Arch Argent Pediatr 2013;111(3):191-195 / 191

Association between the Asthma Predictive Index and levels of exhaled nitric oxide in infants and toddlers with recurrent wheezing

Juan Emilio Balinotti, M.D.[a], *Alejandro Colom, M.D.*[a], *Carlos Kofman, M.D.* [a] *and Alejandro Teper, M.D.*[a]

ABSTRACT

It is difficult to make an early identification of which children with recurrent wheezing will develop asthma in the following years. The Asthma Predictive Index (API) is a questionnaire based on clinical and laboratory parameters used for this end. The measurement of fractional exhaled nitric oxide (FE_{NO}) has been used as a marker of eosinophilic airway inflammation in asthma patients.

Objective. To determine the association between the Asthma Predictive Index and FE_{NO} levels in children younger than 3 years old with recurrent wheezing.

Materials and methods. Observational, cross sectional study. Children younger than 36 months old with 3 or more episodes of bronchial obstruction in the past year who were inhaled corticosteroid-naive or leukotriene receptor antagonist-naive were included. After recording clinical data, FE_{NO} was measured by a chemiluminescence analyzer during tidal breathing (online method).

Results. A total of 52 children aged 5-36 months old were included. Patients with a positive API accounted for 60% of the population and had higher levels of FE_{NO} than those with a negative API, with a median (range) of 13.5 ppb (0.7-31) versus 5.6 ppb (0.1-20.8), respectively ($p < 0.01$). A high FE_{NO} (>8 ppb) was observed in 74% of children with a positive API and in 26% of those with a negative API ($p < 0.01$).

Conclusions. This study found an association between high levels of exhaled nitric oxide and a positive Asthma Predictive Index in children younger than 3 years old with recurrent wheezing.

Key words: *asthma predictive algorithm, exhaled nitric oxide, recurrent wheezing, infants and toddlers.*

http://dx.doi.org/10.5546/aap.2013.191

a. Respiratory Center Dr. Alberto R. Álvarez. Hospital de Niños "Ricardo Gutiérrez", Buenos Aires, Argentina.

E-mail address:
Juan Emilio Balinotti, M.D., juanbalinotti@gmail.com

Funding:
This study was conducted with the support of an annual fellowship grant called the Florencio Fiorini Medical Research Stimulation, year 2009, granted by the Fundación Florencio Fiorini and the Asociación MédicaArgentina.

Conflict of interest:
None.

Received: 10-29-2012
Accepted: 1-18-2013

INTRODUCTION

Cohort studies have demonstrated that approximately half of the infants and toddlers have at least one episode of bronchial obstruction in their first three years of life, and more than 50% of them have one or more recurrent episodes.[1] This is why many infants and toddlers only have transient wheezing in their early childhood, especially during viral infections, while others will have recurrent bronchial obstruction episodes for a longer period caused by different triggering factors. The latter account for the population with a higher risk of having bronchial asthma.[2] Diagnosing asthma at an early age poses a challenge for pediatricians and neumonologists. The Asthma Predictive Index (API) was designed based on the Tucson cohort, and is a questionnaire that has been validated in different populations,[3,4] for the identification of children younger than 3 years old with recurrent wheezing who will develop asthma at school age.[5,6] Though the API's specificity is high (97%), its sensitivity is low (16%). The predictive value of this index enables to ascertain that 77% of patients younger than 3 years old with a positive API will have asthma between 6 and 13 years old, while if the API is negative this probability is only 3%.[7]

Over the past years, the measurement of fractional exhaled nitric oxide (FE_{NO}) has become a potentially useful tool for assessing, managing and diagnosing asthma. It is easy to measure and it enables to non invasively measure the degree of eosinophilic airway inflammation with no need for a bronchoalveolar lavage.[8] Adults and children with asthma and atopy have high levels of FE_{NO} and these values tend to decrease after an anti-inflammatory treatment.[9]

The objective of this article was to establish if there is an association between API and FE_{NO} values in children younger than 3 years old with recurrent wheezing.

MATERIAL AND METHODS

Design

Observational, cross sectional study.

Population

Patients younger than 3 years old with at least three bronchial obstruction episodes in the past 12 months seen at the Respiratory Center of Hospital de Niños "Ricardo Gutiérrez" between March 2009 and April 2010 were included. Children had to be inhaled corticosteroid-naive or leukotriene receptor antagonist-naive and they could not have received systemic corticosteroids in the former month. Patients with a heart condition or identified chronic pulmonary disease (cystic fibrosis, primary ciliary dyskinesia or tuberculosis), and preterm infants (gestational age equal to or lower than 36 weeks) were excluded.

