NEW RESEARCH

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Polysomnographic Characteristics of a Referred Sample of Children with Sickle Cell Disease

Valerie E. Rogers, Ph.D.[1]; Daniel S. Lewin, Ph.D.[2]; Glenna B. Winnie, M.D.[3]; Jeanne Geiger-Brown, Ph.D.[4]

[1]Center for Sleep and Respiratory Neurobiology, Division of Biobehavioral Health Sciences, University of Pennsylvania School of Nursing, Philadelphia, PA; [2]Sleep Disorders Medicine, Division of Lung Diseases, NHLBI, Bethesda, MD; [3]The Pediatric Sleep Center of the Pediatric Lung Center, Purcellville, VA; [4]Work and Health Research Center, Department of Family and Community Health, University of Maryland School of Nursing, Baltimore, MD

Study Objectives: To describe polysomnographic parameters and their clinical correlates in a referred sample of children with sickle cell disease (SCD).

Methods: This was a retrospective medical record review of 55 consecutive children aged 2-18 years with SCD (hemoglobin [Hb] SS and Hb SC genotypes) undergoing polysomnography for evaluation of sleep disordered breathing. Polysomnography values were compared between SCD genotypes, 4 age groups, and adenotonsillectomy status using descriptive and nonparametric statistics.

Results: Obstructive sleep apnea (OSA) was diagnosed in 38/55 (69%) children. Polysomnographic parameters differed significantly between Hb SS and Hb SC genotypes only on arterial oxyhemoglobin saturation (SpO_2; 95.2 ± 3.8 vs. 98.0 ± 0.8, respectively, $p < 0.01$) and percent of sleep time below SpO_2 90% (T_{90}; 8.0 ± 22.0 vs. 0.01 ± 0.02, respectively, $p < 0.05$). Increasing age was associated with decreasing SpO_2 (rho = −0.282, $p < 0.05$), obstructive apnea-hypopnea index (OAHI; rho = −0.364, $p < 0.01$), total arousal index (rho = −0.272, $p < 0.05$) and respiratory arousal index (rho = −0.349, $p < 0.01$). Periodic limb movements in sleep (PLM) averaged 4.7 ± 8.8/h, with a PLM index > 5/h in 5/17 children without OSA. Post- adenotonsillectomy, 8/10 children had OSA, but compared to untreated OSA-positive children they had a lower mean OAHI (4.4 ± 5.5 vs. 8.9 ± 12.5) and a lower T_{90} (1.6 ± 4.2 vs. 9.2 ± 24.9).

Conclusions: Both OSA and PLMs were common in children with SCD. Children with Hb SS experienced more severe nocturnal oxygen desaturation than did those with Hb SC. Post-adenotonsillectomy, most children had OSA, although they experienced fewer obstructive respiratory events and less severe nocturnal oxygen desaturation than did untreated OSA-positive children.

Keywords: Adenoidectomy, tonsillectomy, child, adolescent, sickle cell disease, obstructive sleep apnea, periodic limb movement disorder, polysomnography

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SCIENTIFIC INVESTIGATIONS

Sleep and sleep disorders in children with sickle cell disease (SCD) have been little explored. Sickle cell disease is the most common genetic disorder in the United States, with approximately 1,000 affected infants born each year.[1] In SCD, mutation of the hemoglobin (Hb) molecule (sickle hemoglobin, or Hb S) results in polymerization, or sickling of Hb S under conditions of hypoxemia. Sickling, in turn, contributes to vasoocclusion and hemolysis—events responsible for the high morbidity and mortality associated with SCD.

Existing evidence suggests that children with SCD are at increased risk of disordered breathing during sleep[2] and obstructive sleep apnea (OSA). Excessive adenoidal and tonsillar growth occurs in children with SCD, phenomena attributed to compensatory lymphoid tissue hyperplasia or chronic infection secondary to functional asplenia.[3,4] Adenotonsillar hypertrophy presents the main risk factor for obstructive sleep apnea in childhood,[5] a disease in which obstructed ventilation results in transient periods of hypoxemia. Thus, adenotonsillar hypertrophy presents an important risk factor for OSA in children with SCD, and hypoxemia during obstructed breathing may pose a risk for erythrocyte sickling. Evidence further suggests that children with SCD experience more severe sleep disordered breathing than unaffected children. A recent case-control study of children with SCD matched on age, gender, and ethnicity to healthy controls demonstrated a four-fold increased risk of nadir oxyhemoglobin saturation below 85%, and a 7-fold increased risk of sleep time spent at an end-expiratory carbon dioxide level greater than 50 mm Hg in children with SCD compared to controls.[6]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Little sleep related data has been published on children with sickle cell disease other than overnight pulse oximetry findings. This study aimed to describe full polysomnography findings of a sample of children with sickle cell disease referred for sleep disordered breathing, and to describe differences by genotype, age group and adenotonsillectomy status.

Study Impact: This study contributes to the limited literature describing objective sleep using pediatric scoring criteria in this population. It further highlights implications for clinical care and suggests directions for future research in children with sickle cell disease in whom sleep and the impact of sleep disorders has been largely unexplored.

Disease-specific normative polysomnography data do not currently exist for children with SCD. Few studies report polysomnography data on these children,[6-10] with the exception of

overnight pulse oximetry values.[11,12] Establishing separate diagnostic polysomnographic criteria may be important, however. Dysfunctional hemoglobins in SCD and a right-shifted oxyhemoglobin dissociation curve alter arterial oxyhemoglobin saturation (SpO_2) values measured by pulse oximetry.[13-15] Moreover, nearly half of children with SCD experience nocturnal hypoxemia that is not associated with sleep disordered breathing.[11,16] These disease-related changes cannot be interpreted as inconsequential or normal, yet they suggest a need for interpreting polysomnography based on disease-specific values.

