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RESEARCH ARTICLE

Asthma in Children with Sickle Cell Disease

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ABSTRACT

Sickle Cell Disease is a life-threatening hereditary blood disorder which affects millions of people worldwide. Pulmonary complications are important causes of morbidity and mortality in patients with sickle cell disease. Asthma is a recognised comorbidity of sickle cell disease and may occur in between 15 and 28% of children with sickle cell disease. It has been associated with increased episodes of acute chest syndrome and all cause mortality. Obstructive lung disease, however, is common in children with sickle cell disease, independent of an asthma diagnosis. This review explores the pathophysiology, diagnosis and therapeutic opportunities for asthma in sickle cell disease patients. The diagnostic challenges and inconsistencies in current clinical approaches are highlighted. Convergence of inflammatory pathways in sickle cell disease and asthma occurs, but there is also a heightened level of inflammation unique to sickle cell disease. Thus, wheezing may not be due to asthma but be a manifestation of sickle cell disease per se and the result of the increased pulmonary vascular volume. As a consequence, anti-asthma therapy may not be appropriate for all wheezy children with sickle cell disease and commencing treatment on the basis of a physician's diagnosis alone is inappropriate. Data from paediatric cohorts suggest use of spirometry, aeroallergen sensitisation tests, impulse oscillometry and dedicated interdisciplinary pulmonary clinics could improve diagnosis accuracy. Corticosteroids and bronchodilators are well-established treatments for asthma; observational studies suggest they may provide benefit for some children with sickle cell disease, but therapies such as hydroxyurea may improve respiratory outcomes in others. It is, therefore, essential children are thoroughly investigated and followed-up and a personalised approach taken to their care. Prospective randomised studies are required to establish the effectiveness of asthma therapies in children with sickle cell disease.

INTRODUCTION

Sickle Cell Disease (SCD) is an autosomal recessively inherited haemoglobinopathy affecting millions of individuals worldwide[1]. The average life expectancy of an individual with SCD is between 40 and 60 years although, with improved access to care, the age at death is steadily increasing[2]. It is caused by a mutation in the gene encoding the protein beta-globin, leading to the production of haemoglobin S, which causes impaired red blood cell (RBC) membrane deformability, a decrease in RBC flexibility and the RBCs to become sickle-shaped[3]. This results in a range of clinical manifestations, including anaemia, jaundice, painful episodes and elevated risks of infection and strokes. The increased adhesive properties of RBCs cause them to accumulate in the pulmonary vasculature, leading to hypoxemia, pulmonary hypertension, an asthma-like phenotype and other pulmonary complications[3]. The development of pulmonary complications is associated with a poorer prognosis. Acute Chest Syndrome (ACS) is the leading cause of death amongst individuals with SCD, accounting for up to 16% of deaths in this population[4]. It is estimated to affect 10-45% of individuals with SCD[5]. ACS episodes occur more commonly in children than adults; 50% of children will have had an ACS by ten years of age. Therefore, the early recognition and treatment of these conditions is essential for optimal outcomes. The purpose of this paper is to review the role of asthma in the development of the pulmonary complications of SCD, particularly in children.

Asthma

Asthma is the most common chronic disease of childhood, and it is estimated that it affects 14% of children worldwide[6]. It is a chronic inflammatory disease of the airways characterised by symptoms of wheeze, breathlessness, chest tightness, and cough with associated reversible expiratory airflow limitation. Common triggers include respiratory infections, allergens, irritants and occupational exposures[7].

Asthma exacerbations have been linked to inflammatory and immunological cell infiltration and, likely, their activation. It has been suggested that Th1 and Th2 cells play a role in modulating the severity of asthma exacerbations[7]. Th1 cells are involved in the production of pro-inflammatory cytokines such as interferon-gamma and tumour necrosis factor-alpha, which can contribute to airway inflammation and disease progression. On the other hand, Th2 cells produce anti-inflammatory cytokines such as interleukin-4 and interleukin-10, which can reduce airway inflammation and reduce the severity of asthma symptoms. The intensity and type of inflammatory cells infiltrate varies and can contain eosinophils, neutrophils and lymphocytes, or it can be dominated by only one of these types[6]. When allergens are the trigger, pulmonary T cells appear to trigger an immune response with a strong Th2 component, leading to an eosinophilic infiltration. It is unclear, however, if this shift in balance towards Th2 indicates a weakened Th1 activity, making the patient more susceptible to infections and exacerbations[7]. If the inciting event causes damage to the epithelium, as with infection, the resulting inflammation can lead to a neutrophilic infiltration.

Sickle cell disease and asthma

Asthma may occur in 15 to 28% of children with SCD which is greater than in the general population[8]. In one series the prevalence was higher amongst children aged 5 to14 years than those aged 0 to 4 years (13.9% versus 4.3%). The strongest predictor of asthma in children with SCD was the presence of atopy, which was reported in up to 80% of affected children[8]. Studies have shown that individuals with SCD and comorbid asthma have a higher mortality risk than those with SCD alone. In a review of 81 studies, SCD patients with asthma had a 1.7-fold increased risk of mortality compared to those without asthma[8]. Furthermore, a prospective cohort study of 1,521 SCD patients with asthma and 3,436 without asthma showed that those with asthma had a significantly higher risk of death (OR=2.95, 95% CI 1.72-5.06)[9]. In a study of children aged 4 to 16 years with SCD[10], more than 50% of the participants reported a history of wheezing associated with shortness of breath and, after a mean follow-up of 4.2 years, 45% participants had at least one episode of ACS. Participants with a history of wheeze causing shortness of breath had a significantly higher risk of developing ACS. Both SCD and asthma disproportionately affect minority populations, with African Americans accounting for 8 out of 10 SCD cases who have more than double the prevalence of asthma compared to non-Hispanic whites[7,11]. SCD and asthma are both associated with large economic burdens, with an estimated cost in the USA of $3 billion annually for SCD and over $80 billion for asthma[12, 13]. Making the diagnosis of asthma in children with SCD, however, can be difficult as symptoms of wheeze and shortness of breath are common to both diseases. Hence, many studies have potentially overestimated the prevalence of asthma in SCD since they have used a physician diagnosis or a history of wheeze.

Inflammation

Both SCD (SCD) and asthma are chronic inflammatory diseases in which the immune system becomes overactive and produces an inflammatory response. This response is triggered by various environmental and physiological factors, such as airborne allergens, certain drugs and physical activity. In SCD and asthma, the initial inflammatory trigger causes the release of pro-inflammatory cytokines and other inflammatory mediators, such as leukotrienes and histamine, from mast cells and other inflammatory cells[14]. These inflammatory mediators lead to downstream effects, such as the constriction of the airways or vasculature, increased vascular permeability and activation of immune cells. These effects are common to both SCD and asthma and can result in the development of clinical symptoms, such as shortness of breath, chest tightness, wheezing, and fatigue. Data from a cohort enrolled in the Cooperative Study for Sickle Cell Disease found children with asthma had an increased incidence of ACS (0.39 versus 0.20 events per patient year), painful episodes (1.39 versus 0.47 events per patient year) and an earlier onset of the first episode of ACS compared with children without asthma[15].

Up to 50% of SCD patients have raised IgE levels, compared to 15-20% of the general population[16]. A study conducted in Nigeria reported that the mean IgE levels were significantly higher in SCD patients than those in healthy controls[17] and the raised IgE levels were significantly associated with asthma. This risk was even higher in children 15 years old or younger who had a seven-fold higher risk of having asthma compared to those without raised IgE levels. The increased serum IgE seen in that population is also mirrored in murine models, where the overall IgE levels in sensitised SCD mice were significantly higher than in sensitised wild type mice[18]. These findings suggest that raised IgE is an important risk factor for asthma in SCD patients.

Inflammatory pathways in asthma and SCD overlap[14]. TNF-alpha is a proinflammatory cytokine that plays a role in both asthma and SCD. It is involved in the production of IL-8, which is an important chemoattractant for neutrophils, and IL-1beta, which is a key mediator of inflammation in both diseases. IL-1beta is also involved in the activation of the transcription factor nuclear factor-kappa B (NF-kB), which is a key regulator of inflammatory pathways in both asthma and SCD. In addition, IL-1beta has been shown to be important in the induction of mucus production, which is a hallmark of both asthma and SCD. Other pro-inflammatory cytokines such as IL-3, GM-CSF, and PGE2 are also upregulated in SCD patients [19]. Endothelial activation, a keystone of allergic asthma and initiation of inflammatory pathways, is triggered by upregulation of integrins and selectins in response to allergic stimuli. ICAM-1, VCAM-1, P-selection, and E-selectin are all markers of endothelial activation which are also upregulated in SCD[20]. In allergic asthma and SCD, there is increased survival of eosinophils in the airways, mediated by IL-3 and GM-CSF through increased PGE2 production[19]. Convergence of these common inflammatory pathways in both asthma and SCD is, therefore, likely to contribute to increased prevalence of asthma or an asthma-like phenotype in SCD.

