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Decreased prevalence of asthma among children with high exposure to cat allergen: relevance of the modified Th2 response

Thomas A. E. Platts-MillsCA, John W. Vaughan, Kevin Blumenthal, Judith A. Woolfolk and Richard B. Sporik

Asthma & Allergic Diseases Center, University Health Systems, P.O. Box 801355, Charlottesville, VA 22908–1355, USA

CA Corresponding author Tel: +1 804 924 59 17 Fax: +1 804 924 57 79 E-mail: tap2r@virginia.edu

Introduction

Although there are many possible explanations for the increase in asthma, they can be simplified to three. The first was proposed as early as 1980 and was based on epidemiology from a small group of countries in each of which the increase was related to dust mite sensitivity.1–3 This hypothesis focused on the increase in exposure that had occurred secondary to changes in housing and lifestyle. Over the next 10 years, it became obvious that increases had occurred in many countries and regions where dust mites were not the dominant indoor allergen. In Sweden and Finland, the increase was clearly

Mediators of Inflammation · Vol 10 · 2001
present in areas where the primary allergens were derived from domestic animals. Similarly, in the southwest or mountain states of the USA, the relevant allergens are cat, dog and alternaria. Finally, it became clear that cockroaches were the most important allergen related to asthma in the major cities of the USA. Despite the involvement of different allergens, the time course of the increase appeared similar in many different countries (i.e. progressive over the period from about 1965 through 1995). Without evidence that exposure to these other allergens had increased, or a convincing explanation for an increase in cat or cockroach allergens, it became very unlikely that increasing exposure could explain all of the epidemic. However, exposure to indoor allergens may well have increased because of the increased time spent indoors.

The second group of hypotheses proposed that the increase could be explained by an alteration of immune responsiveness. These proposals focus on the many changes in lifestyle that could have shifted the balance between T helper cell (Th)1 and Th2 responses. The hypothesis is that changes in diet, immunization, antibiotic use and/or a decrease in infectious diseases could have led to an increase in allergic disease. Both of these hypotheses imply that there has been an increase in allergy in general, in parallel with the increase in asthma. The actual data on increases in other allergic diseases are confusing. In England, several epidemiological studies have suggested that hayfever has increased as much as asthma. In the USA, it appears that hayfever increased progressively from 1920 onwards and was already affecting 16% of the population by 1960 (i.e. before the major increase in asthma started). Similarly, comparisons of Hong Kong with Mainland China suggest that the increase in asthma in ‘westernized’ Hong Kong has not been matched by an increase in sensitization. If the increase in asthma represents a selective increase in lung disease or lung symptoms among the allergic population, then there are very different possible explanations.

### Immunity to common indoor allergens

The evidence about a relationship between allergens and asthma is restricted to inhalant allergens and is based on either skin tests or serum IgE antibodies. Thus, there is very little epidemiological data relating to allergens that are not inhaled. In addition, there is no evidence based on T-cell responses or other isotypes of antibodies. At the time when immunoglobulin (Ig)E was discovered, it was already clear that the immune response in allergic individuals included other classes of antibodies, particularly IgG and IgA. Subsequently, it became clear that T-cell responses to purified allergens were common among patients with asthma and that these T cells were characteristically Th2 in type.

Recently, several groups have suggested that responses to dust mite and other inhalants are dictated by events in utero. However, on critical analysis, the lymphocyte proliferation data on which that idea was based is unconvincing. In particular, there is very little data to show that cord blood responses are influenced by the exposure of the mother. Objective data on immune responses to inhalant allergens (i.e. serology or skin tests that can be repeated) is generally not apparent until about 2 years of age. For allergens derived from dust mites, there is evidence from Australia, Europe, the United Kingdom and the USA that the prevalence of sensitization is directly related to exposure. Furthermore, for dust mites, it is possible to define a ‘community’ threshold for exposure above which sensitization to mites will be significantly related to asthma. Although the data for cockroach allergens is less extensive, it appears that both sensitization and the risk of asthma are also directly related to exposure to these insects.

By contrast, the evidence related to cat allergens is not simple. For several years there have been reports from Scandinavia that children raised in a house with a cat were less likely to have asthma. The obvious explanation is that allergic families avoid owning cats. However, the decreased sensitization of children.

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**Table 1. High concentrations of cat allergen are associated with decreased sensitization**

| Exposure to cat allergen Fel d 1 (µg/g) | Sensitization to cat | IgG antibody to cat | IgG antibody and sensitized | IgG antibody and not sensitized |
|---------------------------------------|----------------------|--------------------|----------------------------|------------------------------|
| < 1.6 (n = 75)                        | 12                   | 13                 | 10                         | 3                            |
| 1.7–23 (n = 75)                       | 19                   | 24                 | 41                         | 18                           |
| 23–3840 (n = 76)                      | 10                   | 6                  | 10                         | 31                           |

*Total of 225 middle-school children aged 11 years. Sensitization assessed by skin tests and IgE antibody; data from references 4, 17 and 20.
living in a house with a cat is equally present among children who are atopic as judged by other skin tests. Recently, we have shown that many of the children who are exposed to high concentrations of cat allergen at home have IgG antibodies to Fel d 1 (Table 1). Furthermore, these IgG antibodies include a large proportion of IgG4, an isotype that is fully dependent on interleukin-4. Thus, this immune response to Fel d 1 in children who are not skin-test-positive to cat, and not asymptomatic, we refer to as a 'modified Th2 response'. This evidence that high exposure to an allergen can induce tolerance has many implications. These include: (i) that the response to high-dose animal allergen is not a Th1 response; (ii) that increasing exposure to cat allergens cannot explain the increase in asthma since higher exposure gives rise to tolerance; and (iii) that it is unlikely that changes in 'immune responsiveness' could have produced the same progressive increase in asthma in countries where cat allergen is dominant as in countries where mite is dominant.

