

Temporal Relationship of Asthma to Acute Chest Syndrome in Sickle Cell Disease

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Summary. Acute chest syndrome (ACS) is an important cause of mortality and morbidity in children with sickle cell disease (SCD). An association between asthma and ACS has been reported. Our aims were to determine whether asthma was more common in SCD children than controls and the relationship of the timing of the SCD children's first ACS episode to a diagnosis of asthma. One hundred and sixty-five SCD children median age 8.2 (range 0.3–17.3) years and 151 similar ethnic origin and aged controls were prospectively recruited into the study and a detailed history was taken from all of the children to determine if they were taking anti-asthma medication. The medical records of the SCD children were examined to assess whether they had an ACS episode, the age this episode occurred and when any diagnosis of asthma had been made. A similar proportion of the SCD children and controls were taking anti-asthma medication (7% and 9%). Thirty-three SCD children had at least one ACS episode. More of the children who had an ACS compared to those who had not were taking anti-asthma medication ($P = 0.02$). The ACS children had been diagnosed as asthmatic at a median of 3.5 (range 0.5–7) years prior to their first ACS episode. In conclusion, these results suggest asthma exacerbations may predispose to ACS episodes. *Pediatr Pulmonol.* 2007; 42:103–106. © 2006 Wiley-Liss, Inc.

Key words: asthma; anti-asthma medication; hospitalization; acute chest syndrome; sickle cell disease; diagnosis.

INTRODUCTION

Sickle cell disease (SCD) is the commonest inherited disorder of the African-Caribbean population with between 0.11 and 0.14 per 500 affected infants born in the UK each year.¹ Recently reported studies have highlighted a significant association between asthma and acute chest syndrome (ACS).^{2–4} An aim, therefore, of this study was to test the hypothesis that asthma is commoner in SCD children compared to ethnic and aged matched controls. It is possible that an asthma exacerbation could lead to an ACS episode, in which case diagnosis of asthma would precede the first ACS episode. A further aim of this study then was determine the relationship of the timing of the SCD children's first ACS episode to any diagnosis of asthma.

MATERIALS AND METHODS

Children aged less than 18 years, who had sickle cell anemia (homozygous for sickle hemoglobin (HbSS)) were recruited into a study of pulmonary function in SCD from two specialist clinics in Southeast London. Siblings and

children without HbSS of similar age and ethnic origin to the SCD children were recruited as controls. All the children were Afro-Caribbean. The study was approved by the King's College Hospital Research Ethics Committee and parents gave informed written consent for their children to take part.

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The SCD children and the controls were seen in the Amanda Smith Unit for the prevention and treatment of breathing problems in children. A detailed history was taken, in particular to determine whether the child had been diagnosed as asthmatic and was taking anti-asthma medications. The medical records of the SCD children were examined to determine if and at what age they had an ACS episode. An ACS episode was diagnosed if, during a hospital admission, the child had suffered chest pain, dyspnoea, and pyrexia and had a new pulmonary infiltrate on their chest radiograph.⁶ The medical records of children who had at least one episode of ACS (ACS group), were examined to determine the age at which any diagnosis of asthma was made.

Analysis

Differences were assessed for statistical significance using the chi-square test with the Yate's correction for continuity applied.

Patients

One hundred and sixty-five children with SCD, median age 8.2 (range 0.3–17.3) years and 151 ethnically matched controls median age 7.7 (range 1.2–17.8) years were included in the study.

RESULTS

Twelve (7%) SCD children and 14 (9%) controls had been diagnosed as asthmatic and were taking anti-asthma medication ($P=0.7$). Thirty-three SCD children had at least one ACS episode. Six of the 33 children (18%) who had ACS episodes were currently taking anti-asthma medication, compared to six of the 132 SCD children (5%) who had not suffered an ACS episode ($P=0.02$). The ACS children had been diagnosed as asthmatic at a median of 3.5 (range 0.5–7) years prior to their first ACS episode, when their median age was 1.8 (range 0.2–2.0) years.

