Allergen sensitisation in asthmatic children: consecutive case series

TF Leung, AM Li, G Ha

Objective. To investigate the pattern of sensitisation to aero-allergens and food allergens among asthmatic children in Hong Kong, and to investigate any correlation between atopy and the severity of asthma.
Design. Consecutive case series.
Setting. Paediatric out-patient clinic of a university teaching hospital, Hong Kong.
Participants. Two hundred and four consecutive children with physician-diagnosed asthma who attended from January 1999 through June 2000.
Main outcome measures. Demographic data, questionnaire assessment of asthma control, spirometric evaluation, response to skin prick testing, eosinophil count, and total serum immunoglobulin E concentration.
Results. The median patient age was 8.2 years (range, 5.7-11.3 years), and the median 1-second forced expiratory volume was 95% of the predicted value. The median absolute eosinophil count in the peripheral blood was 0.48 x 10^9 /L and the ratio of total serum immunoglobulin E to the age-adjusted upper limit of the normal range was 2.7. Atopy, as defined by at least one positive response to skin prick testing, was found in 170 (83.3%) of the 204 patients. House dust mites were the most commonly sensitised aero-allergen (n=167; 81.9%). Sensitisation to food allergens was found in 47 (23.0%) of the patients. The self-reported frequency of asthmatic attacks was associated with a positive response to skin prick testing with animal allergens (P for trend = 0.001), whereas spirometric indices correlated with the degree of atopy and the presence of in vivo cockroach-specific immunoglobulin E.
Conclusion. Sensitisation to indoor aero-allergens as determined by skin prick testing, is prevalent among Chinese children with mild-to-moderate asthma, whereas sensitisation to food allergens is not. The severity of asthma is correlated with skin prick test responses to pet and cockroach allergens.

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Key words: Allergens; Asthma; Child; IgE/blood; Skin tests; Spirometry

Introduction

Asthma and allergy are related conditions that are caused by a complex interaction of genetic factors and environmental influences. The occurrence of asthma and wheezing illnesses has been increasing in children and young adults in western countries, as well as in the Far East.[1] The prevalence of self-reported wheeze varies from 3.1% to 13.2% among Chinese children in countries from South-East Asia.[2] Differences in environmental factors are advocated as one of the reasons for this wide fluctuation in asthma epidemiology.[2] Among school-aged children, sensitisation to indoor allergens is the major risk factor for asthma, which is defined as symptomatic bronchial hyperresponsiveness.[3-5] In many humid countries, allergens that derive from house dust mites are the most important cause of sensitisation.[3,6-9] Leung et al[10] have reported that atopic sensitisation is found in approximately 50% of secondary-level schoolchildren in South-East Asia, with allergens from house dust mites and cockroaches accounting for more than 95% of positive responses to skin prick tests (SPTs). Appropriate allergen avoidance measures can be achieved only when the pattern of sensitisation to indoor and seasonal allergens in a particular target population is known.

There have been no well-established, hospital-based data on allergen sensitisation among asthmatic children in Hong Kong. This study aimed to investigate the pattern of sensitisation to aero-allergens and food

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allergens among asthmatic children in Hong Kong, and to investigate any correlation between atopy and the severity of asthma in the study cohort.

Methods

Participants and study design

This study summarises a single-centre experience of evaluating allergen sensitisation in asthmatic children in Hong Kong. Of the children attending the general paediatric out-patient clinic of the Prince of Wales Hospital from January 1999 through June 2000, those in whom asthma had been diagnosed, according to the criteria proposed by the American Thoracic Society,[11] were offered the chance to undergo an allergy assessment. Patients or their parents gave informed verbal consent before the clinical evaluation. All participants had to have been free from infection for 4 weeks prior to the assessment.

Clinical assessment

Demographic data, the severity of asthma during the 1-year period before the assessment, and details of anti-asthma drug treatments used were obtained by using a standardised questionnaire. Any patient history of other allergic diseases, such as allergic rhinitis, eczema, or chronic urticaria; allergies to food, drugs, or vaccines; and any family history of allergic diseases were also recorded.

