Sickle cell disease: an update on management

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Abstract

Sickle cell disease (SCD) is a common inherited disease affecting 12–15,000 individuals in the UK with approximately 250 new births per annum. Life expectancy has improved with the majority of those affected now surviving to adulthood, but it is associated with acute and chronic complications including haemolytic anaemia and intermittent episodes of severe bony pain, which may need hospital admission for management. Other acute complications include acute chest syndrome, stroke, priapism, splenic sequestration and red cell aplasia. Individuals with SCD also have an increased risk of infection and may develop renal dysfunction, respiratory complications and bony complications including avascular necrosis. Newborn screening will identify affected individuals and ensures early entrance into comprehensive care, which should include infection prophylaxis and primary stroke prevention by trans-cranial doppler screening. In addition annual review by a specialist team should continue throughout life. Optimal care provision comes from a strong multidisciplinary approach, with easy access to psychological services and an active community support team. With these measures, patients and their families can be educated to manage the minor complications of SCD with minimal impact to their daily lives and to recognize the more serious complications early, allowing quick and effective intervention to reverse the sickling process. Current treatments options are hydroxycarbamide (hydroxyurea), blood transfusion and haematopoietic stem cell transplant.

Keywords anaemia; hydroxycarbamide; hydroxyurea; sickle cell; stroke; trans-cranial Doppler; transfusion; vaso-occlusive crisis

Introduction

Sickle cell disease (SCD) is one of the most common monogenic disorders in the world. It is estimated that around 350,000 babies are born with the condition every year. In the UK, the national screening programme reveals a birth prevalence of around 1 in 2000. SCD is most common in Sub-Saharan Africa, where carrier frequency approaches 20–25% but it is also common in the Caribbean, Eastern Mediterranean, Middle East, India and in South/Central America. In the past it has been associated with high early mortality but in the UK life expectancy has improved markedly with 99% survival to adulthood.

A single base change in the beta globin gene causes an amino acid change of glutamic acid to valine. This structural variant of the adult haemoglobin, termed sickle haemoglobin or HbS, has unique properties and in the context of hypoxia, acidosis and dehydration can form polymers within the red blood cell. This polymerization can cause a conformational change of the red cell, from its archetypal doughnut shape into the pathognomonic sickle cell shape. This more rigid form causes microvascular occlusion, ischaemia and reperfusion injury. A chronic inflammatory state is established with endothelial and intravascular activation that perpetuates further ischaemia-reperfusion injury. In addition, the chronic haemolysis of sickle cells results in anaemia, hypoxia, cholelithiasis, fatigue, hypercoagulability and vasculopathy.

Several genotypes make up the diagnosis of SCD. The most common and most severe of these is homozygous sickle cell disease, HbSS, which accounts for over 70% of all cases but the sickle phenotype is also seen with compound heterozygosity of HbS in combination with certain other beta globinopathies (HbC, Dpunjab, O-Arab and beta thalassaemias).

National newborn screening programme

Early identification of SCD infants reduces morbidity and mortality. Guidelines from the NHS Sickle Cell and Thalassaemia Screening Programme advise that all newborn infants should be screened for sickle cell disease and this is done as part of the newborn blood spot test (heel prick test), typically on day 5 after birth. Positive results are sent to a named representative in the local service who ensures that parents are informed within 4 weeks of birth, informs the GP so that prophylactic antibiotics can be started and refers for specialist care.

Outpatient management of sickle cell disease

All newborns with a positive screening test should be seen in a haemoglobinopathy clinic within 8 weeks of birth and confirmatory testing should be performed. Clinic review should be offered every 3 months for the first two years of life and every 6 months thereafter. The local unit may offer shared care with a specialist centre, with the latter providing at least annual review. Good communication between local and specialist centre and with primary and community care is vital and parents should be offered follow up at home by the community nurse specialists to provide additional support.

Clinic review should include measurement of height, weight, examination and review of development, blood pressure, urinalysis and oxygen saturations (see Box 1). Blood tests providing steady state levels of haemoglobin (Hb), markers of haemolysis, percentage of fetal haemoglobin (HbF%) and renal function provide important prognostic and clinical information and should be checked at least annually. Many centres have developed proformas to help navigate these consultations. Parental consent should be sought to register the child with the National Haemoglobinopathy Registry (NHR) and data should be updated annually.

