Development of Wheezing Disorders and Asthma in Preschool Children

Fernando D. Martinez, MD

ABSTRACT. Recent longitudinal studies have shed light on the pathogenesis and progression of asthma. The patterns of expression of childhood asthma that persist into adult life have been explored. Distinct asthma phenotypes (transient wheezing, nonatopic wheezing, and atopy-associated asthma) have been identified. Defining which children are at risk for persistent asthma could allow for better management and, potentially, for reduced morbidity and mortality. Pediatrics 2002;109:362–367; asthma expression, phenotypes, wheezing, atopy.

ABBREVIATIONS. IgE, immunoglobulin E; FEV₁, forced expiratory volume in 1 second; RSV, respiratory syncytial virus; IFN-γ, interferon-γ; IL, interleukin.

Much about the natural history of asthma remains unknown; longitudinal studies, however, have shed some light on the pathogenesis and progression of the disease. Asthma is a heterogeneous condition with variable signs and symptoms in patient groups, as well as variability within each individual patient over time. Certain patterns of asthma expression observed during childhood persist into adulthood. Although mild asthma during childhood may resolve, it seems that asthma is a progressive condition in many children, especially those who have severe disease. Early allergic sensitization is an important risk factor for persistent asthma, and the role of allergen exposure during the early years of life in the course of the disease, as well as the role of other factors, has emerged as an important focus. Longitudinal studies of wheezing disorders from childhood to adulthood are necessary for understanding the true progression and the risk factors of what is understood to be asthma.

PATTERNS OF ASTHMA EXPRESSION DURING CHILDHOOD INTO ADULTHOOD

In some young children with mild asthma, wheezing resolves spontaneously; in others, especially those with severe asthma, wheezing continues into adulthood. Defining which children are at risk for persistent asthma could allow for better management and, potentially, for reduced morbidity and mortality. In 1964, a longitudinal study was initiated in Melbourne, Australia, to follow childhood asthma into adulthood. Starting from a cohort of 30,000 children, 401 were enrolled at age 7, based on their parents’ responses to a questionnaire concerning their child’s history of asthma, wheezing episodes, and bronchitis. The children were classified into 4 categories: those who never wheezed (controls, n = 106); those with fewer than 5 episodes associated with apparent respiratory infection (mild wheezy bronchitis, n = 75); those with 5 or more episodes associated with apparent respiratory infection (wheezy bronchitis, n = 107); and those with wheezing not associated with respiratory infection (asthma, n = 113). A fifth group of children with severe asthma (n = 79) was selected from the same cohort at age 10.

Evaluations—including physical examinations, patient questionnaires on symptoms and therapy, laboratory measurements such as eosinophil and immunoglobulin E (IgE) levels, pulmonary function (with spirometry, lung volumes, and histamine challenge), and skin reactivity testing—have been conducted every 7 years. At the evaluation conducted when patients were 35 years old, the participants were categorized as follows: no recent asthma (not having wheezed for 3 or more years previous to the evaluation); infrequent wheeze (having wheezed in the previous 3 years but not in the 3 months before evaluation); frequent asthma (having wheezed less than once per week in the 3 previous months); or persistent asthma (having wheezed at least once weekly in the previous 3 months).

Symptom assessment at age 35 was compared with the categorization established when participants were 7 to 10 years of age (Table 1). Results showed that of the 65 patients who had mild wheezy bronchitis at 7 years of age, 77% (n = 50) had no symptoms at age 35, whereas only 23% (n = 15) had frequent or persistent asthma. Of the 98 participants with asthma at 7 years of age, 50% (n = 49) had no recent asthma or infrequent asthma as adults, whereas 50% (n = 49) had frequent or persistent asthma. Importantly, 75% (n = 50) of those who had severe asthma (n = 67) at age 10 had frequent or persistent asthma at age 35. According to these results, many children do not remit from their asthma, and the more severe their asthma, the less likely they are to remit. These data support the tracking concept of the disease: children with mild disease had remission or continued with mild disease in their adulthood, whereas children with severe asthma suffered persistent severe asthma when they reached adulthood.

