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Mortality, Asthma, Smoking and Acute Chest Syndrome in Young Adults with Sickle Cell Disease

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Abstract
Purpose Sickle cell disease (SCD) patients with asthma have an increased risk of death. Acute chest syndrome (ACS) is a major cause of mortality in patients with SCD, and ACS may be more common in SCD patients who smoke. The purpose of this study was to test the hypothesis that mortality in young adults with SCD would be greater than that of controls during a 10-year period and to determine whether asthma, reduced lung function, ACS episodes, and/or smoking predicted mortality during the follow-up period.
Methods The outcomes during a 10-year period were ascertained of SCD patients and race-matched controls who had taken part in a pulmonary function study when they were between age 19 and 27 years. Smoking and asthma status and whether they had had ACS episodes were determined, and lung function was measured at the initial assessment.
Results Seventy-five subjects with SCD were followed for 683 patient years. There were 11 deaths with a mortality rate of 1.6 deaths per 100 patient years, which was higher than that of the controls; one death in 47 controls was observed for 469 patient years with a mortality rate of 0.2 per 100 patient years ($p = 0.03$). There were no significant associations of body mass index, recurrent episodes of acute chest, steady state haemoglobin, or gender with mortality. Adjusting for baseline lung function in SCD patients, "current" asthma [hazard ratio (HR) 11.2; 95 % confidence interval (CI) 2.5–50.6; $p = 0.002$] and smoking [HR 2.7; (95 % CI 1.3–5.5); $p = 0.006$] were significantly associated with mortality during the 10-year period.
Conclusions Our results indicate that young adults with SCD should be discouraged from smoking and their asthma aggressively treated.

Keywords Sickle cell disease · Smoking · Acute chest syndrome · Lung function

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Introduction

The median survival of patients with sickle cell disease (SCD) in Jamaica is 53 years (95 % confidence interval (CI) 49.3–57) for men and 58.5 years (95 % CI 55.1–67.5) for women [1]. Acute chest syndrome (ACS) is a major cause of mortality in patients with SCD, accounting for 14–50 % [2–4] of reported deaths. In the Cooperative Study of Sickle Cell Disease, it was reported that SCD patients with asthma had a 2.36 greater risk of death at any time in adulthood compared with SCD patients without asthma [5]. Several studies have demonstrated that SCD children with asthma have an increased risk of having ACS episodes [6, 7], and the diagnosis of asthma may predate the first ACS episode [8]. It is, however, unclear whether any excess mortality in SCD patients with asthma is related to them being more likely to have ACS episodes. An increase in ACS prevalence in SCD adults who smoked has been reported [9, 10], but whether mortality is increased

due to ACS episodes in SCD patients who smoke has not been investigated. In 2000–2001, we undertook a pulmonary function study in young adults with SCD aged 19–27 years of age and ethnic-matched controls [11]. We demonstrated that the SCD patients with recurrent ACS episodes were more likely to have reduced lung function [11]. We, therefore, hypothesized that the mortality rate in young adults with SCD would be greater than that of controls, particularly due to adverse pulmonary outcomes. The purpose of this study was to test that hypothesis by determining the outcome 10 years later of those entered into our previous study [11]. In addition, we wished to ascertain whether asthma reduced lung function, ACS episodes, and/or smoking predicted mortality during the 10-year follow-up period, because such data would be important to identify preventative strategies designed to reduce mortality in young adults with SCD.

Materials and Methods

Patients

Eighty patients with homozygous SS disease (Hb SS) and 80 race-matched controls from the Jamaican Sickle Cell Cohort Study (JSCCS) [12] had been recruited into the pulmonary function study [11]. The 80 HbSS patients from the JSCCS were randomly selected from those who were alive and had remained in Jamaica; 80 controls were all those who were alive and remaining in Jamaica. The cohort patients, particularly those with HB SS, were closely followed from birth. The SCD patients were seen every 3–6 months during childhood and then 6 monthly in adulthood. The controls were seen regularly until they were 18 years of age. The clinical histories of both groups were documented in their clinic records.

Ethical approval was granted by the Faculty of Medical Sciences/University of the West Indies/University Hospital of the West Indies Ethics Committee (ECP 176, 2008/2009). All living patients gave informed, written consent. The next of kin were asked to give consent for the inclusion of data from deceased individuals. In three cases, the next of kin were untraceable and the Ethics Committee gave a waiver to allow the inclusion of data from those deceased individuals in the analysis.

