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Sleep Disordered Breathing and Nocturnal Hypoxemia in Young Adults with Sickle Cell Disease

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Abstract

Sleep disordered breathing (SDB) is reported in up to 69% of adolescents and children with sickle cell disease (SCD) [1], but data regarding the prevalence of SDB in adults with SCD are limited. To obtain a preliminary assessment of the frequency and degree of sleep-related hypoxemia and potential associations with cardiovascular function in adults with SCD, we performed overnight sleep studies, 6-minute walk tests, echocardiograms, hematologic and chemistry panels, and administered the Pittsburgh Sleep Quality Index (PSQI), fatigue and health related quality of life measurement in 20 young adults with SCD attending a sickle cell clinic for routine care. Sleep apnea, defined as an apnea-hypopnea index (AHI) >5 events/hour, was found in 50% of subjects. Traditional clinical indicators such as obesity, the presence of snoring, and reported sleep complaints did not reliably differentiate these subjects. Subjects with an AHI>5 had higher mean systolic blood pressure (p =.03), evidence of impaired left ventricular diastolic function (i.e. increased mitral valve E/A ratio, p =.05), a trend toward greater reduction in 6 minute walk distances (p =.06), and lower Health-related Quality of Life scores (p <=.01). Three of nine subjects with more severe anemia (total Hb < 9.0) demonstrated nocturnal hypoxemia in the absence of sleep apnea. As prolonged and frequent hypoxemic episodes likely increase risks for vaso-occlusive, cardiovascular, and neurologic complications of SCD, these results suggest that the prevalence and severity of SDB should be investigated further in studies of larger patient populations. If confirmed, these findings could identify opportunities to prevent or reduce nocturnal hypoxia and improve outcomes.

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Keywords

sickle cell disease; sleep apnea; hypoxia; hypertension

Introduction

Sickle cell disease (SCD) is a genetic blood disease that is classified by the World Health Organization as a global health burden. Hypoxia contributes to polymerization of hemoglobin (Hb) S, which in turn leads to vaso-occlusion and other complications. Sleep disordered breathing (SDB), which is associated with transient hypoxemia and hypercapnea, has been reported in 41% of unselected children and adolescents with sickle cell disease and up to 69% of those with clinical features suggestive of SDB [1,2]. The pathophysiologic consequences of SDB, may include endothelial dysfunction with altered nitric oxide bioactivity, altered redox biology, chronic systemic inflammation, and increased expression of cell adhesion molecules [3, 4]. Each of these processes could contribute to hemolysis and vaso-occlusion. Studies in children and adolescents with SCD have demonstrated associations between nocturnal desaturations and severity of anemia [5], frequency of vaso-occlusive crises and acute chest syndrome [6] cardiac abnormalities including left ventricular hypertrophy and diastolic dysfunction [7], CNS events, impaired cognition and executive function [8, 9], priapism [3], and nocturnal enuresis [3].

Although sleep disordered breathing (SDB) is associated with morbidity in children with SCD, and occurs with increasing frequency with age in the general population, there are fewer studies evaluating SDB in adults with SCD. Sharma et al. identified obstructive sleep apnea in 44% of in 32 adult SCD patients (mean AHI 17 events/hour, (95% CI: 10–24/h) who had been referred to a sleep center based upon SDB symptoms [10], yet no studies have been undertaken to evaluate SDB in the absence of symptoms. Here we report a pilot study to evaluate the frequency and severity of SDB in clinically stable young adults with SCD with no previously identified symptoms of sleep disturbance, cardiac, or pulmonary vascular disease. We have focused this study on individuals less than 30 years of age to identify earlier stages of physiologic compromise that would be potentially modifiable with intervention.

Methods

Subjects and Procedures

Adults with SCD (HbSS, HbS-β thalassemia, or HbSC genotypes), attending a sickle cell clinic for routine care were invited to participate in this study. Exclusion criteria included hospitalization for vaso-occlusive crisis or other acute events within the prior two weeks, blood transfusion within four weeks, a prior diagnosis of pulmonary hypertension or sleep disordered breathing, and participation in a chronic transfusion program. The study was approved by the Institutional Review Board and approved and conducted at the Clinical Research Unit of Howard University Hospital.

