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Peak nasal inspiratory flow in children and adolescents with sickle cell disease: a case-control study

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SUMMARY

OBJECTIVE: Sickle cell disease is the most frequent of the hereditary hemoglobinopathies and it presents multisystemic effects. A manifestation that is commonly found in sickle cell disease is upper airway obstruction, particularly adenotonsillar hypertrophy. This study aims to evaluate the peak nasal inspiratory flow measurements of children and adolescents with sickle cell disease.

METHODS: This is a case-control study on children aged between 8 and 15 years who were diagnosed with sickle cell disease. Peak nasal inspiratory flow measurements were obtained from patients.

RESULTS: A total of 279 patients were enrolled in this study, with 93 in the case group and 186 in the control group. The case group had an 82.83% chance of having lower peak nasal inspiratory flow values than the control group. In the case group, 75% of the peak nasal inspiratory flow values were in the lower standards, whereas in the control group, only 25% were in the lower standards.

CONCLUSION: This study showed a high prevalence of reduced peak nasal inspiratory flow values in children with sickle cell disease and could certainly be incorporated into the day-to-day clinical evaluation of patients as a screening instrument.

KEYWORDS: Sickle cell disease. Hemoglobinopathies. Rhinomanometry. Acoustic rhinometry. Hypoxemia.

INTRODUCTION

Sickle cell disease (SCD) is the most frequent of the hereditary hemoglobinopathies. Its most important pathophysiological aspect is in the red blood cell sickling phenomena with multisystemic effects[1]. Among these effects are manifestations in the upper airways. Furthermore, SCD is a group that is too often neglected in research worldwide. Incidence in Brazil is variable depending on the region, occurring at a rate of approximately 1:1400 to 1:1650 live births in the most prevalent regions[2]. Similar data were found in England at a rate of 1:2000[3]. This represents a high incidence when compared to other countries such as the United States of America, with a rate of 1:6600, according to neonatal screening in the state of California[3].

The infected children and adolescents often suffer from upper airways respiratory diseases. Adenotonsillar hypertrophy (AH) is most commonly found in patients with SCD[4]. It is speculated that this occurs as a result of repeated infections of the upper airways, secondary to functional asplenia[5]. AH is an important causal factor in obstructive sleep apnea syndrome and hypopnea in children[6]. Respiratory sleep disorders are often related to the drop-in oxygen saturation (SaO_2) during the night. Nocturnal desaturation in patients with SCD is associated with high rates of vaso-occlusive pain crises in children, as well as an increase in the probability of events related to the central nervous system (CNS)[7]. Among these CNS events, it is worth highlighting silent infarcts, which produces high morbidity, and leads to significant neurocognitive deficits[7].

Despite the importance of the symptoms related to the upper airways, there are no existing studies in the literature describing objective assessment for nasal air flow in SCD. The peak nasal inspiratory flow (PNIF) is a simple, low cost, and easy-to-use method[8]. Besides this, it presents a reference curve for a pediatric age bracket, which greatly facilitates its use in clinical practice. The assessment of PNIF is useful, informative, and reproducible, particularly when compared to expensive methods such as rhinomanometry and acoustic rhinometry[9]. Since previous studies demonstrated good correlation between rhinomanometry results when compared to PNIF measurements, we decided to use this valuable tool[8,9]. Furthermore, there is a paucity of information in the literature on diagnosing upper airway obstruction in patients with

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SCD, especially in the pediatric population. Therefore, this study is justified to assist the physicians in clinical practice.

The aim of this study was to perform a case-control study evaluation of the PNIF measurements for children and adolescents with SCD ranging in age from 8 to 15 years and to verify the association of the values obtained with variables of interest, such as hematological indices, oxygen saturimetry, past tonsillectomy, and/or adenoidectomy.

METHODS

The case-control study was carried out at the *Fundação Centro de Hematologia e Hemoterapia de Minas Gerais* (Minas Gerais Hematology and Hemotherapy Foundation Center - HEMOMINAS) and at public schools, in the city of Belo Horizonte, Minas Gerais State, Brazil. The case group was composed of children and adolescents with SCD, ranging in age from 8 to 15 years. The control group was composed of children and adolescents without SCD or any upper airway disease ranging in age from 8 to 15 years.

Inclusion and exclusion criteria

Children and adolescents selected by PETN-MG were included in the study composing the case group. All patients had been diagnosed and confirmed at the age of 1 year. The SS and $S\beta^0$ thalassemia genotypes were included, with ages ranging from 8 to 15 years. Children and adolescents from various public and private schools in Belo Horizonte, Minas Gerais State, without SCD were included in the study, composing the control group. All patients from both the groups who presented acute infection of the airways or were unable to perform the respiratory maneuvers were excluded from the study.

Procedures

Data on the case group were collected through interviews, physical assessment, and research of medical records. The interview was performed using a semi-structured questionnaire. Physical assessment was based on the gathering of vital data, including the measurement of weight and height. Research of medical records consisted in retrieving relevant data such as surgery on tonsils and adenoids, chronic transfusion, and hydroxyurea use.

Data on the control group were collected through physical assessment, questionnaire of upper airway symptoms, and PNIF measures (*In-check-inspiratory flow meter*, Clement Clarke, Harlow, England). Before PNIF measurements, the patient performed routine nasal hygiene by gently blowing the nose to eliminate residual nasal secretion. The facial mask was duly placed with participants standing up. They were then told to take a vigorous nasal inspiration from the residual capacity. At least three measurements were taken, and the highest value obtained was considered for analysis. The value noted was compared between the case and control groups.

Statistical analysis

Patient selection was done by non-probability sampling. Descriptive analysis was used to characterize population. With the goal of comparing the results of the two groups of children (case and control – the last one being the compound of two control groups) to the measure of PNIF, withdrawing the effect of the existing differences between each of the groups (blocks), that is, considering the dependence among the three groups of children (case, control 1, and control 2) once they were matched by age and sex, a variance analysis based on block planning with one factor (three groups of children) was performed. The use of block planning aims to withdraw the effect of variation caused by the difference between the experimental units (in this study, the children). The goal of the analysis in this study is to compare the obtained mean values of PNIF by each of the groups (case and control), i.e., to evaluate whether the PNIF measures in both groups presents different mean values or not in a set of paired children. The variance analysis based on block planning with one factor may be understood as an extension of the Student's t-test for paired samples, however, to compare the measures of PNIF performed in three paired groups. The p-value considered statistically significant was lower than 0.05. Univariate analysis was employed to evaluate the correlation between the variables studied through PNIF, tonsillectomy, and oxygen saturimetry. Comparison of the three saturimetry ranges (SaO_2 >98, 95–98, and <98%) was done based on analysis of variance.

Ethical aspects

The protocol and Informed Consent Form were approved by the Research Ethics Committee of HEMOMINAS and the Federal University of Minas Gerais.

RESULTS

The PNIF measurements of 279 individuals were analyzed, of whom 93 were in the case group and 186 were in the control group, comprising control groups 1 and 2. There was no statistically significant difference between the groups of boys and girls in terms of age, weight, height, and PNIF percentage in relation to the expected value (PNIF%). Table 1 shows the descriptive characteristics of the population studied.

The comparison between the PNIF values in the control and case groups by variance analysis showed a probability of

82.83% that the SCD child has a lower PNIF value than the control child, as shown in Table 2.

The mean value of PNIF in the SCD group was 88.5±26.2, and in the control group it was 109.7±16.9, as shown in Table 3.

DISCUSSION

This study found that the majority of the SCD children and adolescents group (75%) presented values of PNIF at the same level as the minority (25%) of the healthy control group, indicating that lower values of PNIF are more prevalent in this population than in the general one. The 82.83% probability of the PNIF values to be lower in the case group than in the control group reinforces that understanding.