Initial Assessment

In 2000–2001, both groups were seen in the pulmonary function laboratory where pulmonary function testing was performed according to the European Respiratory Standards [13] using reference equations derived in the Jamaican population [14]. Gender and age were recorded, oxygen saturation in room air, hemoglobin, weight, and height were measured, and body mass index (BMI) was calculated. Classification of the pulmonary function abnormalities was undertaken using the criteria published by Klings et al. [6, 15]. Obstructive lung function was diagnosed if the FEV_1 (forced expiratory volume in 1 second)/FVC (forced vital capacity) ratio was <70 % of that predicted, the FEV_1 and FVC were <80 % predicted, and TLC (total lung capacity) was either in the normal or elevated range. Restrictive lung function was diagnosed if the FEV_1, FVC, or TLC were <80 % predicted and FEV_1/FVC ratio was in the normal range or the TLC was <80 % predicted but the FEV_1, FVC, and FEV_1/FVC ratio were within the normal range. Individuals were diagnosed as having a mixed, obstructive, and restrictive abnormality if the FEV_1/FVC ratio and FEV_1 were <70 % predicted and the FVC and TLC were <80 % predicted. In those individuals in whom TLC measurements were not available ($n = 11$), classification was made on the basis of the spirometry results. At the time of measurement, individuals were asked to complete a questionnaire. From the results of the questionnaire, they were classified as having "current" asthma if they had ever been diagnosed with asthma by a doctor, had wheezed in the previous 12 months, and/or were currently receiving asthma medication [16]. They were classified as having asthma in the past if they had been diagnosed as asthmatic by a doctor but had no history of wheeze in the past 12 months and were not currently receiving medication for asthma. They were asked if they smoked cigarettes and/or marijuana, currently or in the past. The medical records of the SCD patients were examined to identify whether they had had ACS episodes. An ACS episode had been diagnosed if the patient had suffered an acute onset of abnormal respiratory signs and/or symptoms in association with a new infiltrate on a chest radiograph [17]. Patients were classified as having had no history of ACS episodes, a single ACS episode, or recurrent ACS episodes, which is two or more ACS episodes.

Follow-up

The cohort was followed during the study period and encouraged to have at least yearly clinic visits. In the majority (SCD = 9, controls = 1), the deaths were recorded in the clinic records. In 2010–2011, attempts were made to trace the individuals who had taken part in the pulmonary function study. Initially, they were contacted using the phone number in their medical records. If there was no answer, the last known address was visited. This revealed that two further SCD patients had died. Based on the information available, they were classified as alive, dead, or emigrated.

Analysis

The mortality rate, as deaths per 100 patient years, was calculated using the time period from the date when the individual was recruited into the previous study until the date of their death or the date when their outcome was reviewed in 2010–2011. Asthma, smoking, ACS, and lung function status were based on the data recorded at the pulmonary function assessment [11].

Differences in proportions were assessed for statistical significance using the chi-square test and effect sizes reported as odds ratio (OR) and 95 % CI. The relationship between death and possible explanatory variables was examined using Cox proportional hazard models. This gave quantification of the probability of survival beyond a particular time conditional on the probability of an individual's survival up to that time; the hazard rate (HR). The "time" was defined as the time from the first review until death. Subjects were censored if they were lost to follow-up or were still alive at the second review (2010–2011). Analysis was performed using Stata 12 statistical software for Windows^{TM} (StataCorp LP, College Station, TX).

Results

The outcome of all the SCD patients who remained in Jamaica was determined; five patients had emigrated. The remaining 75 of 80 patients had been followed for a total of 683 patient years since the first assessment, and during that time 11 (14.7 %) patients with SCD had died, giving a mortality rate of 1.6 deaths per 100 patient years. Sepsis was the most common cause of death (Table 1). It was possible to trace 59 of the controls, 12 of whom had emigrated. Only 1 of the 47 controls remaining in Jamaica, who had in total been followed for a total of 469 patient years, had died as a result of trauma, but they had neither smoked nor had asthma. The unadjusted odds of dying, excluding subjects lost to follow-up, was greater in the SCD group compared with the control group (OR 7.9; 95 % CI 1.0–62.0; $p = 0.03$). Adjusting for subjects lost to follow-up, survival remained significantly lower in the SCD patients than the controls ($p = 0.02$; Fig. 1).

