

Prevalence of obstructive sleep apnea in children and adolescents with sickle cell anemia*

Prevalência da apneia obstrutiva do sono em crianças e adolescentes portadores da anemia falciforme

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Abstract

Objective: To estimate the prevalence of obstructive sleep apnea syndrome (OSAS) in children and adolescents with sickle cell anemia (SCA); to investigate the possible correlation between mean annual hemoglobin level and total sleep time with $SpO_2 < 90\%$, as well as between mean annual hemoglobin level and total sleep time with $SpO_2 < 80\%$; and to investigate the possible correlation between apnea-hypopnea index (AHI) and painful crisis. **Methods:** The study involved 85 patients with SCA. The patients completed a questionnaire, were submitted to polysomnography and underwent clinical evaluation (by a pediatrician and an otolaryngologist). An AHI > 1 was considered indicative of a diagnosis of OSAS. **Results:** The prevalence of OSAS was 10.6%. We found a negative correlation between mean annual hemoglobin level and total sleep time with $SpO_2 < 90\%$ ($r = -0.343$; $p = 0.002$), as well as between mean annual hemoglobin level and total sleep time with $SpO_2 < 80\%$ ($r = -0.270$; $p = 0.016$). There was no association between AHI and painful crisis. **Conclusions:** The prevalence of OSAS in this population was high (10.6%). Therefore, it is important to identify signs of OSAS as soon as possible and to determine the mean annual hemoglobin level because of the inverse correlation between that level and the total sleep time with $SpO_2 < 90\%$ or $< 80\%$.

Keywords: Prevalence; Sleep apnea, obstructive; Anemia, sickle cell; Polysomnography; Sleep apnea syndromes.

Resumo

Objetivo: Estimar a prevalência da síndrome da apneia obstrutiva do sono (SAOS) em crianças e adolescentes com anemia falciforme (AF) e investigar a possível correlação entre hemoglobina anual média e tempo total de sono com $SpO_2 < 90\%$ e tempo total de sono com $SpO_2 < 80\%$, assim como investigar a possível correlação entre o índice de apneia-hipopneia (IAH) e episódios de crise algica. **Métodos:** Participaram 85 pacientes com AF, que responderam a um questionário, foram avaliados por um pediatra e um otorrinolaringologista, e submetidos a estudo polissonográfico. O diagnóstico de SAOS foi definido como IAH > 1 . **Resultados:** A prevalência da SAOS foi 10,6%. Observou-se uma correlação negativa entre hemoglobina anual média e tempo total de sono com $SpO_2 < 90\%$ ($r = -0,343$; $p = 0,002$) e tempo total de sono com $SpO_2 < 80\%$ ($r = -0,270$; $p = 0,016$). Não foi observada associação entre IAH e episódios de crise algica. **Conclusões:** A prevalência da SAOS nesta população foi alta (10,6%). Portanto, é importante identificar precocemente os sinais de SAOS e avaliar hemoglobina anual média, devido à correlação inversa entre essa e o tempo total de sono com $SpO_2 < 90\%$ ou $< 80\%$.

Descritores: Prevalência; Apneia do sono tipo obstrutiva; Anemia falciforme; Polissonografia; Síndromes da apneia do sono.

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Introduction

There have been few studies describing the overlap between obstructive sleep apnea syndrome (OSAS) and sickle cell anemia (SCA). Therefore, the exact prevalence, etiology and natural history of OSAS in patients with SCA has yet to be defined.⁽¹⁾ It is known that OSAS is associated with hypoxemia, hypercapnia and acidosis, which might induce the polymerization of hemoglobin S (Hb S), the potentiation of the sickling process and the onset of vaso-occlusive crises.⁽²⁾ In addition, approximately 80% of children with SCA present nocturnal desaturation, which might be the result of OSAS.⁽³⁾

