Fortnightly review

Management of patients with sickle cell disease

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Sickle cell disease is a family of haemoglobin disorders in which the sickle β globin gene (β^S) is inherited. The most common type is homozygous sickle cell anaemia (haemoglobin SS); while other clinically significant conditions include compound heterozygote states for the sickle β globin gene and haemoglobin C (haemoglobin SC) or β thalassaemia (β^0 when no normal β chains are produced and β^+ when reduced amounts of normal β chains are made).¹ The sickle β globin gene is spread widely throughout Africa, the Middle East, Mediterranean countries, and India and has been carried, by 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-Caribbeans² and has reached high levels in these populations because the carrier state protects against malaria.³⁻⁵

In this review we have highlighted the important issues in the management of patients with sickle cell disease. These matters are important to healthcare professionals in most parts of the world. The number of patients in the United Kingdom was estimated at 5000 in 1993,² with the number being estimated as more than 10 000 by 2000.⁶ Patients usually live in urban areas.

The clinical problems encountered in sickle cell disease relate to vaso-occlusion, caused by polymerisation of deoxygenated haemoglobin S. This results in the pathognomonic change in the shape of erythrocytes to the sickle shape (fig 1), which is stiff, deforms poorly, and can adhere to the vascular endothelium.⁷

Fig 1 Characteristic sickle shaped erythrocytes in peripheral blood film of patient with homozygous sickle cell anaemia

Summary points

All patients with sickle cell disease should be registered with and monitored by a specialist clinic

Patients and their families must be fully educated on all aspects of the disease

Analgesia ladders are effective in managing the pain of sickle crises

Patients who are ill should be referred urgently for specialist care

Prophylaxis against pneumococcal infection is effective

Advice should be offered to patients before any travel abroad

The most common clinical problem is the painful vaso-occlusive crisis resulting from blockage of small vessels. However, large vessel disease also occurs, resulting in thrombotic cerebrovascular accidents, the acute sickle chest syndrome (fig 2), and placental infarction.

Search strategy

Our search strategy was to consider all articles in English and French found on a computerised Medline search from 1990 to April 1997. We used "sickle" as the keyword and selected landmark, original papers and comprehensive reviews. This was supplemented by our own collection of published papers, which was started in 1980.

Life expectancy

The clinical variability of sickle cell disease has long been recognised.⁸ Recent work from the United States has shown that the median life expectancy for men and women with homozygous sickle cell anaemia is 42 and 48 years respectively and for men and women who are heterozygous for haemoglobin SC is 60 and 68 years respectively,⁹ while a few patients survive into their

Fig 2 Acute sickle chest syndrome

70s.¹⁰ The most common causes of death in both the United States and the United Kingdom are pulmonary complications, cerebrovascular accidents, causes related to infection, acute splenic sequestration, and chronic organ damage and failure.⁹⁻¹¹ Severe pain, leading to clinic visits, expressed as episodes per year is a marker of clinical severity and correlates with early death in patients over the age of 20 who are homozygous for sickle cell anaemia.¹² Continued production of high concentrations of fetal haemoglobin, which interferes with the polymerisation of haemoglobin S, is associated with a longer life expectancy and amelioration of the clinical course.¹²⁻¹⁴

Screening

The diagnosis of haemoglobin type is easy and cheap and is by means of haemoglobin electrophoresis and the sickle test initially, with specialist tests being required only occasionally. As a person's haemoglobin type remains the same throughout life, patients with sickle cell disease should be given a haemoglobin card to show to health and welfare professionals.

Screening and appropriate counselling should be available and offered to all people who are not of North European origin before general anaesthesia, before conception of a baby or at diagnosis of pregnancy, and neonatally.² Any clinical and genetic implications should be explained and cascade screening, to include partners, should be offered along with prenatal diagnosis for sickle cell disease if appropriate and acceptable.

Clinical complications

Sickle cell disease is highly variable in its manifestations, and the pattern of organ involvement alters with age, as shown in figure 3. Patients are prone to infection, particularly by pneumococcus, salmonella species, and haemophilus, because of hyposplenism resulting from sickling and consequent autosplenectomy.¹⁵ Prophylaxis with daily oral penicillin is effective in reducing both the rate of infection and mortality related to pneumococcal infection.¹⁶ Unfortunately, compliance with oral penicillin is not always optimal,

Fig 3 Age distribution of clinical problems in sickle cell disease

even with repeated counselling, support, and education in a specialist clinic and from specialist nurse practitioners.¹⁷ Poor compliance may contribute to the rising incidence of penicillin resistant pneumococci in the community.¹⁸⁻²⁰ It is, therefore, sensible to immunise children with antipneumococcal vaccine, using half dose at 10-12 months and boosting with full dose at 3 years and every three to five years thereafter. Routine childhood vaccination against *Haemophilus influenzae* type b (Hib) has been adopted in the United Kingdom results in vigorous antibody responses in children with sickle cell disease over the age of 2 years.²¹

Infection with human parvovirus B19 is the main cause of hypoplastic crisis in patients with sickle cell disease,²² and a vaccine is under development. The virus infects developing erythroblasts, causing a cessation of production of mature red cells for a period of 1-2 weeks, so the haemoglobin concentration falls catastrophically, even resulting in congestive cardiac failure, with the need for urgent additive transfusion.