Assessment of the participants every 7 years over...
These abnormalities tracked with age. Adapted from Oswald et al.2 Although in the participants with asthma, the abnormalities were relatively minor (Fig 1). Participants who were classified at age 7 as having mild wheezy bronchitis and wheezy bronchitis had no evidence of airflow obstruction at age 35.2 The patterns of wheezing and asthma expressed early in life generally persisted into adulthood. Conversely, persistent airflow obstruction in adulthood was associated with more troublesome asthma during childhood.2,7

These patterns presented in Fig 1 suggest that no significant additional loss of pulmonary function occurs after the age of 7 to 10 years and up to the age of 35, even in individuals with severe disease. This would imply that children are either born with the deficit of pulmonary function or that there is a loss of pulmonary function after birth, after which no additional loss occurs. The studies from the Tucson Children’s Respiratory Study would argue that the latter is the case.

Children were categorized at age 6 based on the history of their wheezing from before age 3. The categories included the following: nonwheebers (children who had never wheezed); transient wheezers (at least 1 lower respiratory tract illness with wheezing in infants is not associated with a family history of asthma or allergic sensitization.9 The primary risk factor for this phenotype seems to be reduced pulmonary function.1,9 The lower level of pulmonary function seems to track along individual growth curves, and it remains low at age 6.10 Of interest, however, is that children younger than 3 years of age with transient early wheezing had no increased prevalence of methacholine hyperresponsiveness or positive peak flow variability at age 11.1 These results suggest that mechanical pulmonary characteristics, such as reduced airway resistance or increased dynamic compliance,11 play a role in transient wheezing, rather than increased airway lability.1

Other risk factors for transient wheezing include prematurity12 and exposure to siblings and other

### TABLE 1. Distribution of Asthma in 401 Subjects Aged 35 According to Whether They Had Bronchitis or Asthma as Children

<table>
<thead>
<tr>
<th>Asthma at Age 35 N (%)</th>
<th>Infrequent</th>
<th>Frequent</th>
<th>Persistent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild wheezy bronchitis</td>
<td>42 (65)</td>
<td>8 (12)</td>
<td>10 (15)</td>
<td>65</td>
</tr>
<tr>
<td>Wheezy bronchitis</td>
<td>54 (63)</td>
<td>10 (12)</td>
<td>9 (10)</td>
<td>86</td>
</tr>
<tr>
<td>Asthma</td>
<td>29 (30)</td>
<td>20 (20)</td>
<td>18 (18)</td>
<td>67</td>
</tr>
<tr>
<td>Severe asthma†</td>
<td>7 (10)</td>
<td>10 (15)</td>
<td>8 (12)</td>
<td>67</td>
</tr>
<tr>
<td>Total</td>
<td>132</td>
<td>48</td>
<td>45</td>
<td>401</td>
</tr>
</tbody>
</table>

* Values are numbers (percentages) of participants. Eighty-five controls are excluded.
† Patients entered study at age 10.
Adapted from Oswald et al.3

Fig 1. FEV1 as percentage of predicted values in different groups of subjects enrolled in the Melbourne Longitudinal Study of asthma. Subjects were classified according to their diagnosis at time of enrollment: • = control; ■ = mild wheezy bronchitis; △ = wheezy bronchitis; ○ = asthma; □ = severe asthma. Assessment of the participants every 7 years showed that those with asthma and severe asthma at age 7/10 showed diminished lung function as adults, those with asthma having relatively mild abnormalities. These abnormalities tracked with age. Adapted from Oswald et al.2 Used with permission.

#### ASTHMA PHENOTYPES

Most epidemiologic studies have suggested that there are several different asthma phenotypes, reflecting a heterogeneous group of conditions that follow a common final pathway characterized by recurrent airway obstruction. Three of these phenotypes are transient early wheezing (wheezing up to age 3 but not after), nonatopic wheezing of the toddler and early school years, and IgE-mediated wheezing/asthma (Fig 2).1

**Transient Early Wheezing**

In most children, transient early wheezing characteristically resolves by age 3. Generally, transient wheezing in infants is not associated with a family history of asthma or allergic sensitization.9 The primary risk factor for this phenotype seems to be reduced pulmonary function.1,9 The lower level of pulmonary function seems to track along individual growth curves, and it remains low at age 6.10 Of interest, however, is that children younger than 3 years of age with transient early wheezing had no increased prevalence of methacholine hyperresponsiveness or positive peak flow variability at age 11.1 These results suggest that mechanical pulmonary characteristics, such as reduced airway resistance or increased dynamic compliance,11 play a role in transient wheezing, rather than increased airway lability.1

Other risk factors for transient wheezing include prematurity12 and exposure to siblings and other
persistent wheezing. First 3 years of life, was a risk factor for subsequent respiratory tract illness, by itself, and occurring during the Study, was to determine whether RSV lower respiratory tract infection and the relationship between RSV respiratory tract infection and wheezing. The objective of a recently reported longitudinal study, the Tucson Children's Respiratory Study provide important implications. First, although RSV infection is a risk for subsequent wheeze during childhood, RSV-associated wheezing resolves in most children by 13 years of age. Second, the relationship between persistent wheezing up to 13 years of age after RSV infection does not seem to be associated with an increased risk for allergic sensitization.

Nonatopic Wheezing

Most school-aged asthmatic children have a history of airway obstruction during the first 2 to 3 years of life. The most common cause of airway obstruction in infancy is viral infection, most frequently caused by the respiratory syncytial virus (RSV). Several studies have explored the relationship between RSV respiratory tract infection and wheezing. The objective of a recently reported longitudinal study, the Tucson Children's Respiratory Study, was to determine whether RSV lower respiratory tract illness, by itself, and occurring during the first 3 years of life, was a risk factor for subsequent persistent wheezing.

A total of 472 children with lower respiratory tract illness underwent testing for the infecting organism. Of these, RSV was documented in 207 (43.9%) children, parainfluenza in 68 (14.4%), other agents (adenovirus, influenza, Chlamydia, cytomegalovirus, rhinovirus, bacteria, mixed infection) in 68 (14.4%), and no infecting pathogen in 129 (27.3%). Analyses demonstrated that RSV infection significantly increased the risk for wheezing during the first 10 years of life; the risk decreased with age, however, and was no longer significant by 13 years of age (Fig 3). Furthermore, RSV infection during the first 3 years of life was not associated with increased risk for skin test positivity or higher IgE levels later in life compared with other causes of lower respiratory tract infection (Table 3). No relationship of RSV lower respiratory tract infection to allergic sensitization, irrespective of family history of asthma, was identified.

The effect of RSV lower respiratory tract infection on pulmonary function was also assessed. Children who had RSV infection before 3 years of age had significantly lower FEV₁, adjusted for length and gender than children who had not had lower respiratory tract illness. This difference remained independent of current wheezing at 11 years of age ($P = .001$). The children with a history of RSV infection were also more likely to respond to bronchodilatation than their counterparts with no such history ($P < .05$; Table 4). These findings may indicate that the children with lower levels of pulmonary function were either born with reduced function, or had an interaction between the immune system and RSV infection that altered lung growth, or both.

Although additional research is needed to define alterations in airway function secondary to RSV respiratory tract infection, findings from the Tucson Children's Respiratory Study provide important implications. First, although RSV infection is a risk for subsequent wheeze during childhood, RSV-associated wheezing resolves in most children by 13 years of age. Second, the relationship between persistent wheezing up to 13 years of age after RSV infection does not seem to be associated with an increased risk for allergic sensitization.

**Atopic Wheezing/Asthma**

More than half of all cases of persistent asthma start before age 3, and 80% begin before age 6. Among school-aged children with persistent asthma, the onset of symptoms before age 3 is associated with increased severity of the disease and increased bronchial hyperresponsiveness. Patients with early-onset asthma also have significant deficits in pulmonary function growth. Thus, the decisive airway changes seem to begin early in life.

Frequently, asthma that begins early in life is associated with atopy, the genetic predisposition for sensitization to allergens (Fig 4). Early allergic sensitization seems to play an important role in persistent asthma.

The correlation between allergic sensitization and respiratory symptoms of asthma was studied in 380 Australian (Belmont, New South Wales) school children enrolled between 8 to 10 years of age. The
participants underwent skin prick testing to 13 allergens at enrollment and 2 and 4 years later. Three groups of children emerged: those who were sensitized at the time they entered the study, those who became sensitized during the study, and those who never became sensitized during the study. The prevalence of persistent respiratory symptoms (wheeze, exercise wheeze, or night cough) was the same in children who became sensitized during the study and children who did not become sensitized (11% to 12%). The children who were sensitized at the beginning of the study, however, had a prevalence of respiratory symptoms that was significantly greater (approximately 40%) than the other groups, and they were at significantly greater risk for the development of asthma than the other groups.21

These findings underscore the importance of early allergic sensitization in the development of persistent asthma. Interestingly, specific factors have been identified that decrease the risk for persistent disease (Table 5). In these cases, increased exposure to other children, pets, or farm animals in early life may protect against the development of asthma in children.

