ORIGINAL ARTICLE

Predictive Value of Lung Function Trend and FeNO for Difficult Asthma in Children

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Abstract

Objective: The aim of this study was to evaluate the predictive value of lung function and fraction of exhaled nitric oxide (FeNO) for difficult asthma in children.
Patients and Methods: Children with asthma referred to an asthma clinic for uncontrolled persistent asthma on inhaled corticosteroids (ICSs) alone or in combination with a long-acting $ß_2$-agonist and/or a leukotriene receptor antagonist were followed in a prospective 1-year study to identify difficult asthma. At the end of the study period, difficult asthma was considered for children with persistent asthma symptoms and/or frequent moderate/severe asthma exacerbations despite regular intake of ICSs (beclomethasone or equivalent)>800 µg/d for at least 3 months, after correcting for adherence to treatment, inhalation technique, and comorbidities and after implementing an individualized treatment plan. The difficult asthma phenotype was characterized using a multidimensional approach combining clinical features and pathophysiologic features (lung function and inflammation). Unfavorable lung function trend (persistent airway obstruction and fluctuations in forced expiratory volume in the first second of α>0.5) and persistently high FeNO levels (>45 ppb despite increasing ICS doses) were analyzed as risk factors for difficult asthma in the logistic regression analysis together with male sex, atopy, concurrent severe rhinitis, obesity, psychopathology, exposure to tobacco smoke, low socioeconomic status, lack of adherence to treatment, and persistent bronchodilator response.
Results: Forty-six asthmatic children (34 males, 74%) with a mean (SEM) age of 7.55 (3.04) years were enrolled. After 1 year, 24 children (52%) were labeled as having difficult asthma. Independent risk factors for difficult asthma were persistently high FeNO (*P*=.04), obesity (*P*=.04), and severe rhinitis (*P*=.03).
Conclusions: Persistently high FeNO predicts difficult asthma in children, while unfavorable lung function trend does not.

Key words: Asthma. Disease exacerbation. Inflammation. Lung function tests. Risk factors.

Resumen

Objetivo: El objetivo de este estudio fue evaluar el valor del estudio de la función pulmonar (FP) y el óxido nítrico en aire exhalado (FeNO) para predecir el asma de difícil control (ADC) en niños asmáticos.
Pacientes y métodos: Los niños asmáticos con asma persistente no controlada a pesar de tratamiento continuado con corticoesteroides inhalados (CI) solos o en combinación con un beta-adrenérgico de larga acción (LABA) y/o antileucotrienos, enviados a una clínica de asma fueron seguidos de forma prospectiva durante un año para identificar el ADC. El diagnóstico de ADC se estableció al final de estudio para los niños asmáticos que cumplieran los siguientes criterios: síntomas asmáticos persistentes y/o exacerbaciones moderadas o severas, a pesar de tratamiento regular con CI a una dosis igual o superior a 800 microgramos/día de beclometasona o equivalente, durante al menos 3 meses, tras corregir los posibles problemas de adherencia al tratamiento, la técnica de inhalación y las co-morbilidades, e implementar un plan de tratamiento personalizado. El fenotipo de ADC se caracterizó adicionalmente mediante una aproximación multidimensional combinando las características clínicas con los aspectos fisiopatológicos de la enfermedad (FP e inflamación). La tendencia negativa de la función pulmonar (obstrucción bronquial persistente y fluctuaciones del FEV_1 con un alfa > 0,5) y un valor de FeNO persistentemente elevado (> 45 ppb, a pesar del incremento de los CI) fueron analizados como factores de riesgo de ADC en un modelo de regresión logística, junto con las variables sexo masculino, atopia, rinitis grave concurrente, obesidad, trastornos psicológicos, exposición pasiva al humo de tabaco, status socio-económico bajo, falta de adherencia al tratamiento y respuesta broncodilatadora persistente.
Resultados: Se incluyeron un total de 46 niños asmáticos con una edad media de 7.55 ± 3.04, de los cuales 34 (74%) eran varones. Tras un año de seguimiento 24 (52%) niños se consideraron como ADC. Los factores de riesgo independientes para el desarrollo de ADCV fueron: un valor persistentemente elevado de FeNO (p=0.04), la obesidad (p=0.04) y la rinitis grave concurrente (p=0.03).
Conclusión: Un valor persistentemente elevado de FeNO es un factor de predicción de ADC, mientras que la tendencia negativa de la función pulmonar no lo es.