After signing consent, all subjects underwent a complete history and physical examination and completed the Pittsburgh Sleep Quality Index (PSQI), and the SF-36. Medical records were reviewed for ascertainment of clinical data. Complete blood counts, chemistry panels, and brain natriuretic peptide (BNP) levels were obtained. Echocardiographic data obtained for clinical purposes within six months of the study was reviewed or performed, if not available.

Polysomnograms

Overnight sleep studies were performed using a Type III sleep monitor, the NOX-T3 (Carefusion, Inc.), which records snoring, abdominal and thoracic respiratory effort, derived flow (Respiratory Inductance Plethysmography Flow), nasal cannula flow, body position, actigraphy, oxygen saturation, heart rate, and a one channel EEG. Apneas were scored as a ≥ 10 second 90% reduction in flow signal. Hypopneas were scored as a ≥ 10 second 30% reduction in flow accompanied by a 3% or greater drop in saturation or arousal.

Six Minute Walk Tests

On the morning following the overnight sleep study, all subjects underwent a six minute walk test with measurement of ambulatory oximetry according to standardized protocols [11–12].

Statistical Analysis

Continuous data were presented by median (interquartile range). We compared the distribution of continuous data between two groups of patients (based on AHI) with the Kruskal-Wallis test and categorical data with Fisher's exact test.

Results

The study population and results are summarized in Table I. Ten of the twenty subjects (50%) had an AHI > 5, consistent with mild-moderate sleep apnea (mean 8.5 events/hour, range 5.8–15.9 events/hour). There were no differences in age, gender, hemoglobin genotype, hydroxyurea use, narcotic use, smoking history, or history of asthma between the two groups. Subjects with SDB had a higher BMI than those without, (median 23.8 kg/m^2 vs 19.8 kg/m^2, p = .049), but were not obese. A history of priapism was reported solely in subjects with sleep apnea (4 of the 7 male subjects with sleep apnea, 0 of 5 subjects without, p = .08). An abnormal PSQI (total score 5 or greater) showed modest sensitivity for sleep apnea (80%), but less specificity (40%). Three subjects with a greater magnitude of anemia, i.e. total hemoglobin (Hb) levels < 9 g/dl, demonstrated oxygen desaturations which were unrelated to AHI, as shown in Figure 1. The finding of greater duration of oxygen desaturation (oxygen saturation < 90%) with anemia was significant, (Spearman correlation coefficient = − 0.65)

Median systolic blood pressures was 114 mm Hg in subjects with an AHI > 5 vs 103 mm Hg, (p= 0.03) in subjects with AHI < 5. All subjects had a reduced six minute walk distance for age and gender-based standards [11], however, those with an AHI > 5 demonstrated a trend toward a shorter walk distance (median 358 vs 401 meters, p = .06). Echocardiograms

demonstrated that those with AHI > 5 had a higher mitral valve E/A (MV E/A) ratio, (2.0 vs 1.5, p = .04) suggestive of left ventricular diastolic dysfunction. Other echocardiographic parameters were similar between the two groups. Differences were not demonstrated between the groups in BNP levels or tricuspid regurgitant velocity.

Subjects with SCD and an elevated AHI had lower Health-related Quality of Life in the General Health (mean 50 vs 39, p = .01), Emotional (mean 50 vs 38, p = .04), Social (mean 49 vs 37, p = .01), and Mental (mean 53 vs 37, p = .02) Quality of Life domains compared to the subjects without sleep apnea.

Discussion

We prospectively examined a small group of young adults with SCD irrespective of symptoms for SDB, as an initial assessment of the scope of this condition in the young adult population. In the 20 subjects studied, 50% had an AHI > 5 events/hr even though they did not have traditional SDB risk factors. Despite the mild severity of sleep disordered breathing in this group and the small number of patients studied, it was nevertheless associated with a trend toward a reduced exercise capacity, echocardiographic abnormalities suggestive of impaired diastolic function (MV E/A) of the left ventricle, and a diminished quality of life. While blood pressures for both groups were in the normal range, it is possible the relatively higher systolic pressures in this young AHI>5 group may be a precursor for left ventricular remodeling and pulmonary hypertension over time, as some authors suggest that even minor elevations in systolic blood pressures may be deleterious in patients with SCD. [16–19]

Standard clinical screening for sleep apnea, including a history of snoring, obesity, or impaired sleep quality, would have failed to identify most individuals in the AHI >5 group. If adverse physiologic effects from subtle SDB in SCD patients are confirmed in larger studies, it suggests that a more comprehensive screening evaluation with a lower threshold for treatment may be required to identify individuals at risk in comparison to the general population.