In 412 Swedish children, exposure to pets during the first year of life resulted in a lower incidence of allergic rhinitis at 7 to 9 years of age and a decreased frequency of asthma at 12 to 13 years of age. An increased number of siblings also showed an inverse relationship to subsequent development of allergic rhinitis and asthma. Similarly, in a controlled study of secondary school children in rural areas surrounding Quebec City, Canada, children who had been raised on a farm exhibited significantly less wheeze, airway hyperresponsiveness, and allergic skin test positivity during adolescence than did children without exposure to a farming environment.23 The odds ratio among children raised on a farm for having current wheeze was 0.70; for having asthma, 0.59; and for atopy, 0.58. The number of siblings among both groups did not affect the results. These findings have been confirmed in other studies; some investigators, however, question whether heightened early exposure offers protection against airway inflammation or whether increased urban pollutants cause symptoms in children not raised on a farm.24

The possible protective effects of increased early exposure to other children were supported by a study involving 1035 children followed since birth as part of the Tucson Children’s Respiratory Study.13 The risk for asthma (children given a diagnosis of asthma by a physician and who had an exacerbation of their asthma during the previous year) was compared between children with and without older siblings and between children who attended and did not attend day care before 6 months of age.

In children with older siblings in the home and children who attended day care during the first 6 months of life, 12% developed asthma. In children without older siblings in the home and in children

| TABLE 3. Skin Test Positivity and Serum IgE Concentrations at Different Ages in Children With Lower Respiratory Tract Illness Before 3 Years of Age |
|---|---|---|---|---|---|
| Causative Agent | Positive Skin Test (%) | Serum IgE Concentration (IU/μL) |
| | Age 6 Years | Age 11 Years | Age 9 Months | Age 6 Years | Age 11 Years |
| RSV | 37.4 | 59.3 | 4.31 | 33.1 | 58.6 |
| Parainfluenza | 40.7 | 52.9 | 3.25 | 26.0 | 78.5 |
| Other agents | 39.2 | 56.5 | 4.29 | 30.3 | 69.4 |
| Negative tests | 39.8 | 55.8 | 4.24 | 35.1 | 51.7 |
| None | 39.7 | 58.9 | 4.25 | 39.5 | 64.8 |

Adapted from Stein et al.19

**Fig 3.** Adjusted odds ratios (95% confidence intervals) for infrequent and frequent wheeze associated with RSV lower respiratory tract infections before 3 years of age. RSV infection significantly increased the risk for wheezing during the first 10 years of life. The risk decreased with age and was no longer significant at 13 years of age. Results were adjusted for confounding variables including family history of asthma, positive skin test at 6 or 11 years of age, gender, maternal education, birth weight, and current maternal smoking. Adapted from Stein et al.19 Used with permission.
TABLE 4. Mean Baseline FEV1 at 11 Years of Age (95% Confidence Interval)

<table>
<thead>
<tr>
<th>Causative Agent</th>
<th>Baseline</th>
<th>FEV1 After Bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV (n = 110)</td>
<td>2.11 (2.05–2.15)†</td>
<td>2.26 (1.70–2.90)</td>
</tr>
<tr>
<td>Parainfluenza (n = 38)</td>
<td>2.16 (2.07–2.25)</td>
<td>2.29 (1.63–2.67)</td>
</tr>
<tr>
<td>Other agents (n = 32)</td>
<td>2.19 (2.09–2.24)</td>
<td>2.27 (1.69–2.60)</td>
</tr>
<tr>
<td>Negative test (n = 72)</td>
<td>2.14 (2.08–2.20)‡</td>
<td>2.25 (1.83–2.76)</td>
</tr>
<tr>
<td>None (n = 189)</td>
<td>2.22 (2.18–2.25)</td>
<td>2.31 (1.70–2.99)</td>
</tr>
</tbody>
</table>

* P < .001 compared with subgroup having no illness.
† P < .05 compared with subgroup having no illness.
Adapted from Stein et al.19

TABLE 5. Factors Associated With the Onset of Persistent Asthma

<table>
<thead>
<tr>
<th>Increased Risk</th>
<th>Decreased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early allergic sensitization</td>
<td>Exposure to other children early in life</td>
</tr>
<tr>
<td>Sensitization to certain aeroallergens (perennial?)</td>
<td>Exposure to pets</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Exposure to farm animals</td>
</tr>
</tbody>
</table>

was suggested that early exposure to house-dust endotoxin may protect against allergic sensitization via augmentation of T11-type immunity.

