2007

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Acknowledgments: we would like to thank Wayne Morgan, Julio Fontan, Susan Redline and Avijit Datta for the helpful comments and review of this manuscript.

Funding: supported in part by the Doris Duke Charitable Foundation (JHB, MRD) and by the National Institutes of Health, National Heart, Lung and Blood Institute, contract N01-HB-47110, RO1 HL079937 (MRD, RCS), T32 HL07873 (JHB).

Manuscript received May 12, 2006. Accepted May 17, 2007.

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ABSTRACT

An analysis of a prospective cohort of individuals with sickle cell anemia (SCA), enrolled from birth through adulthood, was conducted to determine if asthma is a risk factor for death in SCA. All-cause mortality was determined for participants after adjusting for known risk factors for death in SCA. The study included 1,963 individuals who were followed for 18,495 patient-years. After controlling for established risk factors, individuals with SCA and asthma had a more than two-fold higher risk of mortality (hazard ratio 2.36, 95% CI 1.21 to 4.62, p=0.01). To summarize, asthma is a risk factor for death in SCA.

Key Words: sickle cell anemia, mortality, asthma.

Haematologica 2007; 92:1115-1118

The Co-operative Study for Sickle Cell Disease (CSSCD), a large, multi-center natural history study of sickle cell disease, determined the life expectancy for individuals with sickle cell anemia (SCA) to be in the fifth decade of life after adjustment for previously identified risk factors including white blood cell count (WBC), fetal hemoglobin level (HbF), presence of renal failure, seizures, and acute chest syndrome (ACS.[1] Asthma is a common chronic illness that affects approximately 9% of African-American adults[2] and 15% of African-American children.[3-6] It is associated with an increased incidence of ACS and painful episodes among children with SCA(7). The contribution of asthma to premature death has not been assessed in individuals with SCA. Given the established association between asthma and pain and ACS in this same cohort,[7-9] and the recognized risk of death in patients with even a single episode of ACS,[10] we used data collected prospectively over the 20-year term of the CSSCD to test the hypothesis that a concurrent diagnosis of asthma in patients with SCA is associated with increased mortality.

Design and Methods

Study design

The CSSCD study design has been previously reported.[1,11,12] Participants were assessed at least once for asthma on a supplemental history form and/or a pulmonary function intake form. Original consent and assent were obtained in accordance with the requirements of the human subjects committees at participating clinical centers. Additional Institutional Review Board approval was obtained from Washington University School of Medicine for analysis of the de-identified data held by the National Heart, Lung, and Blood Institute. The cohort for this study included African-American participants with hemoglobin SS enrolled in the CSSCD from birth to 61 years of age. Participants who died before the age of five (n=33) or were not followed beyond the age of five (n=45) were excluded from this study. This is because a diagnosis of asthma is unclear in young children, and death from bacterial infection in children under the age of 5 was frequent in the era of the CSSCD study. Of the 2,557 individuals enrolled, 76.8%

(n=1,963) had adequate clinical data to classify asthma. Follow-up for mortality data was censored for loss to follow-up or bone-marrow transplant.

Classification

Asthma. Asthma was classified by a clinical diagnosis of asthma recorded during the medical history, an acute asthma event during the study period, or use of prescribed asthma medications on a clinic visit form. Based on available evidence, an assumption is made that asthma, a chronic condition, is a life-long illness.[13]

Death. An event reported on a form completed by the CSSCD site investigator at the time of the event. The etiology of death and confirmation of the cause of death was not uniform across the study period. Therefore, for this analysis, all-cause mortality was used.

Outcome measures and statistical methods

Data analysis was performed in SAS, version 9.1. Demographic parameters were compared between subjects classified for asthma using *t*-tests and Fisher's exact test. Time to death was summarized using Kaplan-Meier product-limit estimates and tested by Cox regression. Analysis of deaths included left-truncation of the at-risk interval from birth to date of entry. Mortality (median age at death) was compared for individuals with and without asthma. In addition to asthma classification, Cox regression analysis included the following co-variates and previously established risk factors for death: age, WBC count, renal failure, HbF level, seizure, and ACS.[1] Laboratory values were determined based on the average of all values during follow-up, excluding laboratory values during acute events and HbF percent before the age of 2. The proportional hazards assumption was tested and supported by inspecting martingale residuals and by testing for a time-dependent effect of asthma.

Results and Discussion

Demographics

A total of 1,963 African American individuals with SCA who were classifiable for asthma enrolled in the study and were followed for a total of 18,495 patient-years. The demographic features of the cohort are listed in Table 1. A total of 138 individuals (7.0%) had asthma; 70% (97/138) were classified by a physician's diagnosis, 10% by documentation of an acute asthma event, and 20% by the recorded of use of a prescribed asthma medication (beta-agonist, inhaled corticosteroid, theophylline, inhaled non-steroidal anti inflammatory medication). The 594 individuals who could not be classified for asthma were older (mean age: 16.4 yrs.) and had shorter follow-up (mean follow-up: 7.3 yrs.) when compared to those included in the cohort for analysis.