The purpose of the present study was to describe polysomnography values of a sample of children with SCD referred to a sleep laboratory for evaluation of sleep disordered breathing. A secondary aim was to explore the association between objective measures of sleep and clinical variables including SCD genotype, age group, and adenotonsillectomy status. These findings are intended to contribute to the very limited literature using pediatric scoring of polysomnography data in this population. This study was carried out as part of a more comprehensive retrospective study of the relationship of OSA and severity of SCD in children.[17]

METHODS

Sample

The sample was a retrospective case series of children with SCD referred to a children's hospital-based sleep laboratory for evaluation of sleep disordered breathing between March 2004 and October 2008. Demographic, clinical, and polysomnographic data were collected from the hospital electronic medical record following approval by the institutional review boards of the Children's National Medical Center and the University of Maryland School of Medicine. Inclusion criteria were ages 2 to 18 years with a diagnosis of Hb SS or Hb SC disease. Subjects were excluded for craniofacial abnormality or neuromuscular disorder, current treatment with positive airway pressure therapy, pregnancy, or illness at the time of the sleep study. Eighty consecutive children were screened, and 55 qualified for inclusion.

Diagnostic Criteria for Clinical and Laboratory Variables

Obstructive sleep apnea was defined as an obstructive apnea-hypopnea index (OAHI) ≥ 1.[18] Severity of OSA was further classified into 3 levels (regardless of adenotonsillectomy status): *no OSA*, OAHI < 1; *mild OSA*, 1 ≤ OAHI < 5; or *moderate-severe OSA*, OAHI ≥ 5, utilizing the OAHI categories of the composite score for polysomnography severity proposed by Montgomery-Downs et al.[19] Body mass index (BMI; kg/m^2) was calculated from height and weight measured at the time of polysomnography, and when available checked for accuracy against a height and weight measured during a clinical visit closest to the time of polysomnography. Age groups were defined as 2 to 5 years, 6 to 10 years, 11 to 14 years, and 15 to 18 years of age, dividing the sample approximately equally. For comparisons by adenotonsillectomy status, there were 3 OSA/adenotonsillectomy conditions: *No OSA/No AT*, OAHI < 1 and no adenotonsillectomy; *OSA/No AT*, OAHI ≥ 1 and no adenotonsillectomy; and *AT*, adenotonsillectomy performed for any indication.

Polysomnography

Each child underwent overnight polysomnography (Rembrandt version 7.4, Medcare, Reykjavik, Iceland) with ≥ 6 h of recording time, monitored by registered technicians trained in pediatric polysomnography. The following parameters were continuously recorded: sleep stages, using electroencephalography (C3-A2, C4-A1, O1-A2, O2-A1, Fz-A1); heart rate, by electrocardiography; left and right electrooculogram; submental and tibial electromyogram; oronasal airflow, via thermistor; nasal airflow, via pressure transducer; capnography; chest and abdominal wall excursion using respiratory inductance plethysmography; and SpO_2 via pulse oximeter. Subjects were audio and video recorded. Respiratory events, sleep architecture, arousals, and periodic limb movements during sleep (PLM) were scored using standard criteria[20-23] by a pediatric pulmonologist board certified in sleep medicine.

Polysomnographic parameters were defined as follows. An obstructive apnea was a decrease in nasal airflow of > 90% despite continued respiratory effort for the duration of ≥ 2 missed breaths. An obstructive hypopnea was a decrease in nasal airflow ≥ 50%, despite persistent respiratory effort, lasting for ≥ 2 missed breaths and associated with a drop in SpO_2 ≥ 3%, an awakening, or an arousal. A central apnea was the absence of airflow accompanied by an absence of respiratory effort, lasting ≥ 20 sec or at least 2 missed breaths and associated with an arousal, an awakening, or a desaturation ≥ 3%. A mixed apnea included components of both an obstructive and a central apnea. The OAHI was the sum of obstructive apneas, obstructive hypopneas, and mixed apneas per hour of sleep. Sleep stages are presented as the percent of total sleep time spent in each stage. Non-rapid eye movement (NREM) sleep stage 3 was the sum of reported NREM 3 and NREM 4 sleep stages based on scoring criteria in effect during the study period.

Sleep efficiency was the ratio of sleep time to time in bed (lights out to lights on). Sleep latency was the number of minutes from lights out to the onset of the first of 3 consecutive epochs of NREM 1 sleep or the first epoch of any other sleep stage. Wake after sleep onset was the number of minutes of wake between sleep onset and sleep offset. An arousal was an abrupt shift in electroencephalographic frequency ≥ 3 sec separated by ≥ 10 sec of stable sleep. An index was calculated as the number of events per hour of sleep. Arousal indices were classified as (1) total arousal index, the sum of all-cause arousals; (2) respiratory arousal index, arousals immediately following an obstructive apnea or hypopnea; (3) PLM arousal index, arousals immediately following PLMs; and (4) spontaneous arousals. Periodic limb movements were defined as a series of ≥ 4 consecutive leg movements having a period length (time between onset of consecutive leg movements) of 5-90 sec and lasting 0.5-5 sec (study period 2004-2006) or 0.5-10 sec (study period 2007-2008). Polysomnograms were not available for rescoring PLMs uniformly across the entire study period, thus potentially underscoring PLMs prior to the change in scoring rules in 2007 and presenting a limitation of these analyses. However, no significant difference in the mean PLM index was found between sleep studies performed during the period 2004-2006 (n = 27) and those performed during 2007-2008 (n = 26; $U = 265.5$, $p = 0.12$), suggesting that the mid-study change in scoring of PLMs during sleep did not affect these results. Leg

Table 1—Demographic and clinical characteristics of children with sickle cell disease

