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Association between adenotonsillar hypertrophy, tonsillitis and painful crises in sickle cell disease

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Abstract

Objectives: To determine the prevalence of obstructive adenotonsillar hypertrophy in children and adolescents with sickle cell anemia; to investigate possible associations between the presence of more than five episodes of tonsillitis in the last 12 months and episodes of painful crises in the same period; and to compare the mean annual hemoglobin level in children and adolescents with and without obstructive adenotonsillar hypertrophy.

Methods: Prospective, observational, cross-sectional study involving 85 children and adolescents with sickle cell anemia. All patients answered a questionnaire and underwent a standard otolaryngology examination, including endoscopic endonasal approach. The diagnosis of obstructive adenotonsillar hypertrophy was made according to the Brodsky scale.

Results: The prevalence of obstructive adenotonsillar hypertrophy was 55.3%. Obstructive adenotonsillar hypertrophy was associated with history of difficulty in eating (76.7 vs. 23.5%, p = 0.003), presence of more than five episodes of tonsillitis in the last 12 months (70.6 vs. 29.4%, p = 0.021), loud snoring (73.0 vs. 27.0%, p = 0.004), and sleep apnea (71.8 vs. 28.2%, p = 0.005). Patients with obstructive adenotonsillar hypertrophy had more episodes of recurrent upper airway tract infection (62.5 vs. 37.5; p = 0.010). The presence of more than five episodes of tonsillitis in the last 12 months was associated with episodes of painful crises (median = 12 vs. 2, p = 0.017). There was no significant difference between mean annual hemoglobin levels of patients with obstructive adenotonsilar hypertrophy vs. nonobstructive adenotonsillar hypertrophy: 7.6 vs. 8.2 g/dL, p = 0.199.

Conclusion: The prevalence of obstructive adenotonsillar hypertrophy was 55.3% in children and adolescents with sickle cell anemia; the presence of more than five episodes of tonsillitis in the last 12 months was associated with episodes of painful crises in the same period; there was no difference in the mean annual hemoglobin value among those with or without obstructive adenotonsillar hypertrophy.

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Introduction

Although painful crisis is the most frequent symptom in children with sickle cell disease, its pathogenesis has not been yet fully understood. One of the triggering factors might be hypoxemia, due to upper airway obstruction, which may be caused by compensatory adenotonsillar hypertrophy (ATH).[1] Even though both adenoidectomy and

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tonsillectomy are described as frequent surgical procedures in patients with sickle cell disease, the prevalence of ATH has not been established in this population.

Three hypotheses have been suggested to explain the association between ATH and sickle cell disease:[1] compensatory ATH secondary to autosplenectomy; higher probability of developing recurrent upper airway infections due to decreased opsonization of pathogenic bacteria; and the function of adenoids and palatine tonsils as hematopoietic centers due to hemolytic anemia. However, there has been little research regarding these hypotheses.

The objective of the present study is to determine the prevalence of obstructive ATH in clinically stable children and adolescents with sickle cell disease followed in a referral center for hematology and hemotherapy; to compare the mean annual hemoglobin levels among those patients with and without obstructive ATH; and to investigate a possible association between episodes of tonsillitis in the last 12 months and painful crises during the same period.

Methods

This is an observational, prospective study involving 85 children and adolescents with sickle cell disease who were selected from May 2007 to May 2008 using a non-probability, sequential sampling technique. The subjects were enrolled at a referral center for hematology and hemotherapy and attended the outpatient clinic on Tuesdays and Thursdays (when patients with sickle cell disease were seen at the clinic). For sample size calculation, the Pepi-Sample software was used and the following parameters were set: 95% confidence interval and a 12% prevalence of ATH in children and adolescents. The population from which the sample was drawn comprised approximately 1,000 children and adolescents with sickle cell disease registered at the referral center for hematology and hemotherapy. The acceptable difference in the prevalence was 7%.

In order to comply with the objectives of this study, the sample size was 77 patients, considering the possibility of 10% loss. Thus, the final sample size was calculated at 84 patients. This study is part of a more extensive research project. The inclusion criteria were: to have the diagnosis confirmed by means of quantitative analysis of hemoglobin using hemoglobin electrophoresis or high-performance liquid chromatography performed with the equipment Variant II™ (Bio-Rad); to be aged between 2 and 19 years old; to be clinically stable; to answer the questionnaire and to allow the otolaryngology examination. The exclusion criteria were: other genetic syndromes; disabling diseases; recent craniofacial trauma; and infection during the evaluation or systemic therapy with corticosteroids.