Few studies have attempted to estimate the prevalence of OSAS in children and adolescents with SCA. In addition, those studies had methodological limitations with regard to the populations studied, the number of patients in the samples and the diagnosis of OSAS, which is made through polysomnographic study. The studies described in the literature have not evaluated the problem of OSAS in the general population but rather under specific conditions. For example, the authors of a study conducted in 1992 evaluated a sample composed of children with SCA and children with thalassemia, applying a questionnaire and performing clinical evaluations.⁽⁴⁾ However, since those authors did not perform polysomnography, they were able to determine only the prevalence of sleep-disordered breathing (SDB) in the children with SCA. In 2008, another group of authors conducted a similar study, in which polysomnographic studies were performed.⁽¹⁾ However, the population investigated again comprised children with SCA and children with thalassemia, and only those presenting a daytime $\text{SpO}_2 \leq 94\%$ were included. In the same year, yet another group of authors,⁽³⁾ also in 2008, applied a questionnaire to 100 children with SCA and selected the more severe cases (i.e., suspected cases of SDB) to undergo polysomnography. On the basis of what has been presented, we can state that the prevalence of OSAS in children and adolescents with SCA is unknown. Therefore, the primary objective of the present study was to estimate the prevalence of OSAS in children and adolescents with SCA. The secondary objectives were to investigate the possible correlation between mean annual hemoglobin level and total sleep time (TST) with $\text{SpO}_2 < 90\%$, as well as between

mean annual hemoglobin level and total sleep time with $\text{SpO}_2 < 80\%$ (observed during polysomnographic recording), and to evaluate the possible correlation between the apnea-hypopnea index (AHI) and painful crisis.

Methods

This observational, cross-sectional study involved non-probabilistic sampling of consecutive patients with SCA enrolling for treatment at a referral center for hematology and transfusion medicine between May of 2007 and May of 2008. The study sample comprised 85 patients. The inclusion criteria were as follows: having been diagnosed with SCA through the quantitative analysis of hemoglobin by hemoglobin electrophoresis or HPLC, using the Variant II equipment (Bio-Rad Laboratories, Bossier City, LA, USA); being aged 2 to 19 years; being clinically stable; completing the questionnaire; allowing a pediatric and otorhinolaryngological examination; and undergoing nocturnal polysomnography. The exclusion criteria were as follows: presenting other genetic syndromes, debilitating diseases, acute hepatitis, a history of OSAS treatment or a history of recent trauma; using hypnotics; having been treated with corticosteroids; being pregnant; and presenting an infection during the evaluation. To calculate sample size, the software PEPI-Sample (Sagebrush Press, Salt Lake City, UT, USA) was used, and the following parameters were adopted: confidence level of 95% and prevalence of OSAS in children and adolescents of 5% (a prevalence of 4.9% was an acceptable difference). The population from which the sample was selected was composed of approximately 1,000 children and adolescents with SCA, registered at a referral center for hematology and transfusion medicine. Therefore, to meet the objectives, the calculated sample size was 71 patients. Considering the possibility that the losses would be 10%, the calculated sample was 78 patients.

Age was calculated in whole years from the date of birth. Race was self reported, in accordance with to the official nomenclature of demographic censuses, skin color (white, brown or black—corresponding to White, Mulatto and Black, respectively) being adopted as a reference. Data regarding mean hemoglobin level in the last 12 months (g/dL) were also collected from medical charts.

The patients were weighed using a mechanical scale (model 131; Filizola, São Paulo, Brazil). Height was measured using an anthropometer or stadiometer. These measures were compared with the growth charts of the United States National Center for Health Statistics and converted to Z scores of body mass index and height/age, based on age and gender, using the software Epi Info, version 3.4.1.

All oral examinations were performed by the same otolaryngologist. Pharyngeal and palatine tonsils were classified in accordance with the criteria proposed by Brodsky⁽⁵⁾; those classified as grade 3 or 4 were considered obstructive. Pharyngeal tonsils were observed through nasopharyngoscopy with a flexible optical fiber (Machida, Tokyo, Japan) attached to a light source after the use of three drops of nasal vasoconstrictor in each nostril. These tonsils were scored from 0% to 100%, according to the occupation of the cavum by lymphoid tissue. The size of the pharyngeal tonsil was estimated according to the percentage of the posterior choanae covered by adenoid tissue; the pharyngeal tonsil was considered obstructive when over 70% of this area was occupied. Patients were diagnosed as having obstructive adenotonsillar hypertrophy (ATH) when a grade 3 or 4 palatine tonsil was observed, or when a pharyngeal tonsil occupied more than 70% of the posterior choanae.

