Persistent pulmonary function impairment in children and adolescents with asthma*

Função pulmonar persistentemente reduzida em crianças e adolescentes com asma

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Abstract

Objective: Asthma is the most common chronic pulmonary disease, characterized by bronchial inflammation. Some children with asthma have persistent pulmonary function impairment. The prevalence and etiology of this abnormality in children with asthma in developing countries remain unknown. The objective of this study was to estimate the proportion of patients with impaired pulmonary function who were unresponsive to treatment in a group of children and adolescents with asthma, and to describe the phenotypic characteristics of the sample. **Methods:** Using a standardized questionnaire, we selected outpatients (5-17 years of age) diagnosed with persistent asthma. These patients underwent spirometry and skin prick tests for sensitivity to common aeroallergens. Persistent pulmonary function impairment was defined as an FEV_1/FVC ratio < 0.80, even after 10 days of treatment with bronchodilators and oral corticosteroids. We used the atopic index to differentiate between patients with little or no response to the skin prick test and those with a strong response (cut-off point: 4 allergens). **Results:** We included 96 patients with a mean age of 10.6 years. Of those, 52 (54.1%) were male, and 89 (92.7%) were atopic. Of the 96 patients, 8 (8.3%) had impaired pulmonary function even after the treatment. Among those patients, 8 (100%) were atopic, 7 (87.5%) had moderate or severe asthma, and 7 (87.5%) had a history of hospitalization for acute bronchiolitis. **Conclusions:** Children and adolescents with moderate or severe asthma can present with impaired pulmonary function and be unresponsive to treatment. This clinical situation has been little studied in developing countries, and its risk factors and etiology will be better understood only through birth cohort studies.

Keywords: Asthma; Respiratory function tests; Allergy and immunology.

Resumo

Objetivo: A asma é a doença pulmonar crônica mais comum na infância, caracterizada por inflamação brônquica. Algumas crianças com asma podem apresentar função pulmonar persistentemente reduzida. A prevalência e etiologia dessa anormalidade em crianças com asma em países em desenvolvimento ainda não são conhecidas. O objetivo deste estudo foi estimar a proporção de pacientes com função pulmonar reduzida, sem resposta a tratamento, em um grupo de crianças e adolescentes com asma, e descrever as características fenotípicas da amostra. **Métodos:** Foram selecionados pacientes ambulatoriais (5-17 anos) diagnosticados com asma persistente através de um questionário padronizado. Esses pacientes foram submetidos a espirometria e teste cutâneo para aeroalérgenos comuns. Definiu-se como função pulmonar persistentemente reduzida apresentar relação VEF_1/CVF < 0,80, mesmo após ter recebido tratamento com broncodilatador e corticoide oral por 10 dias. O índice de intensidade de atopia foi utilizado para diferenciar pacientes pouco reatores daqueles multirreatores (ponto de corte: 4 alérgenos). **Resultados:** Foram incluídos 96 pacientes, com média de idade de 10,6 anos. Desses, 52 (54,1%) eram do sexo masculino, e 89 (92,7%) eram atópicos. Dos 96 pacientes, 8 (8,3%) apresentaram redução da função pulmonar mesmo após o tratamento. Desses pacientes, 8 (100%) eram atópicos, 7 (87,5%) apresentavam asma moderada ou grave, e 7 (87,5%) tinham história de hospitalização por bronquiolite aguda. **Conclusões:** Crianças e adolescentes com asma moderada a grave podem apresentar função pulmonar reduzida e sem resposta a tratamento. Essa situação clínica é pouco estudada em países em desenvolvimento, e seus fatores de risco e etiologia serão mais bem entendidos somente com estudos de coorte de nascimento.

Descritores: Asma; Testes de função respiratória; Alergia e imunologia.

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Introduction

Childhood asthma is a chronic inflammatory disease of the lower airways, characterized by airflow limitation and bronchial hyperresponsiveness.[1] Many genetic and environmental factors are involved in the pathophysiology of asthma. The multifactorial and complex character of asthma makes it more difficult to understand the disease in different populations.[2] Atopy is one of the most important risk factors in asthma, being particularly associated with phenotypes with symptoms that are persistent and more severe.[3] However, different phenotypes have been identified, the prevalence of which is high in populations in developing countries.[4-6]

Pulmonary function testing allows an objective assessment of the degree of bronchial obstruction in asthma (including reversibility and variability), contributing to the diagnosis, treatment, and prognosis of the disease.[1,7] Partly because of the etiological complexity of asthma, pulmonary function impairment in children with the disease can have several causes. This abnormality can be transient (being of a reversible nature), congenital, or structural (with irreversible loss of pulmonary function).[8-11] The last of the three, designated airway remodeling, is more severe and is accompanied by bronchial tissue damage, being characterized by structural changes that result in irreversible functional changes.[12] Studies of adults with asthma have demonstrated that, despite appropriate pharmacological treatment, some patients present with airway remodeling and progressive loss of pulmonary function, airway remodeling being often associated with atopy, smoking, and fatal asthma.[13,14] Recent studies of children have demonstrated that airway remodeling seems to occur early in the course of asthma (i.e., in the first years of life).[9,11] In addition, Covar et al. demonstrated that approximately 25% of schoolchildren with mild to moderate asthma in the USA had loss of pulmonary function over a 4-year period, whether or not they had been treated with inhaled corticosteroids.[10]

Persistent pulmonary function impairment in asthma, the onset of which seems to occur early in life, remains a great clinical challenge and is poorly understood, there being little evidence on its etiology and course. The prevalence of treatment-resistant pulmonary function impairment in children with persistent asthma, as well as the clinical characteristics of pulmonary function impairment in those children, including the association between pulmonary function impairment and atopy, remains unknown in Latin-American populations. Therefore, the objective of the present study was to estimate the proportion of patients with impaired pulmonary function who were unresponsive to treatment in a sample of children and adolescents with persistent asthma treated at a pediatric pulmonology outpatient clinic of a tertiary care hospital in Brazil, and to describe the phenotypic characteristics of the sample, particularly the presence or absence of atopy.

Methods

We recruited patients in the 5-17 year age bracket diagnosed with persistent asthma and followed at a pediatric pulmonology outpatient clinic. The diagnosis of asthma was based on the following criteria: having a history of wheezing or recurrent cough in the last 12 months; having used asthma medication in the last 12 months; and having previously been diagnosed with asthma. At the first visit (prior to initiation of prophylactic asthma treatment), all patients were classified according to asthma severity. Persistent asthma and its severity were defined on the basis of symptom-related information and pulmonary function test results, in accordance with the Global Initiative for Asthma criteria,[15] grading having been based on the worst parameter:

- mild asthma—daytime symptoms more than once a week (but less than once a day), nighttime symptoms more than twice a month, or FEV_1 > 80% of predicted
- moderate asthma—daytime symptoms on a daily basis, nighttime symptoms more than once a week, or FEV_1 of 60-80% of predicted
- severe asthma—continuous symptoms, frequent nighttime symptoms, or FEV_1 < 60% of predicted

The patients were routinely classified according to disease severity at the first outpatient visit. All patients were currently using inhaled corticosteroids or a combination of inhaled corticosteroids and long-acting β_2 agonists. This was a convenience sample. We included all patients who met the inclusion criteria during the study period at the aforementioned outpatient clinic.

The exclusion criteria were as follows: having intermittent asthma; having other associated

chronic lung diseases; having experienced an exacerbation of asthma or allergic rhinitis in the last 15 days; having had acute airway infection in the last 15 days; having used oral corticosteroids in the last 2 weeks; having used short-acting bronchodilators 4 h before the test; having used long-acting bronchodilators 12 h before the test; having been born at a gestational age < 37 weeks; presenting with heart disease or neurological disease; presenting with immunodeficiency; and being unable to perform the test properly. The parents or legal guardians were interviewed by previously trained researchers with the use of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire,[16] which addressed patient history and factors known to induce or prevent asthma or allergy. The standardized ISAAC questionnaire has previously been validated for use in Brazil, having been employed by our research group in a previous study.[6]