Age was measured in complete years according to the date of birth informed on the medical record. Ethnic origin was self-defined according to the official terms used in the demographic census, considering skin color as the parameter (white, brown or black).

In order to assess the clinical and sociodemographic variables, a questionnaire developed by the authors was used. The questionnaire was standardized including relevant questions, whose answers were provided by the subjects' parents or guardians as follows: regular school attendance; good school performance; difficulty in eating, nocturnal enuresis; nasal obstruction; predominantly oral breathing; tonsillitis (at least five episodes in the last 12 months); recurrent upper airway infections; sleep chocking; restless sleep; and loud snoring or observed apnea at least three times a week. Possible answers were: yes; no; and I don't know. In addition, parents and guardians were asked to inform the number of days with painful crises in the last 12 months.

The examination of the oral cavity was performed by the same otolaryngologist. Tonsils were classified according to Brodsky's criteria: grade 0 = palatine tonsils located inside the tonsillar fossa; grade 1 = tonsils located beyond the tonsillar fossae, occupying less than 25% of oropharyngeal airspace; grade 2 = tonsils occupying more than 25 and less than 50% of the oropharyngeal space; grade 3 = tonsils occupying more than 50 and less than 75% of the oropharyngeal space; grade 4 = tonsils occupying more than 75% of the oropharyngeal space; grades 3 and 4 were considered obstructive.[2]

After using a nasal vasoconstrictor, a nasal endoscopy was performed using flexible optical fiber (Machida brand) built in a light source device (Endoview). Adenoid hypertrophy was classified according to the following rank: grade 1 = adenoid tissue occupying only the upper segment in the rhinopharyngeal cavity and free choanae (< 25%); grade 2 = adenoid tissue confined to the upper half of the rhinopharyngeal cavity (< 50%); grade 3 = adenoid tissue extending beyond the rhinopharynx, generating partial obstruction of the choana and partial compression of the ostium of the Eustachian tube (< 75%); grade 4 = adenoid tissue obstructing almost the whole choana. Grades 3 and 4 were considered obstructive.[3] The subjects presenting with adenoid or palatine tonsil grade 3 or 4 were considered to have obstructive ATH.

This project was approved by the Research Ethics Committee of the institution under the protocol 197 (report 98/2006). Children and adolescents' parents and guardians signed the written consent form upon agreeing to participate in this study.

The statistical software Statistical Package for the Social Sciences (SPSS) was used for data analysis. Quantitative variables were expressed as mean ± standard deviation or median and interquartile range, being compared using Student's *t* test or Mann-Whitney test. Qualitative variables were expressed as simple and relative frequencies and were compared using Pearson's

chi-square test or Fisher's exact test. P-value < 0.05 was set as statistically significant.

Results

Eighty-five patients, whose mean age was 9.3±3.9 years old, were examined. Of these, 58.8% were males. With regard to the ethnic origin, 71.8% defined themselves as brown, 20% as black and 8.2% as white. The mean hematocrit and hemoglobin levels were 23±4% and 7.9±1.9 g/dL, respectively. The median of painful crisis episodes in the last 12 months was five (interquartile range = 1-20).

Prevalence of palatine tonsils was distributed as follows: grade 0 = 15.3% (n = 13); grade 1 = 43.5% (n = 37); grade 2 = 22.4% (n = 19); grade 3 = 15.3% (n = 13); grade 4 = 3.5% (n = 3). Whereas the prevalence of adenoid was as follows: grade 1 = 15.3% (n = 13); grade 2 = 29.4% (n = 25); grade 3 = 28.2% (n = 24); grade 4 = 27.1% (n = 23). Thus, the prevalence of obstructive ATH was 55.3% (n = 47).

There was not statistically significant difference in terms of association between obstructive ATH, sex and ethnic origin.

ATH mainly affects individuals between 2 and 6 years old, an age group characterized by increase in the lymphoid tissue. Taking the age of 6 years old as a cutoff point, we found that the prevalence of ATH was higher in children aged ≤ 6 years old (17.9 vs. 8.3%; p = 0.003).

Table 1 shows the frequency of otolaryngologic symptoms and the association with obstructive ATH.

We found a greater number of episodes of recurrent upper airway infections in patients with obstructive ATH compared to those with nonobstructive ATH (62.5 vs. 37.5%; p = 0.010).

