Management of sickle cell disease: out-patient and community aspects

Paul T Telfer

Abstract

Sickle Cell Disease (SCD) is the commonest inherited disorder in England, affecting 1 in 2000 births, the majority born in London and of Black African family origins. Newborn bloodspot screening for SCD has now been implemented across the whole of England. This review considers the neonatal screening pathway and aspects of out-patient and community care which should be delivered within comprehensive care networks. Morbidity and mortality during childhood has declined due to implementation of effective care programmes, which include infection and stroke prophylaxis. Children still suffer from complications of SCD affecting long-term health, quality of life, self esteem, school performance and attainment. Treatment options for long-term control of the disease include hydroxycarbamide, regular transfusion and sibling allogeneic bone marrow transplantation. The indications, evidence of efficacy and adverse effects of these treatments are discussed.

Keywords community care; neonatal screening; pneumococcal disease; primary care; specialist centre; sickle cell disease; stroke

Epidemiology

Sickle Cell Disease is now the commonest genetic condition in England with a birth incidence of about 1 in 2000. The highest rates are in London (up to 3 per 1000) and there is a 25-fold difference between high and low-prevalence regions. The high birth incidence reflects the frequency of the sickle cell gene in people whose family origins are Sub Saharan Africa, (carrier frequency 20–25% of the indigenous population). The condition is also common in Caribbean, Eastern Mediterranean, Middle East and Indian tribal populations.

Genetics

There are several genotypes which result in sickle cell disease (SCD). The commonest and most severe is homozygous sickle cell (HbSS). Some other beta globin variants (HbC, D^{Punjab}, O^{Arab}) interact as compound heterozygotes with HbS to produce SCD of variable severity, and HbS also interacts with beta thalassaemia and other thalassaemic mutations (e.g. delta beta thalassaemia, haemoglobin Lepore). HbS does not interact as a clinically significant compound heterozygote with other common haemoglobin abnormalities such as Hereditary Persistence of Fetal Haemoglobin which can be co-inherited with HbS (HbS/HPFH) and is sometimes confused with (HbSS). Co-inheritance of alpha thalassaemia mutations with HbSS may modify the clinical phenotype, but should not confuse the underlying diagnosis of SCD.

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Diagnosis and laboratory monitoring

In the majority of cases the diagnosis is now made at birth with newborn bloodspot screening. However, some older children are still diagnosed after presenting with crisis, or diagnosed as an incidental finding from family studies or pre-operative testing. These are generally very mildly affected children who have moved to the UK from Africa or elsewhere during childhood.

Two methodologies of haemoglobin analysis are used in the newborn screening laboratories in England: High performance Liquid Chromatography (HPLC) and Isoelectric Focusing Electrophoresis (IEF). Direct diagnosis by identification of amino acid substitution in the globin chain by tandem mass spectrometry (TMS) is emerging as a tool for primary diagnosis.

A neonate with HbSS will have about 90% fetal haemoglobin (HbF), 10% sickle haemoglobin (HbS) and no detectable adult haemoglobin (HbA). It is important to note that other genotypes can also give this result (HbS/beta thalassaemia; HbS/HPFH), and the genotype should be confirmed either by checking parental carrier status, or by DNA analysis.

Neonatal screening

Identifying SCD infants early by neonatal screening reduces morbidity and mortality. Interventions which contribute to better outcomes include (i) education and support of parents, (ii) enrolment in a specialist service, (iii) prophylaxis against pneumococcal infection with oral penicillin and pneumococcal vaccine, (iv) abdominal palpation for early identification of acute splenic sequestration, and (v) transcranial Doppler screening for primary stroke prevention. The life expectancy of children has improved dramatically with current estimated survival of up to 97% at age 16 (Figure 1).

Neonatal screening for SCD was introduced across England in 2006, as a component of the National Haemoglobinopathy Screening Programme. It is one of the heel-prick bloodspot tests, recommended to be done on Day 5 after birth by the midwife or health visitor. The screening pathway requires positive neonatal screening results to be transmitted from the regional screening laboratory to a named representative in the local service. There should be an agreed pathway in place for visiting the parents to explain the results, checking parents' carrier status, informing the GP and referral to a comprehensive SCD service for confirmatory testing and enrolment in long-term care.

Out-patient management

Children with HbSS should be seen every 3 months up to age 2, and then 6 monthly. Children with HbSC can be seen every 6 months up to age 5, and then annually. The visit following each birthday should be scheduled as an annual review. Many clinics have developed standard out-patient forms to allow a systematic annual evaluation of the child with SCD, to assess severity and to monitor parameters which may be of prognostic value in the long-term. The National Haemoglobinopathy Register (NHR) has a secure on-line portal for entering clinical data at annual review. This is suitable for those children whose parents have consented

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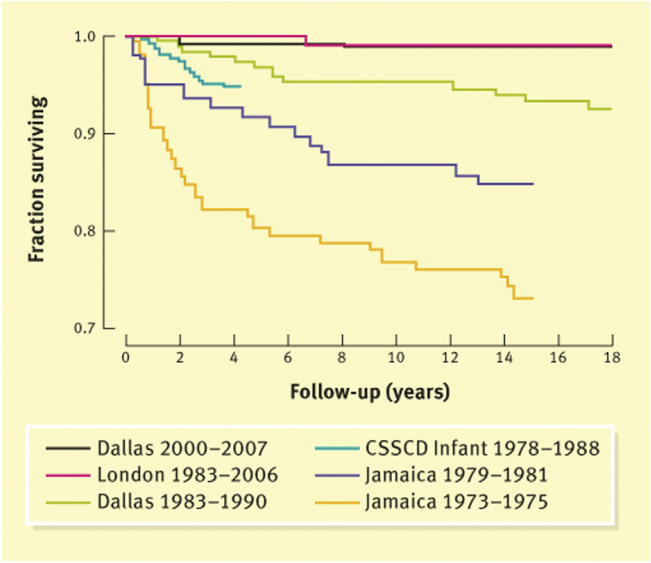

