

The Atopic March: The Pattern of Allergic Disease Development in Childhood

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The developmental progression of allergic disease during early childhood is often referred to as the atopic march. Various epidemiologic and birth-cohort studies have begun to elucidate the evolution of allergic disease manifestations and have identified populations at risk for disease. These studies, along with intervention studies, highlight the effects of genetic predisposition and environmental factors on the atopic march.

The diagnosis of atopic dermatitis or food allergy in the young child is often accompanied by parental inquiries about the prognosis of these conditions, including disease duration and severity. Furthermore, the widespread parental recognition of an atopic march prompts questioning about the child's future in terms of development other allergies or asthma. The rising prevalence of allergic disease and asthma during the past several decades has further increased the importance of early and accurate disease recognition [1,2]. Understanding the natural history of these disorders and the interventions that may modify the development of allergy is essential in determining prognosis and providing advice for children at risk for allergic sensitization and disease.

The atopic march

Parents and clinicians have long recognized that the various manifestations of atopic disease often present in a characteristic sequence, referred to as the

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atopic march, and such a pattern has been confirmed by prospective birth-cohort studies [3–5]. Allergic disease manifestations are rare during the first month of life. The initial signs of allergic disease are atopic dermatitis and food allergies, which typically have their greatest incidence peaks during the first 2 years of life. Nearly half of children with atopic dermatitis develop symptoms within the first 6 months of life, and approximately 85% of individuals with eczema have onset of symptoms by the age of 5 years [6]. The development of food allergy closely parallels the pattern of atopic dermatitis, with the highest rates of food sensitization also noted in the first 2 years of life. The peak incidence of food allergy is 6% to 8% at 1 year of age, followed by a gradual decrease to an incidence of 1% to 2% through adulthood. The development of allergic sensitization to inhalant allergens begins to rise around 3 years of age and often is accompanied by allergic respiratory disease, including asthma and allergic rhinitis. Most children with asthma experience disease onset during the first 5 years of life [7], whereas allergic sensitization to inhalant allergens typically increases in prevalence during the preschool years, with sensitization to perennial allergens (ie, house dust mites, and cat and dog) occurring between 2 and 5 years of age, followed by sensitization to seasonal allergens (ages 3–5 years) [5,8].

Defining the populations at risk

Multiple prospective cohort studies have identified factors that predispose individuals to the development of atopic disease (Table 1). Effective early identification of children at risk for the development of allergic disease may allow focused interventions in an attempt to decrease the likelihood of developing atopic disease. Numerous features thought to be related to or predictive of the development of atopic disease have been investigated, including family history, cord blood IgE levels, skin prick tests for foods and aeroallergens, atopic dermatitis, and the occurrence of wheezing during childhood.

The role of family history

The heritability of allergic disease has been recognized for decades. Family history of atopy places infants at risk for the development of allergic diseases,

Table 1
Risk factors for atopic disease

Personal history	Laboratory data	Other factors
Atopic dermatitis	Allergen-specific IgE (in vivo or in vitro)	Diet
Wheezing	Cord blood IgE	Frequency of infections
Food sensitivity		
Aeroallergen sensitivity		
Family history		

as illustrated by two birth-cohort studies [9,10]. The Isle of Wight birth-cohort study confirmed that a family history of atopy was the single most important risk factor for the development of any atopic disorder by the age of 4 years, with maternal asthma conferring approximately threefold increases in risks for asthma, rhinitis, or any allergic disorder [9]. The Tucson Children's Respiratory Study, a birth-cohort study that examined the factors associated with the development of asthma, evaluated the relationship between parental asthma and the development of allergic sensitization. Maternal asthma was associated with a fourfold increase in the odds of developing persistent wheezing at 6 years of age relative to children who never wheezed during the first 6 years of life [11]. Parental asthma and positive allergy skin tests were also associated with increased prevalence of allergic sensitization at ages 6, 11, and 16 years when compared with children without parental asthma or parental allergic sensitization [10]. In addition, parental asthma and allergic sensitization were associated with clinical manifestations of allergic disease, including frequent wheezing and allergic rhinitis. A personal history of wheezing, however, had a greater influence on the development of aeroallergen sensitization than parental asthma, parental IgE levels, or parental skin test reactivity.