There was not statistically significant difference in terms of mean annual hemoglobin levels between obstructive and nonobstructive ATH: 7.6 vs. 8.2 g/dL; p = 0.199.

Patients affected by more than five episodes of tonsillitis in the last 12 months had more episodes of painful crises during the same period (median: 12 vs. 2; p = 0.017).

Discussion

This study demonstrated high prevalence (55.3%) of obstructive ATH in children and adolescents with sickle cell disease, while the prevalence of obstructive palatine tonsil hypertrophy was 18.8%, and prevalence of adenoid hypertrophy was 55.3%. In children and adolescents without underlying disease, the prevalence of palatine tonsil hypertrophy leading to upper airway obstruction has been reported between 11 and 12.6%,[4,5] whereas the prevalence of adenoid hypertrophy has been between 30 and 37.6%.[5,6] One of the mechanisms that may explain the high prevalence found in our study is the higher susceptibility to severe infections due to asplenia, reduced opsonic capacity, alterations in the reticuloendothelial system and in the phagocytic function.[7-10]

The present study demonstrated that subjects with ATH presented with recurrent tonsillitis and greater number of episodes of recurrent upper airway infections. During

Table 1 - Frequency of otolaryngologic symptoms and association with ATH

	Obstructive ATH (n = 47) n (%)	Without obstructive ATH (n = 38) n (%)	p
Difficulty in eating	23 (49)	7 (18.4)	0.003
Nasal obstruction	40 (85.1)	30 (78.9)	0.459
Recurrent tonsillitis	24 (51.0)	10 (26.6)	0.021
Predominantly oral breathing	39 (82.9)	30 (78.9)	0.636
Passive smoker	34 (72.3)	24 (63.1)	0.366
Loud snoring	27 (57.4)	10 (26.3)	0.004
Observed apnea	28 (59.5)	11 (28.9)	0.005
Sleep chocking	12 (25.5)	3 (7.8)	0.045
Restless sleep	36 (76.5)	17 (44.7)	0.003
Nocturnal enuresis	19 (40.4)	17 (44.7)	0.689
Painful crises	9 (19.1)	5 (13.1)	0.459

ATH = adenotonsillar hypertrophy.

early childhood, children are prone to have splenomegaly due to the congestion caused by the sickle erythrocyte sequestration in the splenic and sinusoid cords. Then, the phagocytic capacity mediated by opsonins and the production of antibodies are impaired because of the persistent splenic aggression.[11,12] Both recurrent upper airway infections and adenotonsillitis are common in these children, with initial viral infections, which make these patients prone to have bacterial infections.[13] Some of the immunological disorders that have been described are: decreased production of interleukin-4, with impairment of B lymphocyte maturation and production of IgM; variable count of T-helper and T-suppressor cells; decreased levels of T-helper and T-suppressor lymphocytes in patients with functional asplenia; fast bacterial multiplication in the blood due to the high levels of circulating iron and transferrin; and inappropriate production of antibodies upon the intravenous administration of polysaccharide vaccines.[14-17] Frequent episodes of adenotonsillitis cause tonsil hypertrophy, which is influenced by the action of antigens.[18]

The main cause of anemia in these patients is the lower survival of erythrocytes; therefore, it is hemolytic anemia, with increased indirect bilirubin, erythroid hyperplasia of bone marrow and higher levels of reticulocytes. However, in addition to hemolysis, there are other factors that can contribute to cause or worsen anemia.[19] There is the hypothesis that adenoids and palatine tonsils would serve as hematopoietic centers due to the hemolytic anemia.[1] Nevertheless, our study did not demonstrate association between ATH and hemoglobin levels lower than 7 g/dL. Such result suggests that obstructive ATH may not be associated with increased hematopoiesis. However, this finding is in agreement with the results obtained by Maddern et al.,[1] which suggest the necessity of anatomicopathological study of the palatine tonsils and adenoids to further improve investigation results.