The patients were accompanied by their legal guardians for the polysomnographic study, which lasted at least 10 h and was conducted in a quiet environment, with appropriate light and temperature. Polysomnography was conducted during spontaneous sleep; no sedation or sleep deprivation was used, and stimulating foods and beverages (coffee, chocolate, soda and black tea) were avoided. Polysomnography was carried out in a hospital environment, using the computer-

ized Sonolab 620 device (Medtron, São Paulo, Brazil). All results were issued by the same observer.

Through polysomnography the following were recorded: electroencephalogram (C4-A1, C3-A2, O2-A1 and O1-A2), electro-oculogram, electromyogram (anterior tibial and mentalis nerves) and electrocardiogram. Respiratory movements were observed using a chest band and an abdominal band, and SpO₂ was observed through pulse oximetry. An oronasal cannula and a thermistor were also used to measure oronasal flow. A microphone was placed near the neck to record snoring.

We used the criteria proposed by Rechtschaffen & Kales for staging of sleep: sleep efficiency was calculated as TST divided by the time in bed. Sleep latency was defined as the interval between the turning off of 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. Arousals were defined as an abrupt change in the frequency of the electroencephalogram lasting 3 s or longer, preceded by at least 10 s of sleep. The total index of arousals corresponded to the number of arousals divided by the total number of hours of sleep.

The following definitions were adopted:

- Obstructive apnea—interruption in airflow, with a duration ≥ 2 respiratory cycles, despite the persistence of chest effort, abdominal effort or a combination of chest and abdominal effort
- Index of obstructive sleep apnea—number of events/h of sleep
- Hypopnea—reduction $\geq 50\%$ in airflow amplitude associated with one arousal or reduction $> 3\%$ in relation to the basal SpO₂

Table 1 - Clinical profile of the sample of children and adolescents with sickle cell anemia.

Variable	With apnea	Without apnea	p
	(n = 9)	(n = 76)	
Age, years	9 $\pm$ 4	9 $\pm$ 3	0.818
Mean annual hemoglobin level, g/dL	7.6 $\pm$ 0.6	7.9 $\pm$ 2	0.295
Z score for body mass index	-0.4 (-2.8-0.5)	-1.0 (-2.2 - -0.2)	0.875
Z score for height/age	-0.5 (-1.7-0.9)	-0.7 (-1.4 - -0.1)	0.775
Painful crises in the last 12 months	12 (3-26)	20 (4-60)	0.936
Size of the pharyngeal tonsils, % of cavum occupation	90 (25-95)	60 (40-70)	0.135

Data presented as mean $\pm$ SD or median (interquartile range).

Table 2 – Comparison of polysomnographic data between the patients with apnea and those without.

Variable	With apnea	Without apnea	p*
	(n = 9)	(n = 76)	
TST, min	332 ± 79	368 ± 63	0.223
Sleep efficiency, %	64 ± 16	73 ± 12	0.047
Stage 2, % TST	50 ± 12	51 ± 7	0.782
Stages 3 and 4, % TST	27 ± 11	28 ± 6	0.939
REM sleep, % TST	17 ± 4	16 ± 4	0.488
Basal SpO ₂ , %	94 ± 2	95 ± 4	0.791
Maximum SpO ₂ , %	98 ± 1	98 ± 2	0.336
Mean SpO ₂ , %	93 ± 3	94 ± 4	0.648
Minimum SpO ₂ , %	81 ± 9	80 ± 12	0.882

TST: total sleep time and REM: Rapid eye movement. Data presented in mean ± SD. *Student's *t*-test.

- AHI—number of obstructive apnea or obstructive hypopnea events/h of sleep
 - Index of oxygen desaturation—all oxygen desaturation events > 3% based on the basal SpO₂/h of sleep
- Patients with an AHI > 1 event/h of sleep were classified as having apnea.