Palabras clave: Asma. Exacerbación. Inflamación. Pruebas de función pulmonar. Factores de riesgo.

Introduction

Difficult asthma in children is described as the presence of persistent asthma symptoms despite regular therapy with high doses of inhaled corticosteroids (ICSs) either alone or in association with a long-acting ß$_2$-agonist (LABA), a leukotriene modifier, or low-dose theophylline [1-3]. In a correct assessment of difficult asthma, it is essential to consider alternative diagnoses, poor adherence to treatment or incorrect inhaler technique, comorbidities, and environmental exposure (allergens, tobacco smoke, and other indoor and outdoor pollutants) [4,5]. Difficult asthma in children is highly heterogeneous and ranges from persistent airway obstruction to brittle asthma. Treatment is particularly challenging due to high morbidity and disease-related costs [5,6].

Unlike in adults, little is known about risk factors or predictors of difficult asthma in children. The combined use of clinical features with measurements of lung function and airway inflammation seems to provide the best characterization of this asthma phenotype.

Lung Function as a Phenotypic Trait

Asthma is a dynamic disease, hence the fluctuating nature of the parameters used to describe asthma phenotypes. Fluctuation analysis is a research tool validated for use in other pathologies or biological processes with a fluctuating character [7-9]. Recent reports have highlighted the value of peak expiratory flow fluctuation analysis in characterizing asthma control during treatment with bronchodilators [10,11] and in predicting response to asthma treatment [12]. No data are available on the relationship between lung function fluctuation and asthma severity, and furthermore, lung function fluctuation has not been evaluated in children with asthma.

Asthma severity is related to the degree of airway remodeling, which is most marked in cases of fatal asthma. Persistent airflow limitation is prevalent in patients with severe or difficult-to-treat asthma, with rates of 60% reported in the TENOR study and of 49% in a European cohort of adults with severe asthma [13,14]. A cumulative end-point merging lung function fluctuation and persistent airflow limitation seems reasonable for predicting severity of asthma.

Airway Inflammation as a Phenotypic Trait

Management of asthma in children is currently guided by assessment of clinical symptoms, exacerbation risk, and lung function measurements. The measurement of the fraction of exhaled nitric oxide (FeNO) has been proposed as a readily determined biomarker that can aid the diagnosis and management of asthma. FeNO has been used to identify steroid-responsive patients, adjust ICS doses, and predict relapse during medication tapering [15]. Exhaled NO levels might predict changes in lung function and the risk of future asthma in wheezy infants and toddlers [16]. In the Children's Health Study, common haplotypes in the promoter of the *NOS2A* gene (encoding for inducible NO synthase) were found to be associated with new-onset asthma and lung function growth [17]. The early enthusiasm generated by these results, however, has been dampened by more recent data suggesting a more limited role for FeNO in asthma management, especially in pediatric asthma [18,19].

Research Hypothesis

In the present study, we characterized the phenotype of difficult pediatric asthma using a multidimensional approach combining clinical features and pathophysiologic features (lung function and inflammation).

Patients and Methods

Study Population and Design

The study was conducted within a private setting. The target group consisted of pediatric asthma patients referred to our asthma clinic by their regular physician for uncontrolled persistent asthma despite use of ICSs either alone or in combination with an LABA and/or a leukotriene receptor antagonist (LTRA). For inclusion the children had to have a physician's diagnosis of asthma based on the American Thoracic Society criteria, and a proven forced expiratory volume in the first second (FEV_1) reversibility of >12% and >200 mL in the last previous 6 months or at the inclusion visit. The local ethics committee approved the study protocol and written informed consent was obtained from parents/legal guardians before all study procedures.

The patients were followed in a prospective 1-year study to identify difficult asthma. Difficult asthma diagnosis was defined as the presence of persistent asthma symptoms (episodic breathlessness, wheezing, cough, and chest tightness) and/or asthma exacerbations requiring oral or systemic corticosteroids and/or an emergency room visit and/or hospitalization for asthma despite regular intake of ICS > 800 µg/day (beclometasone or equivalent) in the last 3 consecutive months of the 1-year observation period and after implementing an individualized treatment plan targeting adherence to treatment, inhalation technique, and control of comorbidities.

Study Procedures

The following evaluations were performed at inclusion:

- Physical examination (including height and weight measurements).
- Asthma duration and treatment.
- History of asthma exacerbations.
- Level of asthma control (Global Initiative for Asthma [GINA] 2010 update).
- History of exposure to tobacco smoke (prenatal and postnatal).
- Skin prick test (SPT). Atopy was diagnosed if at least 1 SPT was positive to the following common aeroallergens tested: house dust mites, cat, dog, molds, cockroaches, grass/tree/weed pollen. An SPT was considered positive for an allergen to histamine wheal diameter of over 1 and a mean wheal size of 3 mm or more.