In the present study, we found that patients younger than 6 years old had a higher prevalence of obstructive ATH than those older than 6 years old. This is an important result, since ATH is the main causal factor for obstructive sleep apnea syndrome (OSAS) in children.[20] OSAS may be associated with silent ischemic stroke, causing several neurocognitive disorders such as learning problems and reduced intelligence quotient. It also affects the frontal lobes, causing attention and executive skill deficits, as well as impairment of active and long-term memory.[21]

The present study allowed us to detect that patients with sickle cell disease and obstructive ATH have difficulty in eating. It has been demonstrated that obstructive ATH causes reduction in the rhinopharyngeal airspace; therefore, the patients tend to open their mouths to breath, deviating the air flow from the rhinopharynx to the oropharynx, where the most common phono-articulatory problems are hypotonia of facial muscles, alteration of the tonus of the lips, cheeks and suprahyoid muscles, and forward position of the tongue at rest, consequently affecting chewing, swallowing and phonation.[22]

We did not find association either between ATH and predominantly oral breathing or nasal obstruction in this study. Predominantly oral breathing has a multifactorial cause that includes rhinopathies, adenoid and/or palatine tonsil hypertrophy, inflammations and infections in the nasal cavity and paranasal sinuses, among others.

In the present study, we found statistically significant associations between ATH and loud snoring, and ATH and observed apnea. These findings are in accordance with the findings by Guilleminault et al.,[20] who found that snoring and breathing difficulty during sleep are responsible for approximately 96% of the most frequent complaints reported by parents or guardians of children with OSAS. From the pathophysiological point of view, all the factors that favor hypoxia, including OSAS, also contribute to the presence of sickle cells in the pulmonary circulation, and might trigger acute chest syndrome.[23] Furthermore, the present study demonstrated the association between ATH and sleep chocking, as well as ATH and restless sleep, which is in agreement with the findings by Souza & Viegas,[24] who characterized these patients' sleep as fragmented, since the number of micro-awakenings, movements in sleep and sleep stage changes was greater than expected for their age.

In our study, patients with ATH did not complain of nocturnal enuresis. A similar result was found by Kara et al.[4] However, ATH is considered the main causal factor for obstructive sleep apnea and hypopnea in children and adolescents; and nocturnal enuresis is associated with the increase in the intra-abdominal pressure secondary to the breathing efforts during episodes of apnea and hypopnea,[25] as well as the decreased secretion of antidiuretic hormone or increased atrial natriuretic peptide, leading to increased urine volume.[26] This higher atrial natriuretic factor seems to be secondary to the episodes of hypoxemia and increased intrathoracic negative pressure in those patients with OSAS.[25]

In the present study, the patients who had at least five episodes of tonsillitis in the last 12 months presented with a greater number of episodes of painful crises in the same period. The pathogenesis of the painful crises has not been fully understood yet. However, it has been established that infection is one of the triggering factors.[27] In addition, it has been described that one of the reasons for the performance of tonsillectomy in sickle cell disease patients is the frequent painful crises.[28] Ijaduola & Akinyanju[28] demonstrated that only tonsillectomy was able to reduce the frequency of the painful crises from 4.7 to 1.5 per patient per year in individuals who had not received prophylaxis with penicillin. These data are important because children with sickle cell disease are 400 times more prone to have episodes of infection

causing a very rapidly progress to death. Infection is the first cause of child mortality in sickle cell disease, and children younger than 5 years old must receive priority treatment, since complications are more easily found in this age group.[29]

Our study suggests the need of researches that include imaging tests in order to define the size of the spleen, as well as anatomicopathological study of the tonsils with the purpose of analyzing a possible correlation between ATH and autosplenectomy and investigating if the tonsils would really serve as hematopoietic centers in this population. Even though the present study did not aim to investigate such aspects, we would like to draw attention to the need of further investigations with the purpose of better understanding the ATH hypotheses in sickle cell disease.

Acquired factors are as important as the genetic variations, since they are responsible for the clinical vulnerability and prognosis of patients with sickle cell disease.[19] Pain, on the other hand, is one of the persistent symptoms of this disease, directly interfering with the patients' quality of life. Therefore, the present study contributes to the literature by showing the need of emphasizing the examination of adenoids and palatine tonsils in children and adolescents with sickle cell disease, since we found that patients with obstructive ATH had a greater number of recurrent upper airway infections and patients who had at least five episodes of tonsillitis in the last 12 months presented with a greater number of painful crises.

Conclusion

The results of the present study showed that the prevalence of obstructive ATH was 55.3% in children and adolescents with sickle cell disease. It was also possible to detect that patients with obstructive ATH were associated with a greater number of recurrent upper airway infections; patients who had at least five episodes of tonsillitis in the last 12 months presented with a greater number of episodes of painful crises during the same period; and there was no difference regarding the mean annual hemoglobin value between those with and without obstructive ATH.

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