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THE ROLE OF INDOOR ALLERGENS IN THE DEVELOPMENT OF ASTHMA

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Abstract

Purpose of review—Asthma prevalence has markedly increased over the past 30 years. While atopy and exposure to environmental allergens is known to exacerbate asthma, recent literature supports a causal role of indoor allergens in disease development.

Recent findings—High risk birth cohorts continue to point to atopy as the main risk factor for developing asthma. Exposure to perennial allergens has also been linked to the development of asthma, though with less consistency. Intervention at the level of exposure mediation and allergic immune response is promising.

Summary—The current model of atopic asthma, the predominant phenotype, incorporates genetic and environmental factors in the development of disease. While genetic factors are less malleable, the environmental component lends itself to analysis and modification. For many, the development of asthma starts with allergen exposure leading to atopic sensitization and subsequent disease. Several studies support the progression from exposure to sensitization with the potential of extremely high levels of exposure leading to tolerance. Likewise, the progression from atopy to asthma is well documented, especially in genetically predisposed children. Recent intervention trials confirm these findings and begin to show promise for the prevention of asthma by interrupting the allergen exposure→allergen sensitization→atopic asthma pathway.

Keywords

Asthma; asthma development; perennial allergens; atopy

Introduction

Asthma prevalence has markedly increased over the past three decades [1]. It is largely accepted that gene-environment interactions are responsible for the development of asthma and that since population genetic variability does not change with such rapidity, changing environmental factors are likely responsible for this increase. For nearly two decades there has been mounting evidence that perennial allergens play a causative role in the development of asthma [2,3]. This review will describe the current evidence for the role of indoor allergens in the development of asthma by investigating the causative effect of early childhood exposure

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and the efficacy of asthma prevention strategies aimed at interrupting the allergen exposure→allergen-sensitization→atopic asthma pathway.

Allergen Exposure, Atopy, and Asthma

Sensitization to indoor allergens correlates well with indoor allergen exposure in young and school age children [4,5,6,**7,8,*9]. In many cases, exposure and sensitivity follow a dose-response relationship [6,*10,11,**12]. Evidence supporting this relationship is particularly strong for HDM [*10,**12] and cat [**7,8,13,14]. The association between atopy and asthma has been well documented[15,16], and recent national survey data in the United States shows that the prevalence of atopy in asthmatics approaches 80% and may be the causative factor in over 50% of asthma cases [15]. Allergen exposure in sensitized individuals with asthma has clear implications on asthma severity, morbidity and utilization of health care resources [17, 18,19]. Furthermore, young children sensitized to aeroallergens are likely to have persistent asthma symptoms into late childhood and adulthood and poorer lung function than those not sensitized [16,20,**21,22,23]. The primary aeroallergens to which these children are sensitized are house dust mite [HDM], furred pets (primarily cat and dog), cockroach, mold, and rodent allergens, with regional variations. The magnitude of exposure is emphasized by U.S. national survey data that shows Americans spend an average of 87% of their time indoors [24]. Infants and toddlers likely spend an even greater proportion of time indoors between home and daycare and are frequently in close proximity to the settled household dust which contains these allergens. [25]

Indoor allergens on the development of Asthma

Several longitudinal birth cohort studies have shown early atopy to be associated with asthma [16,20,**21,22,26]. General population studies have shown that early evidence of elevated total IgE and sensitization by skin prick test (SPT) to aeroallergens separates the population of persistent and late onset wheeze from those with early transient wheeze [16]. Children who are identified as atopic early in life tend to have higher total IgE and larger wheal size compared to those sensitized in later childhood [26] which may indicate a greater immunologic impact of earlier exposure. This also appears to be specific for aeroallergen sensitization and not food or seasonal allergies [20,27]. More recent population-based data from Australia confirms the greater risk of asthma in children with atopy, independent of lower respiratory track infections during infancy [28,29,30].

The strongest evidence of home allergen exposure and asthma development is in children of allergic or asthmatic parents [27,30,31,32,33]. Several recent studies have confirmed the risk of atopy in the development of asthma in high risk birth cohorts [**21,34,35]. The Childhood Asthma Prevention study [**21]showed that even in those without early wheezing illness or allergic manifestations, a positive SPT at 18 months old was strongly correlated with asthma at 5 years old indicating that atopy, independent of early respiratory insult, was at least an indicator of future asthma. Elevated IgE at 18 months also predicted SPT sensitization at 5 years old, echoing the Tucson birth cohort findings [16]. These associations between early atopy and asthma are carried through to early adulthood [22].

The role of atopy in the development of asthma in high risk groups was punctuated in the Multicentre Asthma Study [20] where 90% of the children with non-atopic wheeze in early childhood had remission of their symptoms by age 13 years old in contrast to only 56% of the atopic wheeze group.

While it is clear that atopic children have worse lung function throughout childhood [16,20], exposure to high levels of the offending indoor allergens, measured in the homes of subjects,

has an additional deleterious effect on lung function [20,36]. This may indicate early remodeling or chronic inflammation secondary to exposure to sensitized allergen.

Recent analysis of high risk cohorts has identified viral lower respiratory tract infection in early childhood as an independent risk factor [**21,28,35,37]. This new insight, however, seems to lend more evidence to the risk of allergic sensitization in high risk children to develop asthma. Kusel, et al. [**21] found current wheeze and current asthma at 5 years in association with wheezy and/or febrile lower respiratory illness, but these findings were restricted to those sensitized to allergens by two years old and not later.

Likewise, Chan-Yeung, et al. [35] found an association between RSV prior to 1 year of age and physician diagnosis of asthma at age 7, but the strongest correlation was that of atopy present at any age (tested at 1, 2, and 7years old).

While development of asthma has been clearly linked to early childhood atopy, the direct link to allergen exposures has been more variable [**7,*10,**12,38]

House Dust Mite

House dust mite (HDM) allergy has been strongly associated with asthma [2,19,39,40], asthma severity [41] and morbidity [42,43]. More than 50% of children and adolescents with asthma are sensitized to HDM [44]. It is by far the best studied allergen in the development of asthma, as well. In fact, independent of asthma, the development of sensitivity to HDM appears to predict poorer lung function than those not sensitized [44].

Analysis of HDM effect on the development of asthma attempts to delineate the connection between exposure, sensitivity, and asthma. Though not unanimous [8] [3,39], there is strong evidence for a dose-response relationship of exposure to HDM and sensitization in both cross-sectional [11] [45,46] and prospective studies [3,*10,**12]. The evidence for HDM exposure in general and high risk populations leading directly to asthma has had mixed results [3,47, 48]

Recent work by Tovey, et al. [**12] in a high risk cohort of children showed a non-linear relationship between levels of HDM found in homes and the development of asthma at 5 years of age. The trends showed increasing prevalence of sensitization and asthma correlating with HDM exposure up to a critical point, achieving statistical significance and then sharply dropping at the highest level of exposure (>23.40 μg Der p1/g dust). The immunologic implications of attenuated disease development with high levels of exposure are unclear, but may indicate high concentrations of non-allergenic immune modifiers such as endotoxin [49] and beta-glucans from fungus [50] that may play a protective role and are known to accompany HDM.

Celedon, et al. [*10] also found a dose response relationship between levels of HDM allergen found in the beds of infants of atopic parents at age 2 to 3 months and asthma at school age. These finding may not be disparate from those of Tovey [**12] in that the high allergen threshold for this study was ≥ 10μg/g so the critical concentration found in Tovey's study may not have been attained by any of the subjects or the result folded into the broader group.

Counter to these findings, Torrent, et al [**7] did not find any relationship between home HDM levels, allergic sensitization, or asthma in a prospective multicenter trial involving a general population cohort. Subgroup analysis of high risk infants was similarly unremarkable.

Pet

Clinically, cat allergen is the most insidious of the pet allergens, frequently appearing in dust samples where a cat does not live [51]and in schools and daycares [52,53]. In fact, similar prevalence of sensitivity is found in children who live with a cat and those who do not [40]. Cat allergen exposure in sensitized individuals is deleterious to lung function [36].

Data from the Asthma Multicentre Infant Cohort Study [**7,8,13] have strongly suggested that cat allergen exposure is associated with the development of sensitivity and asthma. Exposure to cat allergen measured during the child's first 3 months of life and sensitivity and asthma outcomes at 6years old showed a dose-dependent relationship up to a plateau of 1μg fel d1/g of dust. Analysis of the high risk subgroup showed an even greater association with asthma diagnosis at 6 years old with odds ratio over 18. This association is corroborated by previously published data [2,13,54].

Similar to findings with HDM, there may be a non-linear correlation of exposure to sensitivity and subsequent asthma [11,55]. In the German Multicentre Allergy Study [56] the infants exposed to the highest levels of cat allergen (fel d1) had decreased cat specific IgE levels and high IgG levels with corresponding low risk phenotype for wheeze. Early exposure to cat has been found protective for asthma in other cohorts, as well [57,58], though the presence of maternal atopy may adversely alter the risk [59].

There are fewer data for dog exposure and asthma. A recent meta-analysis by Takkouche, et al. [58] noted a slightly increased, statistically significant, relative risk of asthma in pet owners, not taking into account allergic sensitization. Other birth cohort studies have found no association [59]

Mold

The presence of IgE-specific mold sensitivity in children approaches 50% [60,61,62]. Alternaria alternata is the best described in relation to immunologically based respiratory symptoms in children and adults, though Cladosporium, aspergillus and penicillium have also been implicated to varying degrees [63]. Alternaria sensitization is independently associated with asthma [64] and responsible for asthma exacerbations and airway hyperresponsiveness in sensitized asthmatic subjects [65,66,67].

The relationship to the development of asthma was suggested by Cantani and Ciaschi [68] in a descriptive study of over 6000 atopic children in Italy. Halonen, et al. [60] provided prospective evidence that Alternaria sensitization at age 6 was the only aeroallergen associated with asthma at age 6 and 11 years old in a semiarid environment. Moreover, new asthma (diagnosed after age 6 years old) was associated with Alternaria sensitivity at age six, suggesting that sensitization to Alternaria was potentially responsible for the development of asthma.

Cockroach and Mouse

Cockroach allergen has been associated with sensitivity and asthma, particularly in urban environments [53,69]. Inner city children sensitized and exposed to cockroach suffer the highest morbidity [4,70]. Cockroach exposure has been shown to increase the risk of wheeze in children of atopic adults in longitudinal studies [71]. Though controversial [38], this effect has been seen in both sensitized and non-sensitized children [72].

T-cell mediated allergic response to cockroach allergen correlates with exposure to elevated levels at 3 months of life [73]. And, clinically, a dose response relationship has been shown

between cockroach allergen exposure and asthma and recurrent wheeze in high risk children [74].

Mouse allergen has also emerged as an important allergen affecting clinical outcomes of asthma [5,75,76]. It is one of the few allergens to span environments from inner city to suburban homes and schools [69,77,78].

Our recent analysis of the data collected as part of the Boston Home Allergens and Asthma Study [*9], which included 500 infants of atopic parents, showed significant association between current mouse exposure and current wheeze through 7 years of age, however early exposure at 2–3 months did not predict wheeze or asthma at 7 years. While it is possible that mouse exposure may influence respiratory status as an irritant [79], the association between early exposure to mouse and prevalence of atopy at 7 years argues that an early life exposure influences later disease through an allergic sensitization pathway [*9].

Further studies are necessary to determine if mouse allergen plays a role in asthma development.

Timing of Sensitization

While it is clear that early sensitization to perennial allergens is associated with asthma in school-age children, the actual timing of sensitization is debated.

There is evidence for T-cell priming in utero for maternal vaccination and fetal viral infection, but it is likely that the immunogenicity of aeroallergens that could potentially pass through the placental circulation is too weak to produce specific allergic immune response in the fetus [80,81]. Circumstantial evidence for *in utero* sensitization has been reported by studying T-cell reactivity in cord blood samples [82] but these have largely been refuted by the lack of evidence of allergen specific cytokine and IgE proliferation, relation to exposed allergens [*83] and correlation to childhood sensitization [**84].

In contrast, elevated IgE levels at 6 months have been shown to predict future allergic sensitization [**84] and at 9 months is associated with persistent asthma outcome [16]. Estimates for the critical window within which allergic sensitization leads to asthma range from birth to 8 years old [*10,20,27,85,86,*87]. More recent data has shown that T-cell induced IL-5 proliferation in response to allergen in 18 month olds neither predicted asthma in this cohort nor was repeatable at age 3 and 5 years old suggesting that early transient sensitization may occur and does not necessarily prognosticate for allergic disease [*87].

Perhaps the most compelling argument for early sensitization is presented by Kusel, et al. [**21] who found significant asthma outcomes in children sensitized by age 2 years old. This is further supported by laboratory evidence of strong TH2 cytokine response in 11 year olds who showed atopy early in life [88].

Prevention of Asthma

If the exposure to indoor allergens and subsequent sensitization lead to the development of asthma, it would be expected that intervention at the level of exposure and/or sensitization would mitigate the final outcome.

Allergen remediation

Secondary prevention of asthma morbidity and severity has been repeatedly shown by removing subjects from their sensitized exposures or remediation of the exposure in their environment [89,90]. Sensitized subjects may also convert their SPT to negative in the absence

of allergen exposure [91]. Based on these findings, allergen avoidance in early life may be expected to reduce or delay the onset of asthma.