- Assessment of asthma comorbidities: atopic dermatitis, gastroesophageal reflux, drug or food allergy, dysfunctional breathing (Nijmegen score >23; a total Nijmegen symptom score of >23 has been reported to have a sensitivity of 91% and a specificity of 95% as a screening instrument in patients with diagnosed hyperventilation syndrome [20]).
- Ear, nose, and throat examination to confirm the presence of rhinitis and exclude other nasal pathologies.
- Psychological profile (performed by a child psychologist; the Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition] DSM-IV symptoms were derived from selected modules of the National Institute of Mental Health Diagnostic Interview Schedule for Children Version IV) [21,22].
- Lung function testing (spirometry; Microlab MK 8, CareFusion) after a washout period of 12 hours for LABAs and of 4 hours for SABAs; postbronchodilator FEV_1 and magnitude of the bronchodilator response were considered.
- FeNO measurement (NIOX MINO, Aerocrine AB); exhaled NO values were corrected for height, male sex, atopy, and infection status [23].

The patients were seen regularly at 1- to 4-month intervals, depending on the level of asthma control achieved. At each visit the following procedures were performed:

- Level of asthma control.
- Lung function testing with assessment of postbronchodilator FEV_1 and magnitude of bronchodilator response.
- FeNO measurement.
- Changes in asthma and/or concomitant medication.
- Adherence to treatment (registration of dispensed medication in pharmacies).
- Status of asthma comorbidities.
- 15- to 30-minute educational session performed by an asthma nurse (basic asthma information, inhalation technique, control of breathing during an asthma attack, avoidance of triggers, recognition of early signs of an exacerbation, reinforcement of adherence to treatment)

An individualized treatment plan was established at each visit and adapted to the level of asthma control, comorbidities, inhalation technique, and socioeconomic status of the patient. If a patient was defined as having uncontrolled or partially controlled asthma, according to the GINA 2010 update, the ICS dose was stepped up to the next concentration. If total control had been achieved, the dose was decreased to the next lowest concentration; if the patient was already on the lowest possible concentration, the dose was maintained. The same ICS was used in each patient, with variations in dosage according to the level of asthma control. LABAs and LTRAs were maintained at the same doses in patients on these drugs.

Risk Factors for Difficult Asthma

A. At inclusion

- Male sex, atopy, obesity (body mass index at or above the 95th percentile), exposure to tobacco smoke, concurrent severe rhinitis (presence of all 4 ARIA [Allegic Rhinitis and its Impact on Asthma] severity items [24]), low socioeconomic status, low adherence to treatment (less then 50% fulfillment of prescriptions), and psychopathology (attention-deficit/hyperactivity disorder, conduct disorder, depression, anxiety, panic disorder).

B. After 1 year

- Persistent bronchodilator response (>12% and >200 mL increase in FEV_1 after inhaled $ß_2$-agonist administration at each visit) [25,26].
- Unfavorable lung function trend, defined as FEV_1 fluctuations with α>0.5 (detrended fluctuation analysis) or persistent airflow limitation (postbronchodilator FEV_1 <80% predicted at each visit).
- Persistently high FeNO levels (>45 ppb at each visit).

Statistics

Results were analyzed with STATISTICA 7 (StatSoft. Inc). Data are presented as mean (SEM) and ranges, unless otherwise stated. The differences between the non-difficult and the difficult asthma subgroups were tested using the Mann-Whitney U test and the χ^2 test for independent samples. Risk factors for difficult asthma were assessed by logistic regression analysis. To avoid falsely positive conclusions, the significance level for each test was set at P<.05.

FEV_1 fluctuations were evaluated using detrended fluctuation analysis (Matlab; The Mathworks Inc.). An FEV_1 time series with α>0.5 indicates a more deterministic behavior of the system,with stronger correlations, which is more likely to be the expression of the stable asthma phenotype.

Results

Characteristics of Participants

Informed consent was obtained from the parents/legal guardians of 52 (69.33%) of the 75 children referred to our clinic for uncontrolled persistent asthma. Forty-six children (88.46%) completed a mean of 12.46 (0.13) months (range, 11-14 months) of observation. The mean age was 7.55 (0.45) years (range, 3-15 years) and 34 (74%) were boys.

