

Risk factors for asthma and atopy

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Purpose of review

The aim of this article is to provide information on risk factors associated with the development of atopy and asthma in childhood.

Recent findings

Several gene polymorphisms have been associated with susceptibility to asthma and allergy; complex gene–environmental interactions, however, appear to play a key role in the development of the disease. Early life sensitization to aeroallergens, presence of atopic dermatitis or allergic rhinitis, maternal smoking during pregnancy and children's environmental exposure to tobacco smoke, lower respiratory tract infections with respiratory syncytial virus and potentially with other viruses including rhinovirus and metapneumovirus, exposure to air pollutants, several perinatal factors other than maternal smoking, are among factors associated with an increased risk for development of chronic asthma.

Summary

The prevalence of asthma and allergic diseases is increasing progressively. Those who are involved in the care of young children should be prepared to recognize risk factors for development of these diseases and to appreciate the role of gene–environment interactions. Preventive measures established at an early age may modify the natural history of asthma and other allergic diseases.

Keywords

allergen sensitization, asthma, gene–environment interactions, respiratory viral infections, risk factors for asthma

Introduction

Over the past 30 years, the prevalence of asthma has increased to epidemic proportions in developed countries, and asthma is the most common chronic disease in children. Evidence indicates that environmental factors acting early in life and interacting with specific genes are key events for the development of the chronic, persistent form of the disease. In this review, we will focus on these gene–environment interactions, with the aim of providing elements which might help identification of risk factors and development of preventive strategies for asthma at an early age.

Atopy and asthma: genetics factors

Asthma is a complex genetic disorder with variable phenotypes, largely attributed to the interactions of the environment and multiple genes [1,2^{••}]. Numerous loci and candidate genes have been reported to show linkage and association of asthma and asthma-associated phenotypes, atopy, elevated IgE levels, and bronchial hyperresponsiveness, to alleles of microsatellite markers and single nucleotide polymorphisms (SNPs) within specific cytokine/chemokine and IgE regulating genes; however, only a few genes conferring significant risk have been mapped. The clinical implications of the genetic variations within these genes remain largely undetermined [2^{••},3,4].

In 1999, Baldini *et al.* [5] showed an association between an SNP in the *CD14* promoter (*CD14* C-159T*), increased serum levels of soluble CD14, and decreased total serum IgE in children, and since then the relationship between *CD14* C-159T* and phenotypes has been extensively investigated. Several studies support a protective role for *CD14* C-159T* in allergy, whereas others have failed to show an association [6^{••}]. It is suggested that these conflicting observations may result from differences in environmental conditions essential to modulate *CD14* gene expression [6^{••}].

Environmental stimuli might induce acquired epigenetic states that affect gene expression and phenotypic outcome, and the interactions are subject to change over time depending on the developmental state and the immunologic milieu, in such a way that an environmental switch may be capable of eliciting different and even opposite immune phenotypes [6^{••}]. The relevance of combinations of multiple genetic and environmental factors in the occurrence and natural history of allergic disorders has been extensively discussed by von Mutius [7^{••}].

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Abbreviations

API asthma predictive index
ETS environmental tobacco smoke
SNP single nucleotide polymorphism

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Accordingly, identification of gene–environment interactions will require large, prospective, population based studies, and better characterization of the immunologic, genetic, and epigenetic mechanisms that underlie the influence of the environment.

In the past 2 years, cloning of two allergy and asthma susceptibility genes, *ADAM33* and *PHF11*, has been reported [8–10]. The expression pattern of *ADAM33* combined with the known function of ADAM family members supports the idea that ADAM33 has a role in airway remodeling rather than in immune-mediated inflammation [8,9]. Regarding *PHF11*, distinct splice variants have been found to be differentially expressed in T and B lymphocytes in different states of activation. One of the PHF11 variants not associated with serum IgE is associated with high concentrations of serum IgM [10].

Gene–environment interactions, asthma and atopy

The risk of having asthma appears to be compounded by a Western lifestyle, including indoor environment, diet, air pollution, and psychological stress [11,12]. The length and type of exposure to infectious agents as well as the time when it happens have been shown either to promote or to suppress an inflammatory process and influence a subsequent history of asthma [13,14^{••}]. Bousquet and co-workers [15] proposed that many of the genes involved in IgE synthesis and airways remodeling in asthma are persistent or reminiscent fetal genes which may not be silenced during late pregnancy or early infancy [15].

Changes in the infectious environment and in the pattern of microbial exposure of children, preventing the shift of allergen-specific responses from the Th2 to the Th1 phenotype, may have been critical for the increase in the prevalence of atopic disorders [16,17^{••}]. However, epidemiologic observations have indicated that the prevalence of Th1-dominated autoimmune disorders is also increasing [18]. A decreased activation of regulatory T cells, including IL-10 producing CD4+CD25+ T cells, also caused by a lower microbial burden, has been proposed [19[•],20].

