Scottish Paediatric & Adult Haemoglobinopathy Network

Introduction to Sickle Cell Disease for Physiotherapists

1. Purpose of this document

To provide background information for physiotherapy staff working with paediatric and adult patients with Sickle Cell Disease. It is intended to be read in conjunction with the SPAH guideline "Physiotherapy management in Sickle Cell Disease"

2. Who should use this document

Physiotherapy staff working with patients with Sickle Cell Disease; including weekend and Emergency Duty staff.

3. Further reference

Reference list included.

4. Published by

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Contents

Scottish Sickle Cell Disease Service

Adult and paediatric patients with Sickle Cell Disease (SCD) receive medical care in primary, secondary and tertiary care centers across Scotland. The Scottish Paediatric & Adult Haemoglobinopathy (SPAH) is a national Managed Clinical Network (MCN) that is funded by National Services Division (NSD) and hosted by National Health Service (NHS) National Services Scotland.

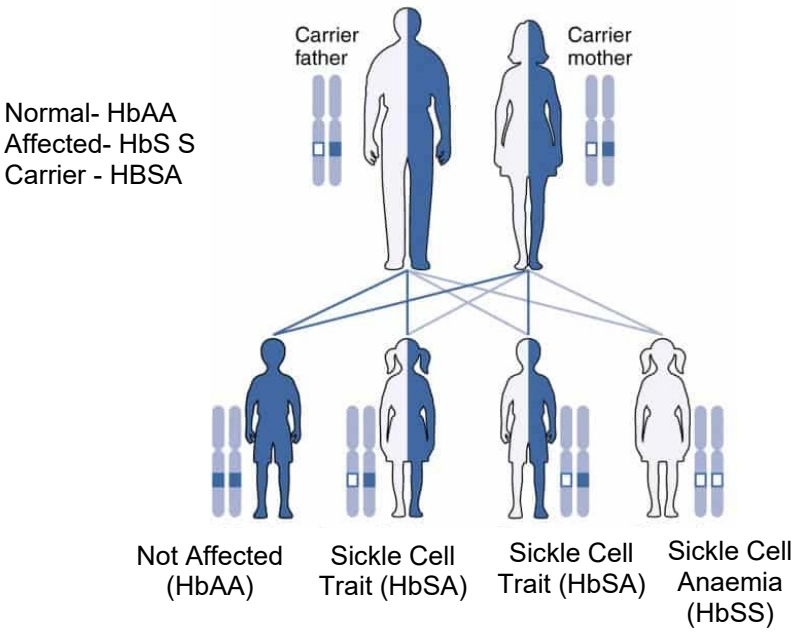
Background Information

Haemoglobin (Hb) is an iron-containing oxygen transport protein found inside red blood cells (RBC). Fetal haemoglobin (HbF) is the main oxygen transport protein in utero and for up to six months in the newborn. After these six months, there are different types of normal Hb such as adult Hb (HbA), minor adult Hb (HBA2) and in some cases fetal Hb (HbF) continues into adulthood.[1]

Abnormal forms of Hb occur due to variations in genetics that can cause alterations in the structure and function of Hb. SCD is a term covering several similar but different lifelong inherited disorders that affect Hb.

The most common types of SCD in the UK are:

- Sickle Cell Anaemia (SCA) (HbSS) is the most common form of SCD. Individuals with SCA have inherited sickle Hb (HbS) from both parents. People with SCA usually have the most severe clinical manifestations[2].
- Sickle Haemoglobin C Disease (HbSC) occurs when someone inherits one HbS gene from one parent and one haemoglobin C (HbC) gene from the other. It often has a milder presentation than SCA but the same health problems can occur.
- Sickle Beta Thalassaemia Disease (HbS/β thalassaemia) occurs when someone inherits one HbS gene from one parent and a beta thalassemia gene from the other parent. There are many different types of beta thalassemia mutation, with presentation ranging from mild to severe.



Pathophysiology

SCD is caused by a mutation in the Haemoglobin beta (HBB) gene. HbS is formed due to the substitution of the amino acid valine for glutamic acid on the beta globulin chain3. Hb transports oxygen around the body and the Hb becomes deoxygenated as the body tissues use the oxygen. In SCD this produces a change in the red blood cell shape from a biconcave disc to a long rigid shape. The process is known as sickling. Hypoxia, acidosis, fever and dehydration increase the rapidity of sickling[4]. Hb polymerisation (shape change) leads to RBC rigidity causing vaso-occlusion (blockage of a blood vessels)[5]. RBC's containing HbS return to their original shape on re-oxygenation but are ultimately damaged by repeated shape changes. This causes the cells to have a shortened life span and haemolysis (the breakdown of RBC's) occurs. Therefore, people with SCD have a reduced RBC count leading to a moderate and persistent anaemia[6]. Intravascular haemolysis (breakdown of RBC's in the vessels) alters the synthesis of nitric oxide (a molecule that contributes to vasodilatation). The normal balance of vasoconstriction to vasodilatation is therefore skewed toward vasoconstriction and endothelial activation (a pro-inflammatory and pro-coagulant state)[7]. This can contribute to some of the clinical manifestations of SCD that are explained later.