Table 1. Demographics of patients with sickle cell anemia that were evaluated for asthma.

	Asthma cases (n=138)	*Controls (n=1825)*	*p value*
Gender – no. (%)			
Male	65 (47%)	872 (48%)	0.93
Age at entry – yrs			
Mean	9.7	14.2	<0.001
Range	0.0 to 47.9	0.0 to 61.4	
Asthma Dx Age[1] – yrs			
Mean	14.0	20.2	<0.001
Range	5.0 to 53.9	5.0 to 67.4	
Follow-up[2] (yrs)			
Mean	10.8	9.3	<0.001
Range	3.0 to 19.6	4.6 to 19.8	

[1]Age is the time when asthma diagnosis was first assessed. [2]Follow-up for the cohort is between date of entry and loss to follow-up or death.

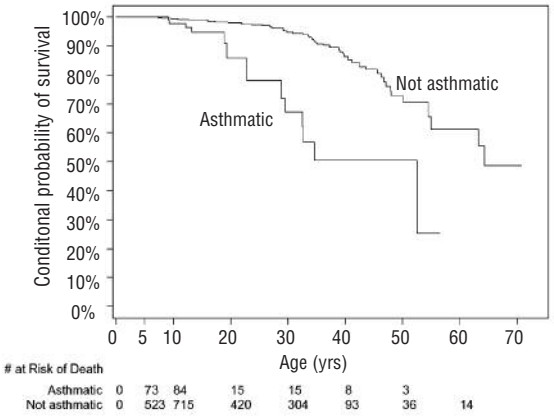

Figure 1. Kaplan-Meier plot of age of death for subjects with sickle cell anemia and asthma (n=138) and those without asthma (n=25) conditional on survival beyond age 5 years. Relative survivorship given here is conservative because asthmatic subjects were enrolled at younger ages and mortality risk increases with age.

Asthma and sickle cell anemia-related mortality

Asthma was associated with a significant increase in the risk of all-cause mortality (Figure 1). The median life span for individuals with and without asthma who survived to the age of 5 was 52.5 and 64.3 years of age respectively. After controlling for age, WBC count, HbF level, renal failure, seizures, and ACS rate, individuals with SCA and asthma had over a two-fold higher mortality risk when compared to children with SCA without asthma (hazard ratio 2.36 by Cox regression, 95% CI 1.21 to 4.62, p=0.01, Table 2). In the CSSCD, the average life span for adults with SCA was determined to be in the fifth decade of life. Several co-morbid conditions including seizures, renal failure, and ACS were determined to be risk factors for mortality in this cohort.[1] However, these analyses did not include an assessment of asthma, a recently described common co-morbid condition that is associated with an increased risk of pain and ACS.[7] The present analysis of data from this cohort has determined that asthma is a sig-

Table 2. Cox regression estimates of mortality predictors, including estimates from both the final multivariate model and each predictor in a univariate model.

	Multivariate Model			*Univariate Models*		
	N	*Hazard ratio (95% CI)*	*p value*	*N*	*Hazard ratio (95% CI)*	*p value*
Age at study entry (yrs)	1828	0.779 (0.709,0.856)	<0.0001	2635	1.005 (0.956,1.057)	0.8496
Fetal hemoglobin (%)		0.929 (0.863,1.000)	0.0511	2407	0.916 (0.878,0.956)	0.0001
ACS rate (<0.2 yr^{-1} vs. ≥0.2 yr^{-1})		2.325 (1.267,4.265)	0.0064	2635	2.418 (1.799,3.249)	<0.0001
Renal insufficiency (Yes vs. No)		7.168 (3.687,13.936)	<0.0001	2635	3.922 (2.536,6.064)	<0.0001
Seizures (Yes vs. No)		1.275 (0.519,3.131)	0.5959	2635	2.405 (1.465,3.948)	0.0005
White-cell count (10^9/L)		1.182 (1.085,1.287)	0.0001	2566	1.107 (1.057,1.160)	<0.0001
Asthma (Yes vs. No)		2.362 (1.208,4.621)	0.0120	1963	3.855 (2.081,7.140)	<0.0001

