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Mini-Symposium: Controversies in the Evaluation and Treatment of Sickle Cell Disease

Acute pulmonary complications of sickle cell disease

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EDUCATIONAL AIMS

- To be aware of the pulmonary complications of sickle cell disease.
- To understand the pathophysiology of the pulmonary complications of sickle cell disease, in particular that recurrent wheezing may not be due to asthma.
- To understand the rationale for the various management strategies for a patient with SCD presenting with an acute respiratory illness.

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SUMMARY

Acute pulmonary problems in sickle cell disease (SCD) patients, in particular acute chest syndrome (ACS), cause significant mortality and morbidity. It is important to differentiate ACS from pneumonia to avoid inappropriate or inadequate treatment. Asthma may increase the risk of ACS and co-morbid asthma and SCD are associated with worse patient outcomes and, in preclinical models, more severe inflammation. Recurrent wheezing, however, can occur in the absence of a diagnosis of asthma; it is likely due to SCD related inflammation and additional therapies than those that treat asthma may be required. Further research is merited to clarify these issues.

INTRODUCTION

Acute chest syndrome (ACS), characterised by the acute onset of pulmonary abnormalities accompanied by the appearance of a new infiltrate on the chest radiograph, can cause significant morbidity and mortality in patients with sickle cell disease (SCD). ACS has a case fatality rate of approximately 3% [1] and may account for as many as 14–25% of sickle related deaths [2,3]. It is second in frequency only to a painful crisis in necessitating admission to hospital. ACS is a risk factor for sickle chronic lung disease [4,5]. ACS is common, with more than 50% of children with homozygous SS disease suffering at least one episode in the first decade of life [6]. To reduce the chronic respiratory morbidity and associated mortality of SCD it is essential to understand the pathophysiology of the acute pulmonary problems seen in SCD and hence identify efficacious preventative and treatment regimens. Over the past decade, several groups have reported that asthma is associated with an increased risk of ACS, [7–10] and other SCD complications, including painful crisis and stroke [8,11,12]. In this paper, the literature is reviewed to describe the acute pulmonary complications of SCD, their aetiology and management and to test the hypothesis that, in certain patients, recurrent wheezing may not be due to asthma, but rather SCD per se.

THE PATHOPHYSIOLOGY OF SICKLE CELL DISEASE

SCD is an autosomally inherited hemoglobinopathy. It is caused by a point mutation in the gene coding for the β-globin chain of haemoglobin (Hb), resulting in the hydrophilic amino acid glutamic acid being replaced with the hydrophobic amino acid valine at the sixth position, producing Hb S. Individuals who inherit an S gene from each parent have homozygous SS disease (sickle cell anaemia) and those who inherit one S gene and another gene causing significant abnormalities in the β chain have other forms of SCD such as Hb SC disease and Hb S β thalassemia disease. In all types of SCD, Hb S is the majority of Hb in the erythrocytes. SCD is characterized by vascular occlusion with ischaemia-reperfusion injury, haemolytic anaemia and chronic inflammation overlaid by acute events [13].

At the intracellular level, the Hb S polymerizes causing sickling of the cell. The changes in the amino acid sequence of the β globin results in an alteration of the quaternary structure of the Hb such

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Table 1
Acute respiratory syndromes: Additional factors to consider in patients with SCD.

Clinical syndrome	Respiratory symptoms and signs and consolidation on the chest radiograph	Recurrent wheezing
Risk factors	- Underlying SCD inflammation - Immune deficiency of SCD - Iatrogenic complications from management of other SCD complications: narcosis, overhydration	- Underlying SCD inflammation - Differences in nitric oxide metabolism? - Lower Vitamin D levels? - Earlier and increased exposure to acetaminophen? - Alterations in the lung microbiomes?
Etiological agents/triggers	- Pulmonary fat embolism	- Haemolysis? (Elevated LDH)
Treatment	- Hydroxyurea - Incentive spirometry patients with a painful crisis - Transfusion - Antibiotic s - *Streptococcus pneumonia* prophylaxis	- Caution with systemic steroids - Hydroxyurea?
Severity	- May be worse than in non-SCD individuals	- May be worse than in non-SCD individuals

that the iron in Hb S is more exposed to the cytoplasm, producing greater concentrations of reactive oxygen species. This has particularly adverse effects as antioxidants, in particular erythrocyte glutathione, are depleted [14,15]. On-going haemolysis releases the cell contents into the circulation, where the free heme overwhelms the haptoglobin and reduces the availability of nitric oxide [16]. The cell membrane is less pliable and also has exposed adhesion molecules which facilitate the adhesion of sickle erythrocytes to each other and to the vascular endothelium [17]. The vascular endothelium becomes injured. Cells adhering to each other and the vascular endothelium cause vaso-occlusion and tissue hypoxia. Release of inflammatory cytokines from the various cell types and endothelium result in a chronic inflammatory state [18]. Acute and chronic inflammation occurs particularly in the lungs, because there the erythrocytes are exposed to relatively low oxygen tensions and the abnormal rheology of the cells results in slow transit times. In addition, the airways and vasculature are in close proximity facilitating transfer of mediators into airways [17].

