Studies of the Relationship between Allergen-Specific IgE Antibodies and Skin Test Reactivity in Patients with Asthma in Kuwait

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Key Words

Skin prick test · Specific immunoglobulin E · Allergy · Asthma · Cockroach sensitization

Abstract

Background: Studies have shown that allergens are important sensitizing agents in asthma. The relationship between various allergy markers has not been documented in Kuwait, although asthma is common. This study was therefore designed to investigate this relationship. **Method:** One hundred and one adult asthmatics were recruited over a 1-year period for this study. After administering a skin prick test (SPT) for common allergens, blood was taken for measuring specific IgE concentrations. **Results:** Eighty-two percent of the patients had positive SPT reactions to at least one allergen. Chenopodium sensi-

zation was the most common, occurring in 47% of cases. Specific IgE was positive in fewer cases, which showed a positive reaction to SPT with the same allergen, the highest being observed with cockroach, occurring in 76% of the cases. There was a positive correlation between the wheal diameter of SPT and the concentration of specific IgE in three of the four allergens tested ($r = 0.376$, $p \leq 0.001$ for Bermuda grass; $r = 0.255$, $p \leq 0.01$ for cockroach, and $r = 0.254$, $p \leq 0.01$ for chenopodium). The sensitivity, specificity and diagnostic accuracy of SPT in the allergens tested were below the reported findings in studies from Western countries. **Conclusion:** This study revealed that SPT had a better predictive value than specific IgE, and there was evidence of increasing sensitization to the cockroach allergen in this environment.

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Introduction

Immunoglobulin E (IgE)-mediated allergy is a major feature of asthma in young patients [1, 2]. Diagnosis of an allergic disorder is largely based on medical history, which can be confirmed by means of measurement of antigen-specific IgE levels or skin tests [3, 4]. In tropical settings where the prevalence of intestinal helminths is high, serum total IgE levels appear to be much higher than in subtropical countries, and this might present a problem in the interpretation of total IgE levels [5]. Epidemiological studies have shown a relationship between certain respiratory symptoms and distinct patterns of various allergy parameters [1, 6, 7]. These findings may not, however, be applicable to the clinical situation. The value of skin tests and allergen-specific IgE for predicting symptomatic allergy in patients has been evaluated in some studies in the Western hemisphere [3, 8–10]. However, to our knowledge, no such study has emanated from this region. Indirect evidence based mainly on the results of skin tests suggests that there are differences in the prevalence of atopy from one area to another [11].

Asthma is the most common respiratory disease in the Middle East. Patients are routinely treated according to internationally accepted guidelines. Neither skin test nor serum IgE (total or allergen-specific) are used in the routine evaluation of patients with asthma in Kuwait. A study of this nature would provide baseline data, which can be used to determine if these allergic parameters are beneficial and relevant to this region in the assessment and monitoring of patients with asthma.

This study has therefore been designed to assess the relationship between skin test reactivity and allergen-specific IgE for common allergens in an environment of low humidity and hot climate with a temperature exceeding 35°C for the greater part of the year. It is also

being investigated if these markers of atopy are of diagnostic value in asthma.

Patients and Methods

This study was conducted at the Chest Clinic of Mubarak Hospital, Kuwait (Kuwait University Teaching Hospital) in collaboration with the Immunopharmacology Laboratory of the Faculty of Medicine, Kuwait University between 1998 and 1999. Patients were adults between 15 and 67 years who were diagnosed as suffering from bronchial asthma using the criteria of the National Heart, Lung and Blood Institute [12]. Some of the patients were on a maintenance dose of salbutamol inhaler and inhaled beclomethasone, but no patient had been on oral corticosteroids for the last 12 months. Patients were randomly selected, and the majority were Kuwaitis. All patients were nonsmokers. Ex-smokers were not included in the study.

A comprehensive history, using a specially prepared protocol, was taken from the patients. This included a history of cough, with or without sputum, shortness of breath, chest tightness, wheezing, duration of symptoms, frequency of exacerbations, history of exposure to the allergen and other irritants, and a previous history of asthma and other chest diseases. Family, socioeconomic and occupational history was taken, while a history of previous and current drug therapy was taken as well. All patients had physical examinations.

Patients with a history and findings suggestive of cardiovascular, renal or hepatic diseases were excluded from the study. Similarly, patients who had been exposed to prednisolone in the last 12 months were also excluded.

All patients gave informed consent. The study was approved by the Ethical Committee of the Faculty of Medicine, Kuwait University, Kuwait.

Blood Samples

Seven milliliters of blood was obtained from each patient on presentation, using a vacutainer, and drawn into vacutubes (vacutainers-SST tubes, Becton, Dickinson, Bedford, N.J., USA). The specