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Pediatric sickle cell disease and obstructive sleep apnea: A cross-sectional study in a tertiary pediatric center in Saudi Arabia

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Abstract:

OBJECTIVE: The aim of the study was to evaluate snoring and obstructive sleep apnea (OSA) in Saudi children with sickle cell disease (SCD).

MATERIALS AND METHODS: This cross-sectional study was conducted among children with SCD attending a hematology clinic were recruited. Demographics, clinical data, and sleep questionnaires were collected and overnight polysomnographies performed.

RESULTS: Seventy children (31 of whom were females) with SCD were included in the study. Their median (interquartile) age was 9 (6.5, 11) years and their body mass index *z*-score was −1.2 (−2.0, −0.4). Seventy-four percent of SCD patients snored and 32 (46%) had evidence of OSA (obstructive apnea-hypopnea index [OAHI] ≥2 events per hour of sleep), 13 of whom had moderate OSA (OAHI ≥5 and <10 events per hour of sleep) and 10 had severe OSA (OAHI ≥10 events per hour of sleep).

CONCLUSION: Snoring and the proportion of OSA were high in children with SCD. This underlines the importance of screening for OSA in all children with SCD.

Keywords:

Obstructive sleep apnea, pediatrics, sickle cell disease

Introduction

Sickle cell disease (SCD) is an autosomal recessive common genetic disorder which results in the production of sickle hemoglobin (HbS) in the blood.[1] This condition is common worldwide, specifically in Saudi Arabia where the prevalence is 24/10,000.[2] The presence of an abnormal HbS molecule is subject to polymerization or sickling under adverse conditions such as dehydration and hypoxia. Frequent polymerization significantly contributes to vaso-occlusion and hemolysis which are implicated in morbidity of patients with SCD.[3] In Saudi Arabia, there are two clinical phenotypes of SCD: the Arab-Indian phenotype and the Benin phenotype, the latter being the more clinically severe one.[4]

Obstructive sleep apnea (OSA) is common in the general pediatric population. OSA has a prevalence of around 2%–5%[5] and is often associated with neurobehavioral morbidity. Adenotonsillar hypertrophy is a common predisposing factor to OSA.[5-8] OSA in children with SCD is highly prevalent and is reported to occur in 10%–70% of all children with SCD.[9-13] Very few studies have assessed the occurrence of OSA within the pediatric population with SCD in Saudi Arabia.[14] Therefore, the primary objective

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of this study was to evaluate the percentage of OSA in Saudi children with sickle cell anemia in our tertiary center. The secondary objective was to compare the different demographic and polysomnographic (PSG) variables between the OSA group and non-OSA group.

Materials and Methods

In this cross-sectional study done between January 2016 and April 2017 in King Fahad Medical City, Riyadh, we prospectively recruited children consecutively from a pediatric hematology clinic to participate. Criteria for inclusion in the study comprised children of both genders between 5 and 15 years of age diagnosed with SCD. Prospective subjects who were identified to be on continuous positive airway pressure therapy as treatment for OSA were excluded from the study.

At the time of recruitment, the demographic and clinical data obtained from the clinical records included age, gender, height, weight, body mass index (BMI) *z*-score, SCD genotype, current medications including hydroxyurea therapy, and additional medical diagnoses as well as occurrence of vaso-occlusive crises (VOC), acute chest syndrome (ACS), and stroke.

Sleep questionnaires were completed at the time of recruitment. The questionnaires in Arabic had not been validated. However, they included common questions pertaining to disordered sleep breathing symptoms that were usually assessed in clinical practice such as snoring and restless sleep. Patients then were referred to the sleep laboratory for PSG.