ASTHMA AS A PROGRESSIVE DISEASE

As reviewed above, many longitudinal studies of asthma have given us important insights into its natural history.1–8,12–15,21–25 There seem to be different forms of asthma, and one of these is a progressive disease that begins mainly during the first years of life. If interventions take place after the age of 6 to 7 years, it seems to be too late to alter the natural course of this form of the disease, and from then on, only symptoms can be controlled. Identifying those children who are or will be affected by this form of asthma before 6 years of age may allow us to treat them by the critical time. The children with this form of the disease seem to be a minority of the children who have asthma, and although they show symptoms early in life and are sensitized early in life, there is no clear way to identify them at present.

The Childhood Asthma Management Program examined the relationships between disease severity and duration in 1041 children aged 5 to 12 years with mild-to-moderate chronic asthma, atopy, and well-preserved pulmonary function.4 Pulmonary function, as determined by PC20FEV1, pre- and postbronchodilator percent predicted FEV1 and pre- and postbronchodilator FEV1/forced vital capacity, declined significantly (P < .001) with each year’s duration of asthma; the strongest association was demonstrated in comparing function before bronchodilator use with that after bronchodilator use.4 Children with a longer duration of asthma also had higher levels of symptoms (P < .001) and greater use of albuterol (P = .064) during a prospective 28-day screening period. These findings are consistent with other ongoing studies showing that persistent asthma is associated with chronic airway inflammation, reduced pulmonary function, and increased asthma symptomatology.

The recently published results of The Childhood Asthma Management Program have shown that inhaled corticosteroids were effective in significantly reducing the subjective measures of asthma, such as symptoms, in children during the 4 years of study, but the course of asthma, as reflected in postbronchodilator FEV1, the primary outcome of the study, was not altered.26 Therefore, if the adverse effects of persistent asthma are to be prevented, diagnosis and intervention would seem to be necessary before the age of 5 to 6 years.

who did not attend day care during the first 6 months of life, however, 21% developed asthma. Similarly, children with older siblings and children who attended day care during the first 6 months of life were less likely to develop frequent wheezing (>3 wheezing episodes during the previous year) when they were older.13 The adjusted relative risk for frequent wheezing at 2 years of age among children with greater exposure was 1.4, but by 6 years old, the adjusted relative risk declined to 0.8, and at age 13 it declined even further to 0.3. Therefore, early exposure to older siblings in the home and day care attendance offers protective effects against frequent wheezing and asthma later in childhood.13 A preliminary investigation suggested that the effects of early exposure to endotoxin in house-dust in early life may protect against the later development of allergic sensitization.25 A total of 61 infants, aged 9 to 24 months with at least 3 episodes of physician-documented wheezing, were included in this study from Denver. The investigators measured the concentrations of house-dust endotoxin and allergens in the children’s homes. Allergic skin tests were performed in all children, and flow cytometry was used to measure proportions of T-lymphocytes producing interferon-γ (IFN-γ), and interleukin (IL)-4, IL-5, and IL-13. Children living in homes with significantly lower concentrations of house-dust endotoxin tested positive on allergic skin testing more often than children living in homes with higher concentrations of house-dust endotoxin. The children living in homes with a greater concentration of house-dust endotoxin also had increased proportions of T-lymphocytes that produced IFN-γ but not IL-4, IL-5, and IL-13. It
CONCLUSION

Asthma is a heterogeneous disease, with variable signs and symptoms among patients as well as significant variability in the individual patient over time. Three phenotypes have been identified in children with asthma: transient wheezing, nonasthmatic wheezing of the toddler and preschool-aged child, and IgE-mediated wheezing. Early allergic sensitization is a risk factor for persistent asthma. Of interest, certain early exposures, including that to older siblings, day care attendees, pets, farm animals, and house-dust endotoxin, seem to decrease the risk for persistent asthma. Some children, particularly those with severe persistent asthma, may experience progressive disease, characterized by decreased pulmonary function and increased asthma symptomatology. Early diagnosis and intervention may be especially important in these patients to prevent adverse effects later in life. Studies are needed to better define the pathogenesis, progression, and outcomes of asthma in preschool-aged children and to define the efficacy of specific interventions in these patients.

REFERENCES

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