A family history of atopy in combination with the presence of atopic dermatitis also increases the likelihood of developing allergic sensitization. The German Multicenter Allergy Study (MAS), a large birth-cohort study designed to identify the risk factors of atopic disease, prospectively evaluated the development of aeroallergen sensitization [12]. By 5 years of age, children with a negative family history of atopy had a 16% risk of developing sensitivity to aeroallergens, whereas children with a positive family history of atopy had 39% risk; these risks were further increased to 50% and 70%, respectively, if the child had eczema. In the absence of a family history or personal history of eczema, the risk of sensitization to inhalant allergens was 14% and increased to 50% if the child had eczema. The augmentation of risk of allergic sensitization in the setting of genetic predisposition (ie, positive family history) and personal history emphasizes the interaction between these two factors in the development of allergic disease.

Cord blood IgE levels as predictors of atopic diseases

Recognition of the genetic control of IgE production led to investigation of cord blood IgE (CB-IgE) levels as predictors of subsequent allergic disease [13]. Although initial studies suggested a relationship between CB-IgE levels and development of atopic disease, more recent studies have demonstrated that CB-IgE levels have low sensitivity, specificity, and predictability for atopic disease. The German MAS found that, although elevated CB-IgE was a strong risk factor for sensitization at 12 months of age, the positive predictive value for sensitization was only 42%, and elevated CB-IgE did not predict wheezing during the first 5 years of life [14].

The relationship between allergic sensitization and the development of atopic disease

Detection of allergic sensitization testing by skin prick tests and allergen-specific IgE levels is helpful in confirming diagnoses of allergic disease in the presence of appropriate clinical manifestations. The role of allergen-specific IgE determinations in predicting the development of atopic diseases is not well defined, however. Numerous studies have evaluated the utility of allergen-specific IgE in combination with history, disease severity, and relationship with other atopic diseases, such as food allergies, in predicting the subsequent development of atopic manifestations.

The German MAS noted that sensitization to hen's egg at 12 months of life was predictive of aeroallergen sensitization at 3 years of age [15]. Other significant predictors of sensitization to inhalant allergens at 3 years of age included a family history of atopy and elevated IgE levels at 12 months of age. The combination of a positive family history of atopy and sensitivity to hen's egg at 12 months resulted in a positive predictive value for aeroallergen sensitivity at 3 years of age of 78% and a specificity of 99%. The sensitivity of egg-specific IgE levels in predicting subsequent allergic sensitization is limited, however, because more than 50% of children with aeroallergen sensitization at 3 years did not have sensitization to hen's egg at 1 year of age. Sensitization to other food allergens (ie, cow's milk and wheat) did not significantly affect the rate of aeroallergen sensitization at 3 years.

In children with a family history of atopy, sensitization to food or aeroallergens increases the risk of having adult asthma. Among a birth cohort of children of atopic parents in Poole, England, sensitization to egg, milk, or both during the first year of life strongly predicted the occurrence of adult asthma (odds ratio, 10.7) [16]. Similarly, allergic sensitization to aeroallergens by age 2 years was also predictive of adult asthma (odds ratio, 7.0). Overall, 60% of adults with asthma had developed allergic sensitization by 2 years of age [17]. These birth-cohort studies confirm early allergic sensitization as a precursor of later manifestations of allergic disease.

Further evidence for the progression from allergic sensitization to allergic disease is provided by studies that examined intervention strategies to reduce subsequent atopic disease. A prospective birth-cohort study of combined maternal and infant food allergen avoidance revealed a lower rate of food allergen sensitization during the first 2 years of life among children whose mothers avoided milk, egg, and peanut during the third trimester of pregnancy, lactation, and the child's first year of life [4]. The group of children who acquired allergic sensitization to egg during the first year of life experienced twice the risk of allergic rhinitis or asthma at age 7 years compared with those without food sensitization.

A longer prospective study revealed that food sensitivity at a young age was associated with aeroallergen-specific IgE at 12 to 15 years of age [18]. Among children with evidence of allergic sensitization to egg white at 2 years of age,

57% developed aeroallergen-specific IgE by age 4 years, and 76% had aeroallergen sensitivity by 12 to 15 years. Similar to the finding of Nickel et al [15], only 48% of children with inhalant allergen sensitization by 4 years of age had evidence of sensitization to egg white at age 2 years, and only 32% with inhalant allergen sensitivity at 12 to 15 years were sensitized to egg white at 2 years of age. Allergic sensitization to egg early in life was associated with the eventual development of atopic symptoms before 12 to 15 years of age in 82% of the children, suggesting a correlation between food-specific IgE levels early in life and the future development of IgE directed against inhalant allergens.

Despite this relationship between allergen-specific IgE and the subsequent development of further sensitizations, questions remain about the appropriate window of time for screening children with a family history of atopy, given the age-dependent nature of this process. Although egg-specific IgE seems to provide the earliest indication for future allergic disease, this possibility has not been examined fully. Further research is required before advocating the use of serum or skin testing as a screening tool in children with a positive family history of atopy.

Allergic sensitization in atopic dermatitis

Children with atopic dermatitis have often have sensitization to food and aeroallergens. A cross-sectional study of East German schoolchildren with atopic dermatitis revealed that, as a group, those with atopic dermatitis had higher median IgE levels than those without atopic dermatitis (118.5 kU/L versus 62.3 kU/L), as well as a fivefold higher likelihood of sensitization to aeroallergens [19].

The age of onset of atopic dermatitis has also been associated with increased allergen sensitization. In Gustafsson's prospective follow-up study [20], onset of eczema before 4 months of age was a significant risk factor (odds ratio, 3.0; 95% confidence interval [CI], 1.0–8.6) for sensitization to inhalant allergens at 36 months or later. The greatest risk factor for sensitization to inhalant allergens was sensitization to food allergens before 36 months of age (odds ratio, 9.7; 95% CI, 2.9–32.9). The German MAS revealed that the presence of atopic dermatitis at 3 months of age resulted in a fourfold increased risk of aeroallergen sensitivity at 5 years of age [21]. The presence of two family members with atopic disease doubled the risk conferred by atopic dermatitis in the first 3 months and translated into a positive predictive value of greater than 75% at 5 years of age. The presence of these factors was strongly predictive of aeroallergen sensitization but was less predictive of the development of allergic airway disease by age 5 years, although children with atopic dermatitis and at least two family members with atopy were still 4.5 times more likely to develop allergic airway disease by 5 years of age.

The severity of atopic dermatitis also affects the natural history of allergic sensitization. A case-control, cross-sectional analysis of German schoolchildren 5 to 14 years of age noted a significant correlation between the severity of atopic

dermatitis and concentrations of allergen-specific IgE to dust mite and cat [19]. Guillet and colleagues [22] examined the relationship between food sensitization and severity of atopic dermatitis in a cross-sectional study of children with atopic dermatitis. All children with severe atopic dermatitis demonstrated allergic sensitization, with aeroallergen sensitization in 40% and food allergen sensitization in 96%. Among children with moderate atopic dermatitis, the rates of sensitization were lower, with only 33% sensitized to an aeroallergen and none sensitized to food. In a prospective evaluation of 29 children with severe atopic dermatitis at 4 months of age, 83% demonstrated persistent food allergen sensitivity at age 3 years, whereas 14% had only inhalant allergen sensitivity, and 69% had both inhalant and food sensitivity. Although patients with less severe atopic dermatitis were not studied in the prospective study phase, the severity of atopic dermatitis correlated with increased likelihood of allergic sensitivity to food and to inhalant allergens.

The development of wheezing

To evaluate the progression from allergic sensitization and atopic dermatitis to wheezing and asthma, the German MAS investigated the relationships between family history, clinical presentation of atopic dermatitis, allergen sensitization, and development of allergic airway disease [23]. Children with atopic dermatitis within the first 2 years of life were more likely to have wheezing during that same time (46%) than children without atopic dermatitis or with atopic dermatitis without scratching (32%). Children with early wheezing and atopic dermatitis had a nearly threefold greater risk of wheezing at 7 years of age than children without early atopic dermatitis. During the first 2 years of life, the presence of atopic dermatitis, along with sensitization to wheat, soy, cat, dust mite, or birch, conferred significant risk for wheezing, bronchial hyperresponsiveness, or reduced lung function at age 7 years. The risk of subsequent wheezing, however, was dependent on the presence of early wheezing, because children with early atopic dermatitis but without early wheezing did not have a greater risk of developing wheezing at 7 years of age than their counterparts without atopic dermatitis. The authors suggest that because the early manifestations of allergic disease, including atopic dermatitis and early wheezing, often begin within a short and overlapping timeframe, the development of childhood atopic disease represents a concurrent rather than sequential process.

