Asthma is associated with acute chest syndrome, but not with an increased rate of hospitalization for pain among children in France with sickle cell anemia: a retrospective cohort study

Asthma and sickle cell disease are two common chronic diseases that may exist as co-morbid conditions. Our group has recently demonstrated that asthma, the most common chronic disease among children, is a distinct co-morbid condition among children with sickle cell anemia (SCA)[1] and has a similar prevalence among children with and without sickle cell disease.[2] Furthermore, we have demonstrated that asthma is associated with an increased rate of both acute chest syndrome (ACS)[2,3] and pain, the most common complication associated with SCA.[2] The majority of the supporting data demonstrating the association between asthma and acute chest syndrome episodes has been documented in the United States. Given that asthma is related to genes and environment, we tested the hypothesis that the strength of the association between asthma and SCA morbidity would be confirmed in another country with a different genetic population and perhaps different environmental factors.

Approval to conduct this retrospective study was obtained from the Institutional Review Board of the Washington University School of Medicine and the Ethics Committee for the Centre Hospitalier Intercommunal Créteil (CHIC). Approval was given to analyze the de-identified data of children with SCA who were followed at the CHIC from 1980 through 2007. Patients were followed at CHIC and were seen at least annually for interval history which consisted of a physical examination and evaluation of SCA-related morbidity, co-morbid conditions, medication histories, and laboratory testing that included complete blood count. Table 1 describes baseline features of children with and without a doctor-diagnosis of asthma. All children regularly receiving medical care in France carry *un carnet de santé*, i.e. a *health notebook*, which is used to document all information regarding their health and hospitalizations. From this health notebook, the lifetime hospitalization history was recorded in a database for all children followed at CHIC.

The start of patient-year accumulation began on the date of birth for those born in France and on the date of the first clinical visit or hospital admission for those not born in France. The end of patient-year accumulation occurred when the earliest date of one of the following was documented: (i) the start of chronic blood transfusion therapy; (ii) the start of hydroxyurea therapy; (iii) the start of hematopoetic stem cell transplant; (iv) death, or (v) 18th birthday. The length of follow-up was at least six months, but not more than 18 years for any subject.

ACS was defined as a new radiographical finding of the lungs associated with fever, respiratory signs or thoracic pain. A pain episode was defined as pain in the extremities, back, abdomen, chest or head that resulted in hospitalization. The diagnosis of asthma was made when a child with sickle cell anemia had 3 or more episodes of bronchiolitis under the age of two years or when wheezing was heard at the time of a visit to the clinic or at hospitalization. Confirmation of the asthma diagnosis was based on an audit by a pediatric pulmonologist documenting more than one episode of wheezing.

The medical records of 324 children with SCA were reviewed. Among this group, 297 children were evaluated for a doctor-diagnosis of asthma, for a total of 1,805 patient-years. Seventy-nine percent of the cohort children were born in France (235 out of 297). In the cohort, 8.4% (25 out of 297) of the children had a doctor-diagnosis of asthma (Table 1).

The rate of ACS was significantly increased in those with asthma diagnosis (0.31 events per patient year for those with asthma and 0.16 events per patient year for those without asthma, p value=0.03). Gender, white blood cell count, percent fetal hemoglobin, and baseline

Table 1. Demographic features of children with sickle cell anemia followed at the Centre Hospitalier Intercommunal Créteil, France with and without a doctor-diagnosis of asthma.

	Children with asthma (n=25)	*Children without asthma (n=272)*	*p*
Gender			0.83
Male	14 (56%)	141 (52%)	
Age at first ACS (years)*		0.39	Mean
3.6	4.3		
Median (Range)	1.7 (1.1–13.3)	3.3 (0.4–16.2)	
Follow-up (years)#			0.28
Mean	7.0	6.0	
Median (Range)	7.2 (0.8–16.5)	4.5 (0.5–18.0)	