The allergen content of homes can be substantially decreased with allergen remediation strategies [92] directed at cat, dog [90], mold, mouse [93]and cockroach [89,94]. Single interventions to reduce allergen exposure have reduced the levels of HDM [95,96,97], and seemed to improve outcomes at early ages. However, long term analyses of single HDM interventions have not prevented allergy and asthma [*87,98]. Some multifaceted interventions were similarly disappointing [86] [99].

Recent meta-analyses have shown multifaceted allergen remediation programs to be protective [*100,**101] against the development of asthma with statistically significant odds ratios between 0.52 and 0.79. The most protective effect was seen in children with greater than 5 years of follow-up [**101], indicating a true decrease in risk to those prone to develop atopic asthma. Macdonald, et al.[*100] found that the decrease in physician diagnosed asthma did not carry over to the outcome of parental report of wheeze. This divergence of findings between physician and parental findings may be more indicative of mitigation of severity rather than prevention of disease. Those without physician diagnosis may not have presented with such significant symptoms to warrant asthma diagnosis.

The single study that has shown the best preventative effect of allergen avoidance was the Canadian Childhood Asthma Primary Prevention Study [102], a multifaceted intervention program in a high risk birth cohort, studied by randomized controlled trial. The interventions were avoidance of house dust mite, pets, and environmental tobacco smoke starting prenatally, and encouragement of breastfeeding with delayed introduction of solids. HDM interventions included encasing parents' and infants' mattresses and box springs, weekly hot water wash of all bedding and application of benzyl benzoate to carpets and upholstery before birth and at 4 and 8 months postnatally. At 7 years old, children in the intervention group had significantly less physician diagnoses of asthma, wheeze in the past 12 months and wheeze apart from colds. The protective effect on physician diagnosed asthma was a relative risk of 0.44 (95% CI 0.25–0.79; P=0.006). Interestingly, there was no difference between the groups for the outcome of atopy despite reduced allergen levels during the intervention [103]. Arshad, et al. [104] also observed significantly fewer asthma symptoms at age 8 years old in a high risk birth cohort intervention focused on HDM and food allergen avoidance in early life, but this cohort did show a significant decrease in atopy at the 8 year time point.

The effectiveness, or lack thereof, of these intervention studies, may not be a decisive verdict of the efficacy of avoidance. First, while many studies show that allergen reduction is possible [99,105], the level of reduction may not be low enough to avoid an allergen mediated immune reaction [106]. Second, several prospective studies used educational programs to enforce their interventions which may have allowed for poor compliance with the stringent avoidance regimens [107]. Finally, in the high risk cohorts that were prospectively studied, it is likely that control group families actively avoid allergen exposures as a consequence of public knowledge and their own allergic tendencies [108].

Immunomodulator evidence for indoor allergens

While mediating indoor allergens has met with variable success in the prevention of asthma, many researchers aim to intervene at a later stage of the atopic march [109].

Specific immunotherapy (SIT) has shown to be effective in preventing the development of asthma in children with seasonal allergies at both 5 and 10 year follow-up of the Preventive Allergy Treatment (PAT) study. This preventative effect continued up to 7 years after the completion of the intervention [**110,111]. In the PAT study, there was no significant

difference in development of SPT sensitivity to HDM between those who did and did not develop asthma, however, other authors have recently reported SITs ability to prevent new sensitization to other allergens in those with monosensitization to HDM [112] or pollen [113]. Sublingual immunotherapy (SLIT) is also promising, but more work needs to be done to prove this modality [114]. All of these studies, however, are not double-blind placebo controlled, and a randomized controlled trial of SLIT is underway to evaluate this question [**115].

The PAT study lower age limit for inclusion was 6 years old. As many children with persistent wheeze and asthma will have developed disease or sensitization prior to school age, it will necessary to study SIT in younger children.

Conclusion

Asthma development depends on complex relationships between genetic predisposition and environmental modifiers of immune function. Persistent wheeze and asthma into the school age, as well as overall decreased lung function, can largely be predicted by phenotypic assessment in early life. While the role of viral infection in this pathway has recently gained significant attention, the role of early and persistent atopy currently remains most important in the development of asthma and asthma severity. Intervention to eliminate exposure to perennial allergens and the ability to temper the allergic tendencies of the immune system with SIT are proven to alleviate allergy and asthma symptoms and are promising, but not definitive, in their role in the prevention of asthma. Further research needs to be done on the role of early environmental exposures in the home and other environments and the development of atopic diseases and asthma in order to design effective primary prevention measures for these diseases.

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