ORIGINAL ARTICLE

Rhinitis Prevalence and Nasal Respiratory Function of Children and Adolescents with Sickle Cell Disease

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Abstract

Introduction: Sickle cell disease is the most frequent of the hereditary hemoglobinopathies and presents significant morbimortality. Upper respiratory obstruction is a common clinical manifestation in these patients. The objectives were quantifying the prevalence of allergic rhinitis and evaluate nasal respiratory function in children and adolescents with sickle cell disease.

Methods: A cross-sectional study was carried out in a reputable Brazilian blood center between July 2017 and October 2017. Patients who were 6-18 years old with a diagnosis of sickle cell disease were included. Current rhinitis symptoms were estimated on the basis of positive answers to the question used in the international study of asthma and allergies in the childhood epidemiological research program. Measurements for peak nasal inspiratory flow, visual analogue scale, and rhinomanometry were taken.

Results: Allergic rhinitis was confirmed in 37.4% of the sample with 99 patients. Approximately 70% of patients with sickle cell disease and allergic rhinitis were not treated for rhinitis and several were unaware of their diagnosis. Means of 96.6% ± 34.3% of the peak nasal inspiratory flow predicted value and 0.35 ± 0.21 Pa/cm^3/second for rhinomanometry were found. Mean visual analog scale was 4.9 ± 3.2.

Discussion: This study did not show a higher prevalence of allergic rhinitis in patients with sickle cell disease, but peak nasal inspiratory flow and rhinomanometry alterations were found in both allergic rhinitis and non-allergic rhinitis groups. Considering the host of complications faced by these patients, it is expected that the recognition and treatment of allergic rhinitis will contribute to improved quality of life.

Keywords: Anemia, Sickle Cell/complications; Adolescent; Child; Rhinitis, Allergic/prevention & control; Surveys and Questionnaires

Introduction

Sickle cell disease is the most common monogenic disease in Brazil, occurring predominantly among Afro-descendants.[1] It is estimated that there are 3,500 new cases per year. Incidence in the state of Minas Gerais is approximately one in 1,400 of live births, according to the Minas Gerais neonatal screening program.[1,2] It is secondary to a mutation in the hemoglobin beta chain gene, transforming normal hemoglobin (HbA) into sickle hemoglobin (HbS).[3] Manifestations of the disease arise from the predominance of sickle-shaped red blood cells, which lead to chronic hemolytic disease and vaso-occlusive phenomena.[4] Sickle cell disease produces multisystem effects, with respiratory complications being an important cause of morbimortality.[5-8]

Children and adolescents with sickle cell disease commonly suffer from respiratory diseases. One respiratory disease of the upper airways, most commonly found in children and adolescents but little studied in the population with sickle cell disease is allergic rhinitis. Allergic rhinitis is defined as an immunoglobulin (Ig) E-mediated inflammation of the nasal lining, after exposure to sensitized allergens,[9,10] and can be detrimental to quality of life due to the disruption of sleep patterns, in addition to a negative impact on academic performance. It favors recurrent sinusitis and impacts asthma control, being considered the most prevalent among the chronic respiratory diseases.[10-12]

In the literature, there are rather few studies on the prevalence of allergic rhinitis and nasal respiratory function in patients with sickle cell disease, despite the importance of the symptoms related to the upper

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airways, particularly in relation to the association of allergic rhinitis in patients with sickle cell disease.
As such, this study aims to quantify the prevalence of allergic rhinitis symptoms in this population as well as evaluate nasal respiratory function, using peak nasal inspiratory flow, analog visual scale, and rhinomanometry.

Methods

Cross-sectional study carried out in the Minas Gerais Hematology and Hemotherapy Foundation Center (HEMOMINAS), Belo Horizonte, Minas Gerais, Brazil, between July 2017 and October 2017. Children and adolescents with sickle cell disease, between 6 and 18 years old, participated in the research.

Inclusion and exclusion criteria

The study included children and adolescents with confirmed sickle cell disease diagnosis at 1 year of life, attending the HEMOMINAS hematology outpatient clinic. SS/Sβ^0 thalassemia genotypes, between 6 and 18 years old were included. We excluded patients:
- Whith other associated neurological or hematological disorders;
- Whith flu-like symptoms at the time of testing;
- Those who did not have the above-cited genotypes for sickle cell disease;
- Those incapable of performing the respiratory maneuvers;
- Those who did not want to participate in the study.