The Tucson Children's Respiratory Study group evaluated the associations between positive skin prick tests and the development of wheezing [11]. Children who wheezed through the first 6 years of life had higher IgE levels at 9 months of age than those who never wheezed during the first 6 years of life or who wheezed during the first 3 years of life but did not wheeze again from ages 4 to 6 years. In addition, more than half of persistent wheezers had positive skin prick tests to aeroallergens at age 6 years, compared with 34% of children who never wheezed. These results emphasize that evidence of atopic tendencies early

Table 2
Asthma predictive index

Major criteria	Minor criteria
Parental history of physician-diagnosed asthma	Wheezing apart colds
Physician-diagnosed atopic dermatitis	Blood eosinophilia $\geq 4\%$
	Physician-diagnosed allergic rhinitis

Stringent index: The child must have a history of early frequent wheezing during the first 3 years of life plus one major criterion or two minor criteria.

Adapted from Castro-Rodriguez J, Holberg C, Wright A, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403–6.

in life, as reflected by IgE levels and skin prick tests, imparts significant risk for the persistence of wheezing throughout the preschool years.

Based upon this birth-cohort study, a clinical index was constructed to help determine (and predict) the risk of asthma in children who experience recurrent episodes of wheezing during early life [24]. The clinical index includes major and minor criteria (Table 2). Presence of one major or two minor criteria at 3 years of age in a child with a history of frequent wheezing resulted in an increased likelihood (2.6–5.5 times) of having asthma at school age in comparison to children who did not have any of these risk factors. Although a positive index predicted the presence of asthma during the school years in 59% to 76% of children, a negative index predicted the absence of asthma between the ages of 6 and 13 years in more than 95% of children. This predictive index confirms the strong association between family and personal histories of asthma and atopy with the development of childhood asthma.

Mechanisms and the genetic basis for the atopic march

The association of family history, allergic sensitization, and personal history of atopic disease suggests an underlying genetic predisposition. Linkage studies in several populations have attempted to elucidate the genetic etiology of the atopic march. Multiple genetic loci are associated with various phenotypes of atopic disease, and three genetic loci are associated with both atopic dermatitis and asthma (5q31-33, 11q13, and 13q12-14) [25]. This finding is consistent with the recognized overlap in immunologic mechanisms that underlie these disease processes, including elevated IgE levels, peripheral and tissue eosinophilia, and production of Th₂ cytokines (interleukin [IL]-4 and IL-5).

The mechanisms responsible for the association between atopic dermatitis and allergic sensitization have also been examined. A murine model of epicutaneous sensitization to ovalbumin provides insight about the underlying immunopathogenesis of atopic dermatitis [26]. Sites of epicutaneous ovalbumin sensitization had increased expression of the Th₂ cytokines IL-4 and IL-5 and the Th₁ cytokine interferon- γ . In addition, total serum IgE was elevated compared

with control. Evidence of systemic sensitization was reflected by the presence of eosinophils in the bronchoalveolar lavage fluid and by airway hyperresponsiveness to methacholine following a single inhalation of ovalbumin.

Prevention of the atopic march

Current treatment of allergic disease remains largely symptomatic and aimed at controlling the underlying allergic process, because most treatment approaches lack disease-modifying properties. Thus, there continues to be intense interest in strategies aimed at the prevention of atopic diseases in infants, especially those with familial and, thus, genetic risk. Prevention approaches can be categorized by the population at risk and the degree of disease manifestation at the time of intervention. Primary prevention involves treatment of a population at risk for disease development but currently without manifestations of the disease process of interest. This approach requires the availability of accurate predictors of disease development so that interventions are provided to those at highest risk and not provided to those at low risk for disease development. Secondary prevention differs from primary prevention in that the target population already has developed evidence of an atopic disease (such as sensitization to foods). The goal of the secondary intervention is prevention of further atopic disease manifestations (such as the development of asthma). Various prevention modalities aimed at reducing the development of atopic features have been examined, including maternal dietary restriction, exclusive breastfeeding, the use of hydrolyzed hypoallergenic formulas, delayed introduction of solid foods, probiotics, the use of antiallergy medications, specific allergen immunotherapy, and environment modifications (Table 3).

Maternal diet and breastfeeding

Manipulation of the maternal diet has been explored as a strategy for decreasing and possibly preventing the development of allergic disease early in childhood. Several studies have evaluated the role of restricting the diet prenatally and postpartum in breastfeeding mothers.

Maternal dietary avoidance of cow's milk and egg from 28 weeks' gestational age until delivery did not alter the manifestations of allergic disease at 5 years of age among children whose mothers had at least one allergic family member [27]. A prospective evaluation of children with a family history of atopic

Table 3
Interventions explored for modulating the atopic march

Diet	Medications	Environmental control
Breastfeeding	Antiallergic medications	Allergen proof covers
Maternal diet restriction	Immunotherapy	Vinyl flooring
Infant diet restriction	Treatment of eczema	High-filtration vacuums

disease reported that the rates of eczema, allergic rhinitis, and asthma at 5 years of age were comparable among offspring of mothers who practiced dietary avoidance during late pregnancy and those who did not. Similarly, a German prospective study compared the effects of three maternal dietary interventions in women with atopic heredity on the development of atopy [28]. The interventions consisted of (1) dietary avoidance of milk and egg during the third trimester and during the (variable) duration of breastfeeding, (2) dietary avoidance of milk and egg after delivery and during the (variable) duration of breastfeeding, and (3) no dietary restrictions. There was no protective effect upon the development of atopic dermatitis or sensitization to milk or egg at 6 and 12 months of age with any of these interventions. The interpretation of these findings is limited because the study was not randomized; the mothers chose which dietary approach they adopted. Overall, these three studies suggest that maternal dietary avoidance during late pregnancy does not influence the emergence of atopic disease during early life, a conclusion supported by a recent review by an expert group of the European Academy of Allergology and Clinical Immunology [29].

Exclusive breastfeeding has also been suggested as being protective against the development of allergic disease. Although numerous studies of the effects of breastfeeding have been conducted, these studies provide discordant results, probably related to the lack of control of the maternal diets. The duration of breastfeeding seems to modulate the development of atopic disease. A prospective, long-term study found that no breastfeeding or breastfeeding for less than 1 month was associated with higher rates of eczema at 5 years of age, food allergy at 2 years of age, and respiratory allergy at age 17 years, and these findings were compounded by an effect of atopic heredity [30]. The group with prolonged breastfeeding (>6 months) had the lowest prevalence of eczema at 1 and 3 years of age and had slightly lower rates of atopy at 17 years of age. The peak prevalence of eczema occurred at 1 year of age, at which time the short-term and intermediate-term breastfed groups had similar prevalence rates, suggesting that short periods of breastfeeding have no effect on the development of eczema in the first year of life. Meta-analyses of the effect of breastfeeding on the development of atopic disease concluded that exclusive breastfeeding for at least 3 months results in a 48% reduction in the odds of asthma during childhood [31] and a 42% reduction in the odds of atopic dermatitis [32]. Family history of atopy, however, seems to modulate these findings, because a family history of atopy seems to be necessary for exclusive breastfeeding to have an effect on the development of atopic dermatitis [32] and of asthma [31] but not of allergic rhinitis [33].

Given the lack of absolute protection afforded by breastfeeding, it is possible that maternal ingestion of allergens during lactation may mitigate the protective effect of breastfeeding. Following maternal ingestion of egg, wheat, and peanut, allergens from these foods have been detected in breast milk [34–36], potentially promoting sensitization in the breastfed child. A prospective birth-cohort study examined the effect of maternal avoidance of food allergens starting in the last trimester of pregnancy on the development of allergic disease in infants

at risk for allergy based on the existence of at least one atopic parent [3,4]. Infants whose mothers avoided dietary allergens were either breastfed or received casein hydrolysate formula as supplements until 1 year of age. In the comparison group, mothers were encouraged to follow standard diets for pregnancy and lactation, and a cow's milk-based formula was provided. At 2 years of age, there was a reduction in food allergy and milk sensitization in the intervention group. This protective effect dissipated by 7 years of age, at which time the prevalence of atopic diseases did not differ between the two groups. In another prospective trial, avoidance of egg, cow's milk, and fish for the first 3 months of lactation was associated with a decrease in the incidence of atopic dermatitis at 6 months of age, but thereafter no difference was noted in terms of atopic manifestations or rates of sensitization to foods [37]. Follow-up studies of this cohort at 5 and 10 years of age revealed no difference in the development of asthma or eczema between the control group and the dietary-restriction group [27,38]. Combined, these studies indicate that altering the maternal diet prenatally or during lactation does not alter the long-term course of the development of atopic disease [29].