Infection prophylaxis

Splenic infarction leads to hyposplenism, usually by the age of 6 months, meaning that patients with SCD are at high risk of

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Key aims of paediatric outpatient services

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- Education and support of parents and patient
- Ensure adherence to prophylaxis against pneumococcal infection.
- Primary Stroke Prevention programme
- Checking developmental milestones
- Ensuring supportive environment at school, including a care plan with school nurse.
- Screening for early signs of chronic organ complications.
- Annual review

Box 1

certain types of infection. Invasive pneumococcal infection is a devastating complication that prior to the widespread use of penicillin prophylaxis occurred at a rate of 10 episodes per 100 patient years and was a major cause of early mortality. A randomised controlled trial in the early 1980s demonstrated that prophylactic oral penicillin reduced the incidence of pneumococcal infection by about 90% and its subsequent introduction vastly improved outcomes in paediatric SCD. Therefore, all patients should be commenced on prophylactic penicillin V by 3 months of age and offered pneumococcal vaccination. This currently comprises a 13-valent conjugate vaccine (Prevenar 13®), given at 2 and 4 months, which protects against 80–90% of serotypes followed by the 23-valent polysaccharide pneumococcal vaccine (Pneumovax®) at 2 years. Unfortunately, whilst covering a wide spectrum of pneumococcal variant, the Pneumovax is poorly immunogenic prior to the age of two years and requires booster vaccinations every subsequent 5 years to maintain efficacy. It is important to ensure adherence to this regimen in clinic.

Patients should also receive vaccination for Hepatitis A and B and Meningitis ACWY as well as the routine vaccines offered to all children. They should also receive the yearly flu vaccine from 6 months onwards.

Primary stroke prevention

A key aspect of paediatric outpatient management is the stroke prevention programme. Untreated, up to 10% of children with HbSS disease will have a stroke by the age of 10 years with an incidence of 1.02% per year between 2 and 5 years. This can leave them with profound long-term cognitive and physical deficits. Furthermore, patients can have smaller infarcts, seen on MRI, but without overt physical signs, termed silent cerebral infarcts (SCIs). These are increasingly recognised to have an impact on IQ and cognitive performance.

Stroke in the SCD population is usually due to a cerebral vasculopathy caused by a combination of microvascular ischaemia-reperfusion injury and the hyperdynamic blood flow typical of patients with SCD. Elevated blood flow velocities which can be measured by performing transcranial doppler (TCD) scanning. The most important measurement is the time-averaged mean velocity (TAMV) taken from the proximal MCA and distal ICA. Those less than 170 cm/second are considered normal, those between 170 and 199 cm/s are termed conditional and those 200 cm/s or greater are considered abnormal and these patients have an annual stroke risk of 10%. The STOP trial showed that if patients with abnormal TCDs are commenced on a blood transfusion program, aiming to maintain the HbS level below 30%, the risk of stroke is reduced by 92%. Since publication of this trial, TCDs have been introduced as standard of care and screening should commence promptly at 2 years of age, and, with ongoing normal measurements, continue on a yearly basis.

Children with abnormal TCDs should be offered long term transfusion but this represents a significant burden, for both the patient and medical services. The STOP 2 trial demonstrated that simply stopping transfusions once TCD velocities had reverted to normal was associated with an increased stroke risk. More recently the TWiTCH trial showed that patients who had completed 12 months of transfusion therapy and with no evidence of moderate or severe stenoses seen on MRA, could be safely transitioned to hydroxycarbamide therapy. Once the patient is on hydroxycarbamide TCD measurements should be monitored trimestially. There is particular interest in this option in low and middle income countries, where disease burden can be high and access to safe blood transfusion services low.

Patients with conditional readings have a higher risk of stroke than those with normal readings, and should be intensively monitored with MRA and repeated TCDs. The role of hydroxycarbamide in reducing TCD velocities in this group is currently being investigated.

The incidence of SCI is 27% and 37% by age 5 and 15 years respectively. The SIT trial enrolled patients with SCI and found that the incidence of further SCI or overt stroke was 14%, but this was reduced to 6% in those commenced on a transfusion programme, suggesting a clear benefit of routinely offering a transfusion programme to these patients. This poses questions about identification of SCIs as MRI screening in young children requires some form of sedation incurring a degree of risk and is resource intense. Currently, UK national guidelines do not advocate routine MRI screening, however, it should be considered in those who are performing below expectation at school and if SCIs are found, patients should be referred for further psychometric assessment and consideration of transfusion.

Stroke is far less common in the milder genotypes of SCD such as HbSC. There is no evidence to support a primary stroke prevention program and centres may offer less intensive TCD screening (e.g. at ages 2, 5 and 10 years of age.)

Respiratory complications

Respiratory complications arise in 20–48% of all children with SCD and are associated with an increased risk of mortality. Asthma is particularly common in children with SCD. Sleep disordered breathing, including obstructive sleep apnoea (OSA) and nocturnal hypoxia, is also very common, and is associated with an increased risk of stroke. It is important to take a good respiratory history and ask about sleeping habits including snoring. If indicated, consider sleep studies and/or pulmonary function tests to assess further. OSA is often secondary to adenotonsillar hypertrophy and these patients may benefit from tonsillectomy.

Renal complications

Renal complications, termed sickle cell nephropathy (SCN) arise in around 30% of children with SCD. Many go on to develop

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