Personal practice

Practical management of sickle cell disease

J P M EVANS

Department of Haematology and Oncology, Hospital for Sick Children, London

Sickle cell disease is a common problem in several inner city populations in this country, but the overall incidence is low. It has been estimated that 5000 people in the United Kingdom have the disease, at least 2000 of these living in London alone.¹ Sickle haemoglobin results from a single amino acid substitution in the β globin chain. The disease is inherited and the important sickling syndromes are homozygous sickle cell disease (Hb SS) and the double heterozygotes, haemoglobin SC disease (Hb SC) and sickle β thalassaemia. Hb SC disease and sickle thalassaemia tend to be milder than Hb SS. There is tremendous variability in the severity of sickle cell disease within all these groups. Some patients are plagued by constant hospital admissions with painful crises and subsequent progressive organ damage; other patients are comparatively symptom free and may not be diagnosed until late in life. Persistently high concentrations of fetal haemoglobin are commonly associated with milder disease and the coincident inheritance of α thalassaemia may also mitigate against severe disease. In most patients, however, the factors responsible for severity are not understood, and the disease course may be hard to predict. This has important implications for genetic counselling and community education programmes.

There are no accurate mortality figures for sickle cell disease in this country, but mortality in an American urban population was of the order of 10% in the first decade of life.² A Jamaican study showed that the highest mortality was during the first five years of life—10% of cases die in the first year, 5% in the second, and 3% in the third.³ It is clear that paediatricians carry the burden of responsibility for ensuring survival of patients with sickle cell disease.

Newborn babies with sickle cell disease have normal blood counts because of normal fetal haemoglobin production and sickle cell disease does not usually present clinically until after the first six months of life when fetal haemoglobin has declined towards adult concentrations. The diagnosis can,

however, be made at birth if sensitive haemoglobin electrophoresis techniques are used.⁴ Because of the high early mortality from potentially preventable or treatable complications it is essential to diagnose patients early. In areas where there is a large population at risk the best method is probably by screening the cord blood of all neonates. In areas with a lower incidence of heterozygote carriers, selective screening of children born to heterozygote mothers may be more appropriate; it is important that the approach is tailored to suit the local population. Once a child is diagnosed as having sickle cell disease, he or she needs a comprehensive programme of care and should be reviewed regularly at a haemoglobinopathy clinic. The diagnosis should be confirmed by repeat testing at three to six months.

Infection

Patients with sickle cell disease are more susceptible to infection than normal subjects, because of hyposplenism, defective opsonisation mechanisms, and other ill defined factors. The organisms to which patients with sickle cell disease are particularly prone include pneumococcus, *Haemophilus influenzae*, and *Salmonella* spp. The risk of infection by pneumococcus is at least 600 times that in the normal population, and the period of greatest risk is within the first three years of life when it is the main cause of death. Continuous prophylactic penicillin in infants aged from 3–36 months results in an 80% reduction in the infection rate, and needs to be started by the age of 4 months and continued at least until adult life.⁵ The role of antipneumococcal vaccine in preventing infection is less clear. There is evidence of both a serological response and efficacy in children with sickle cell disease over the age of 2 years, and giving the vaccine at this age may well provide additional protection.⁶ The role of the vaccine in children with sickle cell disease less than 2 years of age remains to be defined. Parents should

be educated about the risk of infection, and urged to bring children with sickle cell disease who have a fever or who are unwell to hospital for urgent assessment. These young children should be given broad spectrum antibiotics intravenously (including penicillin) without waiting for results of culture. It is always important to look for the source (blood, lungs, bones, meninges, urinary tract) and to treat the infection appropriately. Routine childhood immunisations should be given as usual.

Splenic sequestration

This is the other major cause of mortality in the early years, and may be precipitated by infection. It is characterised by the sudden onset of pallor, breathlessness, abdominal pain, and splenic enlargement. Rapid sequestration of red cells in the spleen leads to sudden anaemia and death. Blood needs to be given without delay and occasionally this may have to be uncrossmatched O negative red cells. It is important to give broad spectrum antibiotics intravenously to cover the pneumococcus and *H influenzae*. Splenic sequestration crises often recur and it is usual to carry out elective splenectomy after the child has recovered from an episode. In children under the age of 2, however, prophylactic red cell transfusion to maintain the level of haemoglobin S below about 30% prevents recurrence and allows a delay in splenectomy until the age of 2 when the risk of postsplenectomy septicaemia becomes less. Parents of young children with sickle cell disease should be warned of the risk of splenic sequestration and taught to look for splenomegaly should the infants become unwell.

