Sickle cell disease, update on management

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Abstract

The article aims to provide a broad overview of sickle cell disorders emphasizing current developments in modern management. The value of neonatal screening, now universal in England, is evaluated with emphasis on the importance of effective measures to reduce the risk of pneumococcal infection. Complications of sickle cell disease are discussed individually with key points of management highlighted, stroke and the use of transcranial Doppler screening as a tool to identify high risk patients is discussed in detail.

The importance of effective, safe and rapid pain relief is highlighted and reference given to new NICE guidelines in this area. Recent changes in commissioning for sickle cell disorders will lead over the next 2 years to more equitable access to both specialist and local care within a multidisciplinary team setting, such arrangements should lead to significant improvements in the quality of care for children with these now common disorders.

Keywords acute chest syndrome; acute splenic sequestration; neonatal screening; pneumococcal septicaemia; sickle cell anaemia; specialist centres; stem cell transplant; transition to adult care; vaso- occlusive crises

Sickle cell disease (SCD) is now the most common genetic condition in England and haemoglobinopathies overall are the world's most common genetic defects. It is estimated that 5% of the population carry a haemoglobinopathy trait worldwide, the most common being sickle cell and thalassaemia carrier states. There are an estimated 300,000 babies born annually worldwide with a severe haemoglobin disorder, with the majority being in low and middle income countries. The national screening programme in the United Kingdom (UK) revealed that there is a birth prevalence of 1:2000 which is higher than that of cystic fibrosis (1:2500), and there is a carrier rate of 1% in all newborn babies in the UK. At present around 350 children are born in England per year with a significant Haemoglobin disorder, 90% of these are sickling disorders.

Definition

Sickle cell disease is a homozygous disorder characterized by polymerization of haemoglobin within the red cell, this changes its shape from a biconcave disk to a sickle or crescent shape when deoxygenated. This physical change in red cell shape leads to a variety of pathologic mechanisms, haemolysis due to shortened red cell survival, vaso-occlusion with both pain and long term organ damage .It is increasing clear that several pathophysiologic mechanisms interact to produce the clinical picture, these include nitric oxide depletion secondary to free haemoglobin depletion of substrate, hypoxaemia, changes in viscosity and interactions of blood cells with endothelium.

Epidemiology and distribution

The highest prevalence of the sickle gene is within the African continent, where the carrier state is believed to have provided genetic advantage, as sickle cells are a relatively poor host for a malaria parasite. It is estimated that at least 5.2% of the world's population carry a significant haemoglobin variant. With reference to sickle cell alone, the sickle haemoglobin variant accounts for 40% of carriers, but is responsible for 80% of haemoglobin disorders, because the gene prevalence is localized in certain areas. Africa is where the majority of individuals affected by sickle cell disorders originate, however the disorder is also seen in some areas of Southern Europe, the Middle East and in some Indian groups, tending in these areas to have a less severe phenotype.

Physiology

Homozygous sickle cell disease is caused by a mutation on chromosome 11 from thymine to adenine, which results in a substitution on the beta-globin chain of the haemoglobin molecule from glutamic acid to valine. Glutamic acid is hydrophilic, whereas valine in hydrophobic. When the cell becomes deoxygenated, there is a shift in the iron atoms, which opens a cavity. This cavity is hydrophobic, because of the valine substitution, and forms a pocket which other mutant molecules become attracted to, and they form bonds. These bonds lock together in double strands and form long fibres or polymers. There are seven double strands to each polymer. It is this polymerization that alters the shape of the cell, and the long fibres also make the cell more rigid.

This polymerization reverses once the cells reach the lungs and become re-oxygenated. Once re-oxygenated the molecules break apart and depolymerize, and the cell will no longer sickle, however the constant changing from polymerization to depolymerization damages the plasma cell membrane, and this makes the cell rigid. This sickling process results in a number of complications. The sickled red blood cells are less deformable, and can get trapped in the capillaries, but the cells also induce inflammatory and coagulation mediators, resulting in the activation of neutrophils which also contribute to the trapping of sickled red blood cells. It is increasingly clear that the interaction of the sickled cell with platelets and the endothelial cell wall, the impact of nitric oxide depletion, hypoxaemia and changes in viscosity all contribute to the eventual clinical picture.

The trapping of blood cells results in vaso-occlusion, which causes ischaemia, stimulating nociceptors, and resulting in pain. This acute pain is termed a 'crisis' and is the most common clinical problem seen in children. Other clinical problems include chronic anaemia, due to a rapid turnover of cells, patients with

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SCD are also at an increased risk of infection, and can experience chest crisis, splenic sequestration, stroke, priapism, avascular necrosis of the bone joints, aplastic crises, gall stones, and multi-organ failure. Many of these complications are serious and some life threatening, they can have a significant impact upon psychological well being, and quality of life.