A complete understanding of gene–environment interactions will require that epigenetic as well as classical genetic mechanisms be taken into account because the expression of the allergic diseases is dependent on a genetic predisposition, environmental interactions and time.

Familial factors and asthma

The familial aggregation in asthma has provided support for a genetic component. The presence of aggregation among related individuals may indicate either shared genes or a common household environment. A study of monozygotic twins showed higher concordance rates than

in dizygotic twins [21]. A history of asthma in the mother is associated with a larger increase in asthma risk. It is feasible that maternal effects on the developing immune system are confined not only to the fetal period but might also influence the postnatal period through breast milk and environmental conditions [22,23,24[•]].

Male sex, asthma and atopy

Male sex is a risk factor for asthma up to the age of puberty. The explanation for this difference is not very clear. Boys have lower maximal expiratory flows at given lung volumes than girls. Probably, in the first years of life, immune factors (boys are more sensitized, atopic) and lung-specific factors are both important. The prevalence of asthma in boys and girls changes during puberty and hormonal changes have been implicated in the reversal of sex ratio, probably including early menarche. Also, airway size increases more rapidly in boys than in girls [22,25,26]. Leptin is a proteohormone produced by adipocytes and it is thought to act primarily through specific receptors at the hypothalamus. Serum leptin levels show a positive correlation with body mass index (BMI) and reflect the body mass. Several studies have shown an association between increased BMI and asthma prevalence. Higher serum leptin levels in asthmatic boys may partly explain the higher prevalence of childhood asthma in male sex [27[•]]. It was also observed that higher rates of early infancy weight gain are associated with impaired lung development [28]. Future investigations of genetic determinants of IgE levels, as shown by sex differences of sensitization to *Blomia tropicalis* in asthma, should include approaches that allow for potential sex differences in their expression [29]. Males have more severe airway hyperresponsiveness; this may be one factor contributing to the higher prevalence of asthma in boys [30].

Maternal effects

Children born from parents with asthma or atopic disorders present an increased risk of developing similar diseases. Maternal factors, placental factors, or both may have an impact on perinatal allergic sensitization [13,24[•],31,32[•]]. Liu *et al.* [32[•]] found that maternal, but not paternal, total IgE levels correlated with elevated infant IgE levels and development of atopy. Maternal asthma has been associated with a higher prevalence of birth of preterm and low weight infants and maternal serum levels or increased gene expression of inflammatory cytokines including TNF α , IL-8 and IL-18, were associated with restriction of intrauterine growth [31].

A recent study [33] demonstrated reduction of the activity of the type 2 11 β -hydroxysteroid dehydrogenase (11 β HSD2) in placenta of asthmatic pregnant women. This enzyme is important in the metabolism of cortisol to inactive cortisone, and it has been shown that cortisol is involved in reduction of fetal growth, particularly lung

growth, in high-risk pregnancies of female fetuses [33]. Pregestational estrogenic effects may have a role in the later development of allergic diseases in the child, including use of oral contraceptives by mothers [34,35] and menarche at a later age [36].

Other perinatal factors identified to be associated with development of asthma and atopic diseases include low birth weight, prenatal exposure to tobacco smoke, severe respiratory infection in the first year of life and lack of breast feeding. Children with increased head circumference, indicating unbalanced fetal growth; those whose mothers received antibiotics during gestation [37]; those born from mothers with uterine complications [38] and those born from cesarean sections [39] also have an increased risk to develop atopy. Duration of labor longer than 12 h has been associated with the presence of bronchial hyperreactivity and atopy by the age of 20 years [40**].

Maternal tobacco smoking during gestation is an important avoidable risk factor associated with elevated levels of IgE in cord blood and subsequent asthma and allergic diseases in childhood [41**,42], and cause reduction of pulmonary function in children [43]. Increased production of IL-13 by cord blood cells has been found in newborns whose mothers had smoked during gestation as compared with those who never smoked [42]. Macaubas *et al.* [44**] reported a direct relationship of maternal tobacco smoking with both low concentrations of IL-4 and IFN- γ in cord blood and increased risk of wheezing by age 6 years.

Increased uptake of n-3 polyunsaturated fatty acids (PUFA) has been associated to reduction of prevalence of asthma in some studies [45,46]. On the other hand, Stoney *et al.* [47] have shown opposite results; they failed to demonstrate a correlation of elevated n3-PUFA levels in colostrum and breast milk, and protection against allergic diseases in high-risk breast fed infants.