ACUTE CHEST SYNDROME AND PNEUMONIA

Patients with SCD who have an ACS episode suffer from fever, cough, shortness of breath, pleuritic chest pain, tachypnoea with crackles heard on auscultation and the appearance of a new infiltrate on chest radiograph [19], which could be mistaken for pneumonia. Acute Chest Syndrome, however, should be considered as a different entity from pneumonia because of certain differences in risk factors, etiological agents, severity of the illness and the treatment required (Table 1). Some risk factors for ACS are similar to those for pneumonia, such as age (increased risk in infants and young children), abnormalities in the immune defences and abdominal surgery, but other risk factors differ. Patients with more severe genotypes (Hb SS disease and Hb S β^0 thalassemia) have a greater risk of having ACS than those with milder genotypes (Hb SC disease and Hb S β^+ thalassemia) [20]. Patients with lower haemoglobin levels and higher Hb F levels are at lower risk of ACS than patients with higher Hb and lower Hb F levels [20]. A higher baseline leukocyte count is also a risk factor for ACS [20]. Unlike pneumonia, ACS is associated with autonomic system dysfunction, whereby patients who had a history of ACS may have less parasympathetic activity than patients who had not suffered an ACS episode [21].

All etiological agents causing community acquired pneumonias can cause ACS [1]. There are, however, some infectious agents, including encapsulated organisms such as *Streptococcus pneumonia*, to which patients with SCD are more susceptible. Atypical bacteria cause ACS at younger ages than they usually cause pneumonia in the general population [22]. Atypical organisms usually result in mild to moderate episodes of pneumonia, but may more frequently cause severe, even life threatening or fatal, episodes of ACS [22,23] A major cause of ACS is pulmonary fat embolism (PFE); in one series it was diagnosed in 16.2% of patients with ACS for whom complete diagnostic data were available [19]. Bony elements, including fat, released into the circulation during a bony painful crisis cause inflammation in the lungs. The inflammatory response to the fat emboli includes release of secretory phospholipase A and the phagocytosis of fat by macrophages [24]. Bronchoscopy of patients with ACS due to PFE demonstrated that their bronchoalveolar lavage fluid had a higher Corwin index of lipid laden macrophages than that of children with aspiration pneumonia [25]. Patients admitted with ACS caused by PFE tend to be older and have a lower mean oxygen saturation at presentation [1]. PFE and infection may together result in an ACS [1]. An ACS episode may be precipitated or worsened by complications of SCD or their treatment, for example chest pain may lead to splinting and hypoventilation and treatment of painful crisis may be associated with overhydration or respiratory depression due to use of narcotics [17].

The treatment of ACS, as for pneumonia, includes supplementary oxygen, antibiotics and fluids. There are, however, differences in how these therapies are used and patients with an ACS episode will frequently require additional treatments. Antibiotic choices for ACS, even in young children, include those which treat atypical bacteria, although clinical trials which have compared antibiotic regimes are lacking [26]. Transfusion, particularly exchange transfusion, may be lifesaving in an ACS episode. Bronchodilators are recommended due to the prevalence of wheezing and airway hyper-responsiveness in patients with SCD, [1] but there are no randomized controlled trials which have appropriately tested their efficacy [27]. Fluids used in the treatment of bony painful crisis should be used judiciously so as not to aggravate vascular leak in the lungs [17]. Incentive spirometry for patients with bone pain, decreases the risk of ACS [28]. Pain management should be optimized to encourage deep breaths and not to the level that respiratory depression will result. Immunization, especially for *Streptococcus pneumonia*, should be life-long [29]. Preventative strategies to decrease the risk of ACS episodes include hydroxyurea [30].

ASTHMA AND SCD

Data from animal models suggest that there may be a synergistic inflammatory response when asthma and SCD co-exist. Sensitization with ovalbumin (OVA) to induce experimental asthma in control white mice (WT), chimeric SCD and hemoglobin (Hb) A mice compared to non-sensitized controls [31] resulted in 10% of the SCD mice dying after the initial sensitization dose, whereas none of the control mice died at that stage ($p<0.01$).