At inclusion, all the children had uncontrolled asthma. They all had daily asthma symptoms with frequent SABA use, 20 (43.48%) reported night awakenings, and 28 (60.87%) reported limitation of daily activities. FEV_1 <80% predicted was recorded in 15 (32.61%) cases, and 22 children (48.83%) had had at least 3 moderate or severe asthma exacerbations in the previous year. The mean ICS dose at inclusion was 575.65 (60.86) µg (range, 200-2000 µg); 21 children (45.65%) were receiving a LABA (formoterol or salmeterol) associated with the ICS, and 11 (24.91%) were receiving an LTRA (montelukast).

After 1 year, 24 asthmatic children (52%) were diagnosed with difficult asthma. At the end of the study, the daily ICS dose in the difficult asthma subgroup was 1450 (46.55) µg (range, 1000-2000 µg) of fluticasone (n=3), budesonide (n=13), or

Table 1. Comparison of General Characteristics of Children With Difficult Asthma and Non-Difficult Asthma[a]

	Non-Difficult Asthma (n=22)	Difficult Asthma (n=24)	*P* Value
Mean age, y	7.36 (0.67) (3-15)	7.71 (0.61) (3-15)	.5750
Asthma duration, mo	37.77 (2.11) (18-56)	39.96 (2.44) (19-64)	.6053
Asthma exacerbations, No.	3 (13.64)	19 (79.17)	<.0001[b]
Mean FEV_1 (% predicted)	103.53 (2.53) (67.66-123.8)	91.13 (3.04) (65.71-119.29)	0.0026[b]
Mean FeNO, ppb	15.85 (2.70) (5-56.33)	26.28 (4.6) (5.5-65)	.2528
Mean ICS dose at inclusion, μg	568.18 (90.49) (200-2000)	572.92 (87.88) (200-1500)	.9299
Mean ICS dose at the end of the study, μg	197.73 (21.36) (100-500)	1.450 (46.55) (1000-2000)	<.0001[b]
Eczema, No. (%) of patients	5 (22.73)	5 (20.83)	.8764
Gastroesophageal reflux, No. (%) of patients	6 (27.27)	11 (48.53)	.1927
Drug allergy, No. (%) of patients	0	0	–
Food allergy, No. (%) of patients	4 (18.18)	9 (37.5)	.1461
Dysfunctional breathing, No. (%) of patients	11 (50)	13 (54.17)	.7775

Abbreviations: FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroids.
[a]Data are expressed as means (SEM) and range unless otherwise indicated.
[b]Statistically significant.

Table 2. Risk Factors for Difficult Asthma Analyzed in Study Groups[a]

	Non-Difficult Asthma (n=22)	Difficult Asthma (n=24)	*P* Value
Male	18 (81.8)	16 (66.67)	.2424
Atopy	19 (86.36)	22 (91.67)	.5638
Obesity	1 (4.55)	6 (25)	.0537
Exposure to tobacco smoke	5 (22.73)	7 (31.82)	.6193
Low socioeconomic status	5 (22.73)	10 (41.47)	.1711
Severe rhinitis	3 (13.64)	16 (66.67)	.0003[b]
Psychopathology	4 (18.18)	15 (62.5)	.0023[b]
Low adherence to treatment	6 (27.27)	10 (41.47)	.3059
Persistent bronchodilator response	13 (59.09)	17 (70.83)	.4036
Unfavorable lung function trend	4 (18.18)	16 (66.67)	.0009[b]
Persistent airflow limitation (post bronchodilator $FEV_1 < 80$ predicted)	1	6	0.0537
FEV_1 fluctuations with $\alpha > 0.5$	3	10	0.0349[b]
Persistently high FeNO	2 (9.09)	8 (33.33)	.0465[b]

Abbreviations: FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in the first second.
[a]Data shown as number (%) of patients.
[b]Statistically significant.

Table 3. Logistic Regression Analysis for Independent Risk Factors for Difficult Asthma

	Wald Statisic	Odds Ratio	CIs		*P* Level
			Lower	Upper	
Male	0.4469	0.2564	0.0047	13.8647	.5038
Atopy	0.0069	1.1638	0.0327	41.4673	.9337
Obesity	3.9913	0.0233	0.0006	0.9312	.0457*
Exposure to tobacco smoke	0.1214	0.5266	0.0143	19.4270	.7275
Low socio-economic status	0.1504	0.4998	0.0150	16.6372	.6982
Severe rhinitis	4.3544	0.0209	0.0006	0.7907	.0369[a]
Psycho-pathology	0.1787	0.5526	0.0353	8.6479	.6725
Low adherence to treatment	0.8200	0.2239	0.0088	5.7110	.3652
Persistent bronchodilator response	0.2230	1.8668	0.1399	24.9027	.6368
Unfavorable lung function trend	3.2596	0.0247	0.0004	1.3729	.0710
Persistently high FeNO	4.1397	0.0297	0.0010	0.8790	.0419[a]

Abbreviation: FeNO, fraction of exhaled nitric oxide.
[a] Statistically significant.

ciclesonide (n=8). This was significantly higher than the dose used in the non-difficult asthma subgroup (Table 1). After 1 year, the daily ICS dose decreased from 568.18 (90.49) μg to 197.73 (21.36) μg in the non-difficult asthma subgroup, while it increased from 572.92 (87.88) μg to 1450 (46.5) μg in the difficult asthma subgroup.

There were no differences between children with difficult asthma and those with non-difficult asthma in terms of asthma duration, mean ICS dose at inclusion, or mean FeNO values. The difficult asthma subgroup had a higher incidence of asthma exacerbations and a significantly lower mean FEV_1 (Table 1). The only differences detected in terms of asthma comorbidities were for severe rhinitis and psychopathology (Tables 1 and 2).

Risk Factors for Difficult Asthma

On comparing children with difficult asthma and those with non-difficult asthma, the former had a significantly increased frequency of severe rhinitis, psychopathology, unfavorable lung function trend, and persistently high FeNO (Table 2). In the logistic regression analysis, only obesity, severe rhinitis, and persistently high FeNO were independent risk factors for difficult asthma (Table 3).

Unfavorable lung function trend was registered for 20 (43.48%) children, 13 of whom had significant FEV_1 fluctuations (α>0.5) and 7 of whom had persistent airflow limitation (postbronchodilator FEV_1 <80% predicted). The number of patients with FEV_1 fluctuations was significantly higher (*P*=.03) in the difficult asthma subgroup (Table 2). The mean α fluctuation coefficient for non-difficult asthma was 0.83 (0.15) (range, 0.60-1.12), while for difficult asthma it was 1.06 (0.22) (range, 0.51-2.58). The difference was not significant (*P*=.6121). There were no significant differences for persistent airflow limitation between the 2 groups. For the only patient with persistently low FEV_1 in the non-difficult asthma subgroup we decided not to increase the ICS doses since he had no daytime or nighttime symptoms, no limitation of activities, and no asthma exacerbations.

Discussion

In the present study, the phenotype of pediatric difficult asthma was characterized using a multidimensional approach combining clinical features with pathophysiologic features (lung function and inflammation). Phenotypes identified in this manner are more complex, but arguably more objective. The multidimensional approach allows validation by replication across different populations and may contribute to a more reliable definition of asthma phenotypes. In addition, both lung function and inflammation were evaluated as dynamic parameters by measuring time trends. We also evaluated the following domains of asthma severity: level of current prescribed treatment, asthma control over the preceding 3 to 4 months, and burden of asthma exacerbations.

Interpretation and Significance of Findings

Incidence of Difficult Asthma in Study Group

After correcting for adherence to treatment, inhalation technique, and comorbidities and after implementing an individualized treatment plan, 52% of the asthmatic children with an entry label of uncontrolled persistent asthma were diagnosed with difficult asthma. This figure is unexpectedly high compared to those described in other reports, but it must be borne in mind that the study was conducted in a tertiary care centre to which difficult asthma cases are referred. The diagnosis of asthma was checked carefully at inclusion and all efforts were made to control comorbidities and reinforce adherence to treatment. Our data are similar to those reported in a recent cross-sectional study conducted in school-aged children diagnosed with problematic severe asthma (defined as insufficient asthma control despite level 4 treatment, according to GINA), where 61% had therapy-resistant asthma, and the

remaining 39% had difficult-to-treat asthma due to identified aggravating factors [27].

After implementing an individualized treatment plan, 48% of the children in our series initially labeled as having difficult asthma achieved good control, thus reinforcing the concept that correctly addressing basic management needs is of prime value in managing uncontrolled asthma before labeling it difficult asthma. The mean daily ICS dose decreased from 568.18 (90.49) μg to 197.73 (21.36) µg in the non-difficult asthma group, which is significant in terms of both safety and disease-related costs.