Procedures

Data was collected based on interviews, physical evaluation, medical record consultation, and the peak nasal inspiratory flow and rhinomanometry measurements taken by one examiner only. The interview was conducted using a semi-structured questionnaire that included questions relating to the symptoms of rhinitis, from the international study on asthma and allergies in childhood (ISAAC), in order to estimate the prevalence of the reported symptoms,[13] namely: Over the last 12 months, have you had problems with sneezing or coryza (runny nose) or nasal obstruction when you did not have a cold or flu? Besides this, the initiative allergic rhinitis and its impact on asthma (ARIA) was adopted in the diagnosis and classification of symptoms as intermittent or persistent, and mild or moderate/severe.[11] The physical evaluation was based on the verification of vital signs, height, and weight. Medical records were examined to find relevant data such as baseline hemoglobin, hydroxyurea use, number of hospitalizations, and acute thoracic syndrome.
After the interview, we recorded the visual analog scale and the rhinitis clinical score as proposed by other authors.[14] Visual analog scale is a scale that ranges from 0 to 10, where zero indicates the absence of nasal symptoms, that is, the patient does not feel any discomfort, and 10 indicates extreme nasal discomfort.[15] The patient was asked to identify the number of the scale that corresponded with the degree of nasal discomfort felt at that given moment. The Wilson score was applied in patients diagnosed with allergic rhinitis and enabled us to quantify the severity of rhinitis symptoms, which ranged from 0 to 18 points, bearing in mind the evaluation of six signals/symptoms, as follows: nasal obstruction, rhinorrhea, sneezing, nasal itching, oropharyngeal pruritus, and ocular pruritus. Scores from zero to three were assigned:
- Zero, for the absence of the given sign/symptom;
- One, in the case of a mild, tolerable sign/symptom that did not interfere with the individual sleep or daily activities;
- Two, when the evaluated sign/symptom caused a certain discomfort but only interfered in activities that required high levels of concentration;
- Three, when the evaluated sign/symptom was intense and difficult to tolerate, inhibiting sleep and the performance of the individual's daily activities.
The total score classified the severity of the allergic rhinitis[15]:
- Mild: 1-6 points;
- Moderate: 7-12 points;
- Severe: 13-18 points.
The peak nasal inspiratory flow measurement (in-check-inspiratory flow meter, Clement Clarke, Harlow, England) was obtained while the patient was standing upright. Before the measurements were taken, the patient performed routine nasal hygiene, gently blowing their nose to eliminate residual nasal secretion. The facial mask was then carefully fitted, whereupon the patient was instructed to vigorously breathe in through the nose with their mouth closed and from a residual volume, until total lung capacity was reached. After at least three measurements were taken, the highest value was chosen. The value noted was compared to the reference value for the age bracket studied, using the predicted values suggested in a previous study.[16]
Rhinomanometry was performed with the rhinomanometer PDD-301/r (Piston Medical, Budapest, Hungary) using transnasal pressure of 150 Pa in accordance with the manufacturer's specifications. The patient remained seated, and a nasal plug of a suitable

size was fitted in the side opposite the one from which the measurement was taken. Next, an appropriately sized face mask was carefully placed to prevent leakage. The patient was instructed to breathe through the open nostril only, and not through their mouth, while the measurement was recorded by the software.[17]

Patient selection was done by non-probability sampling. Descriptive analysis was used to characterize the population. Pearson chi-square tests, Fischer exact test, and the Student's t-test were chosen for independent and paired samples in the comparisons of groups with and without allergic rhinitis. Comparisons of the predicted peak nasal inspiratory flow values with the absolute values found for each group were based on the Student's t-test for paired samples. A Pearson correlation parametric test was used to evaluate the relation between peak nasal inspiratory flow and rhinomanometry. The minimum significance level employed in all statistical tests was 5% ($p < 0.05$).

Results

This study evaluated 99 children and adolescents with sickle cell disease, 50.5% male and average age of 11.4 **± 3.7** years. Table 1 shows the descriptive measurements for the children and adolescents in terms of gender, age, weight, height, and body mass index (BMI).