Children underwent a standard overnight PSG using Alice 5 (Philips Respironics, USA) data acquisition and analysis system as per the standard techniques.[15,16] None of the children had had a PSG performed within 4 weeks of any concurrent illness, including a painful crisis or ACS. PSG measurements included electroencephalograms, electrooculograms, and submental and anterior tibialis electromyograms. Chest wall and abdominal belts were used to measure the chest wall and abdominal movements. Other respiratory measurements included oro-nasal thermal sensor, nasal air pressure transducer, and transcutaneous carbon dioxide and end-tidal carbon dioxide and oxygen saturation (SaO_2) monitors. Video and audio recordings, as well as body positions, were obtained. Sleep architecture[15,16] including sleep stages, sleep time, sleep-onset latency, and arousals was assessed. Recorded respiratory data included counts and indices of obstructive apnea, central apnea, hypopnea, and mixed apneas. All respiratory events were scored according to the American Academy of Sleep Medicine scoring guidelines.[16] OSA severity was graded according to obstructive apnea-hypopnea index (OAHI), the number of obstructive apneas, hypopneas, and mixed apneas per hour of sleep. OAHI of ≥2.0 was considered abnormal and indicative for OSA,[17] OAHI from ≥2.0 to <5 was considered mild OSA; OAHI from ≥5 to <10 was considered moderate OSA, and OAHI ≥10 was considered severe OSA. For the purpose of comparison with other reported OSA prevalence using different OAHI cutoff values, we evaluated the frequency of OSA using cutoff values OAHI ≥1.0 and ≥1.5 events per hour of sleep. The central apnea index was the number of central apneas per hour during sleep. The mean and nadir sleep SaO_2 as well as desaturation index (number of desaturations of ≥3% per hour of sleep) were recorded for each patient from the overnight PSG.

Baseline characteristics and clinical data, questionnaire results, and PSG data were reported as median with interquartile (IQR) for continuous variables and frequencies for categorical variables. The differences in outcomes between OSA and non-OSA were tested using Mann–Whitney nonparametric tests for continuous variables, and a Chi-square test/Fisher's exact was used for categorical variables. The assessment of the correlations between different demographic (age and BMI *z*-score), clinical (hemoglobin), and PSG variables and OAHI was done using Spearman's correlation coefficient test. All statistical analyses were performed using SAS version 9.3 (SAS statistical software, Cary, NC, USA). Statistical significance was set at $P < 0.05$. We estimated that a minimum sample of 60 patients was needed to provide one-sample one-sided test of proportions with 80% power at alpha = 0.05 to detect a 15% absolute increase of the prevalence of OSA than the general pediatric population, given an estimated 5% prevalence of OSA in general pediatric population (SAS version 9.3 statistical software, Cary, NC, USA).

Ethical approval was obtained from the Institutional Review Board/Ethics Committee (Institutional Research Board Review Number 13–128), and informed written consent was taken from all participants and/or their caregivers in the study.

Results

A total of 70 SCD children (44% were females) with a median age (IQR) of 9 (6.5, 11) years completed a full, in-laboratory PSG. Details regarding demographics, clinical information, and questionnaire results are presented in Table 1. The majority of SCD patients (80%) had HbSS genotype. Previous history of VOC was the most common SCD-related complication (99%), and the majority of children with SCD (93%) had a history of receiving blood transfusion. Reported frequencies of snoring and restless sleep were high (74% and 63%, respectively).

Table 1: Demographics and questionnaire results of children with sickle cell disease and in both obstructive sleep apnea and nonobstructive sleep apnea groups[§]

Results[‡]	All SCD (*n*=70) *N* (%)	OSA group (*n*=32) *N* (%)	Non-OSA group (*n*=38) *N* (%)	*p*-Value*
Age (Years) Median (IQR)	9 (6.5-11)	9 (7-10)	9 (6-12)	0.92
Female	31 (44)	11 (34)	20 (52)	0.13
BMI *z*-score Median (IQR)	−1.2 (−2.0-−0.4)	−1.4 (−2.3-−0.1)	−1.1 (−2.0-−0.4)	0.99
Hb (g/l) Median (IQR)	8.2 (7.8-9.0)	8.0 (7.8-8.6)	8.7 (7.9-9.4)	0.01
Genotypes				
HbSS	56 (80)	29 (91)	27 (71)	0.11
HbS β^+	7 (10)	2 (6)	5 (13)	
HbS β^0	7 (10)	1 (3)	6 (16)	
Hydroxyurea use	31 (44)	14 (44)	17 (45)	0.93
History of vaso-occlusive crises	69 (99)	31 (97)	38 (100)	0.27
History of acute chest syndrome	15 (21)	7 (22)	8 (21)	0.93
History of stroke	5 (7)	3 (9)	2 (5)	0.51
History of blood transfusion	65 (93)	30 (94)	35 (92)	0.79
Evidence of pulmonary hypertension	2 (3)	1 (3)	1 (3)	0.92
Previous adenotonsillectomy	6 (9)	2 (6)	4 (11)	0.52
History of snoring	52 (74)	26 (81)	26 (68)	0.22
Restless sleep	44 (63)	25 (78)	19 (50)	0.02
Apnea during sleep	13 (19)	8 (25)	5 (13)	0.21
Wake up at night	49 (70)	23 (72)	26 (68)	0.75
Bed wetting	27 (39)	13 (41)	14 (37)	0.75
Difficult to awaken	32 (46)	12 (38)	20 (53)	0.21
Lack of attention at school	13 (19)	6 (19)	7 (18)	0.97
Excessive sleepiness	6 (9)	3 (9)	4 (11)	0.87
Hyperactivity attention disorder diagnosis	6 (9)	3 (9)	3 (8)	0.83