After routine clinical examination, the patients underwent anthropometric assessment (body weight and height) with a scale and a stadiometer. Subsequently, the patients underwent spirometry with a Koko spirometer (Ferraris Respiratory, Louisville, CO, USA) or a Super Spiro spirometer (Micro Medical Ltd., Kent, UK). The patients performed a deep inhalation maneuver followed by a maximal expiratory maneuver, without a nose clip. The forced expiratory maneuvers were performed after a brief demonstration and training. Tests were considered successful when three acceptable and reproducible curves were achieved. We stipulated a maximum of eight attempts/test, in accordance with the criteria established by the American Thoracic Society.[17] Spirometry was performed with bronchodilator testing (400 μg of albuterol aerosol, with a spacer). After a 15-min interval, spirometry was repeated. The FEV_1, FVC, and $FEF_{25-75\%}$ values in percentage of predicted were normalized and established in accordance with the values obtained with the reference equations described by Stanojevic et al.[18] The data corrected by those equations consider the characteristics of the population in order to set appropriate limits of normality.[18] The patients who continued to have obstructive lung disease (FEV_1/FVC < 0.80) after bronchodilator testing (first spirometric test [S1]) were given a course of pharmacological treatment with an oral corticosteroid (prednisone, 2 $mg \cdot kg^{-1} \cdot day^{-1}$; maximum dose, 40 mg/day) in combination with an inhaled β_2 agonist bronchodilator (albuterol aerosol, 2 puffs, 4 times a day) for 10 consecutive days. At the end of treatment, the patients returned to the outpatient clinic for a second spirometric test (S2), in order to determine whether their pulmonary function values had returned to the normal range (FEV_1/FVC ≥ 0.80). The drugs are prescribed and provided free of charge at the public primary health care clinics in the city. Adherence to treatment was investigated before S2. A diagnosis of treatment-resistant pulmonary function impairment was considered in those cases in which the spirometric values did not return to the normal range even after the treatment with bronchodilators and anti-inflammatory drugs. An FEV_1/FVC ratio ≥ 0.80, which is low for the age group studied, was chosen as the cut-off value for normality in order to reduce the likelihood of false-positive results, thereby allowing the identification of patients who were truly at high risk for bronchial obstructive disease. This was a cross-sectional study in which a subsample was included in a prospective longitudinal study (cohort study).

Skin prick testing was performed with a test kit (FDA Allergenic, Rio de Janeiro, Brazil). The group of allergens tested included *Dermatophagoides pteronyssinus, D. farinae*, *Blomia tropicalis*, cockroach mix, airborne fungal mix, cat dander, dog dander, and pollen, as well as histamine (10 mg/mL, positive control) and a diluent (negative control). The tests were performed in the afternoon (from 1:30 to 4:00). After antisepsis of the volar aspect of the left forearm, which should be free of atopic eczema, a drop of each extract was placed on the skin, leaving a space of 2.0-2.5 cm between drops, at a distance of 5 cm from the wrist and of 3 cm from the antecubital fossa. To that end, marks were previously drawn on the skin with the aid of a pen. Data were collected in accordance with the standardization of the ISAAC protocol.[16] Sterile disposable lancets were used for each of the eight substances (allergenic extracts, as well as negative and positive controls) in order to avoid contamination. Lancets show good reproducibility and accuracy, being easy to use, safe, and well accepted by patients, parents, and collectors.[16]

A reaction was considered positive if the papule diameter was equal to or greater than 3 mm. This

diameter was calculated as follows: ([greatest length + shortest length] ÷ 2) – (length of the negative control). The patients were divided into two groups on the basis of the atopic index.[19] The group of patients with little or no response to the skin prick test comprised those without atopy and those with a positive response to 3 or fewer allergens (< 4), whereas the group of patients with a strong response comprised those with a positive response to 4 or more allergens (≥ 4). The skin reagents were stored in a refrigerator in order to prevent bacterial contamination. All data collectors were previously trained in accordance with the standardization of the ISAAC study.[16]

The parents or legal guardians received all relevant information related to the procedures to be performed, and those who agreed to participate in the study gave written informed consent. The study was approved by the Research Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul.

We analyzed pulmonary function parameters (FVC, FEV_1, FEV_1/FVC ratio, and $FEF_{25-75\%}$) and the data collected with the ISAAC questionnaire. The presence of atopy was analyzed after standardization by means of a quantitative method, based on the number of positive responses to the allergens tested.