There is, however, a heightened level of inflammation unique to SCD, that involves different pathways than those found in allergic asthma and may be a cause of the obstructive disease seen in SCD. A study comparing children with SCD and comorbid asthma with those with asthma only found the SCD group had a higher level of white blood cells and monocytes, while the control asthma group had more pronounced atopic characteristics[21]. Moreover, serum levels of tumour necrosis factor-alpha, interferon gamma inducible protein (IP)-10 and interleukin-4 were all higher in the SCD group. Additionally, exhaled breath condensate levels of monocyte chemotactic protein (MCP)-1 were found to be increased in the SCD group. A negative correlation was observed between forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) in patients with SCD and their IP-10 and LTB4 levels. Therefore, compared with atopic asthmatic patients, inflammatory markers involving Th-1, Th-2 and monocytic pathways were higher in the SCD group, although only Th-1 measures correlated with pulmonary function.

Leukotrienes are inflammatory mediators which are upregulated in asthma. In the lungs they are produced by mast cells, alveolar macrophages and infiltrating eosinophils. Their metabolites bind to vascular endothelium causing increased recruitment of eosinophils in the lung. They bind to receptors and induce bronchoconstriction, mucus secretion, airway oedema, smooth muscle proliferation and fibrotic tissue formation. High levels of urinary cysteinyl leukotriene, a metabolite of leukotrienes, are associated with asthma severity, frequency of exacerbations and exercise induced bronchoconstriction[22]. Cysteinyl leukotrienes and leukotriene B_4 are elevated at baseline in individuals with SCD (171 pg/mg

creatinine in children with SCD compared with 64 pg/mg creatinine in the control group) and are associated with SCD-related morbidity.

Arginine deficiency

Murine models of allergic asthma have established that arginine deficiency causes uncoupling of nitric oxide synthase (NOS) and leads to a decrease in nitric oxide and an increase in peroxynitrite, a pro-contractile molecule, both of which are associated with airway hyperresponsiveness in asthmatic conditions[14]. Cellular uptake of L-arginine is primarily mediated through the Na-independent cationic amino acid transporter (CAT) proteins of the y^+-system[23]. In allergic asthma, polycations are markedly elevated, disrupting the y+ system and hence inhibiting cellular arginine uptake. Arginine deficiency plays a well-established role in the pathophysiology of SCD and low bioavailability of l-arginine, the substrate for nitric oxide synthesis, is associated with pulmonary hypertension and vaso-occlusive events in SCD patients[24]. Decreased NO bioavailability is attributed to two mechanisms: the increased consumption of NO by cell-free plasma haemoglobin which results from haemolysis and the subsequent release of arginase from lysed cells which consumes the L-arginine available for NO synthesis[25]. To counter this effect, NO synthase and non-NO dependent vasodilators are upregulated. In addition, the low concentration of arginine results in the uncoupling of NO synthase, creating reactive oxygen species instead of NO, further decreasing NO bioavailability and aggravating oxidative stress. Studies show that arginase, an enzyme that changes L-arginine into ornithine and urea, is also found in high levels in SCD, also leading to a reduction of arginine bioavailability for NO synthesis. Furthermore, as arginine and ornithine share the same transport system for cellular uptake, an increase of arginase activity would reduce the arginine-to-ornithine ratio, thus further limiting arginine bioavailability for NO production. The presence of concomitant asthma and SCD is associated with an upregulation of baseline inflammation, leading to augmented expression of inducible nitric oxide synthase and arginase, thereby further depleting arginine reserves[26]. It is likely that overall, these mechanisms have a synergistic effect in comorbid disease and may explain the increase in adverse events seen in SCD patients with asthma.

Antibiotic exposure

Individuals with SCD demonstrate a predisposition to bacterial infections, particularly those caused by *Streptococcus pneumoniae*[27]. Consequently, they receive prophylactic penicillin V to inhibit the emergence of pneumococcal septicaemia. Data from meta-analyses including the results of over 12,000 children showed that exposure to antibiotics, particularly within the first year after birth, was significantly associated with development of childhood asthma (pooled OR 2.05)[28]. The association was independent of confounders such as antibiotic use to treat early symptoms of asthma, although there is a risk of reverse causality biasing that relationship[29]. Respiratory microbial communities, including those newly identified within the pulmonary tract, have been linked to the pathogenesis of allergic airway inflammation. It has been hypothesized that distinct microbial populations, notably Streptococcus, Haemophilus and Moraxella species, may regulate immune reactions and consequently modulate the clinical manifestations of airway inflammation[30]. A "critical window" of colonisation during early infancy has been proposed, during which the gut microbial communities modulate immune maturation throughout the body and may increase susceptibility to allergic airway inflammation. The underlying mechanisms of the so-called "gut-lung axis," i.e., how gut microbial communities affect lung immune responses and physiology, have yet to be completely elucidated, but may involve a shift in the differentiation of immune cells associated with asthma and the remote production of metabolites that influence distal sites. Overall, exposure to antibiotics in early life has a long-lasting effect on the gut and respiratory microbiome[31,32]. It is reasonable to hypothesise that these effects may be amplified in SCD due to prolonged and early exposure to antibiotics.