Table 1 Causes of death in the SCD patients

Diagnosis	Number
Ascending cholangitis progressing to *Salmonella* septicaemia	1
Salmonella septicaemia associated with painful crisis	1
Fungemia (*Cryptococcus neoformans*)	1
Pelvic inflammatory disease and sepsis	1
Presumed sepsis* (sudden death at home)	1
Presumed sepsis* (no causative agent found), acute anaemia	1
Acute chest syndrome	1
Cerebrovascular accident	1
Acute on chronic renal failure	1
Trauma	2

The data are displayed as the number of patients affected

* No post mortem available

Because the mortality in the controls was low, further analyses were undertaken in the SCD group only. There was an increased risk of death in subjects with SCD who smoked (HR 5.5; 95 % CI 1.6–18.8; $p = 0.007$) or had current asthma (HR 5.7; 95 % CI 1.5–21.4; $p = 0.04$; Table 2). In contrast, subjects who had ACS episodes were not at increased risk of death. Smokers were not more likely than nonsmokers to have had ACS episodes (62 vs. 57 %, $p = 0.8$). Only one patient died of an ACS episode; they had asthma when assessed previously. Body mass index, steady state hemoglobin, and gender were not significantly associated with mortality. The single patient with obstructive lung function abnormalities survived. There was no significant difference in the proportion of patients dying who had restrictive lung abnormalities compared with those who had normal lung function ($p = 0.09$). Adjusting for baseline lung function, the risk of death for "current" asthma was HR 11.2 (95 % CI 2.5–50.6; $p = 0.002$) and for smoking was HR 2.7 (95 % CI 1.3–5.5; $p = 0.006$).

Discussion

We have demonstrated a high mortality rate amongst young adults with SCD compared with race and age-matched controls. This needs to be interpreted with the caveat that we were unable to trace a quarter of the controls and our sample size to assess mortality data was relatively small. The mortality rate, however, of 1.6 deaths per 100 patient years that we report in SCD patients and 14.7 % of the SCD patients who had died are similar to previous data from Jamaica [1]. From the previous study's results [1], it can be estimated that the mortality rate increases between ages 20 and 40 years from approximately one to three per 100 patient years.

We report that asthma and smoking in young adults with SCD were significant predictors of mortality over the next 10-year period. The pathophysiology of asthma is complex and includes inflammation, hypoxia, and oxidant stress, all of which may contribute to the vasculopathy in SCD, which is important in the morbidity and mortality associated with SCD. Hypoxia also increases the risk of cerebrovascular accident [18]. It remains, however, unclear

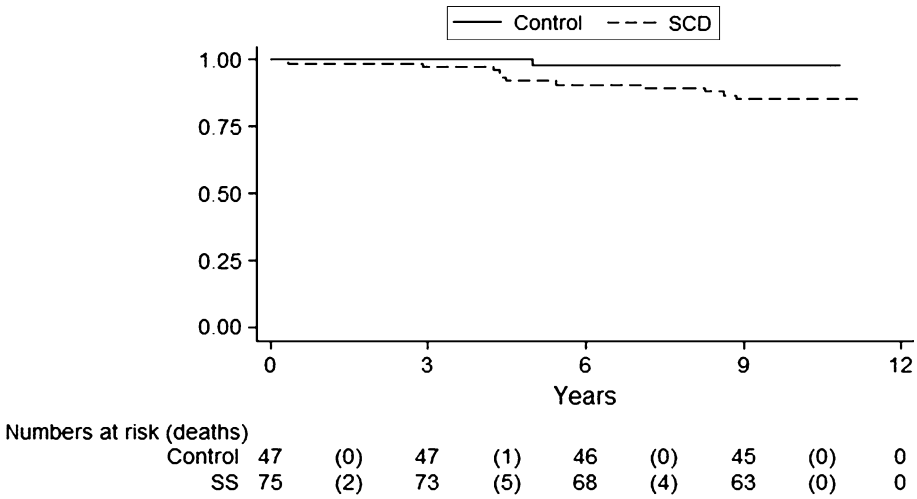

Fig. 1 Survival curve of young adults with SCD and controls

whether asthma/recurrent wheezing in patients with SCD is a complication of their disease or a comorbidity. Nevertheless, our results support the recommendation that any signs of asthma in SCD patients should be carefully investigated and aggressively managed [19].