	Hb SS (*n* = 41)		Hb SC (*n* = 14)	
	N **(%)**	**Mean ± SD**	***N*** **(%)**	**Mean ± SD**
Age (years)	41	9.4 ± 4.6	14	9.9 ± 4.7
Sex, male	20 (48.8)		4 (28.6)	
Body mass index (kg/m²)	41	18.9 ± 6.0	14	19.2 ± 3.7
(BMI z-score)		(0.11 ± 1.25)		(0.58 ± 0.84)
Daytime SpO_2 (%)	39	97.4 ± 2.0	12	99.3 ± 0.6
Systolic blood pressure (mm Hg)	40	114.5 ± 11.2	12	113.5 ± 8.6
Diastolic blood pressure (mm Hg)	40	63.7 ± 7.5	12	67.6 ± 6.6
Hemoglobin (g/dL)	39	8.4 ± 1.3	13	10.6 ± 0.8
White blood count (10^9/L)	39	12.6 ± 4.0	11	9.3 ± 1.9
Hydroxyurea therapy[a] (yes)	14 (34.1)		2 (14.3)	
Chronic transfusion therapy[a] (yes)	3 (7.3)		0	
Adenotonsillectomy (yes)	6 (14.6)		4 (28.6)	

[a]At time of polysomnogram. BMI refers to body mass index; Hb, hemoglobin genotype; SpO_2, oxyhemoglobin saturation.

movements occurring within 0.5 sec of an apnea or hypopnea or following an arousal were not scored as PLMs. A positive screen for PLM disorder was defined as a PLM index > 5 per hour of sleep.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Inc.; Chicago, IL) version 14.0. Alpha was set at 0.05 with Bonferroni correction for multiple post hoc comparisons, and all analyses were two-tailed. Descriptive statistics included mean ± standard deviation, range and percent. Percentages were based on the number of available subjects where data were missing. Data were not normally distributed, so nonparametric statistics were used to test associations and group differences, including Spearman rho, Mann-Whitney (*U*) test, and Kruskal-Wallis test.

RESULTS

Sample characteristics by genotype are shown in **Table 1**. Based on polysomnography, 38 of 55 children (69.1%) had OSA, with 24 (43.6%) having mild and 14 (25.5%) having moderate-severe OSA. The OAHI ranged from 0 to 66.6 events per hour of sleep, with a mean OAHI for the no OSA, mild OSA, and moderate-severe OSA groups of 0.4 ± 0.3, 2.6 ± 1.1 and 16.4 ± 16.0, respectively. Mean SpO_2 ranged from 82.9% to 99.2% and averaged 95.8 ± 2.5, 96.6 ± 2.5, and 94.8 ± 5.5 for the no, mild, and moderate-severe OSA groups, respectively, with no significant difference between groups. The percent of sleep time spent at SpO_2 < 90% (T_{90}) ranged from 0% to 96.6% and increased nonsignificantly across OSA severity groups, averaging 1.9% ± 4.7%, 2.3% ± 10.4%, and 17.0% ± 33.8%, respectively, for the no, mild, and moderate-severe OSA groups. The PLM index ranged from 0 to 56.5 per hour of sleep and averaged 4.7 ± 8.8, with 14 of 53 (26.4%) children in the full sample and 5 of 17 (29.4%) children without OSA screening positive for PLM disorder. The PLM index (n = 46) was highest in the no OSA group, averaging 6.3 ± 13.8, versus 3.6 ± 5.0 and 3.8 ± 5.2 for the mild OSA and moderate-severe OSA groups, respectively, with no significant difference between groups. The PLM arousal index averaged 0.79 ± 1.2 ranging from 0 to 6.6 per hour of sleep, with 15.8% of PLMs associated with arousals.

The average BMI of the sample was 18.9 ± 5.4 (z-score 0.23 ± 1.2), with an average BMI for the no OSA, mild OSA, and moderate-severe OSA groups of 19.9 ± 5.1 (z-score 0.26 ± 0.9), 19.2 ± 4.8 (z-score 0.52 ± 1.0), and 17.4 ± 6.8 (z-score −0.30 ± 1.6), respectively. The BMI was negatively associated with obstructive indices, including the obstructive apnea index (rho = −0.289, p = 0.03), the obstructive hypopnea index (rho = −0.282, p = 0.04), and the OAHI (rho = −0.301, p = 0.03), suggesting that as obstructive indices increased, BMI decreased. The BMI was also negatively associated with peak end-tidal carbon dioxide (rho = −0.375, p = 0.03).

Sleep Parameters by Hemoglobin Genotype

Forty-one children had Hb SS, and 14 had Hb SC disease. Fourteen (34.1%) children with Hb SS did not have OSA, while 16 (39.0%) had mild OSA and 11 (26.8%) had moderate-severe OSA. Among those with Hb SC, 3 (21.4%) children had no OSA, while 8 (57.1%) had mild OSA and 3 (21.4%) had moderate-severe OSA. Sleep parameters by genotype are shown in **Table 2**. Eight children (14.5%) with Hb SS, but none with Hb SC, had an OAHI > 10. Mean SpO_2 was significantly lower (*U* = 139.0, p = 0.004) and T_{90} was significantly higher (*U* = 179.5, p = 0.03) in children with Hb SS than in those with Hb SC. Mean SpO_2 was 93% or lower in 10 of 41 (24.4%) Hb SS children, indicating nocturnal hypoxemia.[21] No child with Hb SC had a mean SpO_2 below 95%. The T_{90} was > 10% for 6 of 41 (14.6%) children with Hb SS, with 3 spending more than half the night below SpO_2 90%, and one child having a T_{90} of 96.6%. Children with Hb SC all had a T_{90} < 1% (0.01 ± 0.02). Nearly 17% (9 of 54) of the sample experienced oxyhemoglobin desaturation below SpO_2 80%, with 2 children, both with Hb SS, having desaturations below 60%. Nadir SpO_2 during a respiratory event was 93% or lower in 33 of 40 (82.5%) children with Hb SS, versus 9 of 14 (64.3%) children with Hb SC.