DISCUSSION

We have demonstrated that a requirement for anti-asthma medication was not more common in SCD children. Children with SCD who had an ACS episode compared to those who had not; however, were more likely to be taking anti-asthma medication and that the asthma diagnosis preceded the first ACS episode. It has been previously demonstrated that children with SCD and asthma, when admitted to hospital for pain, were more likely to have an ACS episode² and we have previously highlighted³ that asthma was more common in those children who had recurrent ACS episodes compared to those who had suffered a single or no ACS episode. The

present study, however, is the first to our knowledge, which has determined the relationship of the timing of the age of diagnosis of asthma to the occurrence of the first ACS episode and hence gives insight into the possible pathophysiology of the relationship between asthma and ACS episodes. It is possible that an asthma exacerbation could lead to an ACS episode. Inflammatory mediators and oxidant species produced during an asthma exacerbation^{7,8} could lead to an increased expression of adhesion molecules⁹ and hence adhesion of the erythrocytes to the vascular endothelium^{10–12} resulting in a vaso-occlusive crisis. In addition, the hypoxaemia associated with an asthma exacerbation could promote sickling in the pulmonary vessels and hence an ACS episode. An alternative hypothesis to explain the association of asthma and ACS episodes is that the increased release of inflammatory mediators and the vascular leak during an ACS episode could increase chronic airway hyperreactivity⁵ and hence asthma. To test such a hypothesis would require examination of the children during an ACS, which was not part of our protocol. Our finding that a diagnosis of asthma occurred prior to the first ACS episode in certain of the SCD children does, however, suggest an asthma attack might precipitate an ACS episode in some SCD children and this merits further study.

A limitation of our study is that we may have underestimated the number of children with asthma. The SCD children, however, were under regular follow up, thus asthma would be more likely to be diagnosed if present in that group than the controls who were not under regular follow up. As a consequence, we do not feel this prevented us from finding an excess of asthmatics in the SCD group had it been present. In adolescents, one third of asthmatics, that is those with asthma-like symptoms and one or more obstructive airway abnormalities may not have been diagnosed as asthmatic by a physician.¹³ Overall, however, the undiagnosed asthmatics had milder symptoms, were less likely to be breathless and had lower methacholine responsiveness.¹³ In this study we, therefore, categorized the children as having asthma not only if they had a physician's diagnosis but also that they were taking anti-asthma medication, thus they were likely to have clinically significant asthma. We have demonstrated that similar proportions of the SCD children and the controls were taking anti-asthma medication, suggesting clinically significant asthma did not differ between the two groups. It is possible, however, that certain of the children who were not taking anti-asthma medication had clinically significant asthma and their lack of treatment represented inappropriate management. All the SCD children, however, as stated above were under regular follow up and, if they did have inappropriately untreated asthma, they would be likely to have become increasingly symptomatic and detected and treated at follow up. Our results are in keeping with findings from epidemiological studies,

which have reported either a similar prevalence^{15–17} of asthma in SCD patients compared to controls, although one other study highlighted a lower prevalence in the SCD children.¹⁴ Using a modified version of the ISAAC questionnaire, we however, demonstrated amongst Jamaican children, a diagnosis of asthma was commoner in those with SCD than the controls,³ but interestingly the proportions of children in the two groups taking anti-asthma medication did not differ significantly. The Isaac questionnaire used in our earlier study³ was modified specifically for use in Jamaican children, using such terms as a “touch” of asthma and thus it would be possible to assess the UK group using the modified questionnaire.

Previous studies have demonstrated a high occurrence of airway hyper-reactivity in SCD children. A positive response to a bronchodilator challenge was found in 30% of a group of SCD children with a normal pattern of lung function, in 67% of those with a restrictive pattern and 78% of those with an obstructive pattern.¹⁸ No controls, however, were studied. In another study,¹⁹ findings in SCD children were compared to sibling controls. Airway hyper-reactivity was documented in 83% of SCD children already known to have asthma, in 64% of those with no history of asthma and in none of the control children. We did not assess hyper-reactivity in all the children who took part in the prospective follow up study, so cannot exclude that airway hyper-reactivity was commoner in SCD children. We have, however, previously reported in a subset of this population a positive response to a bronchodilator challenge was not commoner in SCD children compared to ethnic-matched controls of similar age.²⁰

All the SCD children with asthma who had ACS episodes had been diagnosed as suffering from asthma at 2 years of age or younger. The ability to diagnose asthma in very young children, particularly infants, had been disputed.²¹ Nevertheless, all of the SCD children who had an ACS episode and had been diagnosed as asthmatic were still taking anti-asthma medication when seen at follow up in the study.

In conclusion, in asthmatic SCD children, the diagnosis of asthma preceded the occurrence of their first ACS episode. Although our data do not prove asthma predisposes to or is mechanistically related to ACS episodes, they are consistent with the hypothesis that an asthma exacerbation may predispose to an ACS episode. Whether, then, administration of prophylactic anti-asthma medication, once a diagnosis is made, would reduce the pulmonary morbidity of SCD merits consideration.

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