*Mann-Whitney test was used for continuous variables and Chi-square test/Fisher's exact was used for categorical variables, [§]OSA was defined by total obstructive apnea-hypopnea index ≥2 events per hour. BMI=Body mass index, Hb=Hemoglobin, OSA=Obstructive sleep apnea, SCD=Sickle cell disease, HbS=Sickle hemoglobin

Thirty-two patients (46%) had evidence of OSA, 9 of whom were diagnosed with mild OSA, 13 diagnosed with moderate OSA, and 10 SCD children with severe OSA. Using lower OAHI cutoff values for OSA, the prevalence for cutoff of 1.5 and 1.0 was 39 (56%) and 43 (61%), respectively. Comparisons between OSA group and non-OSA group showed that the OSA group had lower hemoglobin concentration than non-OSA group ($P = 0.01$); however, in the two groups, the remaining demographics and clinical data including a history of previous adenotonsillectomy surgery were similar. There were no significant differences between OSA and non-OSA groups in the sleep questionnaire including a history of snoring, except that there was more reported history of restless sleep by parents of the OSA group (78%) in comparison to non-OSA group (50%), $P = 0.02$ [Table 1]. The OSA group had higher OAHI ($P < 0.0001$), arousal index ($P < 0.0001$), desaturation index ($P = 0.0002$) as well as lower mean wake SaO_2 ($P = 0.03$) and mean and minimal sleep SaO_2 ($P = 0.009$ and 0.01, respectively), which was expected. The remaining PSG variables including sleep architecture did not differ between the two groups [Table 2].

There was weak but significant negative correlation between hemoglobin values and OAHI ($r = -0.28$, $P = 0.02$). There was moderate and significant correlation between OAHI and the arousal index ($r = 0.45$, $P < 0.0001$) and between OAHI and the desaturation index ($r = 0.48$, $P < 0.0001$). There was weak but significant negative correlation between OAHI and mean sleep SaO_2 ($r = -0.29$, $P = 0.02$). These results are not presented in the tables.

Discussion

To the best of our knowledge, this is the largest study in Saudi Arabia that prospectively evaluated the proportion of OSA in children with SCD. There was a high proportion of OSA (46%) in children with SCD. Approximately one-third of SCD patients had moderate-to-severe OSA. As expected, SCD patients with OSA had evidence of lower sleep quality (i.e., higher arousal index) than those without OSA.

Despite the high prevalence of OSA, we did not find any association between OSA and the reported frequency of VOC, stroke, or chest crises. Our findings provide additional support to the limited body of literature that suggests that OSA and its severity are not implicated in SCD morbidity such as VOC.[13,18] These results contradict

Table 2: Polysomnography results in children with sickle cell disease and in obstructive sleep apnea and nonobstructive sleep apnea groups[§]