In the present study, the AHI was adopted for the diagnosis and classification of OSAS for the following reasons: first, because it is relatively uncommon to observe complete obstruction of the upper airways in children; second, because in a study involving OSAS children (diagnosed on the basis of the AHI), the authors reported that the children in which hypopnea was not accompanied by desaturation events had low cognitive scores⁽⁶⁾; third, because in this same study, the children in which hypopnea was accompanied by desaturation events presented arterial hypertension.

The project was approved by the research ethics committee of the institution (Protocol 197; ruling no. 98/2006). The parents or legal guard-

ians of the participating patients gave written informed consent.

For data tabulation and analysis, the software Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA) was used. The quantitative variables were expressed as mean ± SD or as median (Md) and interquartile range, being compared using the Mann-Whitney test. The qualitative variables were expressed as simple and relative frequencies. To test the correlation between the variables, Spearman's test was used. The level of statistical significance was set at *p* < 0.05.

Results

We evaluated 85 patients, 58.8% of whom were male. With regard to race, the patients identified themselves as Mulatto (71.8%), Black (20.0%) or White (8.2%). Table 1 shows the clinical profile of the children and adolescents with SCA.

Table 3 – Comparison of the polysomnographic data between the patients with apnea and those without.

Variable	With apnea	Without apnea	p*
	(n = 9)	(n = 76)	
Sleep latency, min	31 (18-50)	22 (8-45)	0.227
Apnea-hypopnea index, events/h of sleep	1.3 (1.9-5.1)	0 (0-0)	0.000
REM sleep latency, min	205 (98-258)	139 (107-197)	1.000
Stage 0, % TST	154 (107-302)	115 (80-172)	0.141
Stage 1, % TST	3.5 (2.6-5.8)	3.7 (2.5-5.2)	0.732
Arousals, events/h of sleep	57 (30-147)	43 (29-67)	0.145
Desaturations, events/h of sleep	13 (1.5-29)	5 (1-11)	0.083
SpO ₂ < 90% ^a	10 (1-29)	0.6 (0.1-4.9)	0.105
SpO ₂ < 80% ^b	0.1 (0-2)	0 (0-0)	0.021

TST: total sleep time; REM: Rapid eye movement. Data presented as median (interquartile range). ^apercentage of TST during which SpO₂ was < 90%. ^bpercentage of TST during which SpO₂ was < 80%. *Mann-Whitney test.

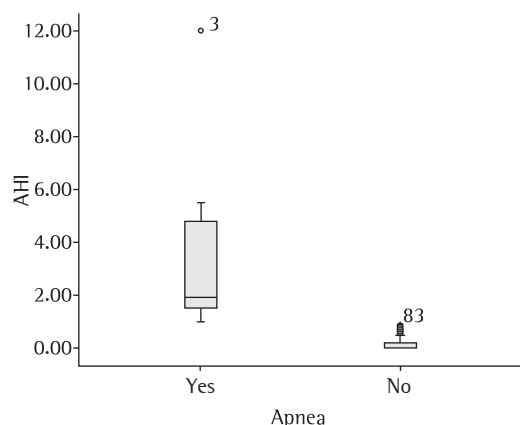


Figure 1 – Box plot graph comparing the apnea-hypopnea index (AHI) in children and adolescents with sickle cell anemia with and without obstructive sleep apnea.

The prevalence of OSAS in the sample was 10.6%; the prevalence of snoring was 44.7%. The distribution of polysomnographic data related to patients with apnea and those without is shown in Tables 2 and 3. We did not find OSAS to be associated with race, gender, age, Z score for body mass index or Z score for height/age.

A box plot (Figure 1) shows that the group of patients that had obstructive sleep apnea presented significantly higher AHIs than the group of patients that did not have obstructive sleep apnea ($p < 0.001$). The number of arousals was not statistically different between patients with apnea and those without ($p = 0.145$). Children and adolescents with sleep apnea presented a significantly higher percentage of

TST with $\text{SpO}_2 < 80\%$ than did those without ($p = 0.021$), as shown in Figure 2.