Quantitative variables are expressed as means and standard deviations, whereas qualitative variables are expressed as percentages. Pearson's chi-square test was used in order to determine the differences among the groups in terms of the categorical variables. The Student's t-test for independent samples was used in order to compare the groups in terms of the means of continuous variables. The paired t-test was used in order to compare the means of continuous variables showing temporal variation, and ANOVA was used in order to determine the differences among three independent groups. The level of significance was set at $p \leq 0.05$. Data analysis was performed with the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

We selected 96 persistent asthma patients with a mean age of 10.6 ± 2.6 years. Of those, 52 (54.1%) were male, and 89 (92.7%) were atopic. According to the classification of severity, 27 patients (28.1%) had mild persistent asthma, 55 (57.2%) had moderate persistent asthma, and 14 (14.5%) had severe persistent asthma. The descriptive characteristics of the patients included in the study and classified according to asthma severity are shown in Table 1. Neither a history of hospitalization for acute viral bronchiolitis (AVB) nor prematurity correlated with disease severity. Neither hospitalization for AVB nor a maternal history of asthma correlated significantly with impaired pulmonary function in the study sample.

Regarding baseline spirometry, the comparison of the pulmonary function indices among the groups of patients classified according to disease severity revealed significant differences between the patients with moderate asthma and those with severe asthma in terms of FEV_1 and FVC ($p = 0.003$ and $p = 0.005$, respectively). We found no significant differences among the groups regarding the remaining pulmonary function indices (Table 1).

In 34 (35%) of the 96 study participants, S1 revealed pulmonary function impairment. In 8 (8.3%), pulmonary function values did not return to the normal range even after the 10-day course of treatment (use of an oral corticosteroid in combination with a β_2 agonist), constituting evidence of treatment-resistant pulmonary function impairment. In this subgroup of patients (n = 8), the mean age was 12.0 ± 2.1 years, and there was a predominance of the following: moderate and severe cases (87.5% *vs.* 72.0% in the sample as a whole); history of hospitalization for AVB (87.5% *vs.* 66.0%); and atopy (100% *vs.* 92.0%). The small number of patients with persistent pulmonary function impairment limits the statistical analysis of these results. Comparing only the baseline values (before bronchodilator testing) found in those patients after the initial tests (S1) with those found after the course of treatment with a corticosteroid (S2), we found no significant differences in the pulmonary function indices. The pulmonary function values of the patients with irreversible loss of pulmonary function are shown in Table 2.

With regard to the skin prick test, there was a predominance of positive responses to house dust mites (> 80%), principally *D. pteronyssinus* (85.4%). The frequency of positive responses to each allergen tested is shown in Figure 1. On the basis of the atopic index, 37 individuals (38.5%) were classified as belonging to the group of

Table 1 - Characteristics of the patients studied, classified by asthma severity.[a]

Characteristic	Asthma severity			p
	Mild	Moderate	Severe	
	(n = 27; 28.1%)	(n = 55; 57.3%)	(n = 14; 14.6%)	
Male gender	11 (40.7)	35 (63.6)	6 (42.8)	NS
Age, years	10.3 ± 2.7	10.6 ± 2.6	11.4 ± 2.3	NS
Atopy[b]	25 (92.5)	52 (94.5)	12 (85.7)	NS
Allergic rhinitis	25 (92.5)	54 (98.2)	13 (92.8)	NS
Atopic dermatitis	10 (37.0)	23 (41.8)	6 (42.8)	NS
MH of asthma	9 (33.3)	17 (31.0)	6 (42.8)	NS
Prematurity	2 (7.4)	5 (9.1)	3 (21.4)	NS
History of AVB	14 (51.8)	39 (71.0)	11 (78.5)	NS
FVC, %	101.5 ± 12.2	108.1 ± 12.5	95.0 ± 18.2	0.003*
FEV_1, %	94.9 ± 12.9	100.9 ± 14.3	86.6 ± 19.8	0.005*
FEV_1/FVC	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	NS
$FEF_{25-75\%}$, %	79.5 ± 22.2	85.6 ± 25.6	73.1 ± 34.4	NS

NS: not significant; MH: maternal history; and AVB: acute viral bronchiolitis. [a]Values expressed as n (%) or as mean ± SD. [b]Atopy: at least one positive skin prick test result (papule ≥ 3 mm in diameter). *ANOVA (Tukey's post hoc test). The difference occurred between the moderate and severe asthma groups.

patients with little or no response to the skin prick test (a group comprising those without atopy and those with a positive response to 3 or fewer allergens, i.e., < 4), whereas 59 (61.5%) were classified as belonging to the group with a strong response (a group comprising those with a positive response to 4 or more allergens, i.e., ≥ 4).

The analysis of the pulmonary function parameters, in relation to the atopic index, showed that there was a significant difference between the group of those with little or no response and the group of those with a strong response only in terms of the FEV_1/FVC ratio (p = 0.032). We found no significant differences between the groups in terms of the remaining pulmonary function indices (Table 3).