Genotypes

The most common form of sickle cell disease is S/S, whereby a sickle S gene is inherited from both parents, however, there are many other possible interactions, haemoglobin S/C, S/β-thalassaemia, and S/D-Punjab are some of the more common combinations seen, all with subtle differences to the structure of the haemoglobin. Patients with haemoglobin SC for example often have spherocytic, dehydrated cells. Forms of SCD other than S/S are generally viewed as less severe forms of the disease, but are at risk of all the same complications, particularly as sickle cell is a very variable disease, the exceptions being sickle in combination with beta 0 thalassaemia and haemoglobin D which both produce a severe disease pattern. Even two siblings with the same genotype can be very differently affected, and the differences in phenotype are poorly understood, this makes it difficult to predict the clinical severity of individual children.

Neonatal screening and routine management

SCD is a complex disorder with a range of common and rarer complications. Within the UK SCD is usually diagnosed from the heel prick test taken shortly after birth. Once a haemoglobin disorder is detected within the laboratory the neonatal screening team will organize for a home visit to inform the family. This visit usually comprises of the nurse breaking the news to the family, and giving them some basic information about the disease.

Families should be invited to bring the newborn to a haemoglobinopathy clinic within 4 weeks of birth and confirmatory bloods will be taken, questions from parents can be answered and some of the common complications can be discussed further. This is also the ideal opportunity for data collection, there is a National Haemoglobinopathy Registry (NHR) onto which patients should be entered following parental consent.

Babies are usually seen monthly initially so that all the verbal and written information can be given to parents in a timely fashion without overloading them. Community nurses specializing in haemoglobinopathies should also be available to go and visit parents at home so they can reiterate all the information given to parents, and provide further support should they need it.

At 3 months of age penicillin V prophylaxis is started, as children with SCD are at increased risk of pneumococcal infection due to auto-splenectomy, this can occur as early as 6–8 months of age and is a painless process. Overwhelming infection has historically been shown to be the biggest cause of death in children under 5 who have SCD. National guidelines for care of children with SCD hence recommend that all children are offered prophylactic penicillin by the age of 3 months. Penicillin is a safe and reliable drug which has been shown to reduce pneumococcal infections by 84%. The dose will be increased at 1 and 5 years of age and additional vaccination with Pneumovax recommended at age 2. The single most important aspect in preventing early death from Pneumococcal infection is alerting the families to the risk and ensuring open access to hospital services.

Blood should be taken at one year of age to establish a baseline haemoglobin level. This can be variable, commonly children will have a steady state haemoglobin of 80–90 g/litre, however some children will have a baseline haemoglobin as low as 60–70 g/litre, it is important to establish this to aid clinical decisions in the future, as a haemoglobin of 58 g/litre for a child who's steady state is 90 g/litre is a significant decrease, but not for a child who's steady state is 60 g/litre.

It is also important to establish baseline foetal haemoglobin levels. Foetal haemoglobin (HbF) levels can be a predictor of disease severity. High levels of HbF are associated with fewer complications, it is believed that the presence of HbF stabilizes the red cells. HbF doesn't interact with any polymerization occurring within HbS molecules within the cell. HbF also lacks the valine to react hydrophobically with the HbS, and has other sequence differences which impede the polymerization process.

Other monitoring is generally dictated by the patient. There is a minimum of yearly follow up so that routine investigations and blood tests can be performed and annual review performed via the NHR.

Annual review should cover an assessment of the overall well being of the child, and assessment of child development. The number of hospital admissions, the number and severity of crises experienced, and the days off school that the child is having should be recorded. Any complications, and management of the complications, and a review of infection prevention, including penicillin prophylaxis and concordance to this, and immunization records should also be discussed.

In addition clinical measurements should be taken including the assessment of growth and development, clinical examination, and blood pressure and oxygen saturations. Urinalysis should also be measured for proteinuria, blood tests reviewed and performed if indicated, and from the age of 2 years annual transcranial Doppler scanning should be available. The annual review is also a good opportunity to update the child and family about SCD, ensuring the child has age appropriate information.

Diagnosis and management of complications

Vaso-occlusive painful episodes

Vaso-occlusive painful episodes are the most common complication of sickle cell disease, and are often termed a 'crisis'. These episodes of pain can last from a couple of hours to a couple of weeks, and they should be treated according to the severity of pain the child is experiencing.

With education many families can manage minor painful episodes at home with simple analgesia. Patients and families should be taught to seek help if analgesia is ineffective, or if they are experiencing other symptoms they are concerned about. There should be a local policy in place to ensure that children are treated for their pain quickly and efficiently. Morphine sulphate is often required, the oral route is preferable in children, in very severe pain patient controlled analgesia (PCA) can be very effective particularly in older children, as it gives them a control over their analgesia. The local policy should be based on recently published NICE guidance and should provide clear guidance on which drugs to use, when and by which route of administration. There should also be guidance on the monitoring for the therapeutic effect of medication, and close monitoring for any side effects.

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