Results[‡]	All SCD (*n*=70) Median (IQR)	OSA group (*n*=32) Median (IQR)	Non-OSA group (*n*=38) Median (IQR)	*p*-Value*
TST, min	344 (295-378)	344 (293-379)	341 (305-378)	0.81
Sleep efficiency, %	85.6 (74.2-92.1)	85.0 (76.3-92.0)	87.2 (71.3-92.5)	0.98
Sleep latency, min	14.2 (4.3-37.5)	7.4 (1.5-28.3)	15.3 (7.0-40.8)	0.06
REM latency, min	134 (100-189)	157 (119-223)	132 (100-176)	0.17
Stage 1% TST	2.9 (1.4-5.4)	2.8 (1.8-6.0)	3.1 (1.4-5.3)	0.69
Stage 2% TST	46.7 (39.4-53.3)	46.8 (37.4-51.0)	46.4 (40.6-54.1)	0.47
Slow wave sleep % TST	32.9 (27.6-39.7)	32.1 (28.5-37.3)	34.3 (26.4-42.4)	0.81
REM % TST	14.7 (10.5-20.2)	16.2 (10.9-20.7)	13.5 (10.0-19.7)	0.66
Arousals index per hour	15.9 (11.5-31.5)	21.5 (16.1-83.0)	12.9 (9.3-16.8)	<0.0001
Mean wake SaO_2, %	98 (96-99)	97 (95-98)	98 (98-99)	0.03
Mean sleep SaO_2, %	97 (96-98)	96 (94-98)	98 (97-99)	0.009
Minimum sleep SaO_2, %	91 (84-94)	89 (81-92)	93 (90-94)	0.01
DI (events/hour)	0.4 (0.2-2.4)	1.8 (0.4-2.7)	0.2 (0.0-0.6)	0.0002
OAHI (events/hour)	1.8 (0.3-6.3)	6.5 (4.3-12.9)	0.4 (0.0-1.0)	<0.0001

*Mann–Whitney test was used for continuous variables, [§]OSA was defined by total obstructive apnea-hypopnea index ≥2 events per hour. DI=Desaturation index, OAHI=Obstructive apnea-hypopnea index, OSA=Obstructive sleep apnea, REM=Rapid eye movement, SaO_2=Oxygen saturation, TST=Total sleep time, SCD=Sickle cell disease

other research findings which used the self-reported Children's Sleep Habit Questionnaire and showed that SCD complications were related to OSA.[19] However, those studies did not use the formal gold standard PSG to diagnose OSA, which makes any conclusions drawn from their results rather tenuous.

We found a high prevalence of OSA in children with SCD compared with the general pediatric population. Although our population consisted of nonreferred SCD pediatric cases, the prevalence was found to be higher than previously published studies with nonreferred cases.[12,13] We evaluated the proportion of OSA in children with SCD using lower cutoff OAHI values and found that the prevalence for cutoff of 1.5 and 1.0 was 56% and 61%, respectively. The results remain higher than the other reported findings.[12,13] This may be explained by the geographic differences between the studies, possibly related to the severity of the SCD phenotype.[4] However, the use of a smaller cohort and recruitment from a single source may have led to differences in the proportion of OSA. On the other hand, one local report found higher prevalence of OSA in Saudi SCD children. However, the evidence of inconsistent and inaccurate results in the tables of that study makes a comparison with our findings inappropriate.[14]

It may be that factors related to SCD itself may promote OSA. It has been shown that upper airway lymphoid tissue hypertrophy possibly following splenic infarctions, recurrent infections, or increased hematopoietic needs may be a cause.[20,21] Another proposed mechanism is that changes in the upper airway size of SCD patients occur as a result of bone marrow effects of the disease.[21] Consequently, narrowing of the airways, even in the absence of lymphoid hyperplasia, may cause upper airway obstruction in these children.

A limitation of this study is the smaller sample size that we had in comparison to the other cohorts. Further, the recruitment was from only one tertiary center[12,13] which might have contributed to the difference in the prevalence of OSA. Moreover, we cannot exclude an association of abnormal neurocognitive function with OSA in children with SCD as described previously[22] since neurocognitive assessment was not done in our institution.

Conclusion

The prevalence of snoring and OSA was high in children with SCD in our center. This underlines the importance of screening for OSA in all children with SCD.

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Conflicts of interest

There are no conflicts of interest.