Based on the questionnaire, socioeconomic data was collected. The family income of the studied population was, on average, 1.6 ± 0.8 minimum salaries. Most of the parents/guardians had not finished high school (62.9%) and the mean number of siblings was 2.2 ± 1.8. Table 2 shows the data for a family history of atopy, smoking at home, and the education level of the parent or guardian.

Allergic rhinitis was confirmed in 37.4% of patients from the sample. Of these, 59.5% had mild and intermittent allergic rhinitis as per the ARIA classification.[11]

There was no difference in hydroxyurea use ($p = 0.221$) between the group of patients with and without allergic rhinitis, 81.8% of the total sample used the medication. No statistically significant difference was noted between the groups in relation to the number of hospitalizations ($p = 0.676$) and the quantity of acute thoracic syndrome ($p = 0.298$). Baseline hemoglobin for the group of patients with allergic rhinitis was 8.7 ± 1.5 g/dL, which was greater than in the group of patients without allergic rhinitis, 8.0 ± 1.0 g/dL ($p = 0.017$). Only a few of the patients were consulting with a pulmonologist, allergist/immunologist, or otorhinolaryngologist, and of those who were, most had allergic rhinitis, although it corresponded only to 16.2% of the patients within this group.

In the group of patients with allergic rhinitis (n = 37), only 36.1% were receiving treatment. In the evaluation of this group, we noted a mean visual analog scale of 4.9 ± 3.2 and Wilson score of 7.9 ± 3.0.

When the parents/guardians were questioned on the presence of allergic rhinitis in these patients, only a few of them were able to provide this information, thereby leading to low agreement between the patient clinical evaluation and the caregiver feedback.

Concerning the variables that evaluated respiratory function, a mean of 96.6% ± 34.3% of the predicted value for peak nasal inspiratory flow was found. For peak nasal inspiratory flow, a value below what was predicted was observed in 57.6% of the sample. This analysis was performed for both the group with allergic rhinitis and the group without allergic rhinitis. In the rhinomanometry, there was no statistically significant difference between the groups with or without allergic rhinitis, the mean value of the groups being 0.35 ± 0.21 (Pa/cm^3/second) (Table 3).

A statistically significant inverse correlation was noted between peak nasal inspiratory flow and rhinomanometry, namely, r = -0.32 ($p < 0.05$), as shown in Fig. 1.

Table 1. Descriptive characteristics of patients (n = 99)

	Descriptive characteristics			
Variable	**Minimum**	**Maximum**	**Mean**	**SD**
Age (years)	6.0	18.0	11.43	3.7
Weight (kg)	17.0	86.0	36.0	15.1
Height (m)	1.10	1.74	1.42	0.18
BMI	12.2	29.7	17.0	3.2

BMI - body mass index, SD - standard deviation.

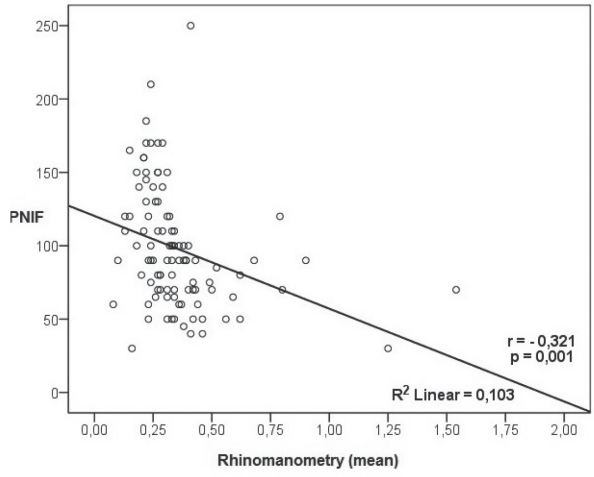
Table 2. Family history of atopy, smoking at home, and the education level of the parent/guardian (n = 99)

Variable	**%**
Family history of atopy	
Rhinitis	19.2
Asthma	26.2
Smokers at home	
Yes	36.1
No	63.9
Education level of the parent/guardian	
Illiterate	3.1
Elementary school incomplete	25.8
Elementary school completed	17.5
High school incomplete	16.5
High school completed	30.9
Third level incomplete	3.1
Third level completed	3.1

Table 3. Descriptive analysis of peak nasal inspiratory flow and rhinomanometry measures in the groups with and without allergic rhinitis

	With allergic rhinitis				Without allergic rhinitis			
Variable	**Minimum**	**Maximum**	**Mean**	**SD**	**Minimum**	**Maximum**	**Mean**	**SD**
Predicted PNIF % (p = 0.650)	40.4	197.3	94.5	36.1	35.7	226	97.9	33.4
Rhinomanometry (p = 0.967)	0.08	0.9	0.35	0.17	0.13	1.54	0.35	0.23

PNIF - peak nasal inspiratory flow, SD - standard deviation.