Methods

One of the investigators was in charge of making the API questions to the parents. Data on peripheral blood eosinophilia ≥4% were obtained from the tests previously performed on the patients. A CBC was requested to those who did not have such data. Children with a positive API were those with one major criterion or two minor criteria, as described in *Table 1*. Then a different investigator, blinded to API results, measured FE_{NO} values. For this measurement, an Ecomedics CLD 88 (Dürnten, Swiss) chemiluminescence analyzer was used with the tidal breathing online method. A DENOX 88 module was added to the equipment to ensure that the patient was breathing in NO-free ambient air and the expiratory flow was regulated at 50 ml/s, according to international standards.[10] Before measuring each patient, the ultrasonic pneumotachograph was calibrated using a 100 ml syringe (Hans Rudolph, Inc.). With the child preferably (and spontaneously) asleep or in a calm waking state, FE_{NO} values were recorded for one minute during tidal breathing through a tight facemask that covered the child's mouth and nose. FE_{NO} values were measured once values were stable (trough phase) at 60-80% of expiratory volume. Results were reported as an average of three technically acceptable maneuvers with a difference of up to 10%. The following secondary outcome measures were also recorded: weight, height, gender, smoking during pregnancy, passive smoking, and attendance to a daycare center or kindergarten.

TABLE 1. *Asthma Predictive Index (API)*

Major criteria

1. One of the parents with a medical diagnosis of asthma.
2. Medical diagnosis of eczema.

Minor criteria

1. Medical diagnosis of allergic rhinitis.
2. Wheezing unrelated to colds.
3. Peripheral blood eosinophilia ≥4%.

API (+) = one major criterion or two minor criteria. Sensitivity: 16%, specificity: 97%, positive predictive value: 77%, and negative predictive value: 68%.

Ethical considerations

The study was approved by the hospital Research and Teaching Committee and the Bioethics Committee. The informed consent was requested to and obtained from one or both parents.

Statistical analysis

The sample size was established at 15 API (+) cases and 15 API (-) cases to get a ≥70% sensitivity, with a 95% confidence interval and a power of 80%. Outcome measure values were indicated as mean or median, and standard deviation or range, as applicable. FE_{NO} values were expressed in ppb (parts per billion) and were considered normal if results were between 2 and 8 ppb.[11] Differences in FE_{NO} values in each group were studied using proportion's test. A value of $p < 0.05$ was considered significant.

RESULTS

Of the 53 patients included (age range: 5-36 months old), only one was excluded because FE_{NO} measurements were not acceptable as per international recommendations. The characteristics of the 52 studied children are detailed in *Table 2*. Of them, 31 patients (60%) had a positive API and 21 (40%) had a negative API. No differences were found in the groups in terms of age, gender, attendance to a daycare center or exposure to tobacco.

The median (range) FE_{NO} values in API (+) patients were 13.5 (0.7-31) ppb, while the values for API (-) patients were 5.6 (0.1-20.8) ppb (Figure 1). A high FE_{NO} (>8 ppb) was observed in 74% of children with a positive API and in 26% of those with a negative API ($p < 0.01$).

DISCUSSION

In this study, an association between high levels of exhaled nitric oxide and a positive asthma predictive index was found in children younger than 3 years old with recurrent wheezing, reflecting the presence of an eosinophilic airway inflammation.

