Young Infants with Recurrent Wheezing and Positive Asthma Predictive Index Have Higher Levels of Exhaled Nitric Oxide

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Objective. The aim of this post hoc analysis was to establish the relationship between FE\textsubscript{NO} levels and the asthma predictive index (API) among infants with recurrent wheezing. Methods. Infants with recurrent wheezing (three or more episodes) were recruited consecutively and online FE\textsubscript{NO} tests at tidal breathing with multiple breaths were performed. Results. Twenty-seven (84%) out of 32 infants (median age of 12 months) who met the inclusion criteria for this post hoc analysis, successfully performed the FE\textsubscript{NO} determinations. Eighteen (66%) infants were classified with positive stringent API. FE\textsubscript{NO} levels were significantly higher among patients with positive API than those with negative (median [IQR] of 12.3 [14.8] ppb vs. 4.1 [7.9] ppb, respectively, \(p = .016\)). Furthermore, FE\textsubscript{NO} and positive API had a significant correlation (Spearman’s \(\rho = 0.4741, p = .0125\)). After logistic regression analysis including FE\textsubscript{NO} levels, gender, age, and use of controller therapy, FE\textsubscript{NO} was the only variable that was marginally related to API (OR = 1.12, 95% CI: 0.99–1.27, \(p = .07\)). Conclusion. Infants with recurrent wheezing who had a positive stringent API already had higher FE\textsubscript{NO} levels than those with a negative API. This finding needs to be corroborated in a larger prospective study.

Keywords asthma predictive index, early childhood asthma, fraction of exhaled nitric oxide, infants, recurrent wheezing

INTRODUCTION

Asthma is the most prevalent chronic disease among children and in the vast majority of the cases it starts before the age of five (1). However, it continues to be one of the most difficult disorders for physicians to diagnose in infants and preschoolers. This is partly because clinical symptoms of asthma are variable and non-specific, given that other wheezing disorders co-exist (e.g., transient wheezing) (2, 3). No accurate screening tests using genetic or single biochemical markers have as yet been developed to determine which young children with recurrent wheezing will develop asthma (4). Therefore, the diagnosis and management of asthma in young children are still primarily based on subjective clinical features and findings from medical examinations. One of the clinical tools most commonly proposed for early prediction of asthma in young children with recurrent wheezing is the asthma predictive index (API) (5).

On the other hand, neither airflow limitation nor airway inflammation, the main pathologic hallmarks of asthma, can be assessed routinely in infants. Recently, a study of preschoolers showed higher markers of airway inflammation (IL-2, -4, -8, and -10 and sICAM) measured in exhaled breath condensate among children with a persistent wheezing phenotype than in those without wheezing (6). The fraction of exhaled nitric oxide (FE\textsubscript{NO}), as a surrogate marker of eosinophilic inflammation of the airways, has been tested in several studies of asthmatic school-age children (7–9). FE\textsubscript{NO} was reported to be higher both among preschoolers with recurrent wheezing bronchitis compared with controls (10) and among preschoolers with atopic compared with non-atopic wheezing (11). FE\textsubscript{NO} also correlated well with preschoolers with probable asthma (12).

Recently, we showed that the determination of online FE\textsubscript{NO} can be successfully performed in infants (13). Using those data, we conducted this post hoc analysis in order to determine whether recurrent wheezing infants with a positive API (high risk to develop asthma) already had evidence of airway inflammation (as measured by FE\textsubscript{NO}) at a young age. Our hypothesis is that infants with a positive API have higher levels of FE\textsubscript{NO} than those with a negative API.

METHODS

The original study was of a cross-sectional design and was carried out in the pediatric pulmonary clinic at the Hospital Universitario Donostia, Spain (13). Briefly, a consecutive sample of 38 patients aged less than 24 months with recurrent wheezing (three or more episodes of confirmed wheezing in the last year) were enrolled in the study. Exclusion criteria for this post hoc analysis included the presence of other chronic respiratory conditions...
(e.g., cystic fibrosis, bronchopulmonary dysplasia, primary ciliary dyskinesia, post-infectious bronchiolitis obliterans, interstitial lung disease, pulmonary malformations, and gastroesophageal reflux), cardiac malformations, neurologic abnormality, and prematurity (<37 weeks of gestational age).