Fig 4 Avascular necrosis of femoral head in patient with heterozygous (haemoglobin SC) sickle cell anaemia

Fig 5 Analgesic ladder for management of vaso-occlusive pain of sickle cell disease in community

Management of painful crises

Pain experienced in a vaso-occlusive crisis results from oxygen deprivation of tissues and avascular necrosis of the bone marrow (fig 4), which is presumed to cause increased intramedullary pressure consequent on the inflammatory response and repair process. Although over 90% of hospital admissions for patients with sickle cell disease are for painful crisis,²³ nearly all sickle pain is coped with in the community.²⁴ Pain has been reported to occur on up to 30% of days,²⁵ with a loss of 10% of schooldays in children.²⁴

Clinical trials are needed because the optimum clinical management of painful crises is still not resolved, but we find that most episodes coped with at home respond to simple oral analgesia, an increased fluid intake, warmth, rest, and, for some patients, massage of the affected area. A simple analgesic ladder, as used in the management of pain caused by cancer, is appropriate,²⁶ starting with paracetamol (fig 5). If this is ineffective, we supplement with a non-steroidal anti-inflammatory drug, followed by codeine phosphate,²⁷ and we ask that patients come to hospital for

Fig 6 Hand-foot syndrome in patient aged 14 months with homozygous sickle cell disease

admission if they require stronger opiate analgesia to minimise the risk of opiate misuse and addiction.

All the large British sickle units which have used pethidine for the management of sickle pain have had patients who developed fits apparently caused by the pethidine, which are, however, difficult to distinguish from sickle related diseases²⁸ so the Central Middlesex management protocol uses morphine infusions.

Emergencies

Patients can be reassured that they will not die of the painful crisis. However, they should be referred for urgent medical care if the pain is uncontrolled in the community and if they develop obvious constitutional upset, tachypnoea, or signs of lung involvement, neurological signs, abdominal distension and pain, splenic or hepatic enlargement, loin pain, severe pallor, and congestive cardiac failure (box).

Complications requiring inpatient management

Pain uncontrolled by non-opiate analgesia
Swollen painful joints
Central nervous system deficit
Acute sickle chest syndrome or pneumonia
Mesenteric sickling and bowel ischaemia
Splenic or hepatic sequestration
Cholecystitis
Renal papillary necrosis resulting in colic or severe haematuria
Priapism
Hyphema and retinal detachment

Intravenous methylprednisolone has been reported in a small, randomised, double blind trial to decrease the duration of severe pain in children and adolescents with sickle cell disease,²⁹ but is not recommended for routine management because of the risks related to the use of high dose steroids, including the development of avascular necrosis of bones in about one third of patients with sickle cell disease.²

Management in the community

Management in the community is based on neonatal screening or early diagnosis of sickle cell disease, with patients being entered into comprehensive care programmes. The consequences of sickle cell disease experienced by patients in the community are jaundice, tiring easily, pain (from vaso-occlusive episodes, avascular necrosis, and leg ulcers), delayed puberty, priapism leading to erectile impotence, and chronic organ damage such as retinopathy and chronic renal failure.

Although patients are at risk of infection from as young as 8 weeks old, pain and other sequelae of vaso-occlusion are unlikely to develop before 4-6 months of age because of the continued high production of fetal haemoglobin. Nearly one third of children with homozygous sickle cell disease or β^0 thalassaemia will have experienced a hand-foot syndrome before the age of 18 months (fig 6),³⁰ with only a small proportion of children who are heterozygous for the disease or have β^+ thalassaemia (<5%) being similarly affected.

Oral penicillin prophylaxis should be started from diagnosis (at 62.5 mg once or twice daily under the age

of 12 months, rising to 125 mg daily, and from the age of 3 years 250 mg daily can be used). It is unclear how long patients should continue to take penicillin, despite the knowledge that the risk remains high throughout life, although diminishing with age. Further confounding factors include the steady rise in prevalence of penicillin resistant pneumococci and the varied antibody responses to vaccination of patients as a result of their hyposplenism. Therefore, our present practice is to ask children and their families to continue daily penicillin treatment until puberty, with vaccination and boosting as discussed earlier.

The combination of pneumococcal prophylaxis and parental and patient education on avoiding situations that can precipitate crisis—for example, cold, dehydration, exhaustion, and prolonged or severe infection—and on how to palpate for splenic size to ensure early presentation of splenic sequestration can significantly reduce deaths associated with homozygous sickle cell disease.^{31 32} Infection should be treated promptly, and any dehydration such as from gastroenteritis should be treated vigorously, even by intravenous rehydration. All patients should be advised to avoid alcohol because of its dehydrating effects and smoking because it may cause the acute sickle chest syndrome.³³

Folic acid supplementation may be necessary if patients do not eat a diet rich in fruit and vegetables. Its use, before conception and in pregnancy, should be encouraged.

