle cell disease (see box on pain management).

Few controlled trials are available, perhaps because of the considerable inter-patient and intra-patient variability in pain severity and the subjective nature of pain assessment.[25] Experts generally agree that paracetamol and hyperhydration are appropriate. A randomised comparison of oral, sustained release morphine with intravenous morphine infusion in children and young adults showed no benefit from intravenous administration.[26] Most studies, however, recommend intravenous administration for severe pain, using either a continuous infusion or patient-controlled analgesia.[23,27] Regardless of the route of administration, the dosage should be titrated to achieve pain relief, particularly as the analgesic effect varies widely across patients.

Pain prevention

Carers and patients can be taught to avoid exposure to cold, fever, dehydration, and stress; to manage mild pain with rest, hydration, and weak opioids (such as codeine or dextropropoxyphene); and to recognise the signs that require an immediate visit to the emergency department.

Two randomised studies assessed the efficacy of hydroxycarbamide in preventing recurrences of painful crises in adults and children with severe sickle cell disease. Hydroxycarbamide acts at least in part by reactivating the synthesis of fetal haemoglobin, which inhibits the polymerisation of haemoglobin S. In a US multicentre study of hydroxycarbamide in adults with sickle cell disease, hydroxycarbamide treatment was associated with decreases in painful crises, acute chest syndrome, and the need for transfusion.[28] In a paediatric study, hydroxycarbamide treatment decreased the number of hospital admissions and days spent in hospital.[29] Uncontrolled long term studies showed that hydroxycarbamide treatment was associated with a 40% reduction in mortality in adults[30] and suggested an acceptable safety profile, most notably in children.[31]

Hydroxycarbamide is currently licensed for use in the United States in adults with recurrent moderate to severe painful crises (at least three episodes over 12 months) and in Europe in adults and children with recurrent vaso-occlusive events. Patients who are unwilling to take hydroxycarbamide or who fail to respond to the drug can be treated with periodic transfusions, whose efficacy in preventing recurrent pain was established by the randomised STOP 1 study (9.7 pain events per 100 patient years in transfused patients versus 27.1 in non-transfused patients, P=0.014).[32]

QUESTIONS FOR FUTURE RESEARCH

- Why is the clinical picture of sickle cell disease so different from patient to patient?
- What is the evidence for safety and efficacy of different therapeutic options (transfusion, hydroxycarbamide, and bone marrow transplantation) for patients with acute chest syndrome, cerebrovascular accident, or severe organ damage?
- Can patients who will have severe complications be identified early on, and does intensification of treatment then prevent the development of irreversible vascular and organ damage?
- Are anti-inflammatory drugs useful in sickle cell disease, and if so which ones?
- How can vascular endothelium dysfunction be prevented and treated?

Treatment of acute chest syndrome

Antibiotics are given routinely, and the high rate of atypical micro-organisms requires combination of a macrolide with intravenous cephalosporin.[23] In a randomised trial, incentive spirometry prevented atelectasis and infiltrates associated with acute chest syndrome in children and young adults admitted with chest or back pain above the diaphragm.[33] Transfusion or exchange transfusion produced improvements in several uncontrolled studies. Available data are not sufficient to support the use of inhaled nitric oxide to treat acute chest syndrome.

Hydroxycarbamide decreased the rate of acute chest syndrome in the multicentre study of hydroxycarbamide cited above[28] (25 episodes in the hydroxycarbamide group versus 51 in the placebo group, $P<0.001$). Periodic transfusion is also effective in preventing recurrences (2.2 episodes per 100 patient years in the transfused group versus 15.7 in the non-transfused group, $P=0.0001$).[32]

Treatment of pulmonary hypertension

There is no proved treatment. Regular blood transfusions or long term anticoagulation are often suggested.[23] Prostacycline analogues, endothelin-1 receptor antagonists, phosphodiesterase inhibitors (including sildenafil), and calcium channel blockers are being evaluated as treatments for pulmonary hypertension in sickle cell disease.

Treatment of priapism

Priapism is an emergency requiring intravenous hydration and analgesia. Although α adrenergic agonists (etilefrine or phenylephrine) are often used,[23] they have not been evaluated in controlled studies. When these drugs are not effective promptly, penile aspiration and irrigation with saline and α adrenergic agents may be performed, together with an exchange transfusion. When this fails, shunting may be considered.[23] No controlled studies of treatments aimed at preventing recurrent priapism are available.[34]

What are the risks of general anaesthesia for surgery?

The complications of sickle cell disease often require surgical procedures such as cholecystectomy, hip replacement, and splenectomy. However, patients with the disease are at high risk of perioperative complications, chiefly acute chest syndrome and pain, which are probably related to hypoxia, hypoventilation, and hypothermia.

The cooperative study of sickle cell disease in the United States found that overall mortality was 1.1% within 30 days of surgery and stated that preoperative transfusion may decrease the risk of postoperative complications.[35] In a multicentre randomised study comparing simple transfusion with exchange transfusion, both given preoperatively, no differences in perioperative complication rates were found.[36] Importantly, the preoperative haemoglobin concentrations were nearly identical in the two groups, and the haemoglobin rise resulting from transfusion, together with the attendant increase in blood viscosity, might have contributed to the lack of difference between the two arms.

What are the risks in pregnancy?

Worsening anaemia, vaso-occlusive crises, and acute chest syndrome may occur during pregnancy. Fetuses are at increased risk of prematurity, low birth weight, or even death.[37] Pregnant women with sickle cell disease must be monitored by an obstetrician and a specialist in the disease working closely together. Although controversial, prophylactic transfusion aiming to maintain a haemoglobin concentration above 90 g/l is recommended by most specialists for women with a history of severe clinical manifestations of sickle cell disease.[23]

Conclusion

Doctors must ensure that neonatal screening, daily penicillin prophylaxis, immunisation, and

ADDITIONAL EDUCATIONAL RESOURCES

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SUMMARY POINTS

Care for patients with sickle cell disease requires a network of doctors

Patients with sickle cell disease should receive annual follow-up investigations, such as blood counts, hepatic and renal tests, transcranial Doppler ultrasonography for children, heart and liver ultrasonography

Immunisation is needed for pneumococcus, *Haemophilus influenzae* type B, meningococcus, and influenza virus

The most frequent complications are painful crises, acute anaemia, and infections

Patients sometimes need admission to intensive care, in particular for treatment of refractory pain and for exchange transfusion

Patients and their families need education and support

Genetic counselling and prenatal diagnosis may be offered to at-risk couples

hydroxycarbamide treatment (when required) are available to all patients with sickle cell disease. Some patients with sickle cell disease require treatments such as regular blood transfusions and bone marrow transplantation, which are often unaffordable. We must help Africans to obtain access to these lifesaving treatments, by developing close ties between physicians in Africa and those in the industrialised world.

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