Although asthma was associated with an increased risk of mortality, we did not find obstructive lung abnormalities to be more common in those who died. Indeed, only one of the SCD patients had an obstructive lung abnormality, which is in keeping with the findings of Kling et al. [15]. Obstructive lung function abnormalities have been demonstrated in children [20], with restrictive abnormalities becoming more common with increasing age [21] and restrictive rather than obstructive lung disease being more

Table 2 Demographics, asthma, lung function and ACS episodes by outcome status of the SCD patients

	Dead	Alive	Hazard ratio	95 % CI	*p* value
n	11	64			
Age, years	23.9 (20.7–24.8)	23.1 (20.8–25.6)			0.8
BMI, kg/m^2	19.0 (17.5–20.8)	19.0 (17.7–21.1)	0.96	0.76–1.21	0.7
Hemoglobin, g/dL	8.4 (6.8–9.5)	8.4 (7.6–9.0)	0.91	0.6–1.38	0.4
Oxygen saturation, %	93.0 (89.0–99.0)	94.0 (92.0–96.0)	0.96	0.7–1.16	0.7
Gender					
Male	6 (55 %)	28 (44 %)	1.44	0.44–2.73	0.7
Smokers	4 (36 %)	4 (6 %)	5.47	1.59–18.82	0.0071
Asthma status*					
Never	7 (64 %)	52 (81 %)	5.72	1.5–21.4	0.01
Historic	1 (9 %)	9 (14 %)			
Current	3 (27 %)	3 (5 %)			
Comparison of lung function**					
Normal	7 (64 %)	25 (39 %)	0.41	0.12–1.41	0.16
Restrictive	3 (27 %)	38 (59 %)			
Mixed	1 (9 %)	0 (0 %)			
Obstructive	0 (0 %)	1 (2 %)			
ACS, number of episodes***					
None	4 (36 %)	28 (44 %)	1.32	0.38–4.5	0.4
One episode	2 (18 %)	16 (25 %)			
Recurrent	5 (46 %)	20 (31 %)			

Data are demonstrated as median (IQR) or *n* (%)

* Comparison of current asthma versus past history or no asthma

** Comparison of restrictive versus normal pattern

*** Comparison of none versus one or more episodes

prevalent in adulthood [11]. We did not, however, find a significant association between restrictive lung abnormalities and an increased risk of mortality. The patients, however, were 19–27 years old when their lung function was measured and then followed for a 10-year period. Powars et al. [22] reported that the median age at which adults were diagnosed with or died from sickle chronic lung disease (SCLD), which is characterized by pulmonary hypertension, hypoxemia, chest pain, and progressively worsening restrictive lung disease, was 32 years. In those diagnosed with SCLD in the previous study [22], an inexorable progression from one stage to the next approximately every 2–3 years has been reported [23]. The results of serial lung function measurements rather than a single assessment might better predict an increased mortality risk.

We highlight that smoking also was significantly associated with an increased risk of dying. Glutathione levels in the alveolar epithelial lining fluid in the lungs of smokers is nearly double that of nonsmokers [24]. In patients with SCD, erythrocyte glutathione levels are decreased [25], which may put them at increased risk of smoking-related oxidant injury, as the antioxidant glutathione protects the lung from oxidant injury. Smoking may adversely affect the immune system regardless of SCD status and thereby increase the risk of having invasive pneumococcal disease, pneumonia, or other infections [26]. An increase in ACS prevalence in SCD adults who smoked has been reported [9, 10]. We did not find such an association, but we did not ascertain whether individuals were smoking cigarettes or marijuana, nor was the quantity of either smoked assessed, which are limitations of this study. Data obtained in the JSCCS in 2000 and 2004 showed that marijuana smoking was very common, particularly in men; more than 60 % of them had smoked marijuana at some time [27]. Two of the four men who died and had smoked died traumatically, which may indicate that smoking was a marker for other high-risk behaviors; Lotrean et al. [28] reported that in young adults smoking was associated with other high-risk behaviors, in particular alcohol-related behaviors and precocious sexual intercourse.

A number of factors have been associated with increased mortality in SCD patients, including male gender [1] and a low level of oxygen saturation, which is associated with pulmonary hypertension [29]. Neither of those factors was significantly associated with mortality in the young SCD adults we studied. Oxygen desaturation, however, may be episodic and in some patients, nocturnal [18]. Thus, a single assessment may not give a totally representative picture. Our sample size was similar to that of previous studies [18, 30], and we did demonstrate significant associations of smoking and asthma with mortality.

Conclusions

Smoking and asthma were found to be independent risk factors for death in young adults with SCD during a 10-year period. Our results indicate that young adults with SCD should be discouraged from smoking and if they have asthma it should be aggressively treated.

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Conflict of interest None.

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