Have lifestyle changes altered the threshold for wheezing?

The increase in asthma prevalence over a 40-year period looks similar to the increase in type 2 diabetes, hypertension or obesity, rather than any known epidemic of infectious disease. In the USA but not in other countries, this increase has been most severe among individuals living in poverty and, in particular, among African Americans living in the cities. It is therefore essential to examine changes in lifestyle in the cities that could be relevant to a progressive change over 40 years. There are three lines of evidence that suggest that lifestyle changes, including a decline in physical activity, could have lowered the threshold for wheezing.

1. Bronchial smooth muscle requires regular full extension, or it will start to contract at a shorter length. In keeping with that, normal individuals will develop broncho hyper-responsiveness (BHR) if they are prevented from taking deep breaths. While it is possible that hormonal or other effects related to obesity influence ‘inflammation’ in the lungs, the more likely explanation is that obesity is a surrogate for decreased activity.

2. Recent reports that obesity is a risk factor for both prevalent and incident asthma. While it is possible that hormonal or other effects related to obesity influence ‘inflammation’ in the lungs, the more likely explanation is that obesity is a surrogate for decreased activity.

3. The lifestyle changes that characterize poverty in the cities of the USA (and could explain the difference from poverty elsewhere in the world) are poor diet, increased sedentary time, and a decline in physical activity.

In some countries, particularly China and the USA, the evidence suggests that the increase in asthma has been primarily an increase in wheezing among allergic individuals. If this is so, then the increase in asthma could be seen as a decrease in the threshold for wheezing. Taking the evidence together, we would ask that these physical activity or prolonged time spent inactive lowered the threshold for wheezing? This effect could be primarily physiological (i.e. related to smooth muscle function); the alternative explanation would be that prolonged exercise plays a role in decreasing inflammation or accelerating the healing of inflammatory foci.

Conclusion

The evidence that children raised in a house with a cat are less likely to become allergic to cat allergens has major implications for understanding the role of immune responses to allergens in the increase in asthma. First, it is clear that the dose response to animal dander is different from that to mite or cockroach, thus the effect of increasing exposure would not be the same. Second, the finding that high exposure to cat allergen can induce a modified Th2 response strongly argues against the hypothesis that a shift from Th1 to Th2 could be the basis for the increase in asthma. Indeed, in our studies, most non-allergic individuals have no serological evidence that they have made an immune response. The results imply that the true explanation for the increase in asthma lies elsewhere. Given the evidence about obesity and the physiological requirement of bronchial smooth muscle for full extension, it becomes increasingly possible that the decline in physical activity has contributed to a progressive lowering of the threshold for wheezing among allergic children.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease clinically and histologically highly similar to allergic contact dermatitis. Recently, it has been proposed to subdivide AD into two distinct forms: the extrinsic form (occurring in the context of sensitization toward environmental allergens), and the intrinsic form (occurring in the absence of any typical atopic background). While the pathophysiology of the intrinsic form remains almost elusive, tremendous progress has been made in the understanding of the extrinsic form. Thus, since IgE plays a major role in other atopic diseases such as asthma and rhinitis, it is assumed that, in this extrinsic form, immunoglobulin E (IgE) also mediated the specificity of the inflammatory conditions in the skin.

Presence of IgE-bearing dendritic cells in patients with AD

The emergence of extrinsic AD (i.e. a cell-mediated inflammation) in atopic patients (i.e. individuals prone to have increased IgE production and to develop IgE-mediated hypersensitivity reactions) remained puzzling until the mid-1980s, when the presence of IgE molecules on the surface of Langerhans cells (LC) from patients presenting AD was first reported. A new pathophysiological concept was proposed in which LC and inflammatory dendritic epidermal cells (IDEC) armed with allergen-specific IgE would trigger an eczematous inflammation.

Molecular structure, regulation and function of FcεRI on human dendritic cells

The identity of the relevant IgE-binding structure of cutaneous dendritic cells (DC) was unclear for some years, until other workers and myself demonstrated the presence of the high-affinity receptor for IgE (FcεRI) on human dendritic cells. It also became clear that FcεRI ligation on APC lacks the classical β-chain and thus, in contrast to effector cells of anaphylaxis (i.e. mast cells and basophils that express an α,β,γ2 conformation), APC display an α,γ2 conformation that implies profound functional consequences. Moreover, its expression and the function may be highly variable, depending on the microenvironment. However, the highest expression is specifically observed in AD skin. One may speculate that FcεRI ligation on APC potently triggers the synthesis and release of mediators that may initiate a local inflammatory reaction, as has been demonstrated for mast cells.

FceRI/IgE-mediated allergen uptake and subsequent antigen presentation has been attributed a key event in the pathogenesis of atopic dermatitis. Using this kind of antigen uptake, APC may, in the presence of antigen-specific IgE, increase their presenting capacity up to 100-fold. This mechanism, also known as ‘antigen focusing’ or ‘facilitated antigen presentation’, has been shown effective by different research groups in different cell systems. The observation that the