nificant risk factor for premature death among individuals with SCA. Prior to the start of this study, we postulated that asthma was a biologically plausible risk factor for premature death in individuals with SCA primarily because asthma increases the prevalence of ACS episodes, a known risk factor for death in this population.[7] The mechanism of an association between asthma and death has not been clarified by this study, but several observations about asthma and SCA support such an association. Firstly, in asthma, lung segments are obstructed by mucus and edema before pulmonary blood flow can adjust.[14] The hypoxemia that results from ventilation-perfusion mismatch promotes local tissue hypoxia and sickling of red blood cells[15] possibly producing disease not only in the lung (ACS episodes), but more distally in other organs affected by SCA. Secondly, asthma is known to be associated with an increased incidence of ACS episodes which in turn may increase the risk of chronic lung disease.[16] Klings *et al*. recently described that pulmonary function abnormalities are common in this cohort affecting up to 90% of individuals;[17] however, no assessment of a physician's diagnosis of asthma was included. Thirdly, asthma[18] and SCA[19-22] are both associated with a pro-inflammatory state. Therefore, individuals with SCA and asthma would also be expected to have additional complications related to asthma and/or SCA. This is supported by evidence from this cohort that suggests individuals with SCA and asthma also have higher rates of pain and ACS.[7] This study does have limitations. The cohort for this analysis did not include children under the age of 5. The diagnosis of asthma is more difficult in young children, and the impact of transient wheezing and remitted asthma on lung function and future SCA-morbidity has not been established.[23,24] This analysis also has only limited ability to check for all factors relating to death in individuals with SCA, such as pulmonary hypertension, a more recently identified risk factor which was not consistently reported in this cohort.[25] In this analysis, we did check for known risk factors for death in this cohort as previously reported. We are unable to identify a direct cause and effect mechanism for the association between asthma and premature death. However, recognition of the association between SCA and asthma is significant since established, evidence-based acute and chronic treatment for asthma is available.

To summarize, based on the analysis of a large, well characterized cohort of individuals with SCA, we have demonstrated that asthma was associated with a significant increase in the risk of mortality. We provide evidence that even after adjustment for the presence of ACS and other known risk factors, asthma is an independent predictor of mortality in patients with SCA. Future prospective studies to classify lung disease associated with SCA and determine the effectiveness of asthma management in preventing SCA-related morbidity and mortality are warranted.

Appendix

The following investigators participated in the Co-operative Study of Sickle Cell Disease: R. Johnson, Alta Bates Hospital, Oakland, CA, USA.; L. McMahon, Boston City Hospital, Boston, USA; O. Platt, Children's Hospital, Boston; F. Gill and K. Ohene Frempong, Children's Hospital, Philadelphia; G. Bray, J.F. Kelleher, and S. Leikin, Children's Hospital National Medical Center, Washington, D.C.; E. Vichinsky and B. Lubin, Children's Hospital, Oakland, Calif.; A. Bank and S. Piomelli, Columbia Presbyterian Hospital, New York; W. Rosse, J. Falletta, and T.R. Kinney, Duke University, Durham, N.C.; L. Lessin, George Washington University, Washington, D.C.; J. Smith and Y. Khakoo, Harlem Hospital, New York; R.B. Scott, O. Castro, and C. Reindorf, Howard University, Washington, D.C.; H. Dosik, S. Diamond, and R. Bellevue, Interfaith Medical Center, Brooklyn, N.Y.; W. Wang and J. Wilimas, LeBonheur Children's Hospital, Memphis, Tenn.; P. Milner, Medical College of Georgia, Augusta; A. Brown, S. Miller, R. Rieder, and P. Gillette, State University of New York Downstate Medical Center, Brooklyn; W. Lande, S. Embury, and W. Mentzer, San Francisco General Hospital, San Francisco; D. Wethers and R. Grover, St. Luke's-Roosevelt Medical Center,

New York; M. Koshy and N. Talishy, University of Illinois, Chicago; C. Pegelow and P. Klug, University of Miami, Miami; M. Steinberg, University of Mississippi, Jackson; A. Kraus, University of Tennessee, Memphis; C. Dampier, Wyler Children's Hospital, Chicago; H. Pearson and A.K. Ritchey, Yale University, New Haven, Conn.; S. McKinlay, D. Gallagher, and D. Brambilla, New England Research Institute, Watertown, Mass, USA; and M. Gaston and C. Reid, National Heart, Lung, and Blood Institute, Bethesda, Md.

The Co-operative Study of Sickle Cell Disease was conducted and supported by the National Heart, Lung and Blood Institute in collaboration with site investigators. This manuscript was not prepared in collaboration with investigators of the Co-operative Study of Sickle Cell Disease and does not necessarily reflect the opinions or views of the Co-operative Study of Sickle Cell Disease or National Heart, Lung and Blood Institute. The principal investigator for this study had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Authors' Contributions

JB contributed to the design of the study, collection and analysis of data, and manuscript preparation and review; EM contributed to the design of the study, statistical analysis and review and preparation of the manuscript; RCS contributed to study design and manuscript review and preparation; MRDB contributed to the design of the study, analysis of the data and manuscript preparation and review. All authors approve the final version of the manuscript.

Conflicts of interest

The authors reported no potential conflicts of interest.

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