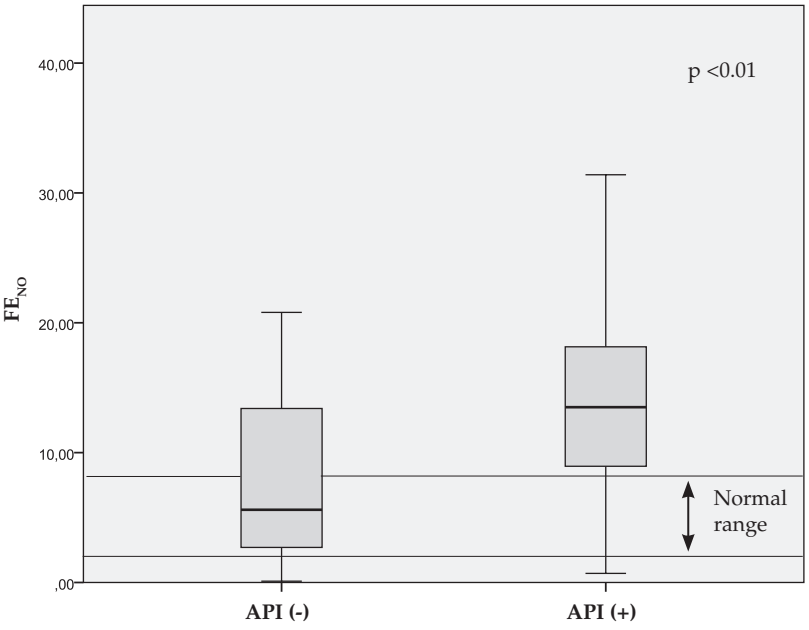
Previous studies conducted in asthma collaborative patients described the association between high FE_{NO} values (single breath method) and an increased number of eosinophils detected in induced sputum, bronchoalveolar lavage, and bronchial biopsy material.[12,13] In non collaborative children, the most commonly used method to measure FE_{NO} is multiple breathing and its reference values have been published by Daniel, et al.[14] Unlike other studies that evaluated the association between the API and FE_{NO} in infants

TABLE 2. *Characteristics of the study population (n= 52)*

Outcome measure	API (+) (n= 31)	API (-) (n= 21)	*p*-value
Age (months), mean ± SD	19.8 ± 11	15.6 ± 8	0.13
Boys	71%	62%	0.66
Weight (kg), mean ± SD	12.2 ± 2	10 ± 3	0.01
Height (cm), mean ± SD	83.5 ± 10	76.8 ± 10	0.02
Only one parent has asthma	51.6%	0%	<0.001
Eczema diagnosed by a physician	29%	0%	0.007
Rhinitis diagnosed by a physician	41.9%	0%	0.001
Wheezing unrelated to colds	96.7%	81%	0.15
Eosinophilia ≥4%	66.6%	11.7%	0.001
FE_{NO} measurement while awake	9/31	7/21	0.56
Attending a daycare center	16%	4.7%	0.38
Prenatal exposure to tobacco	16%	19%	0.78
Postnatal exposure to tobacco	45%	52%	0.60

FE_{NO}: fractional exhaled nitric oxide. API: asthma predictive index.

FIGURA 1. *FE_{NO} values in API (-) and API (+) patients*



FE_{NO} values expressed in ppb (parts per billion). API: asthma predictive index.
API (+) group: median 13.5; interquartile range (8.9-18.1); min. value 0.7; max. value 31.4.
API (-) group: median 5.6; interquartile range (2.7-13.4); min. value 0.1; max. value 20.8.

and toddlers with recurrent wheezing, this study included a larger number of patients who were inhaled corticosteroid-naive or leukotriene receptor antagonist-naive. These drugs reduce airway nitric oxide levels because of the decrease in the expression of the nitric oxide synthase enzyme, which can be induced in the respiratory epithelium of asthma patients.[15,16] In a recently published study, Sardón Prado, et al. obtained similar results with a more limited sample of patients of whom 25% received anti-inflammatory therapy.[17] In addition, even though Moeller, et al. used a different measurement technique whereby exhaled air is collected for a subsequent quantification (off-line method), they reached similar conclusions.[18] Gabriele, et al. compared children younger than 2 years old with bronchopulmonary dysplasia, cystic fibrosis and recurrent wheezing and observed that only atopic children in the latter group had significantly higher FE_{NO} values.[19]

Our study has some limitations. In the first place, the API has a low sensitivity to predict bronchial asthma. It was chosen because it is the most commonly used method to predict asthma and because there is no other tool of greater effectiveness. To overcome this difficulty and to establish the sensitivity, specificity and FE_{NO} validity as an asthma predictor index, these children are clinically followed-up and their nitric oxide levels are measured periodically. In the future, this will allow to establish in what degree the addition of FE_{NO} measurement can modify the API's predictive capacity. Secondly, although the technique chosen to measure nitric oxide in non collaborative children in a clinical environment is the one recommended by international guidelines, it may not be the most sensitive technique. It is probable that FE_{NO} samples obtained using a single compartment facemask (mouth and nose) may contain nitric oxide from the lower and upper airways. We selected it based on its simplicity and practicality, and this can explain results variability and overlapping. FE_{NO} measurement, by separating nasal nitric oxide from lower airway nitric oxide, requires a more complex technique and the sedation of the patient, turning it into a complex and time-consuming method.[20] On the other hand, Franklin, et al. wrote an article describing the ideal method for measuring FE_{NO} in toddlers and infants and found no differences in the measurement of exhaled nitric oxide using the nasal compartment and the levels measured using both the nose and the mouth.[21]

Bronchial obstruction events are very common in the first years of life and many of them tend to improve when children reach school age. API (+) children have a better response to anti-inflammatory treatment than API (-) children, and also have a greater likelihood of developing asthma once they are in the school age.[22]

CONCLUSION

In our study, an association was found between high exhaled nitric oxide levels and a positive asthma predictive index in infants and toddlers with recurrent wheezing. We believe that the measurement of FE_{NO} can help identify subsets of children with similar respiratory symptoms that may have a different course and therapeutic response.■

REFERENCES

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-8.
2. Stein R, Martinez F. Asthma phenotypes in childhood: lessons from an epidemiological approach. *Paediatr Resp Rev* 2004;5:155-61.
3. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.
4. Bacharier LB, Phillips BR, Zeiger RS, Szefler SJ, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122:1127-35.
5. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
6. Castro-Rodríguez JA. Assessing the risk of asthma in infants and pre-school children. *Arch Bronconeumol* 2006;42(9):453-6.
7. Castro-Rodríguez JA. The Asthma Predictive Index. A very useful tool for predicting asthma in young children. *J Allergy Clin Immunol* 2010;126(2):212-6.
8. Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. *Eur Respir J* 1993;6:1368-70.
9. Brussee JE, Smit HA, Kerkhof M, Koopman LP, et al. Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy. *Eur Respir J* 2005;25:455-61.
10. American Thoracic Society 2005 European Respiratory Society 2005 ATS/ERS. Recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med* 2005;171:912-30.
11. Daniel PF, Klug B, Valerius NH. Exhaled nitric oxide in healthy young children during tidal breathing through a facemask. *Pediatr Allergy Immunol* 2007;18:42-6.
12. Djukanovic R, Roche WR, Wilson JW, et al. Mucosal inflammation in asthma. *Am Rev Respir Dis* 1990;142:434-57.
13. Payne DN, Adcock IM, Wilson NM, et al. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. *Am J Respir Crit Care Med* 2001;164:1376-81.

14. Daniel PF, Klug B, Valerius NH. Exhaled nitric oxide in healthy young children during tidal breathing through a facemask. *Pediatr Allergy Immunol* 2007;18:42-6.
15. Moeller A, Franklin, Hall G, Turner S, et al. Inhaled fluticasone dipropionate decreases levels of nitric oxide in recurrenty wheezy infants. *Pediatr Pulmonol* 2004;38:250-5.
16. Ghiro L, Zanconato S, Rampon O, Piovan V, et al. Effect of montelukast added to inhaled corticosteroids on fractional exhaled nitric oxide in asthmatic children. *Eur Respir J* 2002;20:630-4.
17. Sardón Prado O, Pérez Yarsa E, Aldasoro Ruiz A, Korta Murua J, et al. Oxido Nítrico exhalado e índice predictivo de asma en menores de dos años. *Arch Bronconeumol* 2011; 47(5):234-8.
18. Moeller A, Diefenbacher C, Lehmann A, Rochat M, et al. Exhaled nitric oxide distinguishes between subgroups of preschool children with respiratory symptoms. *J Allergy Clin Immunol* 2008;121(3):705-9.
19. Gabriele C, Nieuwhof EM, Van der Wiel EC, Hofhuis W, et al. Exhaled nitric oxide differentiates airway diseases in the first two years of life. *Pediatr Res* 2006;60:461-5.
20. Martinez T, Weist A, Williams T, Clem C, et al. Assesment of exhaled nitric oxide kinetics in healthy infants. *J Appl Physioliol* 2003;94:2384-90.
21. Franklin PJ, Turner S, Mutch R, Stick S. Measuring Exhaled Nitric Oxide in infants during tidal breathing: methodological issues. *Pediatric Pulmonol* 2004;37:24-30.
22. Guilbert TW, Morgan WJ, Zeiger RS, Martinez FD, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354(19):1985-97.