Table 2—Polysomnography parameters in children with sickle cell disease, by genotype

Parameters	Hb SS			Hb SC			
Respiratory parameters	n	Mean ± SD	Range	n	Mean ± SD	Range	p[a]
OAHI (n/h)	41	6.2 ± 11.7	0-66.6	14	3.1 ± 2.1	0.3-7.9	0.53
OAI (n/h)	41	2.0 ± 5.4	0-31.5	14	1.3 ± 1.5	0-4.0	0.41
OHI (n/h)	41	4.2 ± 6.8	0-35.1	14	1.8 ± 1.3	0.3-5.3	0.75
Mixed apnea index (n/h)	41	0.1 ± 0.2	0-0.8	14	0.1 ± 0.1	0-0.3	0.11
Central apnea index (n/h)	41	0.2 ± 0.4	0-1.9	14	0.1 ± 0.2	0-0.5	0.93
Mean SpO_2 (%)	41	95.2 ± 3.8	82.9-99.2	14	98.0 ± 0.8	95.9-99.1	0.004
Nadir SpO_2 (%)	40	85.6 ± 10.5	54.3-98.4	14	90.8 ± 5.1	78.3-98.4	0.07
T_{90} (%)	41	8.0 ± 22.0	0-96.6	14	0.01 ± 0.02	0-0.1	0.03
$P_{ET}CO_2$ (mm Hg)	27	51.9 ± 8.2	36.0-71.0	8	53.1 ± 4.7	46.0-61.0	0.44
Sleep architecture, periodic limb movement index, and arousals							
Total sleep time (min)	41	430.6 ± 81.2	107-548	14	445.6 ± 53.1	335-548	0.73
Sleep efficiency (%)	41	81.5 ± 15.2	21.4-98.1	14	86.2 ± 8.2	70.2-97.8	0.51
Sleep latency (min)	41	53.9 ± 70.5	0-392.0	14	26.1 ± 18.5	0.05-62.5	0.29
REM latency (min)	40	121.1 ± 58.2	49.0-236.0	14	114.6 ± 59.7	44.5-222.0	0.55
Wake after sleep onset (min)	41	46.6 ± 50.6	2-245	14	43.8 ± 28.7	6-110	0.46
NREM 1 (%)	37	3.1 ± 3.2	0.2-14.0	14	3.3 ± 3.0	0.5-11.9	0.52
NREM 2 (%)	37	52.9 ± 9.3	23.4-68.8	14	53.4 ± 6.8	42.6-64.3	0.87
NREM 3 (%)	41	24.8 ± 7.9	12.5-48.8	14	23.3 ± 6.0	11.4-31.2	0.61
REM (%)	41	19.4 ± 4.5	11.4-27.4	14	20.2 ± 4.5	13.2-26.7	0.53
PLM index (n/h)	39	3.5 ± 5.4	0-20.9	14	7.5 ± 14.6	0-56.5	0.39
PLM arousal index (n/h)	34	0.77 ± 1.3	0-6.6	12	0.83 ± 0.98	0-3.3	0.41
Respiratory arousal index (n/h)	41	2.8 ± 4.6	0-21.5	14	1.8 ± 1.2	0.4-4.5	0.31
Spontaneous arousal index (n/h)	41	6.8 ± 3.5	1.1-16.8	14	5.2 ± 2.9	0.4-9.5	0.16
Total arousal index (n/h)	41	12.6 ± 6.5	3.4-28.7	14	9.9 ± 4.3	3.1-17.9	0.17

[a]Mann-Whitney test. OAHI, obstructive apnea-hypopnea index; OAI, obstructive apnea index; OHI, obstructive hypopnea index; $P_{ET}CO_2$, peak end-tidal carbon dioxide; PLM, periodic limb movements during sleep; SpO_2, oxyhemoglobin saturation; T_{90}, percent sleep time below SpO_2 90%.

There were no significant differences between genotypes on sleep architecture, arousals, or PLM index. Children with Hb SS tended to have shorter sleep times, poorer sleep efficiency, more total arousals, increased sleep onset latency, and more wake after sleep onset than did children with Hb SC. Children screening positive for PLM disorder included 8 of 39 (20.5%) with Hb SS and 6 of 14 (42.9%) with Hb SC, a nonsignificant difference.

Sleep Parameters by Age

The average age of the sample was 9.5 ± 4.6 years. Age was negatively correlated with several respiratory parameters, including the OAHI (rho = −0.364, p = 0.006), obstructive apnea index (rho = −0.370, p = 0.005), and mean SpO_2 (rho = −0.282, p = 0.04). Differences in sleep parameters are compared between age groups in **Table 3**.

Of the parameters related to sleep architecture, arousals or PLM index, age was positively correlated with NREM 2 (rho = 0.382, p = 0.006) and negatively correlated with NREM 3 (rho = −0.443, p = 0.001), suggesting that as age increased, more sleep time was spent in lighter (NREM 2) sleep and less was spent in slow wave (NREM 3) sleep. Age was also significantly negatively correlated with total arousals (rho = −0.272, p = 0.04) and respiratory arousals (rho = −0.349, p = 0.009) and approached a negative association with spontaneous arousals (rho = −0.252, p = 0.06), suggesting that arousal indices improved with age. However, age group differences in arousals reflected differences in obstructive indices, in that fewer obstructive events were seen in age groups having fewer total and respiratory arousals. While nonsignificant, the oldest age group had shorter total sleep time, lower sleep efficiency, longer sleep latency, and more wake after sleep onset than the other age groups. There was no significant difference in the PLM index or PLM arousal index between age groups.

