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 β-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 FEV1 >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=0.04), obesity (p=0.04), and severe rhinitis (p=0.03).

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 corticosteroides inhalados (ICI) 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 IC 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 FEV1 con un alfa > 0.5) y un valor de FeNO persistentemente elevado (> 45 ppb, a pesar del incremento de los IC) 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.

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 β₂-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 (FEV₁) 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.
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 [Allergic Rhinitis and its Impact on Asthma] severity items [24]), low socioeconomic status, low adherence to treatment (less than 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 FEV1 after inhaled β2-agonist administration at each visit) [25,26].
• Unfavorable lung function trend, defined as FEV1 fluctuations with <0.5 (detrended fluctuation analysis) or persistent airflow limitation (postbronchodilator FEV1 <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 χ² 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<0.05.

FEV1 fluctuations were evaluated using detrended fluctuation analysis (Matlab; The Mathworks Inc.). An FEV1 time series with χ²<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 (61.33%) completed a mean of 12.46 (0.13) months (range, 8-15 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. FEV1 <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) g (range, 300-2000 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

<table>
<thead>
<tr>
<th></th>
<th>Non-Difficult Asthma (n=22)</th>
<th>Difficult Asthma (n=24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>7.36 (0.67) (3-15)</td>
<td>7.71 (0.61) (3-15)</td>
<td>.5750</td>
</tr>
<tr>
<td>Asthma duration, mo</td>
<td>37.77 (2.11) (18-56)</td>
<td>39.96 (2.44) (19-64)</td>
<td>.6053</td>
</tr>
<tr>
<td>Asthma exacerbations, No.</td>
<td>3 (13.64)</td>
<td>19 (79.17)</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>Mean FEV₁ (% predicted)</td>
<td>103.53 (2.53) (67.66-123.8)</td>
<td>91.13 (3.04) (65.71-119.29)</td>
<td>.0026*</td>
</tr>
<tr>
<td>Mean FeNO, ppb</td>
<td>15.85 (2.70) (5-36.33)</td>
<td>26.28 (4.6) (5.5-65)</td>
<td>.2528</td>
</tr>
<tr>
<td>Mean ICS dose at inclusion, µg</td>
<td>568.18 (90.49) (200-2000)</td>
<td>572.92 (87.88) (200-1500)</td>
<td>.9299</td>
</tr>
<tr>
<td>Mean ICS dose at the end of the study, µg</td>
<td>197.73 (21.36) (100-500)</td>
<td>1.450 (46.55) (1000-2000)</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>Eczema, No. (%) of patients</td>
<td>5 (22.73)</td>
<td>5 (20.83)</td>
<td>.8764</td>
</tr>
<tr>
<td>Gastroesophageal reflux, No. (%) of patients</td>
<td>6 (27.27)</td>
<td>11 (48.53)</td>
<td>.1927</td>
</tr>
<tr>
<td>Drug allergy, No. (%) of patients</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Food allergy, No. (%) of patients</td>
<td>4 (18.18)</td>
<td>9 (37.5)</td>
<td>.1461</td>
</tr>
<tr>
<td>Dysfunctional breathing, No. (%) of patients</td>
<td>11 (50)</td>
<td>13 (54.17)</td>
<td>.7775</td>
</tr>
</tbody>
</table>

Abbreviations: FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in the first second; ICS, inhaled corticosteroids.

aData are expressed as means (SEM) and range unless otherwise indicated.

bStatistically significant.

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

<table>
<thead>
<tr>
<th></th>
<th>Non-Difficult Asthma (n=22)</th>
<th>Difficult Asthma (n=24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18 (81.8)</td>
<td>16 (66.67)</td>
<td>.2424</td>
</tr>
<tr>
<td>Atopy</td>
<td>19 (86.36)</td>
<td>22 (91.67)</td>
<td>.5638</td>
</tr>
<tr>
<td>Obesity</td>
<td>1 (4.55)</td>
<td>6 (25)</td>
<td>.0537</td>
</tr>
<tr>
<td>Exposure to tobacco smoke</td>
<td>5 (22.73)</td>
<td>7 (31.82)</td>
<td>.6193</td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td>5 (22.73)</td>
<td>10 (41.47)</td>
<td>.1711</td>
</tr>
<tr>
<td>Severe rhinitis</td>
<td>3 (13.64)</td>
<td>16 (66.67)</td>
<td>.0003*</td>
</tr>
<tr>
<td>Psychopathology</td>
<td>4 (18.18)</td>
<td>15 (62.5)</td>
<td>.0023*</td>
</tr>
<tr>
<td>Low adherence to treatment</td>
<td>6 (27.27)</td>
<td>10 (41.47)</td>
<td>.3059</td>
</tr>
<tr>
<td>Persistent bronchodilator response</td>
<td>13 (59.19)</td>
<td>17 (70.83)</td>
<td>.4036</td>
</tr>
<tr>
<td>Unfavorable lung function trend</td>
<td>4 (18.18)</td>
<td>16 (66.67)</td>
<td>.0009*</td>
</tr>
<tr>
<td>Persistent airflow limitation (post bronchodilator FEV₁ &lt; 80 predicted)</td>
<td>1</td>
<td>6</td>
<td>.0537</td>
</tr>
<tr>
<td>FEV₁ fluctuations with α &gt; 0.5</td>
<td>3</td>
<td>10</td>
<td>.0349*</td>
</tr>
<tr>
<td>Persistently high FeNO</td>
<td>2 (9.09)</td>
<td>8 (33.33)</td>
<td>.0465*</td>
</tr>
</tbody>
</table>

Abbreviations: FeNO, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in the first second.

aData shown as number (%) of patients.

bStatistically significant.
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).

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 than 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 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 than 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 FEV1) 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 FEV1 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 FEV1 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 FEV1, 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 FEV1 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 FEV1 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 (FEV1 fluctuations or persistent airflow limitation) does not.

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