Original Article

Quality of sleep and pulmonary function in clinically stable adolescents with sickle cell anemia*

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Abstract

Objective: To evaluate quality of sleep and pulmonary function in clinically stable adolescents with sickle cell anemia (SCA). **Methods:** A cross-sectional descriptive study involving 50 patients with SCA submitted to nocturnal polysomnography and spirometry at the Brasília University Hospital. Anthropometric, polysomnographic and pulmonary function data were analyzed. Patients were divided into two groups according to oxygen saturation by pulse oximetry (SpO_2) during rapid eye movement (REM) sleep: $SpO_2 \leq 93\%$; and $SpO_2 > 93\%$. Descriptive statistics, Student's t-test, chi-square test and Pearson's correlation coefficient were used. **Results:** Mean age was 13.9 ± 2.5 years. Total sleep time and REM sleep percentage were lower, whereas REM sleep latency, the number of awakenings, movement during sleep, changes in sleep stage, sleep-disordered breathing index and obstructive apnea index were higher. Two patients (4%) did not present REM. There were statistically significant differences between the groups in most of the polysomnographic variables. The SpO_2 in REM sleep presented a strong positive correlation with waking SpO_2 and with SpO_2 in non-REM sleep, whereas it presented a strong negative correlation with the percentage of total sleep time during which SPO_2 was < 90%. Mean spirometric values were within normal ranges. Residual volume and the residual volume/total lung capacity/functional residual capacity ratio were elevated. **Conclusion:** Sleep impairment in clinically stable patients with SCA is probably due to hemoglobin desaturation and not to individual alterations in pulmonary function.

Keywords: Sleep disorders; Polysomnography; Adolescent; Anemia, sickle cell; Spirometry.

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Submitted: 25 April 2006. Accepted, after review, 22 August 2006.

Introduction

Sickle cell anemia (SCA) is a hereditary disease that presents alteration in the molecular hemoglobin structure caused by a mutation in the beta-globin gene, resulting in hemoglobin S. This alteration promotes physicochemical modifications in the hemoglobin molecule that, due to hypoxia, can undergo polymerization and formation in sickle erythrocytes.[1-3]

Originating from Africa and now the most prevalent hereditary disease in Brazil, SCA affects from 0.1 to 0.3% of the black population.[4] However, due to the high miscegenation rates in our country, it tends to reach distinct segments of the population. In addition, it is estimated that there are 700-1000 new cases annually in Brazil, which makes SCA a public health problem in the country.[1]

The principal complications of SCA are vaso-occlusive crises and acute thoracic syndrome.[3,5] It is known that abnormal pulmonary function can occur even prior to any clinical evidence of these complications,[5,6] and that the restrictive pattern is predominant in young adults.[7,8] Patterns suggestive of asthma or airway hyperresponsiveness, in patients of various ages, have been reported in the literature,[5,7,9] although there is still considerable discrepancy among the results.

The prevalence of nocturnal hemoglobin desaturation in children and adolescents with SCA is over 40%.[5,10] There also seems to be a strong association between nocturnal hypoxemia and the occurrence of neurological events and vaso-occlusive crises.[3,5,11,12] However, the mechanisms of nocturnal desaturation have yet to be clarified. Some authors have tried and failed to establish a cause-and-effect relationship between obstructive sleep apnea syndrome and nocturnal hemoglobin desaturation,[10,13,14] as well as between intrinsic pulmonary diseases and such desaturation.[3,10,12] However, isolated chronic anemia has been shown to be responsible for only a small fraction of desaturation during waking.[15]

In view of these facts, the objective of this study was to evaluate quality of sleep and pulmonary function in adolescents with clinically stable SCA.

Methods

This was a cross-sectional descriptive study involving patients diagnosed and periodically monitored in the Pediatric Hematology Department of the Brasília Support Hospital, which is administrated by the Federal District Department of Health in Brasília. Inclusion criteria were as follows: having been diagnosed with SCA (homozygote SS), being from 10 to 18 years of age, and not having been previously diagnosed with a respiratory disease or sleep disorder. The 10-18 year age bracket was chosen in accordance with the definition of adolescents established by the World Health Organization. Patients diagnosed with other sickle cell diseases and patients presenting fever or infection within the four weeks preceding the polysomnography were excluded, as were menstruating patients.

The patients participating in the study were initially submitted to clinical evaluation, during which weights and heights were determined. During this same phase, a sleep questionnaire adapted to the age bracket was completed by the adolescent with the help of the parents or legal guardians.

For the polysomnographic study, the adolescents reported to the Sleep Laboratory of the Brasília University Hospital at 8:30 pm in the evening of the examination, accompanied by their parents or legal guardians. Electrodes were affixed for electroencephalography, electro-oculogram, electromyogram, and echocardiography. Thoracic and abdominal belts were put in place, as were a microphone, pulse oximeter, and thermistor (to measure respiratory flow; and electrodes on the legs). The polysomnographic recording began at approximately 9:30 pm and ended at approximately 7:00 am the following morning. All of the patients were instructed to maintain their eating habits, in terms of content and schedule, on the day of the test, although they were not allowed to consume stimulants (coffee or soft drinks). Polysomnographic measurements were taken using an Alice 3® Computerized polysomnography system (Healthdyne Technologies, Marietta, GA, USA). The patients were continuously observed by two duly trained technicians and were filmed throughout the sleep period.

The following variables were analyzed: total sleep time (TST); sleep latency; rapid eye movement (REM) sleep latency; change of stage; total number of awakenings; movement during sleep; periodic leg movement; percentage of TST in stage 1, in stage 2, in delta sleep, and in REM sleep; sleep-disordered breathing index; obstructive apnea index; hypopnea index; central apnea index; mean waking heart rate; REM sleep; non-REM (NREM) sleep; percentage of

TST during which hemoglobin saturation was <90% (T90); peripheral oxygen saturation (SpO_2) during waking, during REM sleep, and during NREM sleep; and minimal oxygen saturation during sleep.

On the day after the polysomnography, the patients were conducted to the Pulmonary Function Laboratory of the Brasília University Hospital for spirometry and measurement of pulmonary volumes using the helium dilution method. All tests were conducted by the same technician, using a Vmax®22 series spirometer (SensorMedics, Yorba Linda, CA, USA). The following variables were analyzed: forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) in percentage of predicted; FEV_1/FVC index; forced expiratory flow 25-75% of FVC (FEF_{25-75}); total lung capacity (TLC) and residual volume (RV) in percentage of predicted; RV/TLC ratio; and functional residual capacity (FRC) also in percentage of predicted.

In addition, we observed a response to bronchodilator administration (200 μg albuterol oral spray) when FVC and FEV_1 indexes increased. Venous blood sample collection for hematocrit and hemoglobin tests was performed at the end of the spirometry. During the study, only one patient abandoned the protocol, citing personal reasons.

The statistical analysis was carried out using the Statistical Package for the Social Sciences, version 12.0, and descriptive statistics were performed on all data using mean, minimum, and maximum values, together with standard deviations. Student's t-test was used to compare parametric variables, since, after the patients had been divided into two groups according to SpO_2 during REM sleep (≤93% and >93%), all variables presented normal distribution using the Levene test. Pearson's correlation coefficient and chi-square test were performed when pertinent. Values of $p \leq 0.05$ were considered statistically significant.

The project was approved by the Ethics in Research Committee of the University of Brasília School of Medicine and the State Department of Health of the Federal District. All participants gave written informed consent.

Results

From September of 2004 to May of 2005, we studied 50 patients, 25 (50%) of whom were male. Anthropometric and hematological data are shown in Table 1. The ethnic distribution was 16% White, 34% Black, and 50% Mulatto.

On the sleep questionnaire, 40 patients (80%) reported snoring, and 19 (38%) reported that there were smokers in the home. Mean values for the polysomnographic variables are presented in Tables 2 and 3. Regarding the mean distribution of sleep stages, we observed that, of the TST, a smaller percentage was spent in REM sleep (13 ± 6%), and a greater percentage was spent in stage 2 sleep (57 ± 8%), whereas the remaining stages were within age-normal ranges: 4 ± 3% in stage 1 sleep and 25 ± 9% in delta sleep.

The mean sleep-disordered breathing index (2 ± 3 events/h) was high for the age, and one patient presented 10 events/h. The mean obstructive apnea index was also high (0.2 ± 0.8 events/h), and one patient presented 5 events/h. Polysomnography recorded snoring in 63% of the patients. Waking hemoglobin saturation ranged from 71 to 97% (mean 87 ± 6%), and minimal saturation during sleep ranged from 51 to 96% (mean 73 ± 13%).

The patients were subdivided into two groups regarding SpO_2 during REM sleep: group I (42 patients), with $SpO_2 \leq 93\%$; and group II (5 patients), with $SpO_2 > 93\%$. Two patients did not present REM sleep and were therefore excluded from the analysis. There were statistically significant differences between the groups in > 50% of the polysomnographic variables. These data are shown in Table 4. However, there was no statistically significant difference between the groups in terms of the pulmonary function variables. The variable SpO_2 during REM sleep presented a strong positive correlation with waking SpO_2 ($r = 0.96$, $p < 0.001$), as well as with SpO_2 during NREM sleep ($r = 0.97$, $p < 0.001$). Similarly, there was a strong negative correlation between SpO_2 in REM sleep and T90 ($r = -0.60$, $p < 0.001$). In addition, sleep-disor-

Table 1 - Anthropometric and hematological data.

Variable	Mean	SD
Age (years)	13.9	2.5
Weight (kg)	38.8	11.4
Height(cm)	150.4	13.6
Hematocrit (%)	25.3	3.9
Hemoglobin ($g.dl^{-1}$)	8.3	1.3

SD: standard deviation.

Table 2 - Polysomnographic variables of the group studied.

Variable	Mean	SD
TST (min)	410	64
SL (min)	18	20
REM sleep latency (min)	182	100
SC (number)	86	26
Awakenings (number)	106	73
PLM (number)	0.3	0.8
Mov (number)	29	12
S1 (% of TST)	4	3
S2 (% of TST)	57	8
Δ (% of TST)	25	9
REM sleep (% of TST)	13	6
SE (%)	87	11

SD: standard deviation; TST: total sleep time; SL: sleep latency; REM: rapid eye movement; SC: stage change; PLM: periodic leg movement; Mov: movement during sleep; S1: stage 1 sleep; S2: stage 2 sleep; Δ: delta sleep; SE: sleep efficiency.

Table 3 - Polysomnographic respiratory and cardiac variables.

Variable	Mean	SD
SDB index (n/h)	2	3
OSA index (n/h)	0.2	0.8
H index (n/h)	2	3
CA index (n/h)	0.05	0.2
Waking HR (bpm)	86	12
REMHR (bpm)	81	12
NREMHR (bpm)	79	12
Waking SpO2 (%)	87	6
$REMSpO_2$ (%)	87	6
$NREMSpO_2$ (%)	87	6
MinSat (%)	73	13
T90 (%)	77	40

SD: standard deviation; SDB: sleep-disordered breathing; OSA: obstructive sleep apnea; H: hypopnea; CA: central apnea; HR: heart rate; REMHR: HR during REM sleep; NREMHR: HR during NREM sleep; SpO2: peripheral oxygen saturation; $REMSpO_2$: SpO2 during REM sleep; $NREMSpO_2$: SpO2 during NREM sleep; MinSat: minimal saturation during sleep; T90: percentage of total sleep time during which hemoglobin saturation is < 90%.

dered breathing index was higher in the group with desaturation.