Acute painful crisis

This results from vaso-occlusive episodes and may be provoked by infection or dehydration. Pain occurs in any part of the body but is most frequently seen in the bones, muscles, and abdomen. Young children suffer the 'hand-foot' syndrome characterised by infarcts of the metatarsals and metacarpals and painful swelling of the hands and feet. Crises are often painful and debilitating. There is no specific curative treatment but the child should be given fluid replacement, pain relief, and antibiotics.

Many children with sickle cell disease have reduced tubular concentrating ability, and the continuing fluid loss without adequate replacement causes a reduction in plasma volume with increased plasma viscosity and aggravation of sickling. They require roughly 80 ml/kg of fluid in 24 hours and, although an adequate oral intake can sometimes be

achieved, it is usually necessary to give intravenous fluids to those with severe pain or abdominal symptoms. Intravenous fluids should be continued until the child is free of pain and taking adequate oral fluids and it is important that the oral intake is maintained even when the pain has gone.

Pain caused by vaso-occlusion in sickle cell disease is frequently severe and often underestimated. The aim should be to reduce the pain fully as soon as the child has been assessed. A dose of an intramuscular opiate provides rapid relief and may be followed by an oral analgesic or an opiate infusion. The risks of opiate addiction seem to be small.

It is always important to look for a focus of infection and treat it appropriately. Any child with a high fever or who appears clinically ill should, however, be treated immediately with intravenous antibiotics (including penicillin). The haemoglobin concentration usually remains steady in painful crises and a falling haemoglobin concentration suggests sequestration in lung, spleen, or liver.

Joint effusions and swelling of tissues over infarcted bone often occurs. In children with sickle cell disease there is also an increased incidence of osteomyelitis, often caused by salmonella, which may be multifocal and difficult to distinguish from infarction. If the child is febrile and there is pronounced inflammation, or if fever and swelling fail to settle, blood cultures should be repeated, a radiograph taken of the affected area, and an orthopaedic opinion sought urgently. Acute surgical problems may mimic abdominal crises, and it is always important to consider a wide differential diagnosis.

Chest syndrome

This is more common in older children and adults, and is characterised by lung consolidation on the chest radiograph, which may be bilateral. Chest pain and breathlessness may occur, but physical signs may be scanty. Children with this syndrome may deteriorate rapidly. Antibiotics should be given intravenously as soon as blood and sputum have been obtained for culture. Transfusion should be given if the haemoglobin concentration is falling, and exchange transfusion may be necessary in severe cases.

Stroke

This is one of the most devastating complications of vaso-occlusion and is an indication for acute exchange transfusion. The risk of recurrence is high

and a programme of regular transfusions should be embarked upon to prevent this.⁷

Anaemia

The haemoglobin concentration is reduced in patients with sickle cell disease as a consequence of chronic haemolysis, but remains stable in any individual case. The haemoglobin concentration may be near normal in the SC disease, and children may be misdiagnosed as having sickle trait because of a positive sickling test. It is vital to perform full electrophoresis in all cases. Children do not have symptoms of anaemia, because the shift in the oxygen dissociation curve allows the haemoglobin to give up more oxygen to the tissues. Clinical anaemia may result from various causes including sequestration or reduced marrow activity. All children with sickle cell disease have an increased need of folic acid, and if folate intake is inadequate they may have a megaloblastic crisis as a result of acute folate deficiency. Anaemia may be caused by acute red cell hypoplasia that results from viral infections, particularly by parvovirus. During the period of red cell hypoplasia haemolysis continues unabated, reticulocytes are almost completely absent, and patients may become severely anaemic and require transfusion. Recovery is spontaneous and immunity to the parvovirus lifelong.

Blood transfusion

There is little evidence that blood transfusion during a simple painful crisis either reduces its severity or curtails its length. Repeated transfusions to suppress erythropoiesis and keep the haemoglobin S concentration less than 30% may be used to prevent complications such as splenic sequestration and stroke, and sometimes in preparation for elective operations. In children receiving regular transfusions, iron chelation treatment will become necessary as iron overload begins to develop. Exchange transfusion may be indicated to prevent sickling in acute conditions such as chest syndrome, priapism, or stroke, and occasionally it is necessary in the preparation of a patient for an elective operation. The risks of blood transfusion including reactions, sensitisation, and infection need to be balanced against the potential benefits.

