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Pulmonary Complications and Lung Function Abnormalities in Children with Sickle Cell Disease

Anne Greenough

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Abstract

The pulmonary complications of sickle cell disease (SCD) have a high morbidity and mortality. Fatal pulmonary complications occur in 20% of adults; those with sickle chronic lung disease (SCLD) and pulmonary hypertension have a significantly increased mortality. Treatment of SCLD is only supportive. Recurrent acute chest syndrome (ACS) episodes are the major risk factor for SCLD, and ACS is the leading cause of death. Adults with SCD tend to have restrictive lung function abnormalities, whereas, in children, obstructive abnormalities are more frequent. Lung function abnormalities are common even in young children and may reflect their chronic anaemia and increased pulmonary capillary blood volume, which increases airway obstruction and may be responsible for their increased wheezing. Whether more aggressive treatment of anaemia would improve lung function and long-term outcomes merits testing. Children with SCD experience a decline in lung function, which is most rapid in younger children in whom ACS episodes are most common highlighting the importance of identifying effective strategies to prevent and optimally treat ACS.

Keywords: Sickle cell disease, Acute chest syndrome, Obstructive lung function abnormalities, Restrictive lung function abnormalities

1. Introduction

The pulmonary complications of sickle cell disease (SCD) have a high morbidity and mortality with fatal pulmonary complications occurring in 20% of adults. Despite significant improvements in life expectancy in individuals with SCD, the median age of death for women is 48 years and for men 42 years. Young adults can develop sickle chronic lung disease (SCLD), which consists of restrictive lung disease, abnormal diffusing capacity and hypoxaemia. Those

with SCLD and pulmonary hypertension have a significantly increased mortality. Treatment of SCLD is only supportive. Recurrent acute chest syndrome (ACS) episodes are the major risk factor for SCLD and ACS is the leading cause of death. Prevention and optimum management of ACS episodes then should reduce SCLD occurrence. ACS episodes occur most frequently in young children with SCD and lung function abnormalities are common in childhood. In this chapter, the aetiology, pathogenesis and management of acute chest syndrome are discussed. The presentation of SCLD is briefly summarised as this occurs in adults, but included here as it is an important adverse outcome of ACS episodes. Pulmonary hypertension is discussed elsewhere (see Chapter x), but the impact on those with lung function abnormalities is emphasised in this chapter. Lung function abnormalities in children associated with SCD are described as the factors influencing the deterioration in lung function suffered by children with SCD. Recommendations are made with regard to routine respiratory monitoring.

2. Acute chest syndrome (ACS)

2.1. Presentation

The overall incidence of ACS as indicated by the Cooperative Study of Sickle Cell Disease (CSSCD) is 10.5 per 100 patient years [1]. ACS episodes occur more commonly in children than adults. Fifty percent of SCD children will have an ACS episode prior to the age of 10 years and the highest incidence of ACS occurs in children aged between 2 and 4 years of age [2]. ACS episodes are characterised by fever, chest pain and respiratory symptoms and essential to making the diagnosis with a new pulmonary infiltrate on chest radiograph. Fever and cough are more common in young children who, compared to adults, are more likely to have isolated upper lobe disease. Adults tend to suffer chest pain, haemoptysis and shortness of breath; their middle and lower lobes are more frequently affected than the upper lobes. Severe respiratory failure, necessitating mechanical ventilation, occurs in approximately 10–15% of affected patients. Recurrence is common, occurring in 80% of those who have had a prior episode. Follow-up of 293 patients aged between 3 and 20 years for 21 months demonstrated that a history of acute pulmonary events and younger age were independently associated with developing a new ACS episode [3]. In children less than 4 years of age who had had an ACS episode, one study demonstrated that the majority were hospitalised for ACS or severe pain within 1 year, emphasising the need for an effective therapeutic intervention in that high risk group [4].