Regarding pulmonary function, mean values of spirometric variables were as follows: FVC = 80 ± 10% (ranging from 60 to 101%), FEV_1 = 81 ± 10% (ranging from 61 to 105%), FEV_1/FVC = 88 ± 6% (ranging from 75 to 100%), FEF_{25-75} = 84 ± 21% (ranging from 46 to 133), TLC = 103 ± 16% (ranging from 65 to 144%), RV = 162 ± 49% (ranging from 62 to 275%), RV/TLC = 33 ± 9% (ranging from 10 to 51%) and FRC = 130 ± 38% (ranging from 61 to 223). In the overall analysis, mean values were within normal ranges for the age bracket, except those for RV, RV/TLC ratio and FRC, which were higher. After the individual observation, it was possible to divide the patients into four groups, according to the pulmonary function pattern: normal (57%); restrictive (8%); obstructive (29%); and lower FVC/higher RV without obstruction (6%). A positive bronchodilator response (>200 mL) was observed in 64% of the patients presenting the obstructive pattern.

When the pulmonary function variables and clinical data suggestive of sleep apnea were compared, no statistically significant differences were found between the group of patients that had been exposed to cigarette smoke at home and that of those who had not been exposed, the exception being the variable RV, which was elevated in the group that had been exposed ($p < 0.016$).

Discussion

Although the American Thoracic Society indicates polysomnography for SCA patients who present typical signs and symptoms of obstructive sleep apnea syndrome or frequent vaso-occlusive crises,[16] the possibility of a strong relationship between hypoxemia and neurological events per se only indicated the need to perform a polysomnographic study in order to create a profile of these patients, evaluating the presence of sleep-disordered breathing and identifying nocturnal hypoxemia. In our study, we observed diurnal and nocturnal desaturation in most patients, despite the levels of hemoglobin and hematocrit. There have been few studies using polysomnography to evaluate patients with SCA. Those few date from the 1980s and 1990s, typically involved a small number of patients and did not distinguish between stable periods and crises. Nor did any of those studies describe sleep variables in detail. The exact prevalence of obstructive sleep apnea syndrome in children with SCA remains unknown.[17]

Another challenge regarding SCA is the use of pulse oximetry in the evaluation of hypoxemia of these patients. Some authors[18-20] have suggested that pulse oximetry overestimates oxygen saturation in children with SCA and therefore has low specificity

Table 4 - Comparison of polysomnographic variables between the two groups (with and without desaturation during REM sleep).

Variable	Mean ± SD		p
	$SpO_2 \leq 93\%$ Group (n = 42)	$SpO_2 > 93\%$ Group (n = 5)	
SC (number)	83 ± 23	114 ± 33	0.009
Mov (number)	28 ± 11	43 ± 11	0.004
S1 (% of TST)	3 ± 3	6 ± 4	0.03
Δ (% of TST)	25 ± 8	18 ± 6	0.07
SDB index (n/h)	2 ± 3	0.3 ± 0.4	0.001
H index (n/h)	2 ± 3	0.2 ± 0.3	0.001
Waking SpO2 (%)	86 ± 5	94 ± 2	0.004
$REMSpO_2$ (%)	86 ± 6	95 ± 1	0.001
$NREMSpO_2$ (%)	86 ± 6	94 ± 2	0.003
MinSat (%)	71 ± 13	87 ± 8	0.01
T90 (%)	86 ± 32	8 ± 9	0.001
Waking HR (bpm)	88 ± 12	72 ± 2	0.001
REMHR (bpm)	83 ± 12	68 ± 3	0.001
NREMHR (bpm)	81 ± 12	65 ± 3	0.001

SD: standard deviation; SC: stage change; PLM: periodic leg movement; Mov: movement during sleep; TST: total sleep time; S1: stage 1 sleep; Δ: delta sleep; SDB: sleep-disordered breathing; H: hypopnea; SpO_2: peripheral oxygen saturation; $REMSpO_2$: SpO_2 during REM sleep; $NREMSpO_2$: SpO_2 during NREM sleep; MinSat: minimal saturation in sleep; T90: percentage of TST in which hemoglobin saturation is < 90%; HR: heart rate; REMHR: HR during REM sleep; and NREMHR: HR during NREM sleep.