Discussion

The present study demonstrated that some schoolchildren (8.3%) with persistent asthma can present with treatment-resistant pulmonary function impairment. This group of patients, despite being small in terms of absolute numbers in the present study, does not seem negligible in terms of population if our sample is truly representative of Brazilian children with persistent asthma. This finding has important clinical relevance, considering that it might represent true loss of pulmonary function occurring early in the course of asthma and resulting from bronchial structural changes of irreversible nature.[12]

With regard to asthma severity, 7 (87.5%) of the 8 patients with treatment-resistant impaired pulmonary function had moderate/severe persistent asthma, as well as a history of AVB in the first 2 years of life. In addition, all of the patients with treatment-resistant impaired pulmonary function were atopic. Persistent irreversible airway obstruction in asthma patients seems to be associated with greater disease severity, as well as being predictive of mortality in those patients.[20] The sharp decline in pulmonary function might be related to disease severity and chronic inflammation.[21] When we compared the results of S1 with those of S2 (Table 2), we found a variation in FEV_1 and $FEF_{25-75\%}$ values,

Table 2 - Pulmonary function indices of the patients in whom the first spirometric test showed persistent changes and who received 10 days of treatment with corticosteroids and β_2 agonists (n = 8).[a]

Indices	Baseline spirometry	Post-treatment spirometry	p*
FVC, %	107.33 ± 7.67	110.84 ± 10.75	0.136
FEV_1, %	83.24 ± 5.52	87.31 ± 5.44	0.117
FEV_1/FVC	0.67 ± 0.03	0.68 ± 0.06	0.374
$FEF_{25-75\%}$, %	46.54 ± 6.42	65.33 ± 33.39	0.139

[a]Values expressed as mean ± SD. *Paired Student's t-test.

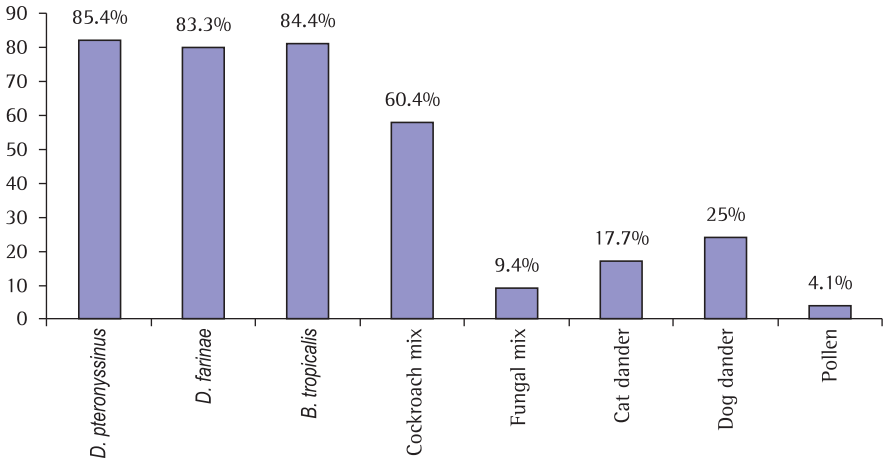

Figure 1 - Positive skin prick test results by allergen tested (n = 96).

although the difference was not significant. This lack of significance was probably due to the small size of this subsample included in the analysis. However, the mean FEV_1/FVC values obtained with S2 (0.68 ± 0.06) demonstrated that, even if there had been a significant variation, the characteristics of obstruction were evident, and there was no trend toward normalization of pulmonary function in those patients.

In a study that followed asthma patients over 30 years after the diagnosis was made, 16% of the patients were found to have developed irreversible bronchial obstruction, a condition that is suggestive of airway remodeling.[22] In addition, a recent study found no direct evidence that the use of anti-inflammatory therapy reduces inflammation or prevents structural changes in the airways, corroborating the findings of our study.[23] Therefore, there is evidence that structural changes are responsible for a varying degree of airway irreversibility, thereby contributing to the phenomenon of loss of pulmonary function, and that frequent exacerbations lead to a decline in pulmonary function, given that they perpetuate the inflammatory process and contribute to the pathogenesis of lung remodeling.[24]

One of the limitations of the present study is that the study design did not allow us to determine whether the treatment-resistant pulmonary function impairment observed was congenital or acquired. Previous studies have demonstrated that children with atopic asthma have a clinical profile that is more severe, with potential loss of pulmonary function during childhood. Cases of transient wheezing, which are more closely associated with impaired pulmonary function at birth, are less likely to show persistent bronchial obstructive disease.[25,26] Our sample of children with persistent asthma and treatment-resistant impaired pulmonary function was characterized by the fact that most presented with atopy, greater disease severity, and a history of hospitalization for AVB. These characteristics are more closely associated with phenotypes of non-transient wheezing, in which pulmonary function is not characterized by being impaired at birth. In order to answer that question, it is essential that birth cohort studies, preferably multicenter studies, be performed in developing countries.