Clinical Correlates of Difficult Asthma

Obesity and severe rhinitis were both independent predictors for difficult asthma.

Most studies suggest that obesity increases the clinical severity of asthma and decreases quality of life in children with asthma [28,29]. In adolescents with asthma, adiposity is associated with poorer asthma control in females, while adiponectin is associated with improved asthma control in males [30]. In our study, weight reduction, which formed part of the individualized treatment plan, was beneficial for gaining asthma control, although it was achieved in less then 50% of the overweight or obese children.

Allergic rhinitis is a common comorbid state in children with severe asthma. In the TENOR study, approximately two-thirds of the 1261 young patients with severe or difficult-to-treat asthma were found to have allergic rhinitis [31], and in a Swedish cohort of children with problematic severe asthma, the prevalence of rhinoconjunctivitis was significantly higher compared to that in children with controlled asthma (P=.01) [27].

Fractional Exhaled Nitric Oxide

In our study, persistently high FeNO was an independent predictor of difficult asthma in children. Since adherence to treatment and correct inhalation technique were reinforced at each visit we can assume that nonadherence to treatment or improper use of ICSs accounted to a minor extent for persistently high FeNO levels, and other causes, such as excessive allergen exposure or corticosteroid insensitivity can thus be suspected. Our results indicating persistently high FeNO as a measure of asthma severity are consistent with the observation that increased FeNO predicts accelerated lung function decline in adults with severe asthma [32]. In another study, conducted in adults, FeNO values of over 30 ppb had a positive predictive value of more then 0.85 for lack of asthma control [33]. In infants with recurrent wheeze treated with ICS, FeNO was well correlated with clinical control [34]. Based on a previous observation that a cutoff of 46 ppb has the best positive predictive value for asthma diagnosis [35], we set the cutoff for persistently high FeNO at 45 ppb, which is higher than the threshold of 20 ppb used in the adult study evaluating lung function decline.

Lung Function Fluctuation and/or Persistent Airflow Limitation

Unfavorable lung function trend (high fluctuation and/or persistently low FEV_1) did not reach statistical significance as an independent predictor for difficult asthma. This is not surprising as, unlike in adults, spirometry is a poor predictor of severity in children [36]. However, unfavorable lung function trend was more common (43.48%) in the difficult asthma group. The prevalence of patients with FEV_1 fluctuations was also significantly higher (P=.03) in this subgroup (Table 2). Our results match those from the Swedish cohort of children with problematic severe asthma who exhibited significantly lower FEV_1 values (P=.02) and increased bronchial hyperresponsiveness (P=.01) [27].

Limitations and Open Questions

The present study has a number of limitations. First, some methodological issues need to be discussed. The numbers are small and it is a single-center study. However, the use of a multidimensional approach in the characterization of the difficult asthma phenotype provides more objectivity and allows replication in future studies. In addition, the sampling rate was not affected by referral patterns since asthma treatment for children, including that in private practice consultations, is fully compensated by the insurance system in our country. The study group comprised both preschool and school-aged children, thus the effect of age on presentation and/or disease course is not considered. As an indicator of asthma severity, we did not evaluate corticosteroid responsiveness in patients needing high daily ICS doses for asthma control. In addition, persistent airflow limitation was defined as persistently low FEV_1 at each visit and not after an oral corticosteroid trial. On the other hand, there is no accepted definition of corticosteroid responsiveness in children and furthermore the correct dose and duration of a corticosteroid trial are not known [4,37,38]. Atopy as a whole was considered a risk factor, with no differentiation between seasonal or perennial allergens or special consideration for fungal sensitization. Most of the atopic children (82%) were polysensitized to both seasonal and perennial allergens, and fungal sensitization was diagnosed in only 2 children. Exposure to smoke was evaluated by history only, not by urinary cotinine levels, so it might be underestimated. Also, we did not perform home visits to truly evaluate chronic exposure to allergens, smoke, and indoor pollutants.

Another drawback is the use of a limited number of data points in the FEV_1 fluctuation analysis. This means that the determination of long-range correlations is less reliable. The actual time over which the data were collected was not the main limitation of the method. Rather, it was the number of data points required to characterize the fluctuation dynamics. To increase the strength of FEV_1 fluctuation analysis in future studies, it would be necessary to extend the length of observation or increase the frequency of data collection.

In conclusion, in children with asthma, lung inflammation (persistently high levels of FeNO) predicts the difficult asthma phenotype while lung function (FEV_1 fluctuations or persistent airflow limitation) does not.

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