Diagnosis

SCD is diagnosed with a blood test. In Scotland, all parents are given the option for their child to undergo a newborn blood spot screening which routinely includes a screen for SCD[8]. If positive, all babies are started on prophylactic antibiotics as patients with SCD have diminished resistance to certain bacterial infection due to hyposplenism[9].

Epidemiology

SCD is the most common serious genetic disease in the UK. The highest frequency of SCD is found in tropical regions; however, it is becoming more common worldwide due to migration[10]. There are an estimated 12,500-15,000 people living with SCD in the UK[11]. In the UK the highest prevalence of SCD is found among black Caribbean, black African and black British communities. The incidence is 1:2000 births but can be as high as 1:300 in some urban areas[12].

Acute Clinical Manifestations

Individuals with SCD are at high risk of developing multi system acute and chronic complications associated with significant morbidity and mortality[13].

Acute medical management is similar during all admissions with the aim of treatment being to break the cycle of sickling, hypoxia and acidosis, which are all exacerbated by dehydration. Dehydration results in acidosis, which causes a shift of the oxygen dissociation curve (Bohr curve), therefore causing Hb to desaturate more readily. Decreased temperature causes vasoconstriction.

General medical management includes:

- Reassurance
- IV access if required
- Warmth
- Identification and treatment of infection
- Regular observations and reassessment[14]
- Analgesia
- Hydration

Vaso-occlusive crisis (VOC)

A vaso-occlusive crisis (VOC) occurs when the microcirculation is obstructed by sickled RBC's, causing ischaemic injury to the organ supplied and can result in extreme pain[15]. It is the most common, debilitating morbidity of SCD[16]. It is common in the bone marrow, resulting in bone marrow infarction typically in the medullary cavity or epiphyses[17]. Dactylitis is swelling of the hands and feet between the age of 6-24 months due to vaso-occlusion in the metacarpals and metatarsals[18].

There is minimal published evidence for musculoskeletal physiotherapy in acute admissions with VOC. One study found the daily use of Fludiotherapy® (a dry superficial heat modality) and a 10-30 minute general strengthening and endurance activity session in paediatric patients with SCD, shortened hospital stays and reduced the amount of analgesia required[19].

Acute Chest Syndrome (ACS)

ACS is a pulmonary complication of SCD that has a high incidence of morbidity and mortality[20]. ACS is defined as a new radiographic opacity in a patient with SCD associated with one or more of the following symptoms: fever, cough, sputum production, dysponea or hypoxia[21].

There is not one specific cause but rather several pathologic processes capable of triggering ACS including infection, fat emboli (secondary to a bony occlusive crisis) and rib infarction[22]. Infection appears to be more common in children and shows seasonal variation being three times more common in winter months, whereas fat embolism occurs more often in adults. The most common virus being RSV and most common bacterial organism in children being mycoplasma pneumonia. Infection can precipitate or complicate ACS[25a].

Sickling within the pulmonary vasculature leads to infarction[23]. Commonly pain in the thorax, upper abdomen or spine leads to hypoventilation, which may be exacerbated by opiate analgesia reducing respiratory drive. Basal hypoventilation leads to regional hypoxia, which triggers localised sickling with subsequent infarction and consolidation. Thus, a vicious circle is set up with sickling leading to progressive hypoxia and in turn to further sickling.

Research in paediatric SCD has shown that starting incentive spirometry immediately on admission, even with patients displaying no respiratory symptoms, can dramatically decrease the rate of ACS[24, 25]. There is no conclusive evidence describing how incentive spirometry prevents ACS but it is presumed it reduces a mismatch of regional ventilation and perfusion and reduces atelectasis, bronchial plugging and hypoxia[26, 27] Incentive spirometry has an important role in perioperative and postoperative supportive care[77]. Significant perioperative pain has been shown to be risk factor for ACS which is also worsened by opiod use[78].

The use of incentive spirometry can be limited by chest wall pain or by difficulty with coordinated inspiration in a young child. A randomised control trial found no significant difference between Positive Expiratory Pressure (PEP) and IS in preventing progression to ACS, patient satisfaction or length of stay[28].

A small study evaluated the effect of non-invasive ventilation (BiPAP) on respiratory distress in children that could not perform incentive spirometry and reported improvement in the oxygenation and in the respiratory distress[29]. In adults, early NiV has been shown to improve respiratory rate and gas exchange but failed to reduce the number of patients remaining hypoxic and was associated with increased patient discomfort.[30]

There are additional risks in children who have had severe ACS with mechanical ventilation, including acute neurological deterioration with seizures, hypertension, and acute white matter abnormalities on MRI scan (Posterior reversible encephalopathy syndrome). The normal course of ACS is for complete recovery with no residual pulmonary damage apparent[78].

Other acute complications

Fever/Infection: Individuals with SCD may be admitted with fever for an infection screen, antibiotics and monitoring for sickle cell crisis[31].

Osteomyelitis/Septic Arthritis

Patients with SCD are at an increased risk of developing osteomyelitis and septic arthritis with several mechanisms postulated including reduced spleen function and the presence of infarcted or necrotic bone[32].