Sleep Parameters by Adenotonsillectomy Status

Thirty-two OSA-positive children had not undergone adenotonsillectomy at the time of polysomnography. Eight children had adenotonsillectomy prior to polysomnography, and 2 underwent polysomnography both before and after adenotonsillectomy. Indications for adenotonsillectomy were largely unreported in this sample but included 2 children with adenotonsillar hypertrophy and 2 children with documented OSA. Two of these 4 children had an additional indication of recurrent otitis media. Sleep parameters by OSA/adenotonsillectomy condition are shown in **Table 4**. Descriptive statistics in this table include both pre- and post-adenotonsillectomy polysomnography data for the 2 children with available data; thus statistical comparisons would violate the assumption of independent

Table 3—Polysomnographic parameters and BMI in children with sickle cell disease, by age group

Parameter	2-5 years		6-10 years		11-14 years		15-18 years	
Respiratory parameters	n	Mean ± SD (Range)	n	Mean ± SD (Range)	n	Mean ± SD (Range)	n	Mean ± SD (Range)
OAHI (n/h)	15	**6.3 ± 5.5**[a] (0.6 - 19.3)	16	7.6 ± 16.8 (0 - 66.6)	14	**2.4 ± 4.6**[a] (0.2 - 18.2)	10	5.0 ± 7.6 (0.3 - 19.5)
OAI (n/h)	15	2.1 ± 3.1 (0 - 12.0)	16	2.9 ± 7.8 (0 - 31.5)	14	0.6 ± 1.3 (0 - 4.2)	10	1.4 ± 3.0 (0 - 9.3)
OHI (n/h)	15	**4.1 ± 4.0**[a] (0.6 - 15.8)	16	4.6 ± 9.1 (0 - 35.1)	14	**1.7 ± 3.4**[a] (0.1 - 13.4)	10	3.6 ± 5.0 (0.3 - 15.2)
Mixed apnea index (n/h)	15	0.2 ± 0.3 (0 - 0.8)	16	0.03 ± 0.04 (0 - 0.1)	14	0.1 ± 0.2 (0 - 0.6)	10	0 (0)
Central apnea index (n/h)	15	0.2 ± 0.2 (0 - 0.7)	16	0.1 ± 0.3 (0 - 1.0)	14	0.2 ± 0.5 (0 - 1.9)	10	0.2 ± 0.3 (0 - 0.7)
Mean SpO_2 (%)	15	96.2 ± 4.3 (84.3 - 99.2)	16	95.9 ± 3.9 (82.9 - 99.1)	14	96.2 ± 2.7 (90.6 - 98.6)	10	95.1 ± 2.7 (89.8 - 98.8)
Nadir SpO_2 (%)	15	84.6 ± 11.4 (56.4 - 94.4)	15	88.8 ± 5.9 (78.3 - 98.4)	14	90.5 ± 4.7 (82.8 - 98.4)	10	82.7 ± 14.1 (54.3 - 94.4)
T_{90} (%)	15	9.8 ± 26.6 (0 - 96.6)	16	5.5 ± 21.7 (0 - 89.6)	14	2.2 ± 5.1 (0 - 15.1)	10	6.1 ± 16.0 (0 - 51.3)
$P_{ET}CO_2$ (mm Hg)	9	51.4 ± 9.6 (36.0 - 70.0)	12	54.3 ± 8.4 (42.0 - 71.0)	9	53.7 ± 4.0 (48.0 - 59.0)	5	46.0 ± 1.2 (45.0 - 48.0)
Sleep architecture, periodic limb movement index, and arousals								
Total sleep time (min)	15	437.6 ± 11.2 (326.5 - 528.0)	16	455.8 ± 47.6 (331.0 - 526.0)	14	454.8 ± 62.5 (347.0 - 548.0)	10	367.0 ± 120.0 (107.0 - 548.0)
Sleep efficiency (%)	15	82.9 ± 11.2 (62.1 - 98.1)	16	86.9 ± 9.0 (64.5 - 96.6)	14	85.2 ± 10.1 (65.0 - 97.8)	10	72.0 ± 22.4 (21.4 - 96.4)
Sleep latency (min)	15	44.1 ± 50.0 (0.5 - 141.5)	16	28.3 ± 20.9 (1.5 - 69.0)	14	43.2 ± 44.6 (0 - 163.5)	10	85.7 ± 116.8 (5.0 - 392.0)
REM latency (min)	15	20.0 ± 5.0 (13.2 - 26.9)	16	19.7 ± 4.1 (14.2 - 27.4)	14	17.9 ± 4.8 (11.4 - 26.7)	10	21.1 ± 3.7 (13.1 - 25.3)
Wake after sleep onset (min)	15	49.3 ± 50.0 (2 - 182)	16	41.7 ± 36.6 (3 - 119)	14	39.1 ± 25.8 (6 - 94)	10	57.2 ± 72.2 (4 - 245)
NREM 1 (%)	15	2.7 ± 2.9 (0.2 - 10.3)	14	2.3 ± 2.6 (0.2 - 9.6)	13	2.8 ± 1.9 (0.5 - 7.0)	9	5.4 ± 4.5 (1.2 - 14.0)
NREM 2 (%)	15	49.3 ± 9.5 (23.4 - 64.9)	14	52.3 ± 8.5 (35.9 - 68.7)	13	57.3 ± 6.8 (47.0 - 68.8)	9	54.2 ± 8.0 (36.4 - 64.3)
NREM 3 (%)	15	27.9 ± 7.4 (19.6 - 48.8)	16	**27.1 ± 6.1**[a] (14.1 - 37.1)	14	**20.9 ± 5.4**[a] (12.5 - 28.9)	10	19.6 ± 7.9 (11.4 - 36.3)
REM (%)	15	20.0 ± 5.0 (13.2 - 26.9)	16	19.7 ± 4.1 (14.2 - 27.4)	14	17.9 ± 4.8 (11.4 - 26.7)	10	21.1 ± 3.7 (13.1 - 25.3)
PLM index (n/h)	14	5.9 ± 6.7 (0 - 20.9)	16	4.8 ± 14.0 (0 - 56.5)	13	4.5 ± 5.0 (0 - 15.1)	10	2.2 ± 3.1 (0 - 8.6)
PLM arousal index (n/h)	13	1.2 ± 1.9 (0 - 6.6)	12	0.4 ± 0.7 (0 - 1.7)	12	1.1 ± 1.0 (0 - 3.3)	9	0.4 ± 0.5 (0 - 1.2)
Respiratory arousal index (n/h)	15	**3.2 ± 2.2**[a] (0.4 - 7.5)	16	3.3 ± 6.1 (0 - 21.5)	14	**1.4 ± 3.0**[a] (0 - 11.6)	10	2.1 ± 3.0 (0 - 8.9)
Spontaneous arousal index (n/h)	15	8.2 ± 3.4 (2.6 - 15.4)	16	6.1 ± 4.0 (0.4 - 16.8)	14	5.1 ± 2.3 (1.8 - 8.7)	10	5.8 ± 3.1 (1.1 - 9.5)
Total arousal index (n/h)	15	**15.0 ± 5.7**[a] (8.6 - 28.7)	16	11.0 ± 6.8 (3.1 - 27.1)	14	**10.3 ± 5.2**[a] (4.0 - 24.4)	10	11.0 ± 6.1 (3.4 - 20.4)
Body mass index	n	Mean ± SD (BMI z - score)	n	Mean ± SD (BMI z - score)	n	Mean ± SD (BMI z - score)	n	Mean ± SD (BMI z - score)
BMI (kg/m^2)	15	16.1 ± 1.8 (0.2 ± 1.2)	16	16.2 ± 1.9 (-0.03 ± 0.8)	14	21.5 ± 6.1 (0.5 ± 1.4)	10	24.1 ± 6.8 (0.4 ± 1.3)