Wheezing in sickle cell disease patients may not always be asthma

Glassberg et al. proposed that wheezing in SCD may be an inherent element of SCD-associated pulmonary disorder, rather than asthma[33]. In a longitudinal study of children with SCD, wheezing was associated with significantly lower FEV_1/FVC and FEF_{25-75} at all time points and was a significant predictor of the decline in lung function. Importantly, although 22% of the patients had a physician's diagnosis of asthma, more (38%) had a history of wheezing[34]. The utilisation of different diagnostic criteria, including physician's diagnosis, patient symptom report, or a reversible diminution in PFT results, may account for the wide disparity in the reported prevalence of asthma in SCD populations.

Increased capillary blood volume causing small airway compression may explain the airway

obstruction observed in certain SCD patients. In a cohort of adults with HbSS disease, two measures of small-vessel size derived from CT scans were independently linked to reduced FEV_1, VC, and FEF_{25-75}, as well as increased respiratory system resistance[35]. These findings were corroborated by results from a cohort of children, where pulmonary capillary blood volume was inversely correlated with FEV_1, VC, and FEF_{25-75} and positively correlated with respiratory system resistance[36]. Increased pulmonary blood volume and airways resistance occurred immediately following blood transfusion in SCD children and were accompanied by significant reductions in FEV_1,VC and FEF_{25-75}. The change in lung function correlated with the increase in pulmonary capillary blood volume[37]. Those correlations suggest that an obstructive defect is related to the elevated pulmonary vascular volume, which is a result of the chronic anaemia experienced by SCD patients. Consequently, SCD-modifying treatments e.g. hydroxyurea, may be more advantageous than asthma therapy in certain patients. Indeed, in children with SCD, the annual decline in pulmonary function tests was halved in those who were receiving hydroxyurea, although this did not reach statistical significance[38].

Exhaled nitric oxide (NO) is increased in individuals with asthma[39]. Comparative studies between SCD paediatric patients and age- and ethnicity-matched controls have demonstrated that SCD patients do not have increased airway NO flux and that those levels were not correlated to airway obstruction[40]. Elevated alveolar pulmonary NO production, however, has been shown to correlate with pulmonary blood flow in SCD children, which may reflect the increased sheer stress due to their hyperdynamic circulation[41]. Airway obstruction and hyper-responsiveness in SCD patients are correlated with markers of haemolysis and IgE levels; however, unlike asthmatics, exhaled NO, eosinophil count, and skin prick test results did not correlate with those parameters[42]. Chaudry et al. demonstrated that despite children with SCD exhibiting airflow obstruction, this was not associated with increased methacholine sensitivity or raised exhaled nitric oxide. In a study of 131 SCD children, steady state exhaled NO was not correlated with an asthma diagnosis, wheezing symptoms, lung function parameters or prior sickle cell morbidity, but was associated with indicators of atopy and increased risk of subsequent ACS episodes[43].

Diagnosing asthma in sickle cell disease patients

A multicentre, prospective study of children with SCD identified three factors that were associated with asthma: parental asthma, wheezing causing shortness of breath and wheezing after exercise[44]. The accuracy of the model was 100% when two or more of the factors were present and 0% when none of the factors were present. In an unselected cohort of 187 children and adolescents with SCD, 45% of those with a physician diagnosis of asthma had at least two skin prick tests positive for common aeroallergens compared with only 15% of participants without asthma[40]. Those results suggest allergy assessment and skin prick testing could be a useful adjunct in making the diagnosis of asthma in SCD patients. The National Heart Lung and Blood Institute recommends asthma screening in SCD. The breathmobile case identification survey (BCIS), a seven-question survey, has been validated in SCD patients[45]. A cohort with a 41% prevalence of asthma completed the BCIS, spirometry, and FeNO testing. The sensitivity, specificity, positive predictive value and negative predictive value of the abbreviated BCIS were 67.3%, 90.8%, 83.3%, and 80.2% for asthma diagnosis respectively.