in determining the true degree of oxygen saturation in such patients. In addition, in patients with SCA, the oxygen-hemoglobin dissociation curve tends to shift to the right, and the upper portion of the curve tends to rise gradually. Therefore, there is no direct relationship between arterial oxygen saturation and SpO_2. However, various authors, including some of the most respected, recommend the use of this tool as a means of *screening*.[2,3,5,10-15] Therefore, exceptions should be made at the outset of treatment, based only on the data obtained with the pulse oximeter.[20]

In the present study, the TST observed (7 h) was lower than that expected for the age bracket (range, 8.5-10 h).[21-23] There might be a bias here related to the fact that the measurements were taken on the first night in the sleep laboratory, which can differ from the nights at home, due to the so-called "first-night effect" that can be marked by decreased TST in children and young adults. However, this would not alter the breathing pattern in sleep-disordered breathing situations.[16,21,24,25] Regarding the quality of sleep of these patients, we noticed that it was fragmented, since the number of awakenings, movement in sleep, and stage changes were high for the age.[26,27] The REM stage was also affected. The duration of REM sleep was shorter, and REM sleep latency was higher. There were two patients who did not present REM sleep.

In order to define oxygen-hemoglobin desaturation, SpO_2 during REM sleep ≤ 93% was used as a cut-off point. This cut-off point was chosen on the basis of the findings of other authors.[3,5] The patients in the nocturnal desaturation group presented lower sleep-disordered breathing index, higher obstructive apnea index, greater time with < 90% saturation during TST, higher heart rate during sleep, and higher waking heart rate. The statistical difference between stage 1 NREM sleep time and stage 1 delta sleep time was not clinically significant.

Although we found a higher sleep-disordered breathing index in the adolescents with desaturation during sleep, we believe that the principal determinant of this is the presence of desaturation during waking. Although this finding is in disagreement with those of one study in literature,[10] we believe that this divergence is due to the greater number of patients examined in the present study.

Our evaluation was based on objective data in order to determine the sleep impairment of these patients when clinically stable. However, there are

reports in literature that pain can affect the quality as well as the quantity of sleep.[28]

Whereas adults with SCA present restrictive ventilatory disorder, probably resulting from repeated pulmonary involvement caused by vaso-occlusive pulmonary episodes,[8,29] the child can present conflicting results.[6,7,9] In our study, although most adolescents presented pulmonary function within normal ranges,[30] it was possible to observe increased RV and RV/TLC ratio. In addition, we observed a relationship between being a passive smoker and increased RV. This might be attributable to airflow obstruction secondary to airway hyperresponsiveness,[7] or to the reduced lung elastic recoil due to acute thoracic syndrome, vaso-occlusive crises, or even silently, without an evident clinical marker.[5]

As a limitation to our study, it might be important to correlate the pulmonary function test results with high-resolution computed tomography scans of the chest in order to evaluate the degree of impairment of the lung parenchyma. It is well known that, in patients with SCA, oxygen-hemoglobin desaturation does not necessarily indicate hypoxemia but rather a decrease in the arterial oxygen content, probably due to the presence of carboxyhemoglobin and methemoglobin, as well as to the decreased affinity of hemoglobin S for oxygen, even with normal SpO_2. Therefore, it might be better to evaluate the patients through arterial blood gas analysis, which was not done in this study since we opted for noninvasive tests.

Finally, our findings suggest that the slightly altered quality of sleep in clinically stable patients with SCA is probably due to desaturation, as determined by SPO_2 measurement, and not to individual alterations in the pulmonary function of these patients.

Acknowledgments

We would like to thank the patients and family members who collaborated in the present study, as well as the technicians of the Sleep and Pulmonary Function Laboratory of the Brasília University Hospital.

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