Post hoc Mann-Whitney test of paired group differences where Kruskal-Wallis test was significant, with Bonferroni correction for number of comparisons, [a]$p \leq 0.008$. Bolded values highlight significant group differences for that variable. BMI, body mass index; OAHI, obstructive apnea-hypopnea index; OAI, obstructive apnea index; OHI, obstructive hypopnea index; $P_{ET}CO_2$, peak end-tidal carbon dioxide; PLM, periodic limb movements during sleep; SpO_2, oxyhemoglobin saturation; T_{90}, percent sleep time below SpO_2 90%.

groups and are not made. Lag time between adenotonsillectomy and follow-up polysomnography averaged 63.4 ± 49.5 months, with a range of 3 to 143 months.

Respiratory indices were generally better in the AT than the OSA/No AT condition, but were often not normal. The largest mean differences between the OSA/No AT and the AT conditions were for the OAHI and the T_{90}. The mean PLM index was higher in children who had adenotonsillectomy than untreated OSA-positive children. Post-adenotonsillectomy, 5 of 9 (56%) children screened positive for PLM disorder, compared with 6 of 31 (19%) in the OSA/No AT condition and 4 of 15 (26%) in the No OSA/No AT condition. The AT condition demonstrated the highest BMI; however, those children were, on average, 2 years older than those in the OSA/No AT condition, which was the youngest group. Pre-adenotonsillectomy polysomnography and BMI were not available for 8 children who had adenotonsillectomy, so change from pre- to post- adenotonsillectomy could not be analyzed.

The 2 children with both pre- and post-adenotonsillectomy polysomnography data, both with Hb SS, continued to have moderate-severe OSA following surgery. The first child was 2 years of age, with a BMI of 17.4 (z-score = 0.94) at the time of initial polysomnography, which increased to 18.7 (z-score = 1.94) at follow-up polysomnography 7 months after initial polysomnography and 4 months post-adenotonsillectomy. This child's OAHI decreased from 17.0 preoperatively to 11.6 postoperatively. Oxygenation parameters were adequate pre-adenotonsillectomy and changed little following surgery (mean SpO_2 = 99.2% pre- vs. 98.9% post-adenotonsillectomy; T_{90} = 0.40% pre- vs. 0.70% post-adenotonsillectomy). The PLM index increased postoperatively (0.0 pre- vs. 5.8 post-adenotonsillectomy). The second child was 7 years of age, with a BMI of 14.8 (z-score = −0.46) at initial polysomnography, which increased to 16.0 (z-score = 0.13) at follow-up polysomnography 7 months after initial polysomnography and 5 months post-adenotonsillectomy. This child's OAHI decreased from 66.6 pre- to 16.9 post-adenotonsillectomy, with continued SpO_2 desaturations below 60%; however other oxygenation parameters improved (mean SpO_2 = 82.9% pre- vs. 92.4% post-adenotonsillectomy; T_{90} = 86.9% pre- vs. 13.4% post-adenotonsillectomy).

DISCUSSION

This study described polysomnography parameters in a sample of children with SCD referred for evaluation of

Table 4—Polysomnography parameters, age, and BMI in children with sickle cell disease, by adenotonsillectomy status