PNIF - peak nasal inspiratory flow.

Figure 1. Correlation between the peak nasal inspiratory flow and rhinomanometry.

Discussion

In the studied population, we noted a prevalence of allergic rhinitis similar to that found in the adolescent population in Belo Horizonte and in another Brazilian multicentric study in 2012, at 35.3%[18] and 37.2%,[12] respectively.

This study indicated that nasal function, as evaluated by peak nasal inspiratory flow and rhinomanometry, showed alterations in the studied population. The study found a high prevalence, 57.6% of the total, for children and adolescents with peak nasal inspiratory flow lower than the minimum predicted value set on the reference curve.[16] These values are particularly high considering that, in a normal population, it is not expected to find more than 2.5% of individuals with peak nasal inspiratory flow below the lower limit.[16] Comparing the results of this study with those from the research conducted in HEMOMINAS in 2014, which also evaluated the peak nasal inspiratory flow values in the pediatric population (n = 94) between 8 and 15 years old, with sickle cell disease, similar values were noted (84.6% ± 23.6% peak nasal inspiratory flow).[19] Nevertheless, there was no difference observed for peak nasal inspiratory flow values when the studied population was divided into patients with and without allergic rhinitis.

In relation to the rhinomanometry, this study found a mean value of 0.35 ± 0.21 Pa/cm^3/second, and there was no statistically significant difference between the group with and without allergic rhinitis. Despite rhinomanometry already being a validated method for investigating allergic rhinitis, there is an absence of studies involving its use in the population with sickle cell disease. There is research that validates its use in allergic rhinitis evaluation, proving that the values are higher than in the population without diseases of the upper airways.[20,21] Normal rhinomanometry values of approximately 0.23 Pa/cm^3/second were already established, ranging between 0.15 and 0.39 Pa/cm^3/second for healthy individuals, while a reasonable upper limit for nasal resistance is 0.30 Pa/cm^3/second.[20] In a previous study, significantly higher values were noted for the allergic rhinitis group than for the healthy group (0.309 *vs.* 0.205 Pa/cm^3/second, respectively).[22]

The high prevalence of allergic rhinitis in this group, as demonstrated in the healthy population, is of concern since it may be related to obstructive sleep apnea syndrome[23] and hypoxemia,[24] factors that trigger vaso-occlusive crises in patients with sickle cell disease.[3]

Another two important findings were the clinical scores for rhinitis (moderate 7.9 ± 3.0) and visual analog scale (4.9 ± 3.2) for patients with allergic rhinitis, as they are important instruments in quantifying the degree of nasal symptoms. The present study has limitations. Despite the Wilson score[14] not being validated yet, it is applied in several studies and in clinical practice since it is easily executed and requires minimum patient collaboration. Therefore, these results should be interpreted with caution. Future studies are needed to confirm these findings in different cities or countries. Visual analog scale, initially used to quantify pain intensity, is currently used on patients with allergic rhinitis both in evaluating severity and in verifying the efficacy of therapeutic intervention,[15] apart from being straightforward and easy to perform.

These results corroborate other findings that correlate sickle cell disease and certain respiratory disorders[6,25,26], although studies that relate sickle cell and allergic rhinitis are still scarce, and that makes this study the first of its kind in conducting this evaluation and associating the measurement of peak nasal inspiratory flow and rhinomanometry, as instruments of great worth in the

assessment of nasal function of patients with allergic rhinitis. Peak nasal inspiratory flow is a quick, painless, and low-cost measurement that is performed using a portable meter developed in 1980, making it an attractive proposition due to its simplicity.[14] A recent review of the literature[27] highlights several studies that confirm the usefulness of the peak nasal inspiratory flow in the pediatric population. Rhinomanometry, despite being a painless, reliable, and well-detailed method that enables the calculation of transnasal air resistance,[17,28,29] is limited in that it is costly, depends on having an experienced professional, suitable location, and the control of temperature and humidity.[17] Due to the peak nasal inspiratory flow ease of use and accessibility, the correlation between it and rhinomanometry was analyzed, and a statistically significant inverse result was noted, that is, the greater the rhinomanometry measurement is, the smaller the peak nasal inspiratory flow measurement, and vice versa. Therefore, the peak nasal inspiratory flow is an appealing choice in the evaluation of nasal respiratory function.

