Testing the Asthma Predictive Index as a diagnostic tool in preschoolers: analysis of a longitudinal birth cohort

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Abstract

Diagnosing asthma in preschool children remains an unsolved challenge, at a time when early identification would allow for better education and treatment to prevent morbidity and lung function deterioration. Objective: To evaluate if the Asthma Predictive Index (API) can be used as surrogate for asthma diagnosis in preschoolers. Methods: Birth cohort of 339 pregnant women enrolled at delivery and their offspring, who were followed for atopy, wheezing, and other respiratory illnesses through 30 months of age. The API was determined at 30 months of age by the researchers; and examined its association with physician-diagnosed asthma during the first 30 months, made independently by the primary care physician not involved in the study. Results: Among 307 offspring with complete follow-up, 44 (14.3%) were API+. Maternal body mass index, maternal education, past oral contraceptive use, birthweight, placenta weight, age of daycare at 12m, gastroesophageal reflux disease at 12m, acute otitis media at 18m, bronchiolitis, croup and pneumonia, cord blood adiponectin were all associated with API+. In the multivariable analysis, API+ was associated with almost 6-fold odds of asthma diagnosis (adjusted OR= 5.7, 95% CI [2.6-12.3]), after adjusting for the relevant covariates above including respiratory infections like bronchiolitis and pneumonia. The API sensitivity was 48%, specificity 92%, 61% PPV, 88% NPV, 6.4 LR+, 0.56 LR-, 0.84 diagnosis accuracy. The adjusted odds for asthma was 11.4. Conclusions: This longitudinal birth cohort suggests, for first time, that API could be used as a diagnostic tool, not only as a prognostic tool, in toddlers and preschoolers.

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Running head: API as an asthma diagnostic tool in preschoolers

ABSTRACT

Diagnosing asthma in preschool children remains an unsolved challenge, at a time when early identification would allow for better education and treatment to prevent morbidity and lung function deterioration.**Objective** : To evaluate if the Asthma Predictive Index (API) can be used as surrogate for asthma diagnosis in preschoolers.**Methods** : Birth cohort of 339 pregnant women enrolled at delivery and their offspring, who were followed for atopy, wheezing, and other respiratory illnesses through 30 months of age. The API was determined at 30 months of age by the researchers; and examined its association with physician-diagnosed asthma during the first 30 months, made independently by the primary care physician not involved in the study. **Results** : Among 307 offspring with complete follow-up, 44 (14.3%) were API+. Maternal body mass index, maternal education, past oral contraceptive use, birthweight, placenta weight, age of daycare at 12m, gastroesophageal reflux disease at 12m, acute otitis media at 18m, bronchiolitis, croup and pneumonia, cord blood adiponectin were all associated with API+. In the multivariable analysis, API+ was associated with almost 6-fold odds of asthma diagnosis (adjusted OR= 5.7, 95% CI [2.6-12.3]), after adjusting for the relevant covariates above including respiratory infections like bronchiolitis and pneumonia. The API sensitivity was 48%, specificity 92%, 61% PPV, 88% NPV, 6.4 LR+, 0.56 LR-, 0.84 diagnosis accuracy. The adjusted odds for asthma was 11.4. **Conclusions** : This longitudinal birth cohort suggests, for first time, that API could be used as a diagnostic tool, not only as a prognostic tool, in toddlers and preschoolers.

INTRODUCTION

As many as 70-80% of children with asthma develop their first symptoms before the age of 5[1]. An early diagnosis of asthma is crucial for several reasons: the increase in asthma incidence in recent decades has been principally explained by rising asthma rates in children <3 years old[2]; significant declines in lung function in may occur during the preschool years; and overall asthma morbidity (activity limitation, sleep disturbance, urgent care and emergency department [ED] visits, and hospitalizations) is higher in young children than in older children and adolescents[3].

Several wheezing phenotypes coexist at the preschool age. Therefore, despite the importance of an early diagnosis, identifying which preschoolers with recurrent wheeze have asthma –as opposed to other, transient causes of wheezing– remains a significant challenge. Several factors make the diagnosis of asthma difficult in this age group, including the fact that parents frequently report wheezing as a catch-all term for respiratory sounds or noisy breathing. Direct observation by a physician and assessment of bronchodilator response is very useful, but objective measures of lung function and reversible obstruction are difficult in young children.

There are several models in preschoolers that attempt to predict an asthma at school and adolescent ages[4]. Among these, the asthma predictive index (API)[5] is widely utilized because it is simple, inexpensive, minimally invasive, and it has been validated in several independent populations[4]. The API has a compelling positive likelihood ratio (LR ˜7.4 when applied by 3 years of age, for predicting a diagnosis of asthma by age 6), making it helpful in the identification of children at high risk for asthma; but its negative LR (˜0.75) is

less helpful in ruling out the risk of incident asthma[4]. A recent cross-sectional study in preschoolers reported that the questionnaire-based diagnosis of asthma is associated with a positive API[6]. Our hypothesis is that the API could be used as a surrogate for asthma diagnosis in preschoolers from a longitudinal birth cohort.

METHODS

Population and study procedures

The details of this birth cohort (NCT02903134) have been published elsewhere[7]. Briefly, pregnant women were recruited during their stay in the delivery ward in Santiago, Chile, after consent was obtained. Information collected included parental sociodemographic, home characteristics, and perinatal characteristics of the offspring, as previously described[7]. Cord blood was collected, processed as previously described[7], and stored for analysis. Children were followed by phone every 6 months through age 24 months, and in-person at age 30 months. At each visit information was collected about feeding characteristics, pets, second-hand tobacco smoking, acute respiratory illnesses, siblings, day care attendance, as well as physician diagnosis of asthma and other atopic diseases. Any diagnoses of asthma and their treatment was made independently by the participants' primary care providers (PCPs), who were not part of the current study. The Edinburg scale for maternal depression postdelivery was performed at 6 months. The study was approved by the Ethics Committees of the participating institutions.

Our primary outcome was physician-diagnosed asthma during the first 30 months (made independently by the PCP not involved in the study). The main risk factor evaluated was a positive API (API+) according to the original stringent criteria: children had to be defined as an early frequent wheezer (more than 3 episodes) during the first 3 yr of life and meet at least one of two major criteria (parental MD asthma or MD eczema in the child) or two of three minor criteria (MD allergic rhinitis, wheezing apart from colds, or eosinophilia)[5]. The API was constructed at the end of this study by us, independently, and blinded to the main outcome of physician-diagnosis asthma made by the PCP not involved in the study.

Biomarkers and cytokines

Biomarkers and cytokines measured in cord plasma included insulin, leptin, interleukins, tumor necrosis factor-α, adiponectin, ultra-sensitive C-reactive protein (CRP), insulin, lipids, 25-hydroxyvitamin D (25(OH)D), and Clara or club cell secretory protein [CC16][7]. At age 30 months, WBC and the following cytokines were measured in a peripheral blood sample: CC16, adiponectin, leptin, CRP, thymic stromal lymphopoietin (TSLP), and serum IgE mixed antibodies with ImmunoCAP Phadiatop®; a Phadiatop serum IgE level [?]0.35 kUA/L was reported as positive.

Statistical Analyses

Bivariate analyses were performed using Fisher's exact test or t-tests as appropriate. Multivariable analyses were then performed using logistic regression to evaluate the association between PCP-diagnosed asthma and API status, adjusting for variables that had p-value<0.10 in the bivariate analysis plus *a priori*factors including gender, C-section, and tobacco exposure. Potential confounders (p-value<0.10) included maternal BMI, education, and oral contraceptive use; birthweight; placenta weight; pets at home at 6 months; age at daycare start; gastroesophageal reflux disease (GERD) by 12 months; acute otitis media (AOM) by 18 months; bronchiolitis, croup, or pneumonia prior to PCP asthma diagnosis; and cord blood 25(OH)D, CC16, adiponectin, and IL12p40. These were retained in the final model if their coefficients were significant, or they contributed significantly to the best model fit. Ap -value<0.05 was considered statistically significant. SPSS$^{(r)}$ v17.0 (IBM, Armonk, NY) was used throughout.

RESULTS

The cohort included 339 pregnant women/offspring enrolled during 2014-2016. Complete data were available for 307 (91%) dyads, including 44 preschoolers with API+ and 263 with API– at 30 months (Table 1). There were no significant differences in baseline characteristics between mothers of API+ and API– children (Table

2). Mothers of API+ toddlers had slightly higher body mass index (BMI), prior contraceptive use, and higher education level, but these did not achieve statistical significance.

At the time of birth, API+ and API– children were similar in terms of most sociodemographic and perinatal characteristics (Table 2); API+ children had slightly higher birth weight and heavier placenta than API– children, but again the differences did not reach statistical significance (Table 2).

During the bi-annual follow-up surveys (Table 3), API+ children had a significantly higher prevalence of symptoms associated with asthma than API– children, including cough after crying, laughing or agitation; as well as higher prevalence reported croup, pneumonia, and antibiotics for respiratory infections. API+ children were also younger at the first episode of bronchiolitis compared to API– children. The API+ group had a higher prevalence of reported physician diagnosis of asthma than the API– group; as well as more frequent oral corticosteroid (OCS) courses, inhaled corticosteroid (ICS) use, ED visits for wheezing, and hospitalizations for wheezing (Table 3). There were no consistent differences between groups in terms of GERD, AOM, paracetamol use, pets at home, or second-hand tobacco smoking (Table 3).

API+ children also had significantly higher adiponectin in cord blood and higher IL-10 at 30 months than API– children, but there were no other significant differences in adipokines or cytokines (Suppl Table 1). The proportion of detectable Phadiatop at 30 months was also similar between API groups (Suppl Table 1).

In order to test the diagnostic accuracy for the API with the physician-diagnosed asthma during the first 30 months, the stringent API+ had sensitivity=48.2% [95%CI: 46.5-50.0], specificity=92.4% [92.2-92.7], positive predicted value (PPV)=61.4% [59.2-63.5], negative predictive value (NPV)=87.78% [87.5-88.0], positive LR=6.4 [3.8-10.9], negative LR=0.56 [0.4-0.7], overall accuracy=83.6% [0.79-0.88], and adjusted odds for asthma=11.4 [5.5-23.4].

After adjusting for potential confounders, including history of bronchiolitis and pneumonia, the API+ was independently associated with physician-diagnosed asthma at age 30 months (adjOR= 5.7 [2.6-12.3]), Table 4.

DISCUSSION

In this prospective birth cohort of 307 children followed through 30 months of age, API+ children showed 5.7-fold higher odds of physician-diagnosed asthma (independent of prior respiratory infections and other potential confounders); as well as higher odds of OCS and ICS use, ED visits, and hospitalizations for wheezing than those who were API-.

Recently, a cross-sectional study in the US demonstrated that the application of the API to a retrospective study for ascertaining asthma status is suitable[8]. The same group demonstrated that using natural language processing (NLP) mining of electronic health records for API criteria allowed for the ascertainment of asthma in children[9]; the NLP-API predicted asthma with sensitivity 86%, specificity 98%, PPV 88%, and NPV 98%[9]. Similarly, a cross-sectional study in 916 Korean preschoolers showed that questionnaire-defined asthma was associated with stringent API+ (sensitivity 72.2%, specificity 82%, PPV 14.1%, NPV 98.6%, and 77% accuracy), but not with spirometry, airway hyperreactivity, exhaled nitric oxide, or atopic sensitization[6]. The authors speculated that the API may serve as a more reliable tool than those tests for the diagnosis of asthma in preschoolers; they also compared the API to other predictive models for asthma, and the API had higher LR+ and lower LR-[6]. Consistent with those results, we did not find an association between atopic biomarkers and API+, although the Phadiatop was performed only in a subsample in our study. Unfortunately, we did not perform infant lung function tests.

Given the difficulties with diagnosing asthma in preschool children, the high specificity, NPV, likelihood ratios, and diagnostic accuracy of the stringent API in both our cohort and the Korean study[6]suggest that the API can provide a simple, non-invasive, and easy-to-implement tool for asthma diagnosis in preschoolers with high confidence. This is important, since for example a recent retrospective study in the Netherlands done in 656 children age 6-18 years who received the diagnosis of asthma by an international code for primary care showed that 53.5% had overdiagnosis of asthma.[10]

A timely asthma diagnosis is important and it should be done as early as possible; often the onset of symptoms happens within the first year of life, and 70% have symptoms by age 3.[11] Despite this, asthma tends to be underdiagnosis in very young children, particularly those who wheeze only with upper respiratory infections.[12] Such patients may be diagnosed with other conditions such a "wheezy bronchitis", "asthma bronchitis", "recurrent pneumonia", "recurrent bronchiolitis".[13] Preschool age is a critical time for intervention since long cohort studies have found that lung function trajectory is established at this time,[14] also inflammation and remodeling have already been found at this age.[15]

There are three primary clinical reasons for making a diagnosis of asthma in young children: to identify the most effective treatment in an effort to alleviate symptoms and possibly prevent morbidity and mortality; to educate the parents or primary caregiver to manage the symptoms and avoid triggers; and to estimate and hopefully modify the prognosis over time.[16] Treatment of asthma aims to reduce symptoms and the risk of future complications, both of which are important motivators for patients and families to seek treatment.[16] However, when asthma symptoms are not present, patients and their families may not be sufficiently motivated to continue treatment unless symptoms recur when the treatment stops.

The present study had limitations. Because the asthma diagnosis was made by independent physicians, we cannot completely rule out an incorrect diagnosis. However, the API was also strongly associated with objective measures such as oral steroids, ED visits, and hospitalizations. Due to the age of the cohort, we did not have lung function studies; further follow-up will allow us to perform spirometry and bronchodilator response when participants are older. Lastly, our findings will need to be replicated in other cohorts, and other biomarkers for asthma diagnosis will need to be tested in future studies.

Conclusions: This longitudinal birth cohort study suggests, for first time, that API+ can act as a proxy for the diagnosis of asthma in the first three years of life. Therefore, the API could be used as a diagnostic tool (not only as a prognosis tool), but more studies are needed to replicate these findings.

REFERENCES

1. Haahtela T, Tuomisto LE, Pietinalho A, Klaukka T, Erhola M, Kaila M, et al. A 10 year asthma programme in Finland: Major change for the better. Thorax. 2006;61:663–70.

2. Radhakrishnan DK, Dell SD, Guttmann A, Shariff SZ, Liu K, To T. Trends in the age of diagnosis of childhood asthma. J Allergy Clin Immunol. 2014;134:1057-1062.e5.

3. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: Are they real? Clin Exp Allergy. 2010;40:1130–41.

4. Castro-Rodriguez JA, Cifuentes L, Martinez FD. Predicting asthma using clinical indexes. Front Pediatr. 2019;7:1–9.

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. Lee DH, Kwon JW, Kim HY, Seo JH, Kim H Bin, Lee SY, et al. Asthma predictive index as a useful diagnostic tool in preschool children: A cross-sectional study in Korea. Korean J Pediatr. 2020;63:104–9.

7. Castro-Rodriguez JA, Forno E, Casanello P, Padilla O, Krause BJ, Uauy R. Leptin in Cord Blood Associates with Asthma Risk at Age 3 in the Offspring of Women with Gestational Obesity. Ann Am Thorac Soc. 2020;17:1583-1589.

8. Wi C Il, Park MA, Juhn YJ. Development and initial testing of Asthma Predictive Index for a retrospective study: An exploratory study. J Asthma. 2015;52:183–90.

9. Kaur H, Sohn S, Wi C Il, Ryu E, Park MA, Bachman K, et al. Automated chart review utilizing natural language processing algorithm for asthma predictive index. BMC Pulm Med. 2018;18:1–9.

10. Looijmans-Van Den Akker I, Van Luijn KRS, Verheij TJM. Overdiagnosis of asthma in children in primary care: A retrospective analysis.*Br J Gen Pract* . 2016;66:e152-e157.

11. McNicol KN, Williams HB. Spectrum of asthma in children—i, clinical and physiological components. *Br Med J* . 1973;4:7-11.

12. Van Schayck CP, Van Der Heijden FMMA, Van Den Boom G, Tirimanna PRS, Van Herwaarden CLA. Underdiagnosis of asthma: Is the doctor or the patient to blame? The DIMCA project. *Thorax* . 2000;55:562-565.

13. Clark CE, Coote JM, Silver DAT, Halpin DMG. Asthma after childhood pneumonia: Six year follow up study. *Br Med J* . 2000;320:1514-1516.

24. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* . 2003;349:1414-1422.

15. Castro-Rodriguez JA, Saglani S, Rodriguez-Martinez CE, Oyarzun MA, Fleming L, Bush A. The relationship between inflammation and remodeling in childhood asthma: A systematic review. *Pediatr Pulmonol* . 2018;53:824-835.

16. Amado MC, Portnoy JM. Diagnosing asthma in young children.*Curr Opin Allergy Clin Immunol* . 2006;6:101-105.

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