# Prevalence of obstructive sleep apnea in children with sickle cell disease at a tertiary hospital in Saudi Arabia

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## ABSTRACT

الأهداف : تقييم مدى انتشار انقطاع التنفس أثناء النوم في الأطفال السعوديين المصابين بمرض الخلايا المنجلية في مستشفى ثالثي في المملكة العربية السعودية عبر دراسة النوم الليلي .

الطريقة : أجريت دراسة مقطعية مستقبلية بين عامي 2012 و 2016 على 65 طفلا تتراوح أعمارهم بين 14-2 سنة في مدينة الأمير سلطان الطبية العسكرية، الرياض، المملكة العربية السعودية مصابين بمرض الخلايا المنجلية . أجاب المرضى على استبيان النوم للأطفال بمساعدة أحد مقدمي الرعاية المرافقين وخضعوا لدراسة النوم في نفس الليلة .

النتائج : شملت العينة النهائية 65 طفلا، متوسط العمر 8.1سنوات . كان هناك 32 صبيا (49.2%) و 33 فتاة (50.8%) وكان متوسط الهيموجلوبين 8.6 (p=0.37) وكان متوسط مؤشر كتلة الجسم 15.6 (p=0.36) وكان انتشار انقطاع النفس أثناء النوم الانسدادي80% 52 مريضا باستخدام مؤشر توقف مؤشر ضعف التنفس ≥1 و 7.7% (5 مرضى) باستخدام مؤشر توقف مؤشر ضعف التنفس ≥5. وكانت نتائج استبيان النوم للأطفال الشخير (73.8%) وانقطاع النفس (32.8%) والتبول اللاإرادي (46%).

الخاتمة : انقطاع النفس أثناء النوم الانسدادي شائع لدى الأطفال المصابين بمرض الخلايا المنجلية .

**Objectives:** To assess the prevalence of obstructive sleep apnea in Saudi children with sickle cell disease at a tertiary hospital in Kingdom of Saudi Arabia (KSA) using nocturnal polysomnography.

**Methods:** A prospective cross-section study was conducted between 2012 and 2016 in 65 children aged between 2-14 years at Prince Sultan Military Medical City, Riyadh, KSA with sickle cell disease. Patients answered a pediatric sleep questionnaire with the help of an accompanying caregiver and underwent polysomnography in the same night.

**Results:** The final sample included 65 children. Median age was 8.1 years. There were 32 boys (49.2%) and 33 girls (50.8%). Mean hemoglobin was 8.6 ($p$=0.37) and mean body mass index was 15.6 ($p$=0.36). The prevalence of obstructive sleep apnea was 80% (52 patients) using an apnea hypopnea index cutoff of ≥1 and 7.7% (5 patients) using an apnea hypopnea index cutoff of ≥5. Results from the pediatric sleep questionnaire were snoring (73.8%), apnea (32.8%), and bedwetting (46%).

**Conclusion:** Obstructive sleep apnea is common in children with sickle cell disease.

Sickle cell disease (SCD) is one of the most common inherited types of hemoglobinopathy in the Kingdom of Saudi Arabia (KSA) and has a high mortality and morbidity risk. In KSA, approximately 4.2% of the population carries the sickle cell trait and 0.3% has SCD. The highest prevalence is seen in the eastern province of the country where approximately 17% of the population has the sickle cell trait and 1.2% has SCD.[1] Clinical and hematological variability exists in SCD in KSA with 2 major phenotypes, a mild phenotype and a severe phenotype.[1] Sickle cell anemia is an autosomal recessive disorder characterized by the presence of homozygous HbSS or heterozygous HbS with another beta globulin mutation (for example, sickle-beta thalassemia). The hallmarks of the disease

are vaso-occlusive phenomena and hemolytic anemia. Vaso-occlusive crises (VOC) can be triggered by cold, dehydration, infection, or hypoxia and can eventually result in acute chest syndromes. Nocturnal desaturation occurs in approximately 80% of patients with SCD.[2,3] The underlying mechanism is thought to be secondary to intrinsic parenchymal lung disease, abnormal oxyhemoglobin affinity, and upper airway obstruction, mainly obstructive sleep apnea (OSA).[4,5] The prevalence of OSA in children with SCD is reported to be 79% compared with the normal general population (1-5%).[2] However, few studies that have investigated OSA prevalence in SCD children were limited to symptomatic patients only.[2,6] One study, conducted a referred sample and evaluated 55 patients with SCD, found 69.1% to have obstructive sleep apnea syndrome (OSAS).[6] In children with SCD, OSAS is primarily secondary to adenotonsillar hypertrophy (ATH).[7] It is not understood why SCD patients are more prone to develop ATH. The main 3 hypotheses on the association include: a) compensatory hypertrophy of adenoid and tonsillar tissues after autosplenectomy; b) an increased incidence of recurrent tonsillitis due to the impaired opsonization to pathogenic bacteria; and c) extramedullary hematopoiesis.[3] The presence of ATH increases the risk for OSAS, and may lead to nocturnal episodic hypoxemia, hypercarbia, and respiratory acidosis; events that can trigger red blood cell sickling and precipitate VOC.[8,9] Obstructive sleep apnea syndrome is associated with various adverse health outcomes including behavioral problems, excessive day time sleepiness, cognitive deficits, cardiovascular changes, and a reduced quality of life.[10] The OSAS is a treatable condition and greater effort is needed to implement and evaluate screening programs, diagnostic tools, and treatment options for OSAS in this high-risk and vulnerable population. The aim of this study was to assess the prevalence of OSA in SCD in Saudi children irrespective of sleep-related breathing disorder (SRBD) symptoms at a tertiary hospital in KSA using nocturnal polysomnography (PSG) and describe the sleep architecture in children with SCD

**Methods.** *Ethical approval.* This study was approved by the Institutional Review Board (No. 761) and was conducted in accordance with the principles contained within the Declaration of Helsinki. All patients and/or their guardians provided written informed consent.

*Participants.* This was a prospective cross-section study of male and female children with SCD (aged 2-14 years) referred from the hematology clinic irrespective of their SRBD symptoms between 2012 and 2016. Two-hundred patients were recruited, but only 65 patients agreed to perform overnight PSG. All patients who agreed to undergo nocturnal PSG were asked to complete a pediatric sleep questionnaire with the help of an accompanying caregiver, and demographic data and histories of medical comorbidities were collected at the same time. Inclusion criteria were patients diagnosed with SCD confirmed by hemoglobin electrophoresis and aged between 2-14 years. Exclusion criteria were patients on active therapy for OSA and patients with debilitating comorbidities.

*Polysomnography.* Patients were accompanied by their legal guardians for the PSG study. The study was conducted in a quiet environment, with appropriate light and temperature, for at least 6 hours. Polysomnography was conducted during spontaneous sleep. No sedation or sleep deprivation was used and patients were asked to avoid any stimulating food or drinks (coffee, black tea, chocolate, soda). The PSG was carried out in a hospital setting using a Philips Alice 6 PSG system (Alice 6 LDxS Base station INT, Philips Respironics, Murrysville, USA). All results were determined by a single observer. The following physiological parameters were recorded: electroencephalogram, leads (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1) were placed according to the international 10-20 system, electro-oculogram, electromyogram (chin electromyography, mentalis and submentalis muscles, right and left leg electromyography, anterior tibialis muscle), electrocardiogram, airflow (signals from a nasal pressure transducer and thermistor) using Pro Tech Sensor (Pro Tech Respironics, Murrysville, USA), microphone recordings, respiratory effort (respiratory inductance plethysmography), body position, and oxygen saturation (SpO2). Sleep studies were scored by a certified sleep medicine technician according to the American Academy of Sleep Medicine (Darien, IL, USA) manual for scoring sleep stages and associated events.[11] Sleepware G3 sleep diagnostic software with version 3.5.1, was used to monitor and score the acquisitions. Sleep efficiency was calculated as total sleep time divided by time in bed. Sleep latency was defined as the interval between turning off the lights and the first

minute of stage 1 sleep. Rapid eye movement (REM) sleep latency was defined as the interval between sleep onset and the first period of REM sleep. Arousal was defined as an abrupt change in the frequency of the electroencephalogram for 3 seconds or longer. The total index of arousals was defined as: number of arousals divided by the total number of hours of sleep. The following definitions were used. Obstructive apnea: interruption in airflow for a duration of ≥2 respiratory cycles, despite the persistence of chest effort, abdominal effort, or a combination of chest and abdominal effort. Index of obstructive sleep apnea: the number of events per hour of sleep. Hypopnea: reduction by ≥50% in airflow amplitude associated with one arousal or reduction of >3% in relation to basal SpO2. Apnea hypopnea index (AHI): the number of obstructive apnea or obstructive hypopnea events per hour of sleep. Index of oxygen desaturation: all oxygen desaturation events >3% based on basal SpO2 per hour of sleep. Patients with an AHI ≥1 event per hour of sleep were classified as having apnea. An AHI cutoff point of ≥5 was used to compare our finding with other studies.

*Pediatric sleep questionnaire.* We reviewed the pediatric sleep questionnaires (PSQ) of all patients, which was translated into Arabic and completed by the accompanying caregiver. The PSQ was validated in 2000,[12] and has a sensitivity of 81% and a specificity of 87%. It comprises 22 questions and is answered with either Yes, No, or Don't know. Each Yes receives a score of 1. A score of 5 or more is a positive questionnaire.

*Statistical analysis.* Microsoft Excel (Microsoft Inc., Redmond, USA) was used to arrange raw data before data were imported into The Statistical Package for Social Sciences version 22 (IBM Corp., Armonk, NY, USA) version 20 for analyses. Continuous data were analyzed using analysis of variance (ANOVA) and results are reported as mean ± standard deviation. Categorical data were analyzed using the Chi squared test. Non-parametric data were analyzed using the Kruskal–Wallis test and results are reported as median and interquartile range. A *p*-value of ≤0.05 was considered statistically significant for associations between variables.

**Results.** The final sample included 65 children. **Table 1** shows clinical profiles of the children with SCD in relation to AHI severity score. Median age was 8.1 years and there were 32 boys (49.2%) and 33 girls (50.8%). Of the patients studied, 90.8% had sickle cell anemia. At AHI cutoff points of ≥1 and ≥5, the male to female ratios were 1:1 (26 boys [50%] and 26 girls [50%] and 1.5:1 (3 boys [60%] and 2 girls [40%]), respectively. There was no significant gender predominance. Sixty percent of SCD patients had a history of blood transfusions; however, there was no significant association with OSA (*p*=0.07). Results from the pediatric sleep questionnaire showed a history of snoring for more than half the time during sleep in 73.8% children (of these 64.6% had an AHI≥1). A history of apnea during sleep was reported in 32.8%(71.4% had an AHI≥1), and bedwetting was reported in 46%(62.1% had an AHI ≥1).

The distribution of cardiopulmonary PSG data stratified by AHI cutoff is shown in **Table 2**. The frequency of OSA in the sample, based on commonly

**Table 1** - Demographic distribution and medical history by apnea hypopnea index categories.

| Characteristics | Total (n=65) | Apnea hypopnea index | | | | P-value |
| --- | --- | --- | --- | --- | --- | --- |
| | | <1 (n=13) | 1-4.9 (n=47) | 5–9.9 (n=4) | 10+ (n=1) | |
| *Demographic characteristics* | | | | | | |
| Age, mean ± SD | 8.1 ± 5.02 | 7.6 ± 4.15 | 8.1 ± 5.43 | 9.5 ± 3.41 | 10 ± 0 | 0.90 |
| *Physiological measurements* | | | | | | |
| Hemoglobin, mean | 8.6 | 8.8 | 8.6 | 8.7 | 6.8 | 0.37 |
| Body mass index, mean ± SD | 14.9 ±29.1 | 15.9 ± 27.7 | 14.7 ± 10.3 | 15.9 ± 3.5 | 14.6 ± 0 | 0.36 |
| *Other medical and/or family history (%)* | | | | | | |
| Blood transfusion | 60.00 | 7.70 | 44.60 | 6.20 | 1.50 | 0.07 |
| Tonsillectomy | 10.80 | 0.00 | 9.20 | 1.50 | 0.00 | 0.66 |
| Adenoidectomy | 9.20 | 0.00 | 7.70 | 1.50 | 0.00 | 0.84 |
| Cigarette smoke exposure | 13.80 | 1.50 | 9.20 | 3.10 | 0.00 | 0.49 |
| Asthma | 20.60 | 4.80 | 14.30 | 0.00 | 1.60 | 0.27 |
| Continuous data with normal distributions are mean ± SD | | | | | | |

used AHI cutoff points and definitions, was 80% (52 patients) if using an AHI cutoff point of ≥1 and 7.7% (5 patients) if using an AHI cutoff point of ≥5. **Table 3** shows sleep PSG data divided by age (≤5, 6-10, and ≥11 years).

**Discussion.** The prevalence of OSA in SCD patients screened for OSA irrespective of SRBD symptoms was 80% at an AHI cutoff point of ≥1 and 7.7% at a cutoff point of ≥5 in the current study. Our results for OSA prevalence were significantly higher than those of the normal population (1–5%).[10,13,14] In children with SCD, the reported OSA prevalence irrespective of SRBD symptoms ranges between 10% and 41%.[3,15]

The high prevalence of OSA in SCD patients in the current study might be secondary to ethnic diversity. Bahammam et al[16,17] reported that 4 in 10 middle-aged Saudi women and one in 3 middle-aged Saudi males are at risk for OSA. Studies in pediatric population are limited.

Cigarette smoke exposure[18] and previous adenotonsillectomy,[19] both known to be associated with OSAS in the general population, were not significantly associated with OSA in this study. We found no significant association between OSA and asthma. However, our asthma assessment did not include a physician's diagnosis, but was inferred from parents' descriptions of asthma symptoms in their children.

**Table 2** - Cardiorespiratory polysomnography variables by apnea hypopnea index cutoff points among 65 children.

| Characteristics | Total (n=65) | Apnea hypopnea index | | | | *P*-value |
|---|---|---|---|---|---|---|
| | | ≤1 (n=13) | 1-4.9 (n=47) | 5-9.9 (n=4) | ≥10 (n=1) | |
| NREM, median (IQR), (range) | 1.3 (11.8) | 0.2 (0.5) | 1.5 (4.3) | 4.6 (1.6) | 11.8 (0) | 0.003 |
| REM, median (IQR), (range) | 1.2 (15.4) | 0.5 (1.4) | 1.7 (11.7) | 6.55 (15.4) | 0 (0) | 0.001 |
| Median (range) | 1.4 (11.5) | 0.3 (0.5) | 1.6 (3.7) | 5.25 (0.8) | 11.5 (0) | 0.000 |
| Central apnea index, median (IQR), (range) | 0.3 (3) | 0.1 (1) | 0.4 (2) | 1.75 (3) | 0.6 (0) | 0.005 |
| Obstructive apnea index, median (range) | 0.35 (10) | 0.1 (0) | 0.45 (10) | 1.75 () | 1.7 () | 0.000 |
| SpO2, % | | | | | | |
| During sleep (TIB), median (IQR) range | 98 (8) | 98 (7) | 98 (8) | 97 (4) | 98 (0) | 0.333 |
| During NREM sleep, median (IQR), (range) | 98 (9) | 99 (7) | 98 (9) | 97 (5) | 97 (0) | 0.219 |
| During REM sleep, median (range) | 98 (9) | 99 (7) | 98 (9) | 97 (5) | 97 (0) | 0.546 |
| Sleep time with SpO2 <95%, median (IQR), % | 1 (99.6) | 0.8 (15%) | 1 (72.7%) | 1.95 (12%) | 1.8 (0.3%) | 0.589 |
| Sleep time with SpO2 <90%, median (IQR), % | 1 (99.6) | 0.8 (15%) | 1 (72.7%) | 1.95 (12%) | 1.8 (0.3%) | 0.403 |
| Sleep time with SpO2 <85%, median (IQR), % | 0.2 (5.6) | 0.3 (34.8%) | 0.2 (63.2%) | 0.1 (0.8%) | 0.4 (1.1%) | 0.77 |
| Heart rate while sleeping, median (SD) | 83.83 (14.8) | 88.77 (12.4) | 82.5 (15.9) | 83.5 (3.6) | 82 (0) | 0.61 |
| Arousal index, median (SD), event/h | 5.9 (3.9) | 4 (3) | 6.3 (3.9) | 6.5 (4.2) | 11.1(0) | 0.18 |