Nocturnal desaturation was observed in 69 patients (81.2%); however, this parameter was not associated with OSAS, obstructive events or obstructive ATH. Of the patients studied, 66 (77.6%) presented a basal $\text{SpO}_2 \leq 94\%$. Among these patients, 6 (9.1%) presented an $\text{AHI} \geq 1$ event/h of sleep.

Obstructive ATH was observed in 55.3% of the patients (previously published finding).⁽⁷⁾ Patients with obstructive ATH, in comparison with those without, presented more episodes of obstructive events (Md: 1 vs. 0; $p = 0.010$), as well as obstructive events that lasted longer (Md: 8.1 vs. 0; $p = 0.015$). However, obstructive ATH was not associated with the number of desaturation events, with the AHI or with painful crises in the last 12 months.

Painful crises in the last 12 months occurred in 47 patients (55.3%). The correlations between polysomnographic data, the size of pharyngeal tonsils and the characteristics of SCA were as follows: sleep efficiency with the AHI = -0.214 ($p = 0.049$); size of pharyngeal tonsils with the AHI = 0.256 ($p = 0.018$); size of pharyngeal tonsils with desaturation = 0.064 ($p = 0.571$); the AHI with painful crises = -0.067 ($p = 0.545$); desaturation with painful crises in the last 12 months = -0.150 ($p = 0.181$); painful crises in the last 12 months with TST at an $\text{SpO}_2 < 80\% = 0.062$ ($p = 0.589$).

Discussion

In the present study, the prevalence of OSAS in children and adolescents with SCA was 10.6%. This result reflects the prevalence of OSAS in the general population of children and adolescents with SCA at a referral center. This result differs from that of the study conducted by Kaleyias et al.,⁽³⁾ who applied a questionnaire to 100 children, selected only the 19 most severe cases of suspected SDB to undergo polysomnography and concluded that 53% of the selected children had OSAS. In another study,⁽¹⁾ only 35% of the 20 patients studied were found to have OSAS. However, the study population was not exclusively composed of patients with SCA, since patients with thalassemia were also included. In addition, only patients presenting a daytime $\text{SpO}_2 \leq 94\%$ and having undergone polysomnography were included. Therefore, the

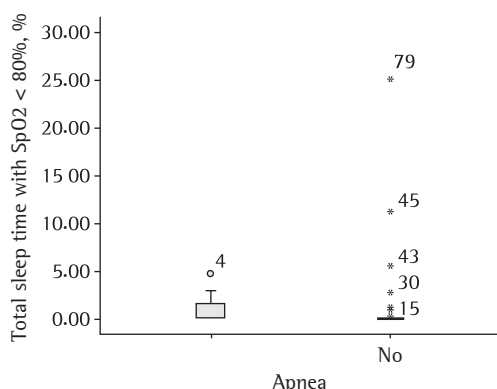


Figure 2 – Box plot graph comparing the total sleep time in which SpO_2 was lower than 80% in children and adolescents with sickle cell anemia, with or without obstructive sleep apnea.

present study is the first study in the literature that investigates the prevalence of OSAS exclusively in children and adolescents with SCA. The present study is relevant because little is known regarding the consequences of the clinical manifestations of OSAS in patients with SCA; it is known, however, that when OSAS is not adequately treated it can lead to serious complications, among which is a delay in the growth curve.⁽⁸⁾ According to one study,⁽⁹⁾ the delay in the growth curve of children with OSAS is related to increased respiratory effort during sleep, which generates increased caloric expenditure; in addition, obstructive events might cause a reduction in growth hormone release.⁽¹⁰⁾ According to one review,⁽¹¹⁾ individuals with SCA present a reduction in serum concentration of growth hormone, as well as a reduced response to growth hormone stimulation, probably secondary to the hypoxic-ischemic injury in the hypothalamic-pituitary axis after one or more episodes of vaso-occlusive crisis, which contributes to a delay in growth.