Hydrolyzed infant formulas

Like the studies of maternal dietary restriction, studies examining the effects of infant formula composition on the development of allergic symptoms are complicated by the variable durations of feedings with various infant formulas. A Swedish group evaluated the efficacy of using either extensively or partially hydrolyzed cow's milk-based formulas in infants who were at risk for developing atopy based on a family history of allergy [39]. All mothers removed cow's milk, egg, and fish from their diets beginning 1 week before the expected date of delivery. When weaning started, the infants were randomly assigned to receive an extensively hydrolyzed formula, a partially hydrolyzed formula, or routine cow's milk formula. No cows' milk was given for the first 9 months of life, and no egg and fish were given up to 12 months of age. Infants receiving the extensively hydrolyzed formula had significantly lower cumulative incidences of atopic symptoms for the first 18 months of life than those receiving standard formula. Despite this finding, the prevalence and severity of atopic dermatitis remained similar for all groups at most time points, including the final observation at 18 months, at which point the proportions of children with a final cumulative diagnosis of atopy were similar in all groups. Wheezing episodes occurred less frequently during the first 18 months in the group receiving extensively hydrolyzed formula. Because the period of observation ended at 18 months of age, the longer-term effects of these interventions remain unclear. Similarly, a Danish prospective, randomized study in infants with a positive family history of atopy evaluated the use of extensively hydrolyzed formula plus delayed introduction of dietary solids until 6 months of age on the prevalence of atopic disease [40]. The group treated with hydrolysate formula had lower prevalence of atopic disease, including wheezing episodes, eczema, and

food allergies, by 18 months of age. Furthermore, several studies confirm the reduction in the rates of atopic dermatitis and cow's milk allergy among children fed extensively hydrolyzed formulas [29], and this effect may extend until 7 years of age [4].

Delayed introduction of solid foods

The introduction of solid foods into infant diets before 4 months of age has been associated with increased risks of eczema [41,42] and food allergy during the first year of life [41] and an increased probability of wheeze during childhood [43].

Modification of intestinal microflora

Other means of altering the infant dietary exposure include the use of probiotics in attempt to alter the gut microflora. The premise of this approach is that probiotics may modify the course of allergic disease by altering IgA production, inducing oral tolerance, and generating transforming growth factor- β . In a double-blind, randomized, placebo-controlled prospective trial, infants at risk for allergic disease based upon a family history of atopic eczema, allergic rhinitis, or asthma were randomly assigned to treatment with the probiotic *Lactobacillus rhamnosus* strain GG or placebo prenatally for 2 to 4 weeks before delivery and for 6 months postnatally. Infants who received *L. rhamnosus* strain GG had a 50% reduction in the rate of atopic dermatitis at 2 years of age, but there was no difference in the rates of allergic sensitization at 6, 12, or 24 months. Among infants who developed atopic dermatitis, *Lactobacillus* treatment did not affect the atopic dermatitis severity scores at 24 months of age. Reassessment of this cohort at 4 years of age revealed persistence in the lower rate of atopic dermatitis in the *Lactobacillus*-treated children but no significant differences in the incidences of allergic rhinitis and asthma between the probiotic and placebo groups [44]. These results suggest that probiotic treatment may have a role in reducing the development of atopic dermatitis during the first 4 years of life but does not significantly affect other elements of the atopic march.