Some subjects with more severe anemia exhibited nocturnal hypoxemia in the absence of sleep apnea, as reported in children with SCD, indicating that other mechanisms for desaturation also need to be considered in patients with SCD [5]. Cardiopulmonary complications, including pulmonary hypertension, are associated with morbidity in SCD and likely contribute to early mortality [13–19]. A growing body of data indicates that sub-clinical vascular changes are progressive in SCD. One potential mechanism for vascular dysfunction in SCD is localized tissue hypoxia, which can lead to pulmonary vasoconstriction, which can contribute to development of decompensated congestive heart failure [18].

We recognize that while these findings are suggestive, in view of the small number of subjects in this pilot study, any conclusions are preliminary. Nevertheless, these results suggest that larger studies are warranted to evaluate the prevalence and severity of SDB and nocturnal hypoxemia in adults with SCD. If confirmed, these findings could provide opportunities to intervene and potentially reduce cardiovascular complications and the

frequency of acute vaso-occlusive events, and to improve the quality of life in this vulnerable population.

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Highlights

- An AHI > 5 was seen in 10 of 20 subjects attending a sickle cell disease clinic.
- Elevated AHI correlated with systolic BP, mitral valve E/A ratio, and QoL scores.
- Hypoxemia occurred in some subjects independently from sleep apnea events.
- Results suggest further study with larger subject numbers is warranted.

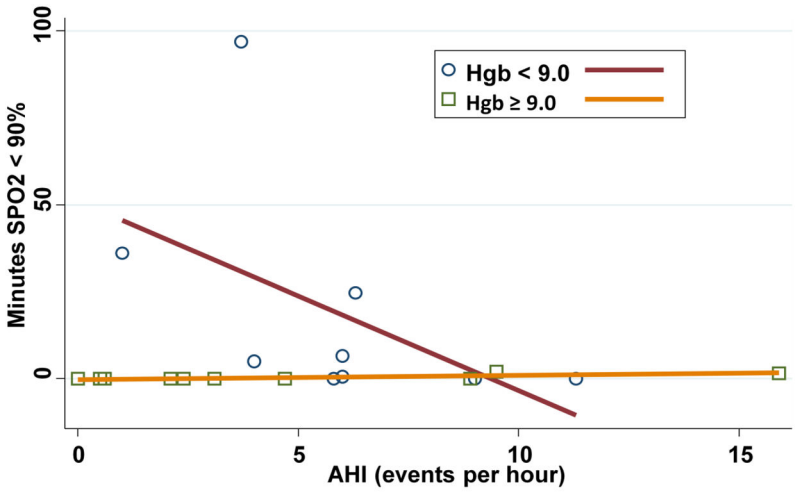

Figure 1.

Minutes of oxygen saturation < 90% and frequency of apnea and hypopnea (AHI) events per hour is shown. The Spearman correlation coefficient in patients with total hemoglobin levels < 9.0 g/dl was −0.65.

Table 1

Demographics and Results

	AHI ≤5 N=10	**AHI>5 N=10**	**p-value**
Age (Median, Interquartile range)	25 (23–27)	28 (22–28)	0.80
BMI (Median, Interquartile range)	19.8 (18.5–24.4)	23.8 (20.7–27.6)	0.05
Female gender, n	5	3	0.70
Narcotic use, n	5	1	0.14
SS genotype, n	8	8	>0.90
Sleep disorder indicated by PSQI, n	6	8	0.60
Snore index (percent of night snoring vs total time in bed)	0.0 (0.0–0.1)	0.8 (0.0–2.1)	0.08
HRQoL General Health Score	50 (46–53)	39 (31–46)	0.01
Systolic blood pressure (Median, Interquartile range)	103 (99–120)	114 (111–130)	0.03
6 MW distance (meters) (Median, Interquartile range)	401 (360–438)	358 (322–383)	0.06
MV E/A (Median, Interquartile range)	1.5 (1.2–1.9)	2.0 (1.8–2.2)	0.04
BNP	47.6 (24.0–105.9)	42.6 (29.9–82.9)	0.9