In the present study, the patients with SCA presented reduced TST. A similar result was observed by one group of authors,⁽¹²⁾ who studied 50 patients with a mean age of 13.9 ± 2.5 years; the authors associated that result with the "effect of the first night" at the sleep laboratory, since the night spent at the laboratory can be different from that spent at home and is characterized by a reduction in TST. In the present study, we observed that sleep architecture was altered, since the values for stages 3 and 4, as well as the percentage of REM sleep, were higher than expected, although an increase in the number of brief arousals was also observed. In addition, sleep latency and REM sleep latency were increased. It was observed that sleep efficiency was reduced and was correlated with the AHI ($p = 0.049$). It is noteworthy that patients with apnea presented lower values for sleep efficiency than did those without apnea ($p = 0.047$). This result coincides with that observed by one group of authors,⁽¹²⁾ who characterized the quality of sleep of patients with apnea as fragmented, since the number of arousals, movements during sleep and changes in sleep stages were increased for their ages. This same group of authors noted impairment of the slow-wave sleep, which was reduced and showed increased latency.

Polysomnography allows the correlation between SpO_2 , respiratory pattern and

arousals during sleep.⁽³⁾ In the present study, the frequency of nocturnal desaturation was increased (81.2%). A similar result was obtained by another group of authors,⁽³⁾ who carried out a study using polysomnography and capnography. Those authors observed that 83% of the patients with SCA presented nocturnal desaturation. Oxygen desaturation is common in patients with SCA and is related to the process of intracellular sickling.⁽¹³⁾ However, when oxygen desaturation occurs during sleep, it can be accompanied by hypoventilation and can be exacerbated by obstruction of the upper airways.⁽¹⁴⁾ The obstruction of the upper airways by ATH is one of the principal causes of OSAS in children,⁽¹⁵⁾ as shown in the present study—patients with ATH presented more episodes of obstructive events ($p = 0.010$), as well as obstructive events that lasted longer ($p = 0.015$); in addition, we found a positive correlation between the size of the pharyngeal tonsils in these patients and the AHI ($p = 0.018$). One group of authors⁽⁷⁾ observed a high prevalence of obstructive ATH in children and adolescents with SCA, reporting a prevalence of obstructive palatine tonsil hypertrophy of 18.8% and a prevalence of obstructive pharyngeal tonsil hypertrophy of 53.3%. The authors attributed this elevated prevalence to the fact that individuals with SCA present a greater susceptibility to severe infections due to asplenia, to the reduced capacity for opsonization and to alterations in the reticuloendothelial system and phagocytic function. Another group of authors⁽⁴⁾ reported that 36% of the patients with SCA presented obstruction of the upper airways. In children, these episodes are frequently associated with ATH, so that the partial occlusion and the complete occlusion of the upper airways during sleep can both be present from the first years of life.⁽¹⁵⁾ In another study,⁽¹⁶⁾ multiple linear regression analysis showed that 74.3% of the upper airway obstructions in individuals with SCA were caused by palatine tonsils, pharyngeal tonsils or the hard palate.

In the present study, there was a negative correlation between mean annual hemoglobin level and TST with $SpO_2 < 90\%$, as well as between mean annual hemoglobin level and TST with $SpO_2 < 80\%$. A similar result was obtained in a study involving 390 patients with SCA, in which basal SpO_2 at routine medical visits ranged from 86% to 99%; however, only 2.3% of the patients

presented $\text{SpO}_2 < 90\%$, and when a multivariate analysis was performed, the authors observed that SpO_2 was inversely associated with hemoglobin level.⁽¹⁷⁾ Hypoxemia has been described as a precipitating factor for painful crises, for vaso-occlusive events at the microcirculatory level⁽¹⁸⁾ and for "silent" ischemic cerebrovascular accident, which causes a number of neurocognitive deficits, such as learning problems and reduced intelligence quotient, affecting the frontal lobes and causing attention deficit and lack of executive functions, as well as short-term and long-term memory loss.⁽¹⁹⁾ In addition, it is believed that patients with OSAS present higher fibrinogen plasma levels, exacerbated platelet activity and reduced fibrinolytic activity than do individuals without apnea, characterizing a state of hypercoagulability. It is likely that the state of hypercoagulability is correlated with OSAS due to the elevated levels of oxidative stress and inflammation. Therefore, some studies have reported that SDB is intimately associated with an increased risk for cerebrovascular accident.⁽²⁰⁾