2.2. Risk factors

The incidence of ACS varies according to the haemoglobin genotype being commonest in those with HbSS and much less common in those with HbSC [2]. In a retrospective review, ACS episodes also appeared less severe in children with HbSC compared to those with HbSS as indicated by a significantly shorter hospital stay [5]. The sickle cell mutation has arisen on at least five separate occasions, on four occasions in Africa and one occasion in

Saudi Arabia or India [2]. The prevalence and recurrence of ACS episodes in Saudi Arabia are relatively low as compared to patients in Africa; this may be due to the interaction between SCD and the 'Asian' haplotype [6], which is known to be associated with a higher fetal haemoglobin (HbF) level. ACS hospitalisation has been shown to be associated with a single nucleotide polymorphism (SNP)-defined beta globin cluster [7]. The risk for ACS is increased by certain endothelin NO synthase gene polymorphisms [8]. A heme oxygenase-1 gene promoter was associated with a reduced incidence of ACS hospitalisation [9]. A gene-centric association study found an association between ACS and rs6141803, the SNP located 8.2 kb upstream of COMMD7, a gene highly expressed in the lung that interacts with nuclear factor-kB signalling [10].

High haemoglobin levels predispose to vascular obstruction and increase the risk of complications, such as ACS. High HbF levels inhibit the polymerisation of HbS and hence the higher the HbF level the lower the occurrence of ACS episodes [2]. Leucocytes release free radicals, elastase, pro-inflammatory mediators and cytokines, hence the occurrence of ACS episodes are directly proportional to the steady-state white blood cell count [11].

In approximately 10% of patients, an ACS is precipitated by a pulmonary fat embolism; affected patients tend to be older, have a lower mean oxygen saturation at presentation and have a more severe clinical course. Typically, the pulmonary signs and symptoms are preceded by bone pain. Affected individuals may have systemic signs of a fat embolism, including changes in their mental state, thrombocytopenia and petechiae. Infarction of the bone marrow may result in fat embolisation. This can activate pulmonary secretory phospholipase A2 liberating free fatty acids. Arachidonic acid causes vasoconstriction and oleic acid upregulation of the vascular cell adhesion molecule (VCAM-1). Splinting resulting from bony thorax infarction leads to hypoventilation and atelectasis with accompanying hypoxia and hence sickling. The hypoventilation can be compounded by suppression of respiration by opioid administration. Infection causes approximately 30% of ACS episodes. The seasonal variation in ACS episodes in young children likely reflects the increase in viral infections in young children during the winter months. Children presenting with fever have an increased risk of developing an ACS episode if they have had a previous ACS episode, upper respiratory tract infection symptoms, non-compliance to penicillin, an absolute neutrophil count greater than $9 \times 10^9/l$ and haemoglobin less than 8.6 g/dl [12]. In a multicentre study, 27 different pathogens were identified, but *Chlamydia pneumoniae* was the most frequent pathogen, followed by *Mycoplasma pneumoniae* and respiratory syncytial virus. Parvovirus B10 has been associated with marrow necrosis and a particularly severe form of ACS.

In the Cooperative Study for Sickle Cell Disease before 6 months of age in which patients were followed beyond 5 years of age, a clinical diagnosis of asthma was made in 17% of the cohort. Asthma was associated with more frequent ACS episodes [13]. In a retrospective review of inpatient episodes for ACS, a previous history of asthma or wheezing was more common in children with HbSC than in those with HBSS causing the authors to speculate that asthma and wheezing may be more significant risk factors for ACS episodes [5].

2.3. Risk factors for recurrent ACS episodes

In a cohort of 159 children followed from birth to a median of 14.7 years, an ACS episode prior to 4 years, female gender, wheezing with shortness of breath and two or more positive skin prick tests were associated with future ACS episodes, but airway obstruction and a bronchodilator response were not [14]. Asthma has been reported to be a risk factor for recurrent ACS episodes in SCD children in Jamaica [15].