This study is pioneer in its analysis of an objective method for measuring nasal inspiratory flow in individuals with SCD and has begun to fill the gap in the literature while serving as base for new studies. Additionally, the originality and lack of studies with similar methodology make it more complex to compare the data from this study with others. The association between SCD and some upper airway respiratory diseases has been demonstrated in publications, especially tonsillar hypertrophy and turbinate hypertrophy[10-15]. Considering that these afflictions have the potential to affect nasal air flow, and PNIF being a method for measuring this flow, it could become an important tool in the evaluation of patients with SCD. The irrefutably altered values noted in this experiment corroborate this possibility. Therefore, this study presents a practical possibility of incorporating a low-cost and easy-to-use device in the physician's clinical practice.

It is important to note that a limitation of the study is that it does not manage to demonstrate the factors that influence PNIF values in patients with SCD. Another significant limitation is that this study was conducted in only one reference center in Minas Gerais; therefore, caution is suggested to generalize outcomes. New studies must be carried out in other reference centers using different methodologies and clinical laboratory parameters.

Table 1. Children participating in the study, distributed by group, age, and sex.

Age (years)	Groups					
	Case		Control 1		Control 2	
	Male	Female	Male	Female	Male	Female
8	5	8	5	8	5	8
9	6	7	6	7	6	7
10	7	7	7	7	7	7
11	4	2	4	2	4	2
12	4	6	4	6	4	6
13	4	7	4	7	4	7
14	7	11	7	11	7	11
15	2	6	2	6	2	6
Total	39	54	39	54	39	54

Table 2. Variance analysis based on a block model comparing the two groups of children regarding the peak nasal inspiratory flow values.

Variation source	Sum of squares	D.F.	Mean squares	F	p
Group	27947.314	1	27,947.314	82.827	**<0.001**
Block	53762.244	92	584.372		
Error	62,422.020	185	337.416		

F: variance analysis statistics based on a block model (93 children), p: test significance probability, D.F.: degrees of freedom. Bold indicates statistically significant value.

Table 3. Descriptive and comparative measures of peak nasal inspiratory flow in both groups of children.

Group	Descriptive measures				p
	Minimum	Maximum	Mean	SD	
Case	40.0	160.0	88.5	26.2	**<0.001**
Control	80.0	160.0	109.7	16.9	

SD: standard deviation. Bold indicates statistically significant value.

Current clinical monitoring of this hematological disease has not yet incorporated objective parameters into the evaluation of nasal flow and is focused more on costly image analysis to clinically evaluate the airways. The use of a functional parameter to evaluate the upper airways could enrich the monitoring process, facilitate treatment decisions and prevent systemic complications. However, to be certain of the effectiveness of PNIF measurements, more studies are needed to address other aspects of the disease's repercussions, relating them to nasal air flow, as well as a comparison with other objective methods for nasal patency evaluation, such as rhinomanometry and acoustic rhinometry.

This study showed the existence of a high prevalence of low PNIF values in individuals with SCD. In this context, more research is needed to determine the cause of this compromised nasal airflow among these patients, as well as the factors associated with reduced PNIF. In the future, it would be interesting to verify the impact of an improvement in the levels of this parameter in the systemic course of the disease. On the contrary, although it may be a preliminary and pioneering study, results provide fundamental information. Hence, in future research, PNIF is incorporated into the methods for the evaluation and follow-up of patients with SCD.

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AUTHORS' CONTRIBUTIONS

AKV: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **CGA:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – review & editing. **CCI:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. R**RD:** Conceptualization, Data curation, Software, Visualization, Writing – original draft, Writing – review & editing. **RMOR:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **MVDB:** Conceptualization, Data curation, Software, Writing – review & editing. **CPB:** Conceptualization, Writing – review & editing.

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