Skin prick testing to detect allergen sensitisation

The same investigator performed all SPTs according to standard procedures, using purified allergen extracts (Hollister-Stier Laboratories, Spokane [WA], United States). The aero-allergens used were divided into five groups: (1) *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* house dust mites; (2) cat and dog dander; (3) mixed American and German cockroaches; (4) mixed ragweed, grass pollens, and tree pollens; and (5) mixed moulds (*Penicillium notatum, Alternaria tenuis, Aspergillus fumigatus,* and *Hormodendrum cladosporioides*). The subjects also underwent SPTs using a panel of the following common food allergens: whole egg, whole cow's milk, mixed codfish, wheat, mixed peanut allergens, and soybean. Positive and negative controls were histamine (10 mg/mL) and normal saline, respectively. Children were considered to be atopic if they had at least one skin test result that showed an induration with a diameter of at least 3 mm greater than the negative control. Each participant was assigned an atopy index, which was the sum of the number of groups of aero-allergen that gave a positive reaction plus the size of the largest reaction (scored as 1 for <4 mm and 2 for ≥4 mm).[12]

Spirometry and blood testing

Patients who were older than 5 years also underwent spirometric assessment using a COMPACT II spirometer (Vitalograph, Buckingham, United Kingdom). The FEV_1, forced expiratory vital capacity (FVC), and FEV_1/FVC ratio were obtained before and 15 minutes after the inhalation of salbutamol 20 μg (Ventolin; GlaxoWellcome, Uxbridge, United Kingdom). The results were compared with the local age- and sex-matched reference values.[13] Participants were then categorised into groups of asthma severity according to the percentage value of their FEV_1 compared with the predicted FEV_1 (mild, >80%; moderate, 60%-80%; or severe, <60%).[14] Furthermore, peripheral venous blood was collected to measure the number of eosinophils using an automatic cell counter and the serum total immunoglobulin (Ig) E concentration using a microparticle immunoassay (IMx analyser; Abbott Laboratories, Abbott Park [IL], United States).

Statistical analysis

The clinical characteristics and results of allergen sensitisation of participants with normal and abnormal lung function were compared using the Student's *t* test, Chi squared test, or Fisher's exact test, as appropriate. The differences in mean values of spirometric measurements between patients with and without allergen-specific IgE were compared using the Student's *t* test. The correlation between SPT responses to aero-allergens and asthma severity was assessed by calculating Pearson's product moment correlation coefficient (*r*). All comparisons were made using two-tailed tests; the cut-off level for statistical significance was taken as P=0.05.

Results

Clinical characteristics of participants

A consecutive series of 204 asthmatic children were recruited, and all participants agreed to be assessed. This sample size was estimated to represent approximately 10% of asthmatic children who were being followed-up in the out-patient clinic. Both parents were Chinese in all but two cases; for two children, one of the parents was a Caucasian. The clinical, spirometric, and laboratory characteristics of the participants are summarised in Table 1. The majority (n=156; 76.5%) of patients had experienced less than five acute asthmatic attacks within the 12 months prior to the evaluation. There was a significant correlation between the eosinophil count and the ratios of serum IgE levels to the upper limit of the normal range in these patients (r=0.414; P<0.001). Based on a spirometric assessment of the FEV_1, 146 (93.0%) of the 157 asthmatic

Table 1. Demographic data, clinical and spirometric indicators of asthma control, and laboratory markers of atopy in asthmatic children (n=204)

Characteristic	Value
Demographic data	
Age at evaluation (years)*	8.2 (5.7-11.3)
Sex (male:female)	128:76
No. with allergic rhinitis (%)	154 (75)
No. with eczema (%)	79 (39)
No. with symptoms suspicious of food allergy (%)	18 (9)
Domestic tobacco smoking (%)	77 (38)
Cats or dogs ever at home (%)	16 (8)
Furry toys in the bedroom (%)	106 (52)
Clinical indicators of asthma severity	
No. of asthma attacks in preceding year	
≤2 attacks (%)	85 (42)
3-5 attacks (%)	71 (35)
≥6 attacks (%)	48 (23)
Use of inhaled corticosteroids (%)	133 (65)
Spirometric assessment	
FEV_1† as % of predicted value*	95 (77-110)
Asthma severity according to FEV_1 (mild:moderate:severe)	112:34:11
FVC‡ as % of predicted value*	110 (92-125)
FEV_1 reversibility after salbutamol as %*	7 (3-13)
FEV_1/FVC ratio in %*	80 (72-89)
Laboratory markers of atopy	
Ratio of serum total IgE level to age-adjusted upper limit of normal range	2.7 (1.0-5.5)
% eosinophils of total leukocytes in peripheral blood	7 (3-10)
Concentration of eosinophils in peripheral blood (10^9/L)*	0.48 (0.25-0.73)