Exclusive breast feeding for at least 4 months has been associated with protection for development of asthma or atopic diseases [48,49*], but other studies have failed to demonstrate protection by breast milk [50]. Botcher *et al.* [51] found no relationship of levels of cytokines (IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, IFN- γ , TGF- β 1, TGF- β 2), chemokines (RANTES, eotaxin) or secretory IgA in breast milk, and development of sensitization or allergic symptoms, or levels of salivary IgA during the first 2 years of life.

Atopic dermatitis and allergic rhinitis as risk factors for asthma

Most patients with asthma present symptoms in the first 2 years of life. Prospective studies have aimed to identify

predictive factors for asthma, and an asthma predictive index (API) has been developed [52,53**]. The API was determined on frequent wheezers, defined as those children who presented more than three episodes of wheezing within a year, during the first 3 years of life. A positive API is met when a frequent wheezer has either one major criterion (physician-diagnosed atopic dermatitis or physician-diagnosed parental asthma) or two minor criteria (peripheral blood eosinophils $\geq 4\%$, wheezing apart from colds, or physician-diagnosed allergic rhinitis). The API has a positive predictive value of 47.5% and a negative predictive value of 91.6% for the development of asthma at age 6 years, and these values have not changed significantly with age, from ages 6 to 13 years [52,53**].

The identification of allergic rhinitis as a risk factor for asthma was highlighted in the guidelines developed by the Allergic Rhinitis and Its Impact on Asthma workshop [54]. The mechanisms by which allergic rhinitis may be a risk factor for asthma have been reviewed in recent studies [55–61]. Peroni *et al.* [55] showed that the presence of rhinitis was a risk factor for physician-diagnosed asthma, asthma symptoms, atopic dermatitis and allergic sensitization in preschool children, using the International Study of Asthma and Allergies in Childhood (ISAAC) protocol. Likewise, a study carried out in São Paulo, Brazil, documented that the presence of concomitant allergic rhinitis and atopic dermatitis was a stronger risk factor for both development of asthma and for more severe asthma, than the presence of each condition separately [62].

Atopic dermatitis, usually the first manifestation of the atopic march, has also been identified as a risk factor for development of asthma [55,63,64]. Evidence suggests that epicutaneous sensitization, potentiated by rubbing and scratching of inflamed atopic skin, can lead to systemic allergic responses and airway sensitization. Migration of Th2 cells from draining lymph nodes through the circulatory system to various sites including nasal and lung mucosa and bone marrow would contribute to maintain a systemic Th2 environment, promoting an allergic response in the airways upon inhalation of allergens [65*]. Therapies aimed at modifying the severity of atopic dermatitis in young children may decrease the risk for development of asthma.

Respiratory tract infections, asthma and atopy

Viral infections have been implicated in at least three ways to the pathogenesis of asthma: inception, prevention and exacerbations [66**]. Asthma inception after early childhood respiratory tract infection might be influenced by genetic, environmental (type of virus and concomitant allergen exposure) and developmental (age at which infections occur) factors. Studies have pointed to an association of respiratory syncytial virus (RSV) bronchiolitis and other

early respiratory tract infections with recurrent wheezing or symptomatic asthma during the first 4–7 years of life [66^{••}]. Results of a long-term study carried out in Tucson, Arizona also demonstrated an association of lower respiratory tract infection caused by RSV early in life with persistent wheezing at 3 and 6 years of age, but this effect was no longer observed by age 13 years [67^{••}]. Term infants with RSV bronchiolitis present large amounts of the Th2 cytokine IL-9 mRNA or protein in the airways, produced mainly by neutrophils, which may be one of the mechanisms underlying persistence of asthma symptoms following RSV infection [68^{••}]. Besides RSV, other viruses including rhinovirus [69[•]] and the previously unrecognized metapneumovirus [70^{••}] have been associated with wheezing illnesses in young children and may be potentially implicated in the subsequent development of childhood asthma. The role of rhinovirus as a major trigger of asthma exacerbations in school-aged children and adults is well recognized [71^{••}].

Similarly to temperate regions, infection with RSV was a major risk factor for acute wheezing among children under 2 years of age living in subtropical Brazil [72^{••}]. Follow-up of these children for 2 years after the index wheezing episode showed that viral infection was not a risk for persistent wheezing. On the other hand, early sensitization particularly to mites and cockroach, at 2–4 years of age, and exposure to high levels of cockroach allergen in the home in the first 2 years of life were both strong and independent risk factors for persistence of wheezing [73]. Previous studies in Brazil showed that daycare centers and schools, in addition to homes, are sources of significant exposure to mite and cockroach allergens, which might contribute to sensitization [74[•],75]. Evaluation of toddler-aged children judged to be at high risk for the development of persisting asthma, participating in the Prevention of Early Asthma in Kids, also revealed a high prevalence of aeroallergen sensitization (54%) [53^{••}].

