

Issues in understanding pediatric asthma: Epidemiology and genetics

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Asthma is a heterogeneous disease characterized by varying phenotypes. Ongoing research is focused on identifying which children who have wheezing early will progress to childhood asthma. Genetic factors, predominantly atopy and a parental history of asthma as well as environmental stimuli, are key components in the development of asthma. Investigation into immunologic processes indicates that atopic children may have a cytokine imbalance or dysregulation in which the transition from T helper 2 (T_H2)-type to T_H1-type immunity is delayed. Several risk factors have been identified in the pathophysiology of asthma, including sensitization and exposure to cockroaches, house dust mites, and the mold *Alternaria alternata*, among other aeroallergens. Viral respiratory infections, primarily those caused by respiratory syncytial virus, are a significant risk factor for the development of childhood wheezing in the first decade of life. A number of prospective epidemiologic studies are investigating, among other issues, the relations among cytokine dysregulation, respiratory tract infections, and allergen exposure and sensitization in the development of asthma. Identifying the pathogenic mechanisms should enable clinicians to identify children at high risk and thereby to treat childhood asthma more effectively. (*J Allergy Clin Immunol* 2002;109:S521-4.)

Key words: Atopy, environment, pediatric asthma, genetics, pathogenesis

Wheezing, especially when related to viral upper respiratory tract infections, frequently begins early in life.^{1,2} Much recent and current investigation has focused on identifying which children who wheeze will have childhood asthma and on identifying risk factors for and markers of such inception and progression. The interactions between genetic and environmental factors appear to be key to unraveling pathogenic mechanisms in childhood asthma. Researchers have long recognized that asthma has specific genetic components, primarily a predisposition for atopy and a family history of asthma, and in particular, a maternal history.²⁻⁵ Because not all children with atopy or a maternal history of asthma have the disease, much still remains to be defined in the patho-

Abbreviations used

IFN- γ : Interferon gamma

RSV: Respiratory syncytial virus

genesis of asthma. This article reviews the current understanding of the role of genetics in asthma and the influence of environmental factors.

RISK FACTORS FOR PEDIATRIC ASTHMA

Several risk factors are associated with the development of asthma, and findings from clinical studies have identified others that are probable (Table I). Atopy, the genetic predisposition for the formation of increased levels of IgE antibody directed toward common environmental allergens, is a predominant risk factor.⁶ Allergic sensitization in atopic children, as indicated by antigen-specific IgE antibody production, may then result in a target organ-specific response. Why some children have only allergic rhinitis whereas some have asthma and allergic rhinitis and still others have atopic dermatitis or anaphylaxis remains unknown. Furthermore, the precise nature of the relation between total serum IgE levels and asthma remains poorly defined.

IgE production not specifically directed toward individual allergens is a significant genetic risk factor for asthma.⁷ High serum IgE levels occur in children with asthma and may be the result of increased IgE production in response to an inflammatory process in the airways.⁸ In addition, the timing of sensitization contributes to asthma risk: Early sensitization to common aeroallergens increases the risk for asthma, whereas late sensitization (after 8 years of age) does not.⁹

One longitudinal study determined the relation between total serum IgE and the risk for wheezing and allergic sensitization during childhood.¹⁰ This study, which included 540 participants (263 boys and 277 girls), analyzed total serum IgE levels in the children at approximately ages 1, 6, and 11 years. Boys were more likely than girls to be sensitized early (39.2% vs 26.4% in girls; $P < .002$) and to have late and persistent wheezing (27.8% and 17.5%, respectively, in boys vs 20.2% and 9.0%, respectively, in girls; $P < .05$). Persistent wheezing occurred infrequently in children who were sensitized late. Overall, total serum IgE tracked with age, with those with high levels at 9 months of age having higher levels at 6 and 11 years of age than those without elevated early levels. Children with persistent wheezing who became sensitized early had the highest levels of serum IgE throughout childhood. These findings support a genetic component for the presence of high serum IgE levels.

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TABLE I. Risk factors for persistent wheezing

Atopy
Parental history of asthma (especially maternal)
Respiratory syncytial virus infections
Male sex
Prematurity
Pulmonary function (flow limitation and airway hyperresponsiveness)
Exposure to passive smoke
Atopic dermatitis
Socioeconomic status
Western lifestyle
Diet
Sedentary lifestyle

The natural history of wheezing during the first 6 years of life confirms the relation between IgE levels and risk for wheezing.² A total of 826 children followed from shortly after birth until age 6 years were categorized into 1 of 4 groups according to their history of wheezing: never wheezed (51.5%), transient early wheezing (19.9%), late-onset wheezing (15.0%), and persistent wheezing (13.7%). Only children with persistent wheezing had significantly elevated IgE levels at age 9 months compared with children who never wheezed ($P < .01$). A direct relation was also demonstrated between serum IgE levels and wheezing in the children with persistent wheezing ($P = .02$), with these children having significantly higher levels at 6 years of age compared with children with late-onset wheezing, as well as those who had never wheezed ($P = .03$).

Exposure to aeroallergens thus induces antigen-specific IgE antibody production (allergic sensitization), although not all children have IgE antibody to the same allergens. For example, many children have IgE antibody to food, in particular to egg white and cow's milk.¹¹ The season of birth may also influence the pattern of aeroallergen sensitization¹²; children born during pollen seasons are at an increased risk for allergy to aeroallergens common during that season. A similar response has been reported with house dust mites for infants born during winter or autumn and with cat dander for infants born in winter.⁵ In US inner cities, cockroaches have been shown to stimulate a response in atopic children.¹³ All of these observations underscore the interaction between hereditary factors and the environment in the natural course of asthma.

Just as cockroaches are prevalent in the inner city, other aeroallergens are specific to certain locales. In the desert southwest, the mold *Alternaria alternata* has been implicated as a prevalent allergen among asthmatic children.¹⁴ In a study among 1246 children, in whom asthma was diagnosed in 9.8% at 6 years of age and in 15.5% at 11 years of age, sensitization to *Alternaria alternata* was the most prevalent among asthmatic children and the only allergen independently associated with increased risk for asthma, compared with other aeroallergens. Persistent asthma, defined as wheezing diagnosed before 6 years of age and persisting up to 11 years of age, was independently associated with the mold at both 6 and 11 years of age, whereas new asthma, defined as that diagnosed after

6 years of age, was associated with *Alternaria* only at 6 years of age.

Although identifying a primary allergen that increases the risk for asthma among children living in a semiarid region, the findings from this study also pointed to one of the problematic issues surrounding the understanding of this disease's pathogenesis: asthma is phenotypically heterogeneous. Children who did not react to *Alternaria* had lower levels of total serum IgE, exhibited no relationship to the frequency of other positive aeroallergen skin tests, were younger at the time of asthma diagnosis, and had more frequent wheezing associated with lower respiratory illnesses during the first year of life.¹⁵ Of greatest significance, however, was the fact that children who had skin test results negative to *Alternaria* were much more likely to undergo a remission of their asthma at age 11 years than those who had positive skin test results. The investigators concluded that dividing children into *Alternaria*-positive and *Alternaria*-negative groups identified 2 subphenotypes distinguished by differences in phenotypic markers and parental influence.

DEVELOPMENT OF THE IMMUNE SYSTEM AND RISK FOR ASTHMA

Although atopy and a parental history of asthma are recognized risk factors for childhood asthma, the genetic basis for these factors remains unknown. Researchers have proposed that the maturation of the immune system plays an important role. Much of the investigative efforts have focused on cytokine imbalance or dysregulation. Placenta-derived T-helper 2 (T_H2)-type cytokines are required for successful gestation and thus are present in utero. After birth, T-cell-mediated responses to signals from the microenvironment appear to be important in the conversion from a predominant T_H2 -type immunity to a balance between T-helper 1 (T_H1)-type and T_H2 -type responses. T_H2 -type responses are associated with the production of proinflammatory cytokines including IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. In turn, these cytokines stimulate production of IgE and induce tissue eosinophilia and airway hyperactivity, which are characteristic of asthma. In contrast, T_H1 -type responses are characterized by an enhanced production of IL-2 and interferon gamma ($IFN-\gamma$).^{16,17} Nonatopic children have a more rapid transition from predominant T_H2 -type responses at birth to more balanced T_H1/T_H2 responses. In contrast, in atopic children, this transition is delayed, which allows T_H2 -type responses to persist.

These relations are depicted in Figure 1.¹⁸ Three important concepts are demonstrated in this hypothetical model: First, in both atopic and nonatopic children, $IFN-\gamma$ production is decreased at birth (T_H2 skewing); however, this decrease is further exaggerated in atopic children. Second, the curve is shifted toward the right in the atopic child, revealing the potential for a critical period in the development of the immune system in which these children may be more vulnerable to environmental interactions with aeroallergens or viruses that may produce adverse conse-

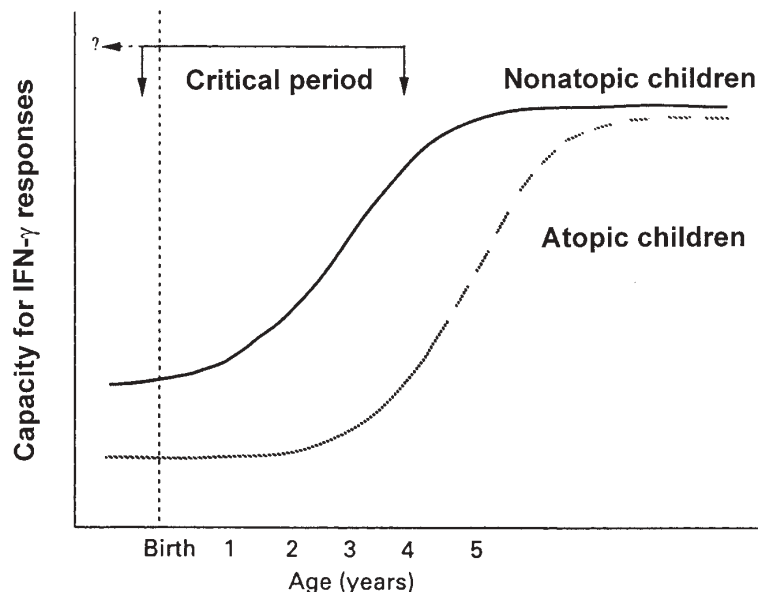


FIG 1. Differences of IFN- γ production in atopic and nonatopic children: Hypothetical model. Curves show differences in the maturation of IFN- γ responses in nonatopic (—) versus atopic (---) children. (Adapted from data in Prescott et al.¹⁸)

quences within the developing airway. Third, differences in cytokine response profiles between nonatopic and atopic children tend to diminish with increasing age.

This critical period in the development of the immune system in early life has been of interest in other contexts. In one study, the effects on day care attendance, specifically during the first 6 months, and the presence of older siblings on wheezing in 1035 children were followed from birth to 6 to 13 years of age.¹⁹ Both factors appear to offer protection against persistent wheezing in later childhood. Specifically, for each additional older sibling, the adjusted relative risk for asthma was 0.8 (95% CI, 0.7 to 1.0; $P = .04$), and that for day care attendance during the first 6 months of life was 0.4 (95% CI, 0.2 to 1.0; $P = .04$). Children with more exposure to siblings at home or day care were more likely to have frequent wheezing at 2 years of age (a time frame in which viral-induced wheezing occurs) compared with those who did not have siblings or did not attend day care ($P = .02$). These children, however, were less likely to have frequent wheezing from age 6 through age 13 years, a time when asthma-related wheezing occurs.

VIRAL INFECTIONS AND ASTHMA

Although the data discussed above suggest that viral infections occurring at a critical period may provide protection from the development of asthma, certain viruses appear to have adverse consequences in this regard. An evaluation of respiratory symptoms, asthma diagnosis, and pulmonary function in children 6 and 11 years of age, with and without a radiologically confirmed diagnosis of pneumonia during the first 3 years of life, showed that respiratory syncytial virus (RSV) was the predomi-

nant infecting pathogen in children with pneumonia (36.4%) and lower respiratory tract infection but no pneumonia (35.6%).²⁰ Exposure to infection during the first 3 years of life had a significant effect on the risk for asthma (Table II). The prevalence of asthma in children at age 6 with lower respiratory tract infection but no pneumonia (10.2%) was more than double that of children with no lower respiratory tract infection (4.6%). Asthma prevalence proved higher yet in children with radiologically documented pneumonia (13.6%). The prevalence of asthma in children 11 years of age who had physician-diagnosed asthma followed the same pattern observed in 6-year-old children. In a separate analysis, no association was observed between RSV infection and an increased risk for allergic sensitization.²¹ Thus, an increased risk for asthma exists during the first decade of life in children who have had RSV infections in the first 3 years of life, but in this cohort, it did not emerge as an important factor in the development of allergic sensitization.^{20,21}

These data stand in contrast to findings from another study of children hospitalized with RSV bronchiolitis as infants.²² In this study, 47 children hospitalized with RSV bronchiolitis during infancy were followed up to age 7.5 years; findings were compared with those from 93 matched control subjects. Skin testing was performed for common food and aeroallergens, and serum IgE levels were determined. There was a significant difference in the cumulative prevalence of asthma between the study and control children (30% vs 3%, respectively; $P < .001$) as well as in the cumulative prevalence of any wheezing (68% and 34%, respectively; $P < .001$). Allergic sensitization was also significantly higher among children with a history of infantile RSV bronchiolitis

TABLE II. Prevalence of current physician-diagnosed asthma at ages 6 and 11 years by pneumonia and lower respiratory infection/no pneumonia during the first 3 years of life (%)

Group	At age 6 y		At age 11 y	
	% (n)	OR (95% CI)	% (n)	OR (95% CI)
Pneumonia	13.6* (59)	3.3 (1.4–7.8)	25.9* (54)	2.8 (1.4–5.6)
LRI/no pneumonia	10.2* (371)	2.4 (1.3–4.2)	16.1† (347)	1.6 (1.0–2.4)
No LRI	4.6 (394)	1	11.0 (373)	1

CI, Confidence interval; LRI, lower respiratory tract infection; OR, odds ratio.

* $P < .01$.

† $P < .05$ for the comparison with no lower respiratory tract infection.

Adapted with permission from Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. Association of radiologically ascertained pneumonia before age 3 yr with asthmatic symptoms and pulmonary function during childhood: a prospective study. *Am J Respir Crit Care Med* 1999;159:1891-7. Official Journal of the American Thoracic Society. © American Lung Association.

than in control children (41% vs 22%, respectively, $P = .059$). Multivariate analysis showed that RSV bronchiolitis was a significant independent risk factor for both asthma and allergic sensitization (odds ratio, 12.7; [95% CI, 3.4 to 47.1] and 2.4 [95% CI, 1.1 to 5.5], respectively) in children at age 7.5 years. Compared with the results discussed previously,²¹ it is possible that the increased risk of allergic sensitization and RSV infection in the latter population of children may be a reflection of the increased severity of lower respiratory tract involvement in hospitalized children.

Despite this strong association between RSV infections and asthma risk in the first decade of life in these two studies, it is important to note that 65% of children acquire RSV infections in the first year of life and nearly 100% by age 2 years. Thus, RSV infections must increase asthma risk either in relation to the timing or severity of infection, or in terms of some host-dependent factor that needs further elucidation. These relations are currently under intense study by a number of research groups.

CONCLUSIONS

Variable phenotypes and incomplete information regarding the pathogenesis of asthma complicate the diagnosis and effective treatment of this disease in childhood. Atopy is an important component in the development of asthma, and emerging data indicate that asthma results from an interaction between genetic and environmental factors, with transition from the T_H2 -type to the T_H1 -type immune response a key constituent. Recent and ongoing investigation into the role that RSV infection, atopy, and other contributing factors play in the pathogenesis of childhood asthma will, ideally, provide information for identification of at-risk children and, ultimately, result in optimal approaches for prevention and treatment.

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