

Serum IgG and IgG4 Antibodies to Fel d 1 among Children Exposed to 20 µg Fel d 1 at Home: Relevance of a Nonallergic Modified Th2 Response

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Key Words

Modified Th2 · Cat allergen · Mite · Asthma · Tolerance

Abstract

Exposure to foreign antigens is an essential element of all immune responses, including allergic sensitization. For some allergens (e.g. mite and cockroach), the prevalence of sensitization is directly correlated with exposure. However, for allergens derived from domestic animals, several studies have suggested that children with a cat in the home have a decreased risk of sensitization and asthma. We have now shown that many children exposed to greater than 20 µg of Fel d 1/g of dust at home made an IgG and IgG4 antibody response to Fel d 1 without IgE antibody. This modified Th2 response is not associated with symptoms and should be regarded as a form of immunological tolerance. The fact that the dose-response relationship between cat exposure and sensitization is bell shaped, while that for mite exposure and sensitization is linear, is highly relevant to understanding the role of allergens in the increase in allergic disease.

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Introduction

In 1970, Morrisson Smith reported that there had been an increase in asthma among school children in Birmingham, England over the decade from 1958 to 1968. He also showed that positive skin tests to dust mite were much more common among the children with asthma than among those without symptoms. Those studies essentially defined a problem that subsequently became obvious in many different countries and has persisted for 40 years. Although there are many possible explanations for the increase, 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 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* [4, 5]. Finally, it became clear that cockroaches were the most important allergen related to asthma in the major

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cities of the USA [6, 7]. 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 rationale for a progressive increase in cat or cockroach allergens, it became very unlikely that increasing exposure could explain all the epidemic. However, with a large proportion of time spent indoors, increased exposure to indoor allergens may well have contributed.

The second group of hypotheses proposed that the increase could be explained by an alteration of immune responsiveness [8]. These proposals focus on the many changes in lifestyle that could have shifted the balance between Th1 and Th2 responses [9, 10]. The hypothesis is that changes in diet, immunization, antibiotic use and/or decrease in infectious diseases could have led to an increase in allergic disease. It is important to realize that both of the first two 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 is confusing. In England, several epidemiological studies have suggested that hay fever has increased as much as asthma [11]. In the United States it appears that hay fever 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.

Relevance of the Immune Response to Inhalant Allergens

The epidemiological 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 data relating to foods or to any other noninhaled allergen and no epidemiological evidence related to other aspects of the immune response. In particular, there is no evidence based on T cell responses or other isotypes of antibodies. At the time when IgE was discovered, it was already clear that the immune response in allergic individuals included other classes of anti-

bodies, particularly IgG and IgA [12]. 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. Several groups have suggested that responses to dust mite and other inhalants are dictated by events in utero [13, 14]. 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 [15]. 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 [16]. For allergens derived from dust mites, there is evidence from Australia, Europe, UK and the USA that the prevalence of sensitization is directly related to exposure [1]. 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. This threshold value of 2 µg group 1 mite allergen/g should be seen as a statistical value for a population, not on an individual basis. Although the data for cockroach allergens is much less extensive, it appears that both sensitization and the risk of asthma are also directly related to exposure to these insects [7, 17]. 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 [18, 19]. The obvious explanation is that allergic families avoid owning cats. However, the decreased sensitization of children living in a house with a cat is equally present among children who are atopic as judged by other skin tests [17]. 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 which is fully dependent on IL-4 [20]. Thus, this immune response to Fel d 1 in children, who are not skin test-positive to cat and not symptomatic, should be seen as a modified Th2 response. This evidence that high exposure to an allergen can induce tolerance has many implications. These include (1) that the response to high dose animal allergen is not a Th1 response, (2) that increasing exposure to cat allergens cannot explain the increase in asthma since higher exposure gives rise to tolerance, and (3) 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.

Table 1. High concentrations of cat allergen are associated with decreased sensitization but increased IgG (and IgG4) antibodies to Fel d 1

	Exposure to cat allergen (Fel d 1), µg/g			p value
	<1.6 (n = 75)	1.7–23 (n = 75)	23–3,840 (n = 76)	
Sensitization to cat	12	19	10	NS
IgG Ab to cat	13	24	41	<0.001
IgG Ab and sensitized	10	6	10	NS
IgG Ab and not sensitized	3	18	31	<0.001

225 middle school children aged 11 years. Sensitization assessed by skin tests and IgE antibody [data from 4, 17, 20].

The Third Hypothesis: Lifestyle Changes Have Changed the Threshold for Wheezing

These progressive increases in asthma prevalence over a 40-year period look 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 American 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 be have lowered the threshold for wheezing: (1) The bronchial smooth muscle requires regular full extension, or it will start to contract at a shorter length [21]. In keeping with that, normal individuals will develop bronchial hyperresponsiveness if they are prevented from taking a deep breath for as little as 30 min [22]. (2) There is recent evidence that obesity is a risk factor for asthma and the onset of wheezing in the USA [23, 24]. 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 which characterize poverty in the cities of the United States (and could explain the difference from poverty elsewhere in the world) are poor diet, increased sedentary time, and a decline in physical activity [25].

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: Has decreased 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 nonallergic 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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