REVIEW ARTICLE

Assessing the Risk of Asthma in Infants and Pre-School Children

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Childhood asthma is a heterogeneous inflammatory disease with several wheezing phenotypes (transient, atopic, nonatopic, and obese) and various clinical expressions of multifactorial origin. All forms, however, follow a similar course characterized by recurrent episodes of airway obstruction. Studies have shown that the onset of disease occurs early in life for the great majority of asthmatics, that airway inflammation and remodeling are present in schoolchildren with asthma, and that even infants with persistent wheezing present airway inflammation. The difficulty lies in the early identification of infants with recurrent wheezing who are at risk of suffering persistent asthma later in life. The Asthma Predictive Index, a simple tool validated in a longitudinal study, has been suggested for early identification of infants with recurrent wheezing who are at risk of developing asthma and whose lung function has undergone major irreversible damage during the first years of life.

Key words: *Wheezing. Phenotypes. Asthma. Asthma predictive index. Children.,*

¿Cómo evaluar el riesgo de asma bronquial en lactantes y preescolares?

El asma infantil es una enfermedad inflamatoria heterogénea con diferentes fenotipos (con sibilancias transitorias, no atópicos, atópicos y obesos) y diferente expresión clínica y multifactorial, pero que siguen una vía común, caracterizada por cuadros recurrentes de obstrucción de la vía aérea. Se ha demostrado que la inmensa mayoría de asmáticos comienza su enfermedad en los primeros años de vida, que la inflamación y la remodelación de la vía aérea están ya presentes en escolares asmáticos e incluso que hay inflamación en lactantes con sibilancias persistentes. El problema consiste en identificar tempranamente qué lactante con sibilancias recurrentes tiene riesgo de presentar posteriormente asma persistente. Se postula el uso del Algoritmo Predictor de Asma (Asthma Predictive Index), que es una herramienta simple, validada en estudios longitudinales y que nos permite identificar tempranamente ese fenotipo de lactantes sibilantes (cuya función pulmonar presenta su principal deterioro irreversible en los primeros años de vida) con riesgo de desarrollar asma.

Palabras clave: *Sibilancias. Fenotipos. Asma. Algoritmo predictor de asma. Niños.*

Most longitudinal epidemiological studies show that childhood asthma is a heterogeneous inflammatory disease with several phenotypes and clinical signs dependent on age, sex, genetic background, and environmental exposure. All forms, however, follow a similar course characterized by recurrent episodes of airway obstruction.[1] Treatment must be started as early as possible in order to improve prognosis. Inflammation of the airways is known to be present in school children with bronchial asthma[2] and even in infants with persistent wheezing.[3] Airway remodeling has also been reported in asthmatic children,[4] however, and, more seriously still, there is evidence that the thickness of the reticular basement membrane in children with uncontrolled asthma is the same as in adults with severe asthma and is unrelated to the duration of the disease.[5] It has been suggested that early intervention and treatment could prevent this irreversible airway damage.[6-8] For this reason, early detection of infants with wheezing which could develop into bronchial asthma in the future is very important.

A recent cohort study carried out in the region south of Santiago de Chile[9] showed that 43% of children aged under 1 year had recurrent wheezing (3 or more episodes). However, there are several phenotypes of 5- to 6-year-old children with recurrent wheezing or asthma. Nearly 10 years ago, 3 distinct phenotypes of asthma were clearly defined in young children.[10] Recently, a fourth, late-onset asthma has been described, related to girls and obesity during puberty, but it is not discussed in this article.

The first phenotype includes children with transient wheezing who made up about 20% of a cohort in Tucson, Arizona, in the United States of America[10] and 29% of a cohort from the region north of Santiago de Chile.[13] The obstructive events and wheezing in these children are nearly always resolved by the age of 3 and they do not have a family background of asthma or allergic sensitization (negative skin test and total serum

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IgE within the normal range). The main risk factor for this phenotype is to be born with reduced pulmonary function.[10] Pulmonary function continues to be impaired in these children at the age of 6, and despite improving slightly at the age of 11, it continues to be lower than that of healthy controls at 18.[14] Another characteristic of this phenotype is that methacholine does not cause bronchial hyperresponsiveness and bronchial variability is not observed on the flowmeter (peak expiratory flow) when measured at 11 years of age.[15,16] These results suggest that a characteristic of this phenotype is altered pulmonary mechanics involving, for example, reduced airway resistance or increased dynamic compliance but not increased airway lability, as noted in a review of the subject.[17] In a recent longitudinal study, airway resistance was measured using the MicroRint® system (Micro Medical, Rochester, Kent, UK), confirming that children with transient wheezing have less resistance than those with persistent wheezing.[18] Other risk factors associated with transient wheezing are prematurity,[19] exposure to siblings and other children in nurseries and kindergartens,[20] maternal smoking during pregnancy, and exposure to tobacco smoke during the first years of life.[21]

The second phenotype includes children with wheezing or nonatopic asthma. Of all the children who continue to wheeze after the age of 3 years, 40% belong to this second phenotype. Unlike children with transient wheezing, these children are born with lung function that is similar to that of the control group and that remains statistically normal up to the age of 18 years,[14] but they show bronchial hyperresponsiveness to methacholine. These children generally have episodes of bronchial obstruction secondary to viral infections–particularly respiratory syncytial virus (RSV)–during the first years of life. Stein et al[22] showed that children who had had RSV in the first 3 years of life had significantly more risk of wheezing than controls up to the age of 11 years (regardless of atopy) but that after this age the risk was the same. Children with a background of RSV infection had diminished pulmonary function and greater response to bronchodilators than controls at 11 years of age, suggesting that children of this nonatopic phenotype present bronchial obstruction as a result of impaired control of airway tone. It is important to note that nonatopic asthma has a clinical picture that is less severe, less persistent, and less prevalent than the third phenotype–atopic asthma–particularly in developed countries. There is evidence, however, that in developing countries nonatopic asthma is more prevalent than atopic asthma. A study in Lima, Peru, for example, showed that asthma in school children was not associated with allergic sensitization or with other atopic markers,[23] and more and more studies are showing that at least 40% of asthma in school children is not atopic even in developed countries.[24,25]

The third phenotype includes children with wheezing or classic atopic asthma. We know that in nearly 80% of persons with persistent asthma, the disease starts early, usually before the age of 6.[26] According to several epidemiological studies,[10,27-30] the main factors associated with this phenotype are atopy and bronchial hyperresponsiveness. Patients with atopic asthma are born with normal pulmonary function, statistically the same as that of healthy controls, but function deteriorates significantly and quickly within the first 6 years of life, continues to do so during the first 18 years,[14] and is not recovered during adulthood.[28,29] It must be emphasized, however, that the main loss of lung function occurs in the first 5 years of life,[14] clearly indicating that changes in the physiology of the airway could occur at a very early age.[10] Early sensitization increases the risk of more obstructive disease and airway inflammation and involves greater risk of pulmonary function decline in this phenotype of atopic asthma. Lowe et al[31] showed that children with atopy had reduced pulmonary function at 3 years of age. Several studies have observed that recurrent wheezing patterns during childhood are closely associated with high titers of IgE and sensitization to local aeroallergens.[32-34] Early sensitization before 8 years of age–but not late sensitization–has been associated with increased risk of bronchial hyperresponsiveness and asthma.[35,36] In a study of the Tucson cohort, Sherill et al[37] also showed that high concentrations of IgE at 9 months of age was directly related to greater risk of persistent wheezing, indicating that there is already a type of sensitization mediated by IgE in early childhood. These findings suggest genetic predisposition for sensitization to certain aeroallergens, and that this predisposition is also associated with symptoms of asthma that appear in early childhood. It must be emphasized that atopy is a serious risk factor for persistence and severity of asthma symptoms[38,39] and also for relapses during adolescence.[27,40]

In summary, within this large group of children with recurrent wheezing, early identification is essential. This means that children who will develop atopic asthma, or whose clinical picture suggests they will, should be identified before the age of 5 or 6 years. Therapeutic intervention can then be used to try to prevent pulmonary function deterioration and to lower the risk of disease development or relapse during childhood and adolescence.

Curiously, a Swiss study revealed that it was precisely asthmatic children under 6 years of age who received the poorest treatment of their disease in comparison with asthmatic children aged 13 to 16 years: control of the disease was achieved in only 38% of patients under 6 years old compared with 66% in the older group.[41] Early identification is important in this group of infants and preschool children with recurrent wheezing at risk for asthma considering that in nearly 80% of asthmatic patients the disease commences in the first 6 years of life[26] and that asthma is a progressive disease in which symptoms tend to remain on track as children grow: children with severe asthma will continue to present the same severity when adults, most children with mild asthma will continue to have mild asthma when adults, and reduced pulmonary function presenting in childhood will also continue into adulthood.[14,27-29]

Unfortunately, no specific biological markers have been found to date that are reliable and easily measured at all levels of health care to distinguish infants with

How Do We Predict Whether an Infant With Recurrent Wheezing or Bronchial Obstruction Events Will Have Asthma in the Future?