* Results are expressed as median (25th to 75th centiles)
† FEV_1 1-second forced expiratory volume
‡ FVC forced vital capacity

children who had spirometry performed showed mild-to-moderate airflow limitation (≥60% of the predicted value). Keeping pets at home, having furry toys in the bedroom, and the presence of domestic tobacco smoke did not affect any of the spirometric measurements in this cohort (data not shown).

Atopy and allergen sensitisation

The SPT responses to aero-allergens and food allergens are shown in the Figure. Atopy, as defined by at least one positive response to skin prick testing, occurred in 170 (83.3%) of the patients, with the median atopy index being 4 (range, 0-7). The three major environmental allergens in this hospital-based cohort of asthmatic children were house dust mites (n=167; 81.9%), animal dander (n=84; 41.2%), and mixed cockroaches (n=61; 29.9%). There was a significant correlation between sensitisation to *D pteronyssinus* and *D farinae* (r=0.840; P<0.001). The mean percentage eosinophil count and ratio of serum IgE levels to

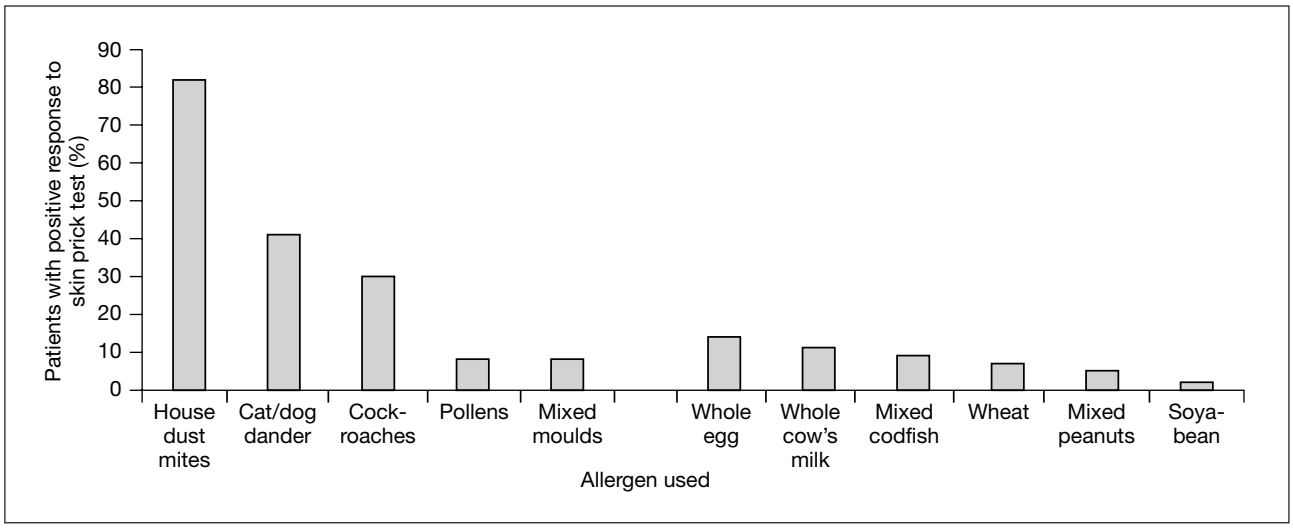

Fig. Sensitisation to aero-allergens and food allergens as measured by skin prick testing

Table 2. Correlations between atopic markers and spirometric measurements of asthma severity

Characteristic	Pearson's product moment correlation coefficient (*r*)			
	FEV_1*	FVC†	FEV_1/FVC	FEV_1 reversibility
Ratio of serum total IgE level to ULN‡	0.082	0.046	0.036	0.079
% eosinophils in peripheral blood	0.083	0.058	0.022	0.207‖
In vivo atopy testing by skin prick testing§				
Dermatophagoides pteronyssinus	-0.037	-0.021	-0.110	0.054
Dermatophagoides farinae	-0.094	-0.090	-0.097	0.065
mixed American and German cockroaches	-0.300¶	-0.317¶	-0.009	0.221**
cat dander	-0.108	-0.109	-0.062	-0.028
dog dander	-0.115	-0.127	-0.005	-0.010
mixed moulds				
Atopy index	-0.091	-0.074	-0.101	0.184‖

* FEV_1 1-second forced expiratory volume
† FVC forced vital capacity
‡ ULN upper limit of normal range
§ Reactions to individual allergens, as measured by diameter (mm) of wheals, were used in the correlation analysis
‖ P <0.05
¶ P<0.001
** P<0.005

the upper limit of the normal range differed significantly between atopic and non-atopic patients (8.2% versus 2.6% [P<0.001] and 7.7 versus 0.7 [P<0.001], respectively). On the other hand, sensitisation to at least one food allergen was found in 47 (23.0%) patients. Twenty-eight (13.7%) asthmatic patients had specific IgE to egg allergen, as indicated by the SPT response, whereas sensitisation to other foods was uncommon (2.0% to 10.8%). The prevalence of atopy did not differ among patients with and without inhaled steroid treatment (84.8% versus 79.9%; P=0.392). A positive SPT response to cat and dog allergens, but not to others, was significantly associated with the self-reported frequency of asthmatic attacks in the preceding year (56% for those with one or two attacks, 30% for those with three to five attacks, and 33% for those with five or more attacks; P for trend = 0.001).

Spirometric evaluation

The mean reversibility of FEV_1 following inhalation of a bronchodilator in atopic and non-atopic patients differed significantly (10.0% versus 4.1%; P<0.001). The measured FEV_1 and FEV_1/FVC ratio did not differ between the two groups but were similar between patients with and without a positive reaction to food allergens (data not shown). The Pearson's product moment correlation coefficients between spirometric measurements and markers of atopy are shown in Table 2. The degree of atopy and eosinophil count in the peripheral blood correlated with the reversibility of FEV_1 (r=0.184 [P<0.05] and r=0.207 [P<0.05], respectively). There was also a significant and consistent correlation between sensitisation to cockroach allergens and the measured FEV_1, FVC, and FEV_1 reversibility following inhalation of a bronchodilator.

Discussion

The role of the environment in the pathogenesis of asthma has become increasingly obvious as the evidence for regional variation in the prevalence of allergic diseases has accumulated.[1,2,10,12,15] Although an increasing number of gene loci have been linked to asthma and atopy,[16] genetic factors alone cannot explain the marked differences in the prevalence of allergic diseases in population-based studies. Among the proposed environmental factors related to asthma pathogenesis, allergen sensitisation has been the most widely implicated in susceptible individuals. Sensitisation to house dust mites and cat dander has been associated with the development,[6,9,17] exacerbation,[8,18] and severity of asthma symptoms.[19]

Leung et al[10] studied 1062 schoolchildren in Hong Kong and found that 58% of them had at least one positive SPT response to aero-allergens. Only a small proportion (6.6%) of the children studied, however, were found to have asthma. Using similar methodology, this study has shown that more than 80% of a group of 204 asthmatic children in Hong Kong were atopic. This prevalence is much higher than the figures reported in other studies involving Chinese subjects.[10,12] The main reason for this difference is that the former studies involved non-selected schoolchildren who had a high rate of asymptomatic allergen sensitisation.

In contrast, this study was performed in a hospital-based cohort of asthmatic children; hence, the participants were at the more severe end of the spectrum of atopic manifestations. This bias was lowered, however, by the fact that most (93.0%) of the 157 patients who underwent spirometric assessment had only mild-to-moderate asthma. About one quarter of these patients

had more than one asthmatic attack every 2 months, and just 11 (7.0%) had severe impairment of FEV_1 as found by spirometry (<60% of predicted values). Based on these indicators of asthma severity, the current study may underestimate the degree of allergen sensitisation and its correlation with asthma development and severity in Chinese children with severe asthma.