	No OSA, no adenotonsillectomy			OSA, no adenotonsillectomy			Adenotonsillectomy		
Parameters	**n**	**Mean ± SD**	**Range**	**n**	**Mean ± SD**	**Range**	**n**	**Mean ± SD**	**Range**
Age (years)	15	11.7 ± 3.9	2.5-17.6	32	7.8 ± 4.5	2.4-17.6	10	10.6 ± 4.6	3.0-17.1
Respiratory parameters									
OAHI (n/h)	15	0.4 ± 0.3	0-0.9	32	8.9 ± 12.5	1.0-66.6	10	4.4 ± 5.5	0.4-16.9
OAI (n/h)	15	0.1 ± 0.1	0-0.5	32	3.0 ± 5.9	0-31.5	10	0.8 ± 1.1	0-2.9
OHI (n/h)	15	0.4 ± 0.3	0-0.9	32	5.8 ± 7.1	0.3-35.1	10	3.5 ± 4.8	0.3-14.2
Mixed apnea index (n/h)	15	0.01 ± 0.03	0-0.1	32	0.1 ± 0.2	0-0.8	10	0.1 ± 0.1	0-0.4
Central apnea index (n/h)	15	0.2 ± 0.3	0-1.0	32	0.1 ± 0.2	0-0.7	10	0.3 ± 0.6	0-1.9
Mean SpO_2 (%)	15	95.5 ± 2.5	90.6-99.1	32	95.7 ± 4.1	82.9-99.2	10	96.9 ± 2.5	92.3-98.9
Nadir SpO_2 (%)	15	89.9 ± 3.4	82.8-94.4	31	84.1 ± 11.6	54.3-98.4	10	88.0 ± 11.4	57.6-95.0
T_{90} (%)	15	2.1 ± 5.0	0-15.4	32	9.2 ± 24.9	0-96.6	10	1.6 ± 4.2	0-13.4
$P_{ET}CO_2$ (mm Hg)	9	48.9 ± 4.0	45.0-58.0	22	52.8 ± 8.8	36.0-71.0	6	53.3 ± 4.6	46.0-58.0
Sleep architecture, periodic limb movement index, and arousals									
Total sleep time (min)	15	447.3 ± 113.6	107-548	32	431.3 ± 58.8	244-528	10	431.9 ± 59.6	335-520
Sleep efficiency (%)	15	81.3 ± 19.9	21.4-96.6	32	82.3 ± 14.5	21.4-98.1	10	85.5 ± 8.9	70.2-96.0
Sleep latency (min)	15	67.2 ± 99.9	4.5-392.0	32	42.2 ± 43.4	0.5-151.0	10	24.8 ± 19.6	0-55.5
REM latency (min)	15	92.6 ± 42.0	49.0-170.0	32	120.6 ± 59.6	44.5-236.0	10	150.5 ± 56.9	46.0-224.0
Wake after sleep onset (min)	15	34.2 ± 43.0	4-182	32	51.0 ± 49.5	2-245	10	48.3 ± 33.4	3-110
NREM 1 (%)	12	3.1 ± 3.8	0.5-14.0	31	2.9 ± 2.6	0.2-10.3	10	4.7 ± 3.6	0.2-11.9
NREM 2 (%)	12	55.4 ± 8.7	36.4-67.4	31	51.3 ± 8.7	23.4-68.7	10	53.5 ± 9.1	37.1-68.8
NREM 3 (%)	15	21.5 ± 7.3	11.4-36.4	32	26.5 ± 7.0	14.2-48.8	10	22.0 ± 6.9	12.1-31.1
REM (%)	15	19.9 ± 4.5	12.3-27.4	32	19.8 ± 4.4	12.7-26.9	10	19.8 ± 5.4	11.4-27.3
PLM index (n/h)	15	6.8 ± 14.7	0-56.5	31	3.3 ± 5.1	0-20.9	9	4.6 ± 3.5	0-9.5
PLM arousal index (n/h)	14	0.6 ± 0.8	0-2.0	28	0.8 ± 1.4	0-6.6	5	1.3 ± 1.4	0-3.3
Respiratory arousal index (n/h)	15	0.3 ± 0.3	0-1.1	32	4.0 ± 4.8	0-21.5	10	1.7 ± 1.3	0-4.5
Spontaneous arousal index (n/h)	15	4.8 ± 2.8	0.4-9.2	32	7.1 ± 3.7	0.9-16.8	10	6.2 ± 2.2	1.8-9.5
Total arousal index (n/h)	15	7.5 ± 2.7	3.1-11.0	32	14.1 ± 8.6	4.2-28.7	10	11.5 ± 4.1	5.7-17.9
Body mass index	**n**	**Mean ± SD**	**z-score**	**n**	**Mean ± SD**	**z-score**	**n**	**Mean ± SD**	**z-score**
BMI (kg/m^2)	15	19.2 ± 4.4	0.1 ± 0.8	32	17.7 ± 5.1	0.04 ± 1.3	10	22.3 ± 6.3	1.2 ± 0.9

Data includes pre- and post-adenotonsillectomy data on 2 subjects. BMI, body mass index; OAHI, obstructive apnea-hypopnea index; OAI, obstructive apnea index; OHI, obstructive hypopnea index; OSA, obstructive sleep apnea; $P_{ET}CO_2$, peak end-tidal carbon dioxide; PLM, periodic limb movements during sleep; SpO_2, oxyhemoglobin saturation; T_{90}, % sleep time below SpO_2 90%.

sleep disordered breathing. Sleep parameters were compared across SCD genotypes, age groups, and OSA/adenotonsillectomy conditions. Two-thirds of the sample was diagnosed with OSA, suggesting that children with SCD are either at increased risk of OSA or that recognition of sleep disordered breathing and referral for polysomnography is delayed in these children. Our data also suggest that sleep is comparable between Hb SS and Hb SC genotypes, with the exception of respiratory indices influenced by the hemolytic process, affecting oxygen-carrying capacity in Hb SS more severely than in Hb SC disease. Mean SpO_2 was significantly lower and T_{90} was significantly higher in children with Hb SS than those with Hb SC disease, findings that replicate other studies.[11-16] A consideration when interpreting these data, however, is that pulse oximetry measurement in SCD differs from that of people with normal adult hemoglobin on whom oximetry was validated, because of altered oxyhemoglobin affinity and the presence of dysfunctional hemoglobins. Studies of pulse oximetry measurement in children with SCD have both underestimated and overestimated SpO_2, depending on the standard of comparison (e.g., co-oximetry, arterial blood gas analysis) and method (arterial or capillary blood), although are generally within 5% of co-oximetry values.[13-15] Even between SCD genotypes, the shift in oxyhemoglobin dissociation and amounts of dyshemoglobin differ,[24] and thus could account for differences in hypoxemia observed between subjects with HbSS and HbSC in this study. However, the magnitude of differences in oxygenation parameters in this study; for example, an average T_{90} of 8% in Hb SS versus virtually 0% in Hb SC subjects, and nadir SpO_2 as low as 54% in Hb SS versus 78% in Hb SC, are unlikely to be explained solely by discrepant oximetry measurement.