2.4. Pathogenesis

The levels of inflammatory cytokines are increased in ACS. Nitric oxide (NO) levels, however, are reduced; this is due to a number of reasons. 'Free' haemoglobin in the plasma scavenges NO. Hypoxia reduces NO production by inhibition of NO synthase and activated macrophages and leucocytes release free radical species that inactivate NO. Adhesion is increased when there are low NO levels as NO inhibits the upregulation of VCAM-1. NO also inhibits endothelin-1 production. In addition, there is a lack of inhibition of platelet activation and further potentiation of microvascular occlusion and the release of vasoconstrictor metabolites such as thromboxane A₂. Sickle red blood cells, due to the greater auto-oxidation of HbS compared to HbA, produce greater levels of oxygen-related radicals including superoxide, hydrogen peroxide and peroxynitrite. There are also lower levels of antioxidant enzyme systems, e.g. superoxide dismutase, catalase and glutathione peroxidase. The sickle cells occlude vessels causing vascular injury, especially to organs with sluggish circulation such as atelectatic areas of the lung. Neutrophils are more adherent to endothelin cells in SCD patients and this has been associated with ACS episodes.

2.5. Management

Broad spectrum antibiotics should be given, including macrolides or quinolones to treat atypical organisms. The choice of antibiotics should be guided by the patient's clinical condition and the 'local' pathogens. Oxygen therapy should be used to treat any hypoxaemia. There may, however, be a poor correlation of pulse oximetry readings with arterial oxygen tensions (see below) and hence blood gas analysis should be undertaken if there is suspicion of hypoxia. Indications for escalation of respiratory support, which is most likely in those with extensive, pulmonary involvement, are increasing hypoxia and dyspnoea and the pH following below 7.35. In such patients, non-invasive ventilation has been demonstrated to improve oxygenation and reduce heart rate [16], but may be poorly tolerated. Patients should be carefully rehydrated as SCD patients are susceptible to fluid overload; hydration should be limited to 1.5 times the maintenance fluid volume to avoid further impairment of lung function by aggravating vascular leak in the lungs. In ACS patients with hypoxia, simple or exchange transfusion can rapidly increase oxygenation [17]. An alveolar-arterial oxygen gradient >30 mmHg has been associated with a worse severity score and higher need for transfusion [17]. To improve the oxygen-carrying capacity of the blood and reduce the proportion of sickle haemoglobin a transfusion is given. In those patients with a relatively high haematocrit an exchange transfusion is administered, as a simple transfusion under such circumstances would increase the viscosity of the blood. Non-randomised trials have not shown any benefit of

exchange transfusion over simple transfusion [18, 19]; nevertheless in more severe cases requiring mechanical ventilation, particularly if a simple transfusion has not improved the patient, exchange transfusion is recommended [2]. Indications to proceed to an exchange transfusion include increasing hypoxia, increasing respiratory rate, reducing platelet count and multilobar disease. The aim being to keep the haemoglobin level at 10–11 g/dl. Analgesia should be given to control pain, but the amount limited to avoid respiratory depression. Patient controlled analgesia devices may reduce the risk of narcotic-induced hypoventilation [20]. Intercostal nerve block with a long acting local anaesthetic can alleviate chest wall pain and has the advantage of reducing the amount of systemic analgesia needed to control pain [2]. Inhaled NO (20–80 ppm) in patients with ACS and pulmonary hypertension has been reported to result in rapid and significant pulmonary vasodilation and improvement in oxygenation [21, 22]. Inhaled NO increases the oxygen affinity of HbS. A large prospective randomised trial, however, failed to show any significant differences in the time to resolution of crisis, length of hospitalisation, pain scores, cumulative opioid usage and rate of ACS between the nitric oxide and the placebo groups [23]. Approximately 25% of patients wheeze during an ACS episode and may benefit from bronchodilator administration [18], but the effect of bronchodilators on long-term outcome has not been investigated in randomised controlled trials. In a small Randomised controlled trial, dexamethasone administered to children with mild to moderately severe ACS was associated with a 40% reduction in the length of hospitalisation, a shorter duration of supplementary oxygen requirement and less need for analgesia [24]. Such outcomes are biologically plausible, as corticosteroids modulate endothelin cell adhesion molecule expression including VCAM-1 and have an inhibitory effect on phospholipase A2. Readmission after an ACS episode, however, has been demonstrated to be more common in those who reported use of an inhaler or a nebuliser at home or had received corticosteroids for the ACS episode [25].