Figure 1 Comparison of overall survival for children with sickle cell anemia (HbSS and HbS/sickle beta^0 thalassaemia). Cohorts are the first and last thirds of the Jamaican cohort, the infant cohort of the Cooperative Study of Sickle Cell Disease, the East London Cohort, and the first and last eras of the Dallas Newborn Cohort. Note that the y-axes (fraction surviving) of all panels do not begin at 0. (Reproduced from Quinn CT et al. Blood. 2010 Apr 29; 115(17):3447–52, with permission.).

for enrolment on the NHR (http://www.nhr.nhs.uk/). Measurements of height, weight and pubertal development are essential for assessing growth and development. Blood pressure, urinalysis and oxygen saturation may be predictive of long-term complications. Steady state blood parameters (including Full blood count, reticulocyte count, renal function, percentage HbF and lactate dehydrogenase) have important prognostic and clinical value and should be assessed annually.

It is important to assess the parent/carer's ability to provide care and support for the child. This depends on socioeconomic factors as well as on the level of engagement and understanding about the condition. In some cases, there is a persistent denial of the condition and an unwillingness to divulge the diagnosis even to close family members. Erratic adherence to prophylactic medication (especially oral penicillin), irregular attendance at out-patient visits and a tendency to under-estimate the significance of the condition and the need to attend hospital are warning signs. These should trigger intensified efforts to engage with the family, to identify reasons for non-attendance and to offer appropriate support.

Prevention of invasive pneumococcal disease (IPD)

There is a striking increased susceptibility to IPD. Before pneumococcal prophylaxis was introduced in the USA, the rate of IPD in infants was about 10 episodes per 100 patient years of follow-up. IPD was a major cause of childhood death in the Jamaican Sickle Cell Cohort Study and the Infant Cohort study of the Co-operative Study of SCD in the United States.

A randomised controlled trial done in the early 1980's showed that prophylaxis with oral penicillin in children less than 5 years of age reduced the incidence of IPD by about 90%. A further trial was undertaken in the USA to determine if it was safe to stop oral penicillin prophylaxis after the age of five, but lacked sufficient statistical power to draw firm conclusions. Although the incidence is definitely reduced, IPD is still a significant cause of mortality and morbidity in older children and adults, and UK guidelines still recommend long-term prophylaxis.

Polysaccharide pneumococcal vaccine (PPV) was introduced in the 1980's, and the current 23-valent vaccine (Pneumovax®) in combination with oral penicillin, appears to be effective in preventing IPD. One major problem with Pneumovax is that it is poorly immunogenic before the age of two, and does not induce immunological memory. Pneumococcal Conjugate vaccines (PCV) were developed to induce long-lasting immunological protection in infants. Antibody responses to the 7-valent PCV (Prevenar®) in children with SCD are similar to non-SCD population and the vaccines have been associated wth a marked decline in morbidity and mortality from IPD. A thirteen-valent conjugate vaccine (Prevenar 13®) has now replaced 7v PCV in the routine childhood immunization schedule in N America and most of Europe. It includes six additional serotypes that are known to cause severe IPD, and should protect against 80–90% of serotypes causing IPD in most parts of the world. In Sub-Saharan Africa Prevenar 13® or alternative high valency vaccines could substantially reduce childhood morbidity and mortality from SCD. It is likely that these vaccines, in combination with regular boosters of Pneumovax® in older children, will reduce IPD rates still further, and one wonders whether oral penicillin prophylaxis is still needed for SCD children who are fully vaccinated. However, reports of IPD due to non-vaccine serotypes suggest that one should take a conservative approach.

Prevention of stroke

Transcranial Doppler (TCD) enables an assessment of cerebral blood flow velocity and can identify early stenotic lesions in the distal internal carotid artery (ICA), proximal middle cerebral (MCA) and anterior cerebral arteries (ACA): the most commonly affected segments of the vasculature in children with SCD (Figure 2). An abnormal scan is defined as a time averaged mean of the maximal blood velocity (TAMMV) $\geq$200 cm/seconds measured on at least two occasions. About 30% of children with abnormal scans have an ischaemic stroke within 4 years, and regular transfusion, keeping HbS below 30%, has been shown to reduce the risk of ischaemic stroke by 90%. (The Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial). TAMMV in the range 170 and 199 cm/seconds is categorised as 'Conditional', and in some cases will progress to abnormal. This risk of progression is higher (up to 50%) in young children with velocities in the 'high conditional range of 185–199 cm/seconds. Children with conditional velocities need to be scanned more frequently (at least every 3 months).

There are national quality standards and a standard protocol for undertaking TCD scanning and interpreting the results. TCD findings are very operator dependent, and it is quite easy for an inexperienced operator to obtain a false negative result. Annual TCD screening is part of routine management of children age 2 to 16 with HbSS or HbS/beta thalassaemia, but scanning is not required for children with HbSC. The identification of a child with abnormal TCD result is often a shock for the parent. Paradoxically, this group tends to have less frequent painful crises.

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