Development

Children with sickle cell disease are usually thin, and their weight tends to be lower at all ages. Puberty is often delayed and the growth spurt is accordingly delayed, but the final height is usually near normal.

Enuresis is a common problem, probably as a result of high fluid intakes and urinary volumes, but it eventually resolves.

It is important to manage all these problems with reassurance rather than inappropriate investigation or intervention.

Comprehensive care

One of the most important developments in the management of sickle cell disease has been the recognition of the importance of a comprehensive programme to cover all aspects of health and development, and the development of specialist haemoglobinopathy clinics. In areas with a high incidence of the disease it is now common to employ sickle counsellors to liaise among the medical, social, and educational services. They play a vital part in the health education of affected communities and of the children and families. Some children miss a lot of schooling and it may be necessary to arrange for tuition at home during periods when complications are preventing attendance at school. An adequate standard of housing is probably of great importance in maintaining the health of children with sickle cell disease, cold and damp are likely provokers of crises and stress may also contribute to a poor clinical course. The employment achievements of people with sickle cell disease have been poor⁸; this is at least in part related to poor educational achievement as a result of chronic illness.

Regular clinical review forms an important part of the management of sickle cell disease. Chronic organ damage may become a problem in teenage children and adults; liver, lungs, heart, and kidneys may all be affected. Regular attendance at clinics also provides the opportunity to ensure compliance with penicillin prophylaxis and folic acid treatment.

Antenatal diagnosis

Sickle cell counsellors, supported by the haemoglobinopathy clinic and the laboratory, are beginning to assume a vital role in antenatal diagnosis and counselling. Antenatal diagnosis for sickle cell disease by chorionic villous biopsy is now possible in the first trimester of pregnancy, and it is important that good non-directive counselling that takes account of the variable clinical course is available for affected couples. The recent introduction of haemoglobinopathy cards by the Department of Health reflects increased awareness of the need for community health education. Failure to provide adequate backup by qualified counsellors, however, is likely to prevent success.

Future directions

Despite a clear understanding of the molecular basis of sickle cell disease, the development of specific treatment has been disappointing. Numerous anti-sickling agents have been tried over the years and have been found to be either ineffective or toxic. Vasoactive drugs and attempts to promote persistence of fetal haemoglobin have been equally unsuccessful.

Bone marrow transplantation has been successfully carried out, but the risks of graft versus host disease and of the marrow ablative treatment required for this approach are too high to allow it to become generally applicable. Gene treatment is viewed with great interest and optimism but it is still far from having a clinical application.

For the time being, management hinges around supporting the child and family and preventing and treating complications.

References

- ¹ Brozovic M, Anionwu E. Sickle cell disease in Britain. *J Clin Pathol* 1984;**37**:1321–6.
- ² Powars DR. Natural history of sickle cell disease—the first 10 years. *Semin Hematol* 1975;**12**:107–26.
- ³ Sergeant CR. Observations on the epidemiology of sickle cell disease. *Trans R Soc Trop Med Hyg* 1981;**75**:228–33.
- ⁴ The British Society for Haematology. Guidelines for haemoglobinopathy screening. *Clin Lab Haematol* 1988;**10**:87–94.
- ⁵ Gaston H, Verter J, Woods G, *et al.* Prophylaxis with oral penicillin in children with sickle cell anaemia: a randomised trial. *N Engl J Med* 1986;**314**:1593–9.
- ⁶ Ammann AJ. Current status of pneumococcal polysaccharide immunisation in patients with sickle cell disease or impaired splenic function. *Am J Pediatr Hematol Oncol* 1982;**4**:301–6.
- ⁷ Powars D, Wilson B, Imbus C, *et al.* The natural history of stroke in sickle cell disease. *Am J Med* 1978;**65**:461–71.
- ⁸ Franklin IM, Atkin K. Employment of persons with sickle cell disease and sickle cell trait. *J Soc Occup Med* 1986;**36**:76–9.

Correspondence to Dr JPM Evans, Department of Haematology and Oncology, Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.