If a Child Under the Age of 3 Presents:
Frequent Wheezing (>3 Events/Year)
+
1 Major Finding or 2 Minor Findings

⇓

If the API is Positive There Is 77% Certainty That the Patient Will Present Atopic Asthma at School Age

If, However, There Are No Findings and the API Is Negative, There Is a 68% Chance That Wheezing Episodes Will Cease Over Time and the Child Will Not Have Atopic Asthma in the Future

Children With a Positive API Have 7 Times More Risk of Asthma at School Age Than Children With a Negative API

Major Findings:
– Medical Diagnosis of Eczema in the First 3 Years of Life
– At Least 1 Parent With a Background of Asthma

Minor Findings:
– Medical Diagnosis of Allergic Rhinitis in the First 3 Years of Life
– Wheezing Not Associated With Colds in the First 3 Years of Life
– Peripheral Blood Eosinophilia of at Least 4% in the First 3 Years of Life

Figure 1. Algorithm for the Asthma Predictive Index (API)[43] (Scientific Prize for Respiratory Research of the International Union Against Tuberculosis and Lung Disease, Montreal, October 2002).

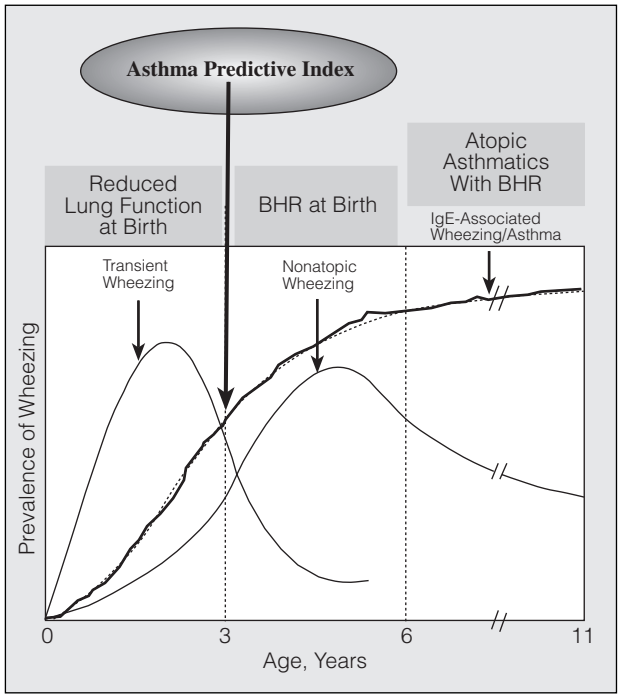

Figure 2. Wheezing phenotypes or asthma in young children. BHR indicates bronchial hyperresponsiveness; IgE, immunoglobulin E (modified from Stein et al[15]).

persistent wheezing (atopic asthma) from those with other wheezing phenotypes.[42] As mentioned above, atopic asthmatic children are born with normal pulmonary function, present irreversible deterioration in the first 5 years of life, and have more persistent severe symptoms as well as a higher relapse rate.[14,37-40]

Infants with recurrent wheezing patterns or obstructive bronchitis and who will develop atopic asthma can be identified using an index which includes clinical criteria and simple laboratory tests: the Asthma Predictive Index (API).[43] Castro-Rodríguez et al[43] studied the Tucson cohort and selected infants with more than 3 episodes of wheezing or obstructive bronchitis a year during the first 3 years of life and who had also had 1 major finding or 2 minor findings, and called them API positives. The major findings were medical diagnosis of eczema in the first 3 years of life and having a parent diagnosed with asthma. The minor findings were a medical diagnosis of allergic rhinitis in the first 3 years of life, wheezing episodes unrelated to colds in the first 3 years of life, and eosinophilia in peripheral blood of 4% or more (Figure 1). The sensitivity, specificity, positive predicted value, and negative predicted value for predicting which infants with recurrent wheezing would develop asthma by school age (6-13 years) were 16%, 97%, 77%, and 68% respectively. In other words, if an infant with recurrent wheezing is attended at a health care center and the API is applied and is positive, we can be 77% sure that the infant will have asthma at school age; however, if the API is negative we can be 68% sure that the infants will cease to have wheezing events at school age. Infants with positive API had 7 times greater risk of asthma at school age than those with a negative API (odds ratio, 7.1; 95% confidence interval, 3.5-14.1).

In conclusion, with the simple API method, applicable at all levels of health care, we can identify infants with recurrent wheezing with the highest risk for pulmonary function deterioration and for higher rates of persistence, progression, and relapses of asthma, in other words, atopic asthma patients (Figure 2). Future trials of medical interventions to control the disease, such as inhaled corticosteroids at correct doses and during appropriate periods, should include this group of wheezing infants at risk (API positive) to see whether early application of drug treatment can modify the natural course of asthma.

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