Use of antiallergy medications

Antihistamines have been a mainstay in the management of allergic disease for several decades. The Early Treatment of the Atopic Child trial examined the effect of cetirizine, a second-generation H_1 receptor antagonist that also inhibits allergen-induced eosinophil trafficking into the skin, nose, lungs, and conjunctiva, on the development of asthma in children 1 to 2 years of age with active atopic dermatitis and a first-degree relative with atopy [45]. This double-blind, placebo-controlled trial compared the effects of cetirizine 0.25 mg/kg two times per day versus placebo for 18 months on the time to onset of asthma. After completing the 18-month treatment phase, the patients entered an 18-month

observational period to detect the time of asthma onset. Overall, the cetirizine and placebo groups had similar cumulative prevalence rates of asthma. Subgroup analysis indicated that only the cetirizine-treated children with sensitivity to grass pollen experienced a decreased rate of onset of asthma during the 36 months compared with the placebo-treated grass pollen-sensitized group. Sensitization to egg white, house dust mite, grass pollen, or cat was a significant risk factor for the development of asthma in the placebo group. These results suggest that cetirizine therapy in young children with atopic dermatitis and a family history of atopy may delay the onset of asthma, especially in children with grass pollen sensitivity, although the effect beyond 36 months after onset of therapy is not yet known.

Ketotifen is another antiallergy/asthma drug that has been shown to improve symptoms of many allergic conditions. A randomized, double-blind, placebo-controlled trial examined the effect of treatment with ketotifen on the development of asthma in children aged 1 to 36 months with moderate atopic dermatitis unresponsive to dietary elimination [46]. At the end of this 1-year study, 13% of the ketotifen-treated children had developed asthma compared with 42% of children in the control group. Thus, antiallergy medications may attenuate the development of allergic airway disease in high-risk children, but these effects may be confined to certain subgroups of patients, such as those with grass pollen allergy and atopic dermatitis. Furthermore, longer follow-up is necessary to understand the long-term effects of these therapies.

Role of immunotherapy

Allergen immunotherapy is an effective treatment for pollen allergy and has been demonstrated to reduce airway hyperresponsiveness in patients with asthma [47]. Johnstone and Dutton [48] reported that children with perennial asthma treated with immunotherapy experienced a significant reduction in asthma prevalence at 16 years of age. A recent prospective European study evaluated the effect of 3 years of specific immunotherapy on the development of asthma in children between the ages of 6 and 14 years with seasonal allergic rhinoconjunctivitis to grass or birch pollen [49]. Although family history and personal history of food allergies and atopic dermatitis were not reported, the study population had positive skin prick tests to birch or grass pollen. Children with allergic sensitization to other allergens were excluded from the study. After 3 years of treatment, the immunotherapy group was 2.5 times less likely to develop asthma and demonstrated a reduction in methacholine responsiveness compared with the placebo group. This finding suggests that treatment of children with seasonal allergic rhinoconjunctivitis who are sensitized to an inhalant allergen may prevent the development of asthma over a 3-year period. More study is needed to determine the duration of the protection given by allergen immunotherapy against the development of asthma, the optimal timing for initiation of immunotherapy, and the populations likely to benefit from this approach.

Environmental controls

Exposure to environmental allergens, especially house dust mite, is a significant risk factor for the development of asthma [50]. Thus, the reduction in environmental exposures early in life may serve as an approach to prevent the allergic march. A randomized, prospective trial examined the effect of pre-natal and postnatal environmental modification on the development and severity of wheeze and atopy in infants from families with and without histories of atopic disease [51]. Allergen-proof covers, high-filtration vacuum cleaners, and vinyl flooring were used. In children 1 year of age, environmental control measures were associated with a decreased incidence of several respiratory symptoms, including severe wheeze with shortness of breath, use of medications for wheezing, and wheezing with vigorous activity, but had no effect on the development of eczema or food allergies. Because the study of environmental measures could not be completed in a blinded fashion, bias may have contributed to the results. The use of environment modification, as with most other interventions early in life, requires further long-term study to elucidate the efficacy of these approaches over time.

Summary

Clinical impressions and numerous clinical studies confirm the occurrence of an atopic march. A multitude of risk factors and treatment modalities have been evaluated in efforts to define the populations at risk and to alter the development of allergic disorders in the context of the rising prevalence of allergic disorders during the past several decades. It is evident that genetic background plays an important role, although environmental factors also contribute significantly, and these environmental factors may be amenable to modification. More accurate detection of the populations at risk for development of allergic disease and the development of novel intervention strategies may allow more effective treatment and prevention of the atopic march.

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