In relation to the use of hydroxyurea, it was noted that a large part of the studied population already used the medicine. It has a direct effect on the pathophysiological mechanism of sickle cell disease in increasing the synthesis of the fetal hemoglobin and promoting a reduction in the number of neutrophils and erythrocyte adhesion molecules.[30]

Despite the statistically significant difference found in relation to the baseline hemoglobin values in the groups of patients with and without allergic rhinitis, there is little clinical relevance in this finding, since the values are higher than 7.0 g/dL[31] and it is considered as one of the factors in sickle cell disease severity.

This study did not show a higher prevalence of allergic rhinitis, but alterations in nasal respiratory function were found in sickle cell disease patients, using peak nasal inspiratory flow and rhinomanometry measurements. Moreover, it is noteworthy that 70% of patients with sickle cell disease and allergic rhinitis were not receiving treatment for their rhinitis and several patients were unaware of their diagnosis.

Even though it is a preliminary and pioneering study, the results provide relevant information on the prevalence of allergic rhinitis and nasal function in Brazilian children and adolescents with sickle cell disease. It is hoped that the results achieved may contribute to the recognition of this condition and promote the appropriate treatment with a view to contributing to an improved quality of life for these patients.

WHAT THIS STUDY ADDS

- Overall, a high prevalence of allergic rhinitis and alterations in nasal respiratory function in patients with sickle cell disease.
- It is noteworthy that 70% of patients with sickle cell disease and allergic rhinitis were not receiving treatment for their rhinitis and several patients were unaware of their diagnosis.
- The results provide relevant information on the prevalence of allergic rhinitis and nasal function in Brazilian children and adolescents with sickle cell disease.
- These results should be interpreted with caution. Future studies are needed to confirm these findings in different cities or countries.
- The results achieved may contribute to the recognition of this condition and promote appropriate treatment with a view to contributing to an improved quality of life for these patients.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Prevalência de Rinite e Função Respiratória Nasal de Crianças e Adolescentes com Doença Falciforme

Resumo:

Introdução: A doença falciforme é a mais frequente das hemoglobinopatias hereditárias e apresenta morbimortalidade significativa. A obstrução respiratória superior é uma manifestação clínica comum nesses pacientes. Pretendeu-se quantificar a prevalência de rinite alérgica e avaliar a função respiratória nasal em crianças e adolescentes com doença falciforme.

Métodos: Foi realizado um estudo transversal num hemocentro brasileiro de renome, entre julho e outubro de 2017. Foram incluídos pacientes com idade entre 6-18 anos com diagnóstico de doença falciforme. Os sintomas atuais de rinite foram estimados com base em respostas positivas à pergunta usada no programa de pesquisa epidemiológica do estudo internacional de asma e alergia na infância. Foram realizadas medições de pico de fluxo inspiratório nasal, escala visual analógica e rinomanometria.

Resultados: A rinite alérgica foi confirmada em 37,4% da amostra de 99 pacientes. Aproximadamente 70% dos pacientes com doença falciforme e rinite alérgica não foram tratados para rinite e vários desconheciam o seu diagnóstico. Foram encontradas médias de 96,6% ± 34,3% do valor previsto do pico de fluxo inspiratório nasal e 0,35 ± 0,21 Pa/cm^3/segundo para a rinomanometria. A média de escala visual analógica foi de 4,9 ± 3,2.

Discussão: Este estudo não mostrou uma maior prevalência de rinite alérgica em pacientes com doença falciforme, mas o pico de fluxo inspiratório nasal e alterações de rinomanometria foram encontradas nos grupos de rinite alérgica e não rinite alérgica. Considerando a série de complicações enfrentadas por esses pacientes, espera-se que o reconhecimento e o tratamento da rinite alérgica contribuam para a melhoria da qualidade de vida.

Palavras-Chave: Adolescente; Criança; Doença Falciforme/complicações; Inquéritos e Questionários; Rinite Alérgica/prevenção & controle