2.6. Prevention

Fetal haemoglobin (HbF) inhibits polymerisation of deoxyhaemoglobin S and the level of HbF predicts the severity of the condition being inversely related to the mortality. There are a number of agents that raise HbF levels. One such is hydroxyurea that is a ribonuclease reductase inhibitor blocking DNA synthesis. The HbF level is raised due to the resultant bone marrow suppression. Additionally, hydroxyurea as an NO donor reduces VCAM-1 production and hence decreases sickle cell adhesion to the vascular endothelin. In an RCT involving adults, hydroxyurea reduced the incidence of ACS [26]. The systematic review of studies to date concluded that hydroxyurea is effective and safe in adults severely affected by sickle cell anaemia. The Pediatric Hydroxyurea Phase 3 Clinical Trial (BABY HUG) was an RCT of daily oral hydroxurea in children with sickle cell anaemia aged 9–18 months. The trial failed to achieve its primary aim which was to determine whether daily hydroxyurea would reduce spleen and renal damage by at least 50%. There were, however, significantly fewer sickle cell disease related events in the hydroxurea group, including ACS episodes [27]. Hydroxyurea, however, may cause cytopenias and patients must be carefully monitored, especially early in the administration of therapy, which may explain why some physicians are reluctant to prescribe it [28]. The summary of the 2014 evidence-based report by expert panel members

gave a recommendation of moderate strength regarding offering treatment with hydroxyurea without regard to the presence of symptoms for infants, children and adolescents [29]. Chronic transfusion in patients with a history of recurrent or severe episodes has been demonstrated by both retrospective review [30] and randomised trial [31] to reduce the frequency of ACS episodes. Routine use of incentive spirometry is recommended in SCD patients admitted to hospital with chest or bone pain. Such management in a randomised trial was associated with a lower rate of pulmonary complications (atelectasis or infiltrates) as seen on a subsequent chest radiograph [32]. A retrospective review demonstrated that introduction of an evidence-based guideline initiating mandatory incentive spirometry in children with SCD admitted for non-respiratory complaints resulted in a reduced number of transfusions and ACS episodes [33]. Stem cell transplantation in adults and children has been associated with no recurrence of painful crisis in those with stable engraftment [34]. The best results were obtained in young children who have HLA-identical sibling donors and transplanted early in the course of their disease [35]. In certain paediatric populations the success rate is 85–90% [36].

2.7. Outcome

The overall mortality for ACS is 3%, but 9% in adults [18]. The primary cause of death is respiratory failure from pulmonary emboli and bronchopneumonia. In one study [37], 60% of severe ACS episodes were associated with pulmonary hypertension which is associated with a higher risk of death. The incidence of acute kidney injury is higher in patients with ACS and pulmonary hypertension and correlates with the severity of the ACS [38]. Young children with a greater number of ACS episodes have a greater decline in lung function (see below) [39]. In young adults, the greater the number of ACS episodes the greater the reduction in lung function [40].

3. Pulmonary hypertension

In a screening study, 32% of patients had a tricuspid regurgitant jet velocity (TRV) by Doppler echocardiography of greater or equal to 2.5 m/s which corresponds to a Pulmonary artery systolic pressure of 25–35 mmHg (approximately two standard deviations above the mean). Despite mildly elevated TRV values, the prospective mortality was high with a tenfold increase in the odds ratio for death [41]. Echocardiography, however, may overestimate the prevalence of pulmonary hypertension [42]. Pulmonary hypertension in SCD is characterised by progressive obliteration of the pulmonary vasculature. Possible causes include chronic hypoxic stress causing irreversible remodelling of the pulmonary vasculature, recurrent pulmonary thromboembolism, sickle cell related vasculopathy and pulmonary scarring from recurrent ACS episodes. An elevated TRV has been reported in 11–31% of children and adolescents with SCD [43, 44]. The clinical significance is not known although an elevated TRV in children has been associated with a decline in exercise capacity [45].