Educational needs

Sensitive neuropsychological testing has shown that subtle, but important and widespread, neuropsychological defects result from sickle cell disease and may be present even in the absence of neurological complications.³⁴ This damage is probably responsible for the decreased intellectual ability of about five points in IQ (intelligence quotient) in patients with sickle cell disease as a group, when compared with controls on meta-analysis of published studies. This reduction indicates a twofold risk for significant learning difficulties and the need for remedial education compared with their peers.³⁵

Travel

All patients travelling abroad should be advised to obtain medical insurance. Preparative red cell transfusion and supplementary oxygen are not necessary for travel in commercial pressurised aircraft. 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, as is 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.

Hospital management

Good hospital care for patients with sickle cell disease is multiprofessional, involving not only haematologists, paediatricians, orthopaedic surgeons, obstetricians,

ophthalmologists, neurologists, and renal physicians but also nurse specialists, midwives, and all the staff of accident and emergency units and admitting wards.³⁶ All professionals who may be involved in the care of such patients should be aware of the protean manifestations of the disease, the life threatening complications, and their optimal management.

Splenic sequestration and fulminant sepsis including septicaemia and meningitis should be watched for in infants. Splenic sequestration presents as an enlarging spleen, worsening anaemia, abdominal pain, and ultimately cardiac failure, shock, and death unless the child receives an emergency blood transfusion. Acute cerebrovascular accidents are most common in childhood, but occlusive and haemorrhagic events can occur at all ages. Such patients should have an emergency exchange transfusion and urgent referral to a centre with both sickle and neurological skill for continuing care.

The acute sickle chest syndrome is rare before puberty but thereafter is the most common cause of death in Britain in patients with sickle cell disease. Although the aetiology remains unclear, the clinical syndrome is now well recognised: dyspnoea, sickle pain in the thoracic cage, arterial desaturation, the development of pulmonary consolidation with radiological changes. The onset can be insidious or rapid and fulminant, leading to death in untreated patients within hours. Inspired oxygen, continuous positive airways ventilation, and exchange transfusion are the present therapeutic options. Occasionally ventilation may be necessary.

Blood transfusions

We recently reviewed the role of blood transfusion in sickle cell disease.³⁷ Transfusion may also be required regularly to suppress production of haemoglobin S.^{38 39} All hospital blood banks should have in place written guidelines respecting the choice of red cell phenotype and the components to be used for patients with sickle cell disease.³⁷

Patients should be monitored regularly in specialist clinics for their growth, development,⁴⁰ and organ function so that active management may be considered before organ failure develops.

Future management

Although life expectancy continues to improve in patients with sickle cell disease, few patients are likely to live a normal lifespan with the present regimens of supportive care. Bone marrow transplantation offers the opportunity for cure and has been reported in over 100 children to date.⁴¹ The box shows the selection and exclusion criteria defined by the British Paediatric Haematology Forum, a subcommittee of the British Society for Haematology; these are similar to those used elsewhere.⁴²

Overall survival is 90-95%, with graft rejection of around 10-15%.⁴² Sadly, however, not all children who have a matched HLA sibling and satisfy the criteria for bone marrow transplantation are being referred to centres for consideration of the procedure. Interestingly, the proportion of children in clinics reported to satisfy eligibility seems to be indirectly related, albeit loosely, to the size of the clinic.⁴³

Criteria for bone marrow transplantation

Acceptance

Informed family (including patient) consent
Under 16 years old with sibling who is matched for HLA

Presence of one or more of:

Neurological deficit related to sickle cell disease, cerebrovascular accident, or subarachnoid haemorrhage
Two or more episodes of acute sickle chest syndrome or stage I and II chronic sickle lung disease
Recurrent severe and debilitating pain from sickle cell disease

Problems anticipated for future medical care

Exclusion

Presence of one or more of:

Karnofsky performance score <70%
Major intellectual impairment
Moderate and severe portal fibrosis
Renal impairment (glomerular filtration rate <30% of predicted values)
Stage III and IV sickle lung disease
Cardiomyopathy
HIV infection

Donor has important haemoglobinopathy

Pharmacological approaches that raise fetal haemoglobin concentrations are under development and include the use of hydroxyurea and short chain fatty acids. In a randomised, double blind, controlled trial hydroxyurea ameliorated the clinical cause in adults with homozygous sickle cell disease who had three or more painful crises a year.⁴⁴ The authors reported a longer median time from start of treatment to development of both first and second crisis with treatment compared with placebo, as well as significantly fewer treated patients developing the acute sickle chest syndrome and requiring treatment with blood transfusion for the duration of the study.

The mechanism of action of hydroxyurea has not been fully elucidated, and concerns remain about its myelosuppressive and teratogenic effects and its possible long term toxicity. It is not yet licensed for use in sickle cell disease and, although early studies suggest it is also efficacious in children, it should still be used only on a named patient basis with close haematological supervision.

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