An epidemiological survey of Hong Kong Chinese schoolchildren showed that allergic sensitisation to moulds and animal allergens, but not to other indoor allergens, was associated with asthma.[10] In contrast, studies involving two other Chinese populations have shown that exposure to house dust mites was the dominant risk factor for asthma.[10] Each target patient population should establish its own spectrum of allergen sensitisation, so that appropriate avoidance measures can be sought. Samplings of major aero-allergens in the domestic environment of 40 randomly selected residential homes have demonstrated that *Der p* 1, *Fel d* 1, and *Bla g* 2 are the predominant allergens in Hong Kong.[20] This observation is consistent with the finding that house dust mites, animals, and cockroaches were the major reactive aero-allergens in this case series.

Sensitisation to animal dander in this study showed significant negative correlation with the self-reported frequency of asthmatic attacks. Approximately 50% of patients who experienced three or more asthmatic attacks a year had positive SPT responses to cat or dog dander, unlike those who experienced less frequent exacerbations. The reason for this observation remains unclear. Owing to the design of this study, data on the details of environmental control in the patients' homes were limited. This drawback precludes accurate assessment of domestic exposure of the participants to animal dander, house dust mites, and cockroaches. Asthma control in sensitised patients may worsen if they are exposed to large amounts of the reactive aero-allergens at home, and highly sensitised individuals may experience asthmatic episodes when they are exposed to these allergens.

Alternatively, these atopic patients might practise meticulous avoidance measures against exposure to animal dander, which would account for the less frequent asthmatic attacks within the year prior to this evaluation. It was also observed that just 16 (7.8%) of participants ever kept cats or dogs at home, which is inconsistent with the finding that approximately two fifths of the participants were sensitised to animal dander. Further studies involving a more detailed evaluation of environmental factors for asthma control in the local population are needed.

Several previous reports have suggested that allergen avoidance against house dust mites might be helpful in the control of asthma in Caucasian populations.[17,21,22] Although this study confirmed that sensitisation to house dust mites is prevalent in Chinese children with asthma, this factor did not correlate with either the frequency of asthmatic attacks or spirometric indicators of asthma severity.

Frederick et al[22] failed to show any long-term clinical benefit of a dust mite–proof bed-covering system in asthmatic children, in terms of asthma symptoms, bronchodilator use, or bronchial hypersensitivity. Peat et al[7] have also reported that the overall prevalence of sensitisation and asthma are both unrelated to the levels of exposure to house dust mite allergens in six Australian centres. The same group have found similar levels of allergen sensitisation and asthma prevalence in seven regions of New South Wales, despite differences in climatic conditions and allergen exposure.[23] Based on the above clinical findings, the efficacy of avoidance measures against exposure to house dust mites in the prevention of asthma development and exacerbation remains to be shown.

Parents of asthmatic patients commonly complain that certain foods aggravate respiratory symptoms in their children. A variety of foods are also implicated in causing bronchial hyperresponsiveness and respiratory symptoms in patients with asthma.[24-26] Yazicioglu et al[24] showed that two fifths of 50 asthmatic children aged 1.5 to 6 years had SPT reactions to egg and milk. On the other hand, food allergy occurred in only 4% of their study population, as diagnosed by double-blind placebo-controlled food challenge testing, which is the gold standard in the diagnosis of food allergy. This study revealed that approximately one quarter of the cohort had positive SPT responses to one of the six food allergens tested. The clinical significance of sensitisation to foods in these patients remains uncertain, because positive SPT reactions are well known for their poor specificity and positive predictive values for food allergy.[27] Hence, food challenges are required to confirm the results. This study nevertheless provides local allergologists with data on the prevalence of food allergen sensitisation, which can be used to plan further research and treatment strategies.

In conclusion, sensitisation to indoor aero-allergens, as determined by skin prick testing, is prevalent among Chinese children with mild-to-moderate asthma, whereas sensitisation to food allergens is not. The severity of asthma is correlated with skin prick test responses to pet and cockroach allergens.

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