Table 3 - Pulmonary function test results according to the atopic index, as determined by the skin prick test.[a]

Variable	Atopic index < 4 (n = 37)	Atopic index ≥ 4 (n = 59)	p*
FVC, %	104.58 ± 14.19	104.15 ± 14.17	0.88
FEV_1, %	99.25 ± 13.84	95.75 ± 16.49	0.28
FEV_1/FVC	0.84 ± 0.07	0.80 ± 0.08	0.03
$FEF_{25-75\%}$, %	88.02 ± 25.02	78.35 ± 26.62	0.08

[a]Values expressed as mean ± SD. *Student's t-test.

The overall analysis of our sample revealed that the patients with severe asthma had significantly lower FEV_1 values than did those with moderate asthma. This finding strengthens the quality of the study, validating, to a certain extent, the asthma severity classification used. Although this classification is influenced by subjective criteria, the differentiation between moderate and severe asthma correlated well with the objective data on pulmonary function.

Considering that a small group of asthma patients with greater disease severity seem to have an unfavorable course, with irreversible loss of pulmonary function, it is important to investigate factors that might be associated with severity or that are useful for the early identification of those patients. Clough et al.[27] found that atopic children in the 7-8 year age bracket with cough and wheezing had significantly lower FEV_1 values than did those who were nonatopic. Another group of authors[25] recently suggested that atopic and nonatopic asthma have different clinical, functional, and epidemiological characteristics. That study demonstrated that atopic asthma is associated with exacerbations that are more severe, as well as with a greater number of emergency room visits and hospitalizations.[25] According to Bottini et al.,[26] in addition to clinical and epidemiological differences, there are pathophysiological and genetic differences between atopic and nonatopic asthma. Atopy seems to be strongly associated with pulmonary function abnormalities and persistent wheezing in adolescence.[28] Although the mere presence of atopy might not be the most appropriate way to identify patients at risk of having more pronounced loss of pulmonary function, there are other quantitative methods for the analysis of skin prick test results.[19,29]

The atopic index[19] uses the total number of positive responses to different allergens and can provide a better idea of the intensity of the response to multiple allergens. In the present study, we divided our sample into two groups: individuals with little or no response to the skin prick test (i.e., those without atopy and those with a positive response to 3 or fewer allergens) and individuals with a strong response (i.e., those with a positive response to 4 or more allergens). We observed that the patients with a strong response had significantly higher indices of airway obstruction than did those with little or no response. One group of authors[19] demonstrated a significant correlation between the atopic index for indoor home allergens in childhood and the persistence of asthma into puberty.[19] Another study[30] reported associations between those allergens and reduced FEV_1 values in children aged 6-12 years. These results support the hypothesis that indoor home allergens are involved in or are markers of greater asthma severity, playing an important role in the pathogenesis of the disease, probably early in life.[30] The analysis including atopic index data demonstrated the relationship between atopy intensity and asthma severity. However, when we consider that the proportion of patients with persistent loss of pulmonary function (i.e., 8.3%) was relatively small in comparison with the total number of asthma patients in our sample, the small number of patients with persistent loss (n = 8) makes it difficult to analyze the factors associated with this outcome.

In conclusion, our results demonstrated that a significant group (nearly 10% of the cases) in a sample of schoolchildren with asthma in Brazil had treatment-resistant pulmonary function impairment. This finding might be associated with airway remodeling and should be further studied in populations in developing countries. We also demonstrated that the atopic index is associated with impaired pulmonary function and that this might be indicative of greater disease severity. Therefore, early identification of patients with loss of pulmonary function, as well as the use of clinical and biological markers, such as the atopic index, can be useful in determining the group of children who should be tested for novel therapeutic targets that might change the natural history of a disease that has a poorer prognosis.

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