A postprandial FeNO was determined at tidal breathing over multiple breaths without sedation. An online system was used with a stationary chemiluminescence analyzer (CLD 88 sp; Eco Physics AG, Duernten, Switzerland). A mask was used to separate airflow from the oral and nasal cavities (Hans Rudolph Inc, Kansas City, MO, USA), with an expiratory flow between 40 and 60 ml/s (14). The mask was connected to a disposable antibacterial antiviral filter. Mean FeNO was obtained during the spontaneous respiratory cycles (inspiration–expiration) of the subjects over a 60-s period. FeNO was measured at the end of the respiratory cycle, in the stable plateau phase when the expiration of 60–80% of the total tidal volume had been exhaled. All subjects performed three valid determinations with a variability ratio of less than 10% among them, and the mean calculated from these measurements. The determinations ranged between 0.1 and 5000 parts per billion (ppb). The determinations were carried out with NO-free (<5 ppb) room air to avoid environmental contamination. Daily calibration of flow and volume verified the precision of these measurements, as did a calibration of NO to zero. Likewise, the NO gas was calibrated monthly (13).

Data on demographic characteristics, use of controllers, parental medical diagnosis of asthma, medical diagnosis of dermatitis and rhinitis, episodes of wheezing apart from colds and peripheral blood eosinophils (determined in a venous blood sample by a fully automated blood cell counter and expressed as the percentage of total leukocyte count) was taken during the first visit. API was based on the original definition using the stringent index (5), which requires recurrent episodes of wheezing (≥3 episodes/ year) during the first 3 years of age and one of two major criteria (physician-diagnosed eczema or parental asthma) or two of three minor criteria (physician-diagnosed allergic rhinitis, wheezing without colds, or peripheral eosinophilia ≥4%) (5).

The study was approved by the hospital’s Ethics and Research Committee and written informed consent and permission were obtained from both parents and/or guardians.

Data Analysis

Given that there is limited reliable data on methodology and the lack of standardization of FeNO determination techniques, both in general and for infant populations, no sample size was determined a priori. A univariate analysis of the positive and negative API groups was conducted, as well as a chi-square test for associations among categorical data. The distribution of numerical variables was evaluated using the Shapiro–Wilk test and described as median and interquartile range (IQR). Spearman’s coefficient between FeNO and API was calculated. Logistic regression analysis was used to test for significant associations between API and factors known to influence FeNO levels (age, sex, and the use of controller therapy). Two-tailed p values of <0.05 were considered significant. STATA 8.0 (Stata Corp, College Station, Texas, USA) statistical software package was used for the analysis.

RESULTS

Twenty-seven (84%) of the 32 original infants who successfully performed the FeNO determinations met the inclusion/exclusion criteria for this post hoc analysis. The median (IQR) age was 12 (2.5) months, 64.8% were males, and the median (IQR) expiratory flow of FeNO was 62 (4.4) ml/s.

There were 18 (66%) patients with positive stringent API. Among this group the prevalence of parental doctor asthma diagnosis, atopic dermatitis, allergic rhinitis, wheezing without viral infections, and eosinophilia were 44%, 56%, 0%, 70%, and 44%, respectively. There were no significant differences in gender, weight, antiasthmatic drug use, number of reproducible maneuvers, and FeNO determinations between infants with positive and negative API (Table 1). However, those in the positive API group were significantly older than negative API group: median (IQR) of 13.5 (6.3) months versus 11 (8) months, respectively, p = 0.033 (Table 1).

Infants with positive API had significantly higher FeNO levels than those with negative API: median (IQR) of 12.3 (14.8) ppb versus 4.1 (7.9) ppb, respectively, p = 0.016 (Table 1 and Figure 1). Furthermore, FeNO and positive API were significantly correlated (Spearman’s rho, ρ = .4741, p = .0125). Logistic regression analysis of FeNO, gender, and age and the use of controller therapy showed that FeNO was the only variable marginally related to API (OR = 1.12, 95% CI: 0.99–1.27, p = .07).

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Characteristics of the infants with positive and negative original asthma predictive indices (API).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive API</strong></td>
<td><strong>Negative API</strong></td>
</tr>
<tr>
<td>n = 18</td>
<td>n = 9</td>
</tr>
<tr>
<td>Males (%)</td>
<td>75</td>
</tr>
<tr>
<td>Age (months)</td>
<td>13.5 (6.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>10 (6.3)</td>
</tr>
<tr>
<td>Controller therapy (%):</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>61.1</td>
</tr>
<tr>
<td>ICS</td>
<td>22.2</td>
</tr>
<tr>
<td>LTRA</td>
<td>5.5</td>
</tr>
<tr>
<td>ICS and LTRA</td>
<td>11.1</td>
</tr>
<tr>
<td>FeNO (ppb)</td>
<td>12.3 (14.8)</td>
</tr>
<tr>
<td>Expiratory flow (ml/s)</td>
<td>61.7 (8.8)</td>
</tr>
<tr>
<td>Reproducible maneuvers (%):</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>27.8</td>
</tr>
<tr>
<td>Three</td>
<td>72.2</td>
</tr>
</tbody>
</table>

Note: Numbers are express as % or median (interquartile range). ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; FeNO, fraction of exhaled nitric oxide; ppb, parts per billion.

*p < 0.05.
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DECLARATION OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES