Allergol Immunopathol (Madr). 2016;xxx(xx):xxx-xxx

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

# Airway tone dysfunction among pre-schoolers with positive asthma predictive index: A case–control study

V. Lezana[a,b], A. Gajardo[b], L. Bofill[b], M. Gutierrez[a], S. Mora[a], J.A. Castro-Rodriguez[c,*]

[a] *Hospital Naval Almirante Nef, Viña del Mar, Chile*
[b] *Department of Pediatrics, School of Medicine, Universidad de Valparaiso, Chile*
[c] *Division of Pediatrics, School of Medicine, Pontificia Universidad Catolica de Chile, Santiago, Chile*

Received 18 April 2016; accepted 27 May 2016

**KEYWORDS**
Asthma;
Wheezing;
Preschool;
Asthma predictive index;
Lung function;
IOS;
Spirometry

**Abstract**
*Objective:* To measure lung function by impulse oscillometry (IOS) and spirometry in recurrent wheezer pre-schoolers according to their asthma predictive index (API) condition.
*Methods:* We performed a case–control study enrolling all pre-schoolers with recurrent wheezing episodes (>3 episodes confirmed by physician) who presented at a paediatric pulmonology clinic. The population was divided according to stringent API criteria into positive or negative.
*Results:* In the nine-month period, 109 pre-schoolers were enrolled. After excluding one patient (due to lung function technique problems) 108 pre-schoolers (56 males, age range from 24 to 72 months) completed the study; 50 belong to positive API and 58 to negative API group. There were no differences in demographics between groups. More use of ICS was found in those with positive API than with negative API (62% vs. 12%, respectively, $p = 0.001$). No differences in basal lung function and post-bronchodilator response to salbutamol (by IOS or spirometry) were found between positive and negative API pre-schoolers. However, those positive API pre-schoolers with ICS had significantly higher central basal airway resistance (RA at 20 Hz) and higher post-BD response (% change in $FEF_{25-75}$ and in $FEV_{0.5}$) than those positive API without ICS.
*Conclusion:* Recurrent wheezer pre-schoolers with positive API and ICS used may have airway dysfunction. More studies are needed to confirm this finding.


## Introduction

Wheezing is a common symptom in the first years of life, but a minority of children will continue to experience wheezing symptoms in school years and beyond.[1] Based on the epidemiological data on the natural history and temporal

* Corresponding author.
*E-mail address:* jacastro17@homail.com
(J.A. Castro-Rodriguez).

http://dx.doi.org/10.1016/j.aller.2016.05.006
0301-0546/

patterns of wheezing, several childhood wheezing phenotypes have been described. However, the use of these ''epidemiological'' phenotypes of wheezing is limited, since they can only be identified retrospectively; indeed, they were defined using statistical inference on longitudinally collected data, and not useful in the present as they are defined by events that will occur in the future.[2] Thus, it has been proposed that wheezing phenotypes be based on the trigger(s) and temporality of symptoms (such as episodic viral wheeze [EVW] and multiple-trigger wheeze [MTW]) which can be ascertained in a clinic and could be more practical for making treatment decisions.[3] However, it was reported that EVW and MTW had considerable overlap[4]; showing conflicting results as these differ in clinical features and have limited value in predicting asthma at school age.[5]

In the past 15 years, the diagnosis of asthma has hinged on the ability to predict the persistence of asthma at six years.[6] Several asthma predictive rules have emerged. The Asthma Predictive Index (API)[7] used clinical parameters (paternal asthma, rhinitis, dermatitis, wheezing without cold and eosinophils in peripheral blood) and originally developed in the Tucson cohort study, is the most widely used. The API is simple and cheap, and its major strength is its good positive likelihood ratio ~7.4 (the post-test probability of disease can improve from 2 to 7 times) and high specificity (~97%).[8]

Children with persistent wheeze, frequent asthma exacerbations, and multiple early atopy have diminished lung function (measured by specific airway resistance [sRaw]) throughout childhood, and are at risk of a progressive loss of lung function from age 3 to 11 years; these effects are more marked in boys.[9] One study from the Tucson cohort suggested that for persistent wheezers the deficit in lung function is not present soon after birth (lung function measure at age four weeks by chest compression technique [RCT]), but is acquired by age six years (measured by spirometry).[1]

However, few studies on lung function and bronchodilator response were performed in children with API characteristics. A study on young Spanish children with a positive API had significant lower lung function (measured by RCT) than those with negative API.[10] A trial in recurrent wheeze preschoolers with positive API or a positive screening test for atopy treated with inhaled corticosteroids (ICS) for 24 weeks modestly reduces wheeze exacerbation rates and improves lung function (measured by spirometry).[11] A previous trial showed that ICS for 24 months improves lung function, but the effect disappears after the treatment is discontinued.[12] However, no group of pre-schoolers with negative API was involved in those trials.

The objective of this case–control study is to compare the lung function (measured by impulse oscillometry [IOS] and spirometry) and post-bronchodilator (post-BD) response to salbutamol among pre-schoolers with positive and negative API.

## Methods

We prospectively enrolled all the recurrent wheezing preschoolers attended at the paediatric pulmonology clinic at Hospital Almirante Nef, Viña del Mar, Chile, during a nine-month period (May 2012 to February 2013). In accordance with international guidelines, their paediatricians treated each child with ICS (fluticasone propionate 125 mcg bid or budesonide 200 mcg bid by metered dose inhaler and spacer with face mask) or montelukast (4 mg/d).[13] The study was approved by the local ethics committee and parents gave written informed consent. Inclusion criteria: aged two to six years of age with recurrent wheezing, defined as having three or more wheezing episodes (confirmed by paediatrician) in the previous year; received ICS or montelukast for at least six months; and correctly performed IOS and spirometry according to ATS/ERS recommendation.[14] Exclusion criteria: cardiac or other chronic respiratory diseases (e.g. cystic fibrosis, bronchopulmonary dysplasia, post-infectious bronchiolitis obliterans, ciliary dyskinesia), airway malformations, endocrinological and neurological diseases, prematurity (<37 weeks), low weight for gestational age, undernourishment, parental or guardian failure to sign the informed consent form.

A predefined questionnaire with demographic data and peripheral blood sample (during asymptomatic period) were performed on the children. According to the presence of stringent API[6] we divided the population into two groups: positive API if they had one major or two minor criteria, or negative API if they did not fulfil those criteria.

Pulmonary lung function was performed only if the child was free of respiratory symptoms in the previous four weeks and following this protocol: first basal IOS, then basal spirometry, and finally post-BD measurements by IOS and spirometry after 15 min of using two puffs (100 mcg/puff) of salbutamol (Fesema®, GSK, Aranda de Duero, Spain) administered with three minutes of separation in between puffs and using a spacer with face mask (AeroChamber Plus® Flow-Vu®, Monaghan Medical Corp., USA). ICS treatment was not discontinued at the moment of lung function measurement. Weight and height were measured before lung function.

The IOS was done by one paediatric lung function technician (SMO). For all subjects, three replicate measurements of impedance respiratory (Zrs) were obtained using the system software (MasterScreen-IOS, Jaeger® Co, Germany). Impedance measurements were retained for analysis if reproducible, that is, if the coefficient of variation between replicates measurements was <10%. Briefly, the sitting child was asked to breathe for 15–20 s using a rigid oval mouthpiece with a tongue guard, with the head in a neutral position, nose clip in place, and while supporting both cheeks. For the respiratory system, resistance represents the effective resistance of lungs and chest wall, whereas reactance is the net effect of the two opposite (one compliant and one inertial) components. Each recording on the MasterScreen IOS assessment yielded both the expiratory resistance (R5 and R20) and reactance (X5) [kPa/l/s] at different oscillatory frequencies between 5 Hz and 35 Hz within the flow range of normal tidal breathing. R5 measure the total resistance (central and peripheral), R20 the central resistance and X5 the peripheral reactance. In addition, the resonant frequency (Fres) [i.e. the frequency at which the reactance was zero] was also computed.

The spirometry (Jaeger Master-Screen®) was also performed by SMO. None of the participants had performed a spirometry before; each child did all possible expiratory force curves over a 15-minute period, with a nasal clip (unless it was not tolerated) and standing. Sometimes,

Please cite this article in press as: Lezana V, et al. Airway tone dysfunction among pre-schoolers with positive asthma predictive index: A case–control study. Allergol Immunopathol (Madr). 2016. http://dx.doi.org/10.1016/j.aller.2016.05.006