Stroke

Stroke is a devastating complication of SCD, particularly during childhood however the incidence has dramatically reduced with the use of transcranial Doppler (TCD) ultrasonography that identifies those with SCD who are at high risk for stroke and allows early treatment with transfusions to reduce this risk [33,34,35].

Acute Splenic Sequestration Crisis

Acute Splenic Sequestration Crisis (ASSC) is defined as acute splenic enlargement with a fall in the Hb level[36]. Acute intrasplenic sickling traps blood in the spleen, leading to a decrease in the circulating blood volume[37].

Aplastic Crisis

An aplastic crisis is a temporary cessation of RBC production. As RBC's have a shortened life span in SCD an interruption in production will lead to a rapidly decreasing Hb[38].

Venous Thromboembolism

There is evidence of enhanced thrombin generation in children with SCD[39]. There is lack of research into the incidence of deep vein thrombosis (DVT) and pulmonary embolisms (PE) in children and adolescents with SCD but the majority of adolescents admitted with pain will be started on thromboprophylaxis as a precaution[40]. This is based on the known increased incidence of pulmonary embolism in hospitalised adult patients with SCD[41].

Chronic Clinical Manifestations

Long-term medical management is individually tailored for each patient.

Blood transfusions are often done to enhance oxygen-carrying capacity, improve tissue oxygen delivery and reduce HbS concentration to reduce sickling[42]. Transfusions are associated with several different complications including hyper viscous blood; alloimmunization (immune response to foreign RBC) and iron overload[43]. Many patients will require medication to treat iron overload.

Hydroxycarbamide is a drug that reduces the frequency of painful crises, dactylitis hospitalisation and chest syndrome in patients with SCD[44,45] The exact mechanism of action is under investigation but is likely to include the induction of HbF production and inhibiting sickling within the cell[46]. Patients need to attend regular clinics for full blood counts. The side effects include myelosuppression (decrease in bone marrow activity), gastrointestinal disturbance and liver dysfunction[47].

Cardiopulmonary complications

Patients with SCD often have a high cardiac output to compensate for their low Hb concentration, often associated with left ventricular enlargement and hypertrophy[48].

Pulmonary Hypertension (PH) can rarely occur in children with SCD. An elevated tricuspid regurgitant jet velocity (TRV>2.5m/s) is seen in around 30% of adult patients with SCD and can, in some cases, be a marker of pulmonaryhypertension. Elevated TRV is associated with increased mortality[49]. Screening by echocardiography can lead to early detection and intervention that may potentially reduce the impact of this disease process[50].

Asthma appears to be more common in children with SCD than ethnically matched controls and appears to be associated with an increased incidence of SCD-related morbidity, including ACS and painful episodes[53,54].

Sleep disordered breathing; most commonly Obstructive Sleep Aponea (OSA) is more common in children and young adults with SCD[55] resulting in oxygen desaturations overnight[56-59]. Paediatric patients may be admitted for a tonsillectomy, which has been shown to reduce the risk of OSA and cerebrovascular ischemia in SCD[60]. Sleep disordered breathing is also known to occur in adults with SCD[61].

Lung function of children with SCD has been shown to differ significantly from that of controls matched for age and ethnic origin[62]. Some studies suggest that paediatric SCD is associated with chronic inflammation that initially affects the smaller airways even in the absence of other clinical symptoms. Long standing inflammation could initially contribute to obstructive lung disease but may lead to fibrosis in later stages[63]. The development of restrictive lung disease may be attributed to a variety of factors ranging from lung fibrosis to disproportionate growth of limbs and thorax resulting in a small chest cavity[64,65]. It may also be related to the age of the patient at the first pulmonary insult, the severity of episodes of ACS/VOC and the type of treatment regime they have received[66]. Longitudinal changes in lung function in children with SCD have been reported,

with one study reporting an average loss of approximately 3% of forced expiratory volume in one second per year[67,68]. Children with SCD showed a lower functional capacity for exercise than that predicted for their age [69,70]. Up to 90% of adults with sickle cell disease have been shown to have abnormal pulmonary function[71].

Avascular Necrosis

Avascular necrosis (AVN) occurs when vaso-occlusion results in the infarction of the articular surfaces and heads of the long bones. The true prevalence of AVN in SCD is difficult to determine due to the small number of studies using MRI but is estimated at up to 27% in the paediatric population, increasing into adulthood[72,73].

The most common sites of AVN are the femoral heads followed by the head of the humerus, knee, and small joints of the hands and feet[74]. The mean age for a total hip replacement in SCD is 38[75].

Osteopenia/ Pathological fractures

In the fetal skeleton, red marrow is present throughout. After birth, red marrow undergoes a gradual conversion into yellow or fatty marrow. In a healthy adult, red marrow is only present in the axial skeleton. In SCD there is a demand for increased production of RBC that stops the conversion to yellow marrow in the peripheral skeleton. The constant RBC production leads to a widening of the medullary spaces and thinning of cortical bone, which may result in pathological fractures and osteopenia[76].

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