Oxygen desaturation events were not correlated with the size of pharyngeal tonsils or the AHI. A group of authors⁽²¹⁾ investigated the mechanisms of nocturnal desaturation in 20 children and adolescents with SCA and concluded that, although nocturnal hypoxemia was common in those children, OSAS did not appear to play a central role; the authors also reported the need to consider desaturation as the result of chronic pulmonary involvement due to the repetitive episodes of acute chest syndrome, leading to pulmonary fibrosis, chronic hypoxemia and consequently to the development of pulmonary hypertension,⁽²²⁾ or due to the reduced affinity of HbS for oxygen.⁽²³⁾

In the present study, the size of the pharyngeal tonsils correlated with the AHI. It is known that the air space of the pharynx tends to be smaller in children with OSAS than in individuals without OSAS.⁽²⁴⁾ Sedated children (mean age of 4.8 years) were studied using magnetic resonance imaging, and a positive linear correlation was observed between tonsil volume and the AHI ($r^2 = 0.26$).⁽²⁾ In another study involving children (mean age of 9.5 years) who were not sedated, it was observed that the transverse area of the palatal tonsils, of the hard palate and of the region posterior to the hard palate, as well

as the volume of the oropharynx, were strongly correlated with the AHI.⁽²⁵⁾

Of the patients studied, 77.6% presented basal $\text{SpO}_2 \leq 94\%$; among these, 9.1% presented an AHI ≥ 1 event/h of sleep. The percentage of TST with $\text{SpO}_2 < 80\%$ was higher for individuals with OSAS than for those without ($p = 0.021$); however, we did not find a statistically significant correlation between these variables and painful crises. Similarly, a group of authors⁽²⁶⁾ did not observe a correlation between the frequency of painful crises and OSAS; however, they described the association between painful crises and recurrent infections ($p = 0.02$). Studies have suggested that OSAS can induce the polymerization of HbS, potentiating the sickling process and the development of vaso-occlusive crises.⁽²⁾ Based on what has been reported, we should consider that conditioning factors can enhance or impair the sickling process. For the aggregation of HbS molecules, a high concentration of deoxygenated molecules is necessary, which facilitates the association between the molecules. The sickling process is not instantaneous, occurring after an interval. Therefore, if hemoglobin is oxygenated during this interval, cell sickling does not occur. As a consequence, cell sickling does not occur in most red blood cells at each cycle through the capillaries. It occurs in a small percentage of cells, since the cells that become oxygenated resume their normal aspect. Therefore, the sickling process, for a large number of red blood cells in a blood vessel, is principally caused by the lack of time for red blood cells to pick up oxygen, leading to vaso-occlusion, and not only by deoxygenation itself.⁽²⁷⁾

The principal limitation of the present study is related to the wide age bracket of the patients, which ranged from 2 to 18 years. According to one study,⁽²⁸⁾ a great increment in growth tends to occur in the first years of life; at birth, the craniofacial skeleton of a white American corresponds to 60% of the cephalic size of an adult; at 6 months, it corresponds to 80%; at 3 years, it corresponds to 90% and, at 9 years, the craniofacial skeleton has developed almost entirely, corresponding to 95% of the cephalic size of an adult. Therefore, further studies should focus on more specific age brackets to investigate the possible correlation between craniofacial characteristics and OSAS in individuals with SCA.

The present study is relevant because it is the first investigation of the prevalence of OSAS in children and adolescents with SCA, which allowed the understanding of the high prevalence of OSAS (10.6%) in this population. The data draw attention to the need for the early identification of the signs of OSAS and for the evaluation of certain factors, such as mean annual hemoglobin level, since we observed a negative correlation between mean annual hemoglobin level and TST with $SpO_2 < 80\%$. Although there are reports in the literature indicating that hypoxia favors the sickling process, no association between the AHI and painful crises was observed in the present study. These data can contribute to minimize the clinical manifestations of SCA, a pathology that does not have a specific treatment yet but a treatment based on prevention and control of symptoms.

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