References

1. Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med 2010;38:S512-21.
2. Al-Qurashi MM, El-Mouzan MI, Al-Herbish AS, Al-Salloum AA, Al-Omar AA. The prevalence of sickle cell disease in Saudi children and adolescents. A community-based survey. Saudi Med J 2008;29:1480-3.
3. Lionnet F, Hammoudi N, Stojanovic KS, Avellino V, Grateau G, Girot R, *et al*. Hemoglobin sickle cell disease complications: A clinical study of 179 cases. Haematologica 2012;97:1136-41.

4. Jastaniah W. Epidemiology of sickle cell disease in Saudi Arabia. Ann Saudi Med 2011;31:289-93.
5. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 2008;5:242-52.
6. Löfstrand-Tideström B, Hultcrantz E. The development of snoring and sleep related breathing distress from 4 to 6 years in a cohort of Swedish children. Int J Pediatr Otorhinolaryngol 2007;71:1025-33.
7. Montgomery-Downs HE, O'Brien LM, Holbrook CR, Gozal D. Snoring and sleep-disordered breathing in young children: Subjective and objective correlates. Sleep 2004;27:87-94.
8. O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner JL, Raffield TJ, *et al.* Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. Pediatrics 2003;111:554-63.
9. Lehmann GC, Bell TR, Kirkham FJ, Gavlak JC, Ferguson TF, Strunk RC, *et al.* Enuresis associated with sleep disordered breathing in children with sickle cell anemia. J Urol 2012;188:1572-6.
10. Goldstein NA, Keller R, Rey K, Rao S, Weedon J, Dastgir G, *et al.* Sleep-disordered breathing and transcranial Dopplers in sickle cell disease. Arch Otolaryngol Head Neck Surg 2011;137:1263-8.
11. Rogers VE, Lewin DS, Winnie GB, Geiger-Brown J. Polysomnographic characteristics of a referred sample of children with sickle cell disease. J Clin Sleep Med 2010;6:374-81.
12. Rosen CL, Debaun MR, Strunk RC, Redline S, Seicean S, Craven DI, *et al.* Obstructive sleep apnea and sickle cell anemia. Pediatrics 2014;134:273-81.
13. Salles C, Ramos RT, Daltro C, Barral A, Marinho JM, Matos MA, *et al.* Prevalence of obstructive sleep apnea in children and adolescents with sickle cell anemia. J Bras Pneumol 2009;35:1075-83.
14. Al-Otaibi T, Al-Qwaiee M, Faraidi H, Batniji F, Al-Otaibi F, Al-Harbi A, *et al.* Prevalence of obstructive sleep apnea in children with sickle cell disease at a tertiary hospital in Saudi Arabia. Saudi Med J 2017;38:616-20.
15. Rechtschaffen AK. A Manual of Standardized Terminology: Techniques and Scoring System for Sleep Stages of Human Subjects: UCLA Brain Information Service. Angeles, CA: Brain Research Institute;1968.
16. Berry RB, Gamaldo CE, Harding SM, Marcus CL, Vaughn BV; For the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.0. Darien, Illinois: American Academy of Sleep Medicine; 2012.
17. Marcus CL, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG, *et al.* A randomized trial of adenotonsillectomy for childhood sleep apnea. N Engl J Med 2013;368:2366-76.
18. Brooks LJ, Koziol SM, Chiarucci KM, Berman BW. Does sleep-disordered breathing contribute to the clinical severity of sickle cell anemia? J Pediatr Hematol Oncol 1996;18:135-9.
19. Daniel LC, Grant M, Kothare SV, Dampier C, Barakat LP. Sleep patterns in pediatric sickle cell disease. Pediatr Blood Cancer 2010;55:501-7.
20. Strauss T, Sin S, Marcus CL, Mason TBA, McDonough JM, Allen JL, *et al.* Upper airway lymphoid tissue size in children with sickle cell disease. Chest 2012;142:94-100.
21. Samuels MP, Stebbens VA, Davies SC, Picton-Jones E, Southall DP. Sleep related upper airway obstruction and hypoxaemia in sickle cell disease. Arch Dis Child 1992;67:925-9.
22. Hollocks MJ, Kok TB, Kirkham FJ, Gavlak J, Inusa BP, DeBaun MR, *et al.* Nocturnal oxygen desaturation and disordered sleep as a potential factor in executive dysfunction in sickle cell anemia. J Int Neuropsychol Soc 2012;18:168-73.