4. Sickle chronic lung disease (SCLD)

SCLD is a progressive disease with an insidious onset progressing to end-stage respiratory failure, characterised by hypoxemia, restrictive lung disease, cor pulmonale and chest radiograph evidence of diffuse interstitial fibrosis. Recurrent ACS episodes result in damage to the lung parenchyma resulting in restrictive lung disease. In a study of 319 adults with SCD, 74% had restrictive lung function abnormalities [46]. The mean survival of SCD patients with chronic lung disease and elevated pulmonary artery pressures can be as short as 2 years. Sudden death in SCLD patients with pulmonary hypertension is common due to pulmonary thromboembolism, systemic hypotension and cardiac arrhythmia. Adult SCD patients, therefore, should be screened for pulmonary hypertension with echocardiography as, although initially the patients may be asymptomatic, their condition progresses and they suffer worsening hypoxia and chest pain with impaired exercise tolerance.

5. Asthma and outcomes of SCD

Asthma has been associated with adverse outcomes in SCD patients. Asthma has been reported to be more common in those with ACS [13] and in particular with recurrent ACS episodes [15]. In one series, after controlling for established risk factors, individuals with sickle cell anaemia and asthma had more than a two fold increased risk of mortality [47]. In another series [48], after adjusting for baseline lung function, current asthma and smoking were significantly associated with mortality during a 10-year period in young adults [48]. Patients with SCD frequently wheeze and asthma may have been over diagnosed in previous studies that used a physician's diagnosis of asthma rather than more objective tests such as determination of bronchial responsiveness. In a retrospective study, asthma and wheezing were independent risk factors for increased painful episodes and only wheezing was associated with more ACS episodes [49]. In an observational study in SCD adults, the ACS rate, lung function or risk of death was not significantly related to a diagnosis of asthma. Whereas those who had recurrent severe episodes of wheezing compared to those without wheeze had twice the number of ACS episodes, poorer lung function and an increased risk of death [50].

6. Lung function abnormalities

Obstructive lung abnormalities are reported in young children [51, 52] with restrictive abnormalities becoming more prominent with advancing age [53]. Airway hyper-responsiveness (AHR) to methacholine has been reported to be more common in SCD children, but not related to signs or symptoms of allergy [54]. There is great variation reported in the response to bronchial challenges from 0% in one study [55] to 78% [56] in another. Similarly, the response to bronchodilator varies from no difference compared to controls [53], but others [15, 57] reporting a much higher response. Nocturnal desaturation episodes, possibly due to obstruc-

tive sleep apnoea, may occur in up to 40% of children and adolescents. Oxygen saturation monitoring, however, may be inaccurate as oximeters do not differentiate between oxyHb and carboxyhaemoglobin which is raised in some patients.

6.1. Exercise capacity

There have been few studies investigating the cardio-respiratory responses of patients with sickle cell anaemia to exercise. Children with SCD have been reported to have more adipose tissue with reduced fitness and exercise performance [58]. Exercise capacity has been reported to be related to the baseline degree of anaemia and be significantly lower in subjects with a history of recurrent ACS [59]. The metabolic changes imposed by exercise may initiate sickling and vaso-occlusive episodes. Patients, therefore, are advised to start exercise slowly and progressively, to maintain hydration and avoid sudden changes in temperature [60].

6.2. Longitudinal changes in lung function

A cross-sectional study suggested that restrictive abnormalities may increase with increasing age in childhood [53]. A longitudinal study of children aged 5–18 years demonstrated at baseline the children mainly had obstructive lung function abnormalities [61]. At follow up 4 years later, the number of children with obstructive or restrictive lung function abnormalities had increased, but obstructive abnormalities were more common [61]. Retrospective analysis of results from 413 SCD children aged between 8 and 18 years, however, demonstrated an increased prevalence of restrictive abnormalities with increasing age [62]. In two cohorts of SCD children, one of which was followed for 2 years and the other for 10 years, lung function deteriorated in the SCD children compared to contemporaneously studied ethnic and age matched controls. This was the first longitudinal study to include contemporaneously studied ethnic and age-matched controls [39]. In the cohort followed for 10 years restrictive abnormalities became more common. The rate of deterioration in lung function was greater in the younger children in whom ACS episodes were more common [39].