Continuous data with normal distributions are mean ± standard deviation (SD). Data with non-normal distributions are medians (IQR), IQR - interquartile range, NREM - non-rapid eye movement, REM - rapid eye movement, SpO2 - oxygen saturation, TIB - time in bed.

**Table 3** - Sleep polysomnography variables by age in yearsamong 65 children.

| Characteristic | Total (n=65) | Age in years | | | *P*-value |
|---|---|---|---|---|---|
| | | ≤5 (n=19) | 6-10 (n=31) | ≥11 (n=15) | |
| Total sleep time (min), Mean | 372.38 | 387.61 | 376.68 | 344.2 | 0.31 |
| Sleep latency (min), Mean | 12.7 | 13 | 13 | 7.9 | 0.71 |
| REM latency (min), Mean | 168.75 | 166 | 149 | 186.5 | 0.67 |
| Sleep efficiency (%) Median | 76.9 | 73.4 | 89.8 | 68 | 0.05 |
| NREM stage 1 sleep (%) Median | 4.7 | 4.9 | 4.24 | 5.5 | 0.45 |
| NREM stage 2 sleep (%) Median | 51.5 | 48.8 | 51.4 | 55.3 | 0.11 |
| NREM stage 3 sleep (%) Median | 29.8 | 29.14 | 30.8 | 28.5 | 0.72 |
| REM sleep (%) Median | 15.3 | 22.13 | 13.4 | 10.6 | 0.05 |

REM - rapid eye movement, NREM - non-rapid eye movement

Nocturnal oxygen desaturation in patients with sickle cell disorders ranges between 50%[20,21] and 80%,[2,3] and is associated with an increase in red blood cell sickling and increased VOC and acute chest syndromes. In the current study, nocturnal oxygen desaturation reached 72.7%, consistent with what is reported in the literature .[2,3] Also, the arousal index was high in the severe AHI group. Our second aim was to describe sleep architecture in children with SCD, but we could not draw conclusions from the findings for sleep stages in the current study due to the small sample size, which made it difficult to compare the patients in the 3 age groups. Future local studies with larger sample sizes are needed to describe the sleep stages by age groups in SCD patients. A strength of the current study was that we studied children with SCD irrespective of their SRBD symptoms.

*Study limitations.* There was a large variation in ages in our sample and there were both patients with sickle cell anemia and sickle beta-thalassemia, in addition to small sample size. Our sample comprised patients referred from a specialized clinic at a tertiary hospital and might not reflect the actual population of SCD patients in the community.

In conclusion, in the setting of a Saudi tertiary hospital, OSA is very common in children with SCD. Appropriate care of these patients should include routine evaluation for OSAS to improve overall health and prevent possible OSAS-related complications.

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