**Eighteen of 25 (72%) asthmatics and 118 of 272 (43%) non-asthmatics experienced ACS events. Mean age at first ACS event was given and compared. #Length of follow-up in years: (i) entry date was date of birth, if born in France, or date of first clinical visit or of first hospital admission, whichever was earlier, if not born in France; (ii) truncation date was date of last clinic visit, initiation date of hydroxyurea, initiation date of chronic blood transfusion therapy, initiation date of stem cell transplant, or date of death, whichever was the earliest; (iii) length of follow-up between 0.5 and 18 years was assessed in this study. *Age denotes age at date of truncation; i.e., date of last clinic visit, initiation date of hydroxyurea, initiation date of chronic blood transfusion therapy, initiation date of stem cell transplant, or date of death, whichever was the earliest.*

Table 2. Acute chest syndrome and pain incidence rate (events per patient-year of follow-up), rate ratio, 95% confidence interval and *p* values for acute chest syndrome and for children with (n=25) and without asthma (n=272).

	Rate among those with/without asthma	*Rate ratio*	*95% lower confidence interval*	*95% upper confidence level*	*p*
Acute chest syndrome	0.31/0.16	1.88	1.07	3.29	0.03
Pain	0.72/0.60	1.19	0.68	2.09	0.53

hemoglobin level were not significant predictors of ACS events. The rate of pain was not increased in those with asthma diagnosis (0.72 events per patient year for those with asthma and 0.60 events per patient year for those without asthma, p value=0.53). Furthermore, baseline white blood cell count, percent fetal hemoglobin and baseline hemoglobin were not significant predictors of pain episodes (Table 2). When compared to the remaining group of children without asthma (n=280), children taking daily inhaled corticosteroids (n=17) had an increased rate of ACS (0.43 events per patient-year *vs.* 0.16 events per patient-year; p-value=0.002) and no significant increase in rate of pain (0.99 events per patient-year *vs*. 0.59 events per patient-year; p=0.122) .

Evidence from previous studies suggested that asthma is associated with increased rates of ACS events[2,3,4] and pain episodes.[2] The results of this study confirmed previous data indicating an association between asthma and ACS events, but did not reveal an association between asthma and pain events. The reasons for the lack of association between asthma and pain in the Créteil population are not known, but may be related to differences in how care is delivered in that center and/or unmeasured environmental factors. Two studies have assessed the impact of the environment on SCD-related pain episodes.[5,6] Both studies demonstrated that local environmental factors may contribute to the rate of hospitalization for pain.[5,6]

The background rate of asthma among the children with SCA in France, 8.4%, was not significantly different from a comparable cohort of children of African descent living in France, 9.1%.[7] Taken together, these studies provide no evidence that a physician diagnosis of asthma occurs more frequently among children with sickle cell disease when compared to children without sickle cell anemia.

In summary, we provide further support that asthma is a potentially treatable risk factor associated with ACS. Future prospective studies to classify lung disease associated with SCA and to determine the effectiveness of asthma management in preventing SCA-related morbidity are warranted.

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Clinical and biological features of acute promyelocytic leukemia patients developing retinoic acid syndrome during induction treatment with all-trans retinoic acid and idarubicin

Although all-trans retinoic acid (ATRA) is generally well tolerated, some patients develop a potentially severe and life-threatening complication referred to as retinoic acid syndrome (RAS). We analyzed here the biological and clinical characteristics of 110 consecutive patients with genetically proven APL, with the aim of identifying predictive features of developing RAS.

All patients described were treated with AIDA[1] or AIDA 2000[2] protocols, between January 1993 and December 2005 at the University "La Sapienza" of Rome. Diagnosis was confirmed at the genetic level by RT-PCR identification of the PML/RARa hybrid as previously described.[1] The presence of FLT3 internal tandem duplication (ITD) was investigated in 80 cases using the technique previously reported.[3] Immunophenotype was performed by flow-cytometry using a wide panel of monoclonal antibodies including CD13, CD33, HLA-DR, CD34, CD2, CD7, CD15, CD9, CD117, CD56, MPO (Becton Dickinson, Mountain Flow, CA, USA), considering a sample antigen-positive if >20% of the cells reacted with a specific monoclonal antibody, whereas for CD34 a cut-off of >10% was used. According to Frankel *et al.*[4], the diagnosis of *definitely present* RAS was clinically established by the presence of at least three of the following signs: weight gain, respiratory distress, unexplained fever, interstitial pulmonary infiltrates, pleural or pericardial effusions. For statistical analysis, the Wilcoxon-Mann-Whitney test was per-