Early sensitization has been associated with an increased risk for persistent asthma and bronchial hyperresponsiveness and with a greater loss of lung function [76]. Sensitization to house dust mites and other aeroallergens was shown to be an important risk factor for hospital admissions for wheezing and adverse responses to viral infections, particularly those caused by rhinovirus, in 3–18-year-old children [71^{••}], highlighting the synergistic effect of sensitization, allergen exposure and concomitant viral infection in augmenting inflammatory responses in the airways.

Repetitive viral infections might confer protection to development of asthma, on the basis of their ability to skew the immune system away from the Th2-type response [66^{••},77[•]]. Daycare attendance or siblings

significantly increased the likelihood of contracting RSV or rhinovirus infections, and increased the risk of rhinovirus-induced wheezing at an early age. Neonatal IFN- γ responses were lower in infants with high frequency of respiratory infections; conversely, frequent infections were associated with a smaller decline of IFN- γ responses during the first year of life, indicating that preexisting immunologic factors may influence the expression of viral infections in infancy [77[•]].

Indoor and outdoor air pollution

Perceived ambient air pollution as a surrogate for exposure to outdoor air pollutants including nitrogen oxides, carbon monoxide and sulfur dioxide, and parental atopy were significantly associated with physician-diagnosed asthma among children 6–15 years of age of both sexes living in Taiwan [78]. Among 8–11-year-old asthmatic children followed prospectively, high exposure to nitrogen dioxide, mainly emitted from gas cooking appliances and motor vehicle exhausts, in the week before the start of a respiratory viral infection, was associated with an increase in the severity of a resulting asthma exacerbation [79^{••}]. Few studies have evaluated exposure to air pollutants prospectively and its relation to the development of asthma. Exposure to gas stoves and wood burning stoves, measured NO₂ concentrations and persistent mold increased the risk of persistent cough or wheeze in the first year of life among infants with an asthmatic sibling [80[•]]. The effect of these exposures varied among children whose mothers had physician-diagnosed asthma and children whose mothers were not asthmatic, indicating a role for genetic differences in susceptibility to specific environmental agents.

Environmental tobacco smoke

There is a strong body of evidence to support the role of exposure of children to environmental tobacco smoke (ETS) in increasing the incidence of asthma, wheeze, cough, bronchitis, bronchiolitis, pneumonia and impaired pulmonary function. ETS increases both the prevalence and severity of asthma, as judged by increases in the frequency of attacks, the number of emergency room visits and the risk of intubation [41^{••},44^{••}]. The risk associated with parental smoking seems to be greater at younger ages. Although a dose–response relationship between ETS exposure and respiratory outcomes has been demonstrated, at present there is no threshold dose of ETS exposure below which an effect will not occur, and therefore active intervention measures and policies to reduce or eliminate children's exposure to ETS should be strongly encouraged [41^{••}]. A home-based, individualized, intervention study [81^{••}] carried out among inner city children with atopic asthma which included education and remediation for exposure to both allergens and environmental tobacco smoke, resulted in reduction of asthma associated morbidity.

Conclusion

Atopy and asthma are related conditions, involving both environmental and genetic factors. Some environmental factors are amenable to prevention, including pre-natal and postnatal environmental tobacco smoke exposure, and exposure to food and inhalant allergens and air pollutants, whereas most respiratory viral infections including those caused by RSV and rhinovirus remain difficult to avoid, with no treatment available. Evidence suggests that events taking place between 2 and 3 years of age might be crucial determinants for the development of asthma. Treating children at this age with inhaled corticosteroids may alter the course of the disease and prevent loss of lung function, and this possibility is currently under investigation [53^{••}]. Alternative strategies have focused on manipulating the environment of high-risk individuals as an attempt to reduce the prevalence of asthma in children. At present, six primary prevention controlled studies are in progress [82[•]]. The longest follow-up reported has been from the Isle of Wight study. Stringent allergen avoidance measures instituted at birth, aimed at reducing exposure to house dust mites and preventing food sensitization, resulted in a significant decrease in current wheeze, nocturnal cough and symptomatic asthma, in addition to reduction in sensitization to allergens at age 8 years. Likewise, outcomes of the Canadian Primary Prevention Study on high-risk infants have been reported at age 2 years, showing that intervention comprising avoidance of mite, pet allergens, and environmental tobacco smoke, as well as dietary regimen resulted in reduction of asthma in the intervention group. Initial results from other cohorts look promising, but further follow-up will be necessary before any recommendations can be made [82[•]].

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