In adults, the presence of an obstructive picture on spirometry, with a ratio of FEV_1/FVC <70% and associated reversibility following administration of bronchodilator is in keeping with asthma[7]. Furthermore, in adult SCD populations, an FEV_1 <70% predicts earlier mortality and a higher ACS incidence rate[46]. In a large multicentre study in the USA, only 31% of patients with SCD aged between 5 and 34 years, comorbid asthma and a history of ACS had undergone spirometry[47]. Guidelines do not recommend routine monitoring of children with SCD for asthma. Although, in a retrospective study of 127 children, obstructive lung disease and asthma were significantly associated with a history of ACS[48]. In addition, data from case studies demonstrates bronchodilator reversibility in children with SCD and supports the use of FEV_1 measurement, especially in acute exacerbation[49]. A challenge, however, especially in paediatric populations, is that spirometry results are frequently in the normal range when measured during stable disease and even in patients with severe asthma[50].

SCD children with wheezing should undergo assessment for bronchial hyper-reactivity according to their baseline lung function. Those with airway function less than 70% predicted should receive a bronchodilator challenge and those with lung function better than 70% predicted either a cold air or exercise challenge. A methacholine challenge should not be used as this can precipitate an ACS. The most rapid

deterioration in lung function occurs in young children who may not be able to undertake spirometry. Impulse oscillometry is an effort independent pulmonary function test which measures total airway resistance and reactance and has been successful in monitoring asthma in children under six years of age. A comparative study found impulse oscillometry was a more sensitive diagnostic tool than spirometry in individuals with asthma and SCD, diagnosing 20 participants compared to seven diagnosed using FEV_1[51].

Treatment of asthma in sickle cell disease

Inhaled bronchodilators relax the smooth musculature of the airways to provide relief from the manifestations of bronchial constriction[7]. Some studies demonstrate an increase in FEV_1 in a subset of individuals with ACS and reactive airways disease, however, the ability of bronchodilators to enhance other clinical outcomes in that population is uncertain[8]. A recent Cochrane review found no randomised controlled trials exploring the use of bronchodilators for ACS in SCD[52]. One study showed bronchodilator use in children with ACS and SCD resulted in a 13.2% increase in length of stay, however in the subgroup identified as having comorbid asthma, bronchodilator use was associated with a 17.9% reduction in length of stay[53]. On the other hand, a cross-sectional study in children with and without SCD receiving asthma treatment found that SCD children had lower baseline heart rate variability and higher vagal tone[54]. This was further worsened by administration of salbutamol, suggesting there is underlying impaired parasympathetic control and sympathetic overactivity in SCD patients.

Corticosteroids are potent immunomodulators. Methylprednisolone in vaso-occlusive crisis significantly decreased the duration of analgesic therapy and hospitalisation in ACS[55]. Dexamethasone administered to 43 children with mild to moderately severe ACS in a randomized, double-blind, placebo-controlled study[56] resulted in a reduction in the duration of hospitalisation, requirement for transfusion due to deteriorating anaemia, duration of fever, need for supplementary oxygen and analgesia. Unfortunately, there have been associated adverse events related to corticosteroids, including recurrent episodes of painful exacerbations necessitating hospital readmission, serious vaso-occlusive crises, ACS, stroke, renal infarction, coma and mortality[57]. Between 15 and 27% of patients treated with corticosteroids have been reported to have had a rebound pain crisis and required readmission[55,56]. In contrast, another study found short courses of dexamethasone therapy did not have an effect of readmission rates[58]. Most recently, a large American study found corticosteroids were associated with an increased length of stay and a higher three day readmission rate[59]. In a randomized, double-blind, placebo-controlled clinical trial assessed the efficacy of montelukast in SCD patients[60], there were no significant differences in sVCAM levels or any of the secondary outcomes between the two groups.

Conclusion

Asthma is associated with increased SCD complications and hence it is imperative that acute asthma exacerbations in SCD are identified and treated promptly, since hypoxia can trigger further red cell sickling and induce ACS episodes. Wheezing, however, can be due to SCD per se, hence a physician's diagnosis is insufficient to determine optimum therapy. Children with SCD and wheeze require pulmonary function testing with assessment of bronchial hyper-responsiveness and skin prick testing to determine if anti-asthma therapy would be appropriate. In those who cannot perform spirometry, impulse oscillometry assessments should be undertaken.

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