6.3. Aetiology of the lung function abnormalities

The obstructive lung function abnormalities seen in SCD children could be due to asthma. An increased prevalence of asthma was reported in one study [15], but other studies have indicated a similar incidence to that of non-SCD populations [63, 64]. Exhaled nitric oxide is elevated in asthma due to the enhanced expression of inducible nitric oxide synthase in inflamed airways. Yet in prospective study of 50 SCD children and 50 controls the exhaled NO levels between the two groups were similar and airway obstruction in the SCD children was not associated with increased methacholine sensitivity or eosinophilic inflammation [55]. An alternative explanation for the airway obstruction in SCD is the hyperdynamic pulmonary circulation due to a raised cardiac output resulting from chronic anaemia [65]. Furthermore, in a study of 18 SCD children compared to 18 ethnic and age-matched controls, the SCD children had a significantly higher respiratory system resistance, alveolar NO production and pulmonary blood flow, but not airway NO flux. There was a significant correlation between alveolar NO production and pulmonary blood flow, but not between airway NO flux and respiratory

system resistance [66]. SCD patients have an increased pulmonary capillary blood volume resulting from their chronic anaemia. In a study of 25 SCD children and 25 ethnic origin matched controls, the SCD children had significantly both higher airway obstruction and pulmonary capillary blood volume before and after bronchodilator. In the SCD children there was a significant correlation between the pulmonary capillary blood volume and the increased airways airway obstruction [67]. Furthermore, transfusion in SCD children has been shown to acutely increase airway obstruction and this was significantly related to an increase in pulmonary capillary blood volume [68]. Those results suggest that the airway obstruction seen in SCD children, at least in some, relates to their increased pulmonary capillary blood flow rather than bronchial hyper-reactivity. The clinical implication of those results is that SCD children with airway obstruction may have only limited benefit from bronchodilators and this should be formally tested (see below). Strategies to reduce anaemia and the increased pulmonary capillary blood volume, such as hydroxyurea, may be beneficial in those who remain symptomatic despite optimisation of bronchodilator therapy.

7. Recommendations regarding routine respiratory monitoring

The most rapid deterioration in lung function occurs in very young children [39], thus routine respiratory monitoring should begin early, that is, as soon as the child can undertake the measurements (usually from 4 years of age) on an annual basis. Such monitoring is to enable early detection of a child whose respiratory function is deteriorating and needs escalation of treatment. Equally paired lung function assessments can determine the efficacy of treatment for an individual (see below). Young children, however, have limited ability to perform lung function tests and detailed lung function testing is not available in all centres. As a consequence, in those less than 5 years of age, impulse oscillometry is recommended as this does not require volitional input by the child; in older children spirometry gives additional information. Both techniques are applicable to developed or low resource settings (if in the latter a hand-held spirometer is used). Assessment of lung volume is also additive in older children as this will identify those starting to develop restrictive abnormalities, but the relevant techniques are expensive, particularly plethysmography. Assessment of lung volume by measurement of functional residual capacity by helium gas dilution is more generalisable in developed settings. It is important that children with wheeze are not assumed to have asthma as wheeze in SCD may have other causes. It is therefore important that they undergo assessment for bronchial hyper-reactivity according to their lung function, those with airway function less than 70% of predicted should receive a bronchodilator and those with better airway function, better than 70% predicted, should receive either a cold air or exercise challenge. A methacholine challenge should not be used as this can precipitate an ACS. To ensure all children are appropriately diagnosed as having AHR undertaking both a cold air and exercise challenge should be considered, as some children respond only to one type of challenge and not the other [69]. Theoretically, any bronchial challenge could precipitate a crisis although this has only been reported with a metacholine challenge. An alternative approach in a child with recurrent wheeze, particularly if they have an atopic family history, is to give

them a trial of inhaled steroids, but importantly assess whether there has been any positive effect using respiratory diary cards and preferably lung function assessments. Clinical trials are required to evaluate the effectiveness of therapy for asthma in patients with SCD and coincident asthma and whether this influences their respiratory outcomes.

Author details

Anne Greenough

Address all correspondence to: anne.greenough@kcl.ac.uk

Division of Asthma, Allergy and Lung Biology, King's College London, London, UK

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