In our sample, obstructive indices decreased as age increased across the first three age groups, increasing again slightly in the oldest age group. The increase in obstructive events in adolescents with SCD was not associated with an increase in BMI, but appeared more pronounced in those who were underweight. This finding contrasts with findings in unaffected children in which the bimodal peak of OSA during adolescence appears to be related to obesity.[25]

Most arousal indices were higher in children with Hb SS than in those with Hb SC, while sleep efficiency was decreased, latency to sleep was longer, and wake after sleep onset was greater. Other chronic anemic states have been associated with sleep fragmentation. Tarasiuk et al., for example, found severe sleep fragmentation, defined by the number of arousals and awakenings per hour of sleep, in children with two hereditary hemolytic anemias, β-thalassemia and congenital dyserythropoietic anemia type 1 (27.8 and 23.8 events/hour, respectively).[26] In our sample, arousal indices were not abnormally elevated, and sleep fragmentation based on the above definition was similar in our subjects with SCD to that found in their controls[26] (13.9 vs. 12.1 events/hour, respectively). Yet, sleep disruption was evident in children with Hb SS in our sample. While indices measured during polysomnography may not reflect sleep quality at home, they suggest that children with Hb SS experience poorer quality sleep than those with Hb SC disease.

This study provides preliminary evidence that adenotonsillectomy improves OSA in children with SCD, although it appears that obstructive events continue to be present, or reoccur, in many patients. Following adenotonsillectomy, the first-line treatment of OSA in the pediatric population, 8 of 10 children had OSA. Referral bias may explain this phenomenon, in that children with signs of continued or recurrent obstruction are more likely to be referred for follow-up polysomnography. Despite this, nearly all respiratory parameters were better in the AT than in the OSA/No AT condition, including a mean OAHI for the AT condition that was half, and a T_{90} that was 20% of the mean values of the OSA/No AT condition.

There are several possible explanations for the elevated obstructive indices found in this sample post-adenotonsillectomy. While highly effective in reducing severity of OSA, adenotonsillectomy does not cure all children. A recent systematic review of studies of adenotonsillectomy for the treatment of OSA in children found that when cure was defined as an OAHI < 1, only 59.8% of children were cured.[27] The high frequency of OSA following adenotonsillectomy in our sample may also be related to the higher mean BMI found in post-adenotonsillectomy children compared to children with OSA who had not undergone surgery. While obesity has historically been rare in children with SCD because of high metabolic demands,[28] the current trend toward increasing BMI among children may well be affecting this population. In our study, 4 children had a BMI ≥ 30. It is possible that some subjects in the AT condition were overweight prior to surgery, and adenotonsillectomy is not only less likely to cure OSA in children who are overweight,[29] it may contribute to the development of obesity.[30]

The elevated PLM index in children with SCD is a new finding. Periodic limb movements during sleep are unusual in children. In a large sample of children referred for polysomnography, for example, investigators found that 1.2% of the sample had a PLM index exceeding 5 per hour of sleep when other comorbidities such as OSA and attention deficit hyperactivity disorder were excluded.[31] In the present study, the prevalence of PLM disorder was 29% in subjects who did not have OSA. Reasons for the elevated PLM index in children with SCD are unknown. In pediatric studies of PLM disorder and restless legs syndrome, PLMs have been associated with low to low-normal serum iron and ferritin levels.[32,33] Low iron levels are unusual in children with SCD because of blood transfusions and acute phase response to vaso-occlusive tissue damage.[34] Yet there is evidence that iron deficiency is not uncommon in this population, particularly before the age of 6 years in untransfused patients.[35] The present study lacked measures of iron storage, yet a nonsignificant difference in the PLM index between age groups makes low iron stores an unlikely cause of the elevated PLMs.

The findings of this study highlight several implications for the clinical care of children with SCD. Foremost is the need to screen every child with SCD for sleep disordered breathing and other sleep related problems at every contact. Validated sleep questionnaires for use in children and adolescents are available.[36] Referral for polysomnography should be initiated promptly when parents report symptoms suggestive of sleep disordered breathing including snoring, gasping, witnessed apneas and excessive daytime sleepiness. Providers should be aware that OSA can present at any age and in the absence of common comorbidities such as obesity. Close follow-up of OSA-positive children treated with adenotonsillectomy also appears to be required. Serious consideration should be given to performing routine post-adenotonsillectomy polysomnography to evaluate for residual disease, as eradication of OSA and not merely improvement in respiratory indices must be the goal of treatment.[27]

This observational, retrospective study had some limitations. All cases were referred for polysomnography for assessment of sleep disordered breathing. Consequently, the prevalence of OSA found in this sample likely overestimates its prevalence in the general population of children with SCD. Analyses were limited by data and variables that were unavailable retrospectively (pre-adenotonsillectomy polysomnography and BMI), lag times between adenotonsillectomy and follow-up polysomnography were long in some cases, and the number of children having adenotonsillectomy was small. Thus, the ability to draw conclusions regarding the effect of adenotonsillectomy on the presence and severity of OSA was limited.

In conclusion, children with SCD may have a unique susceptibility to developing sleep disordered breathing and other sleep-related disorders, warranting further investigation. Areas of future research should include the prevalence, causes and consequences of OSA in children with SCD. For example, OSA has been associated with pulmonary hypertension in adults,[37] a disease which, in SCD, carries a high risk of mortality. A potential association between OSA and pulmonary hypertension presents an important area of investigation in children with SCD given the apparent high prevalence of each disease in this population.[38,39] Effectiveness of treatments of OSA, particularly adenotonsillectomy, deserves investigation. Finally, the finding of elevated PLMs in children with SCD requires further inquiry into their causes and long-term consequences. Expanded research in these areas is essential to improve outcomes of children with a disease that causes progressive, lifelong decline in health and quality of life.

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Address correspondence to: Dr. Valerie E. Rogers, 307D Claire M. Fagin Hall, 418 Curie Boulevard, Philadelphia, PA 19104-4217; Tel: (215) 746-4447, Cell: (410) 794-6485; Fax: (215) 573-7507; E-mail: vrog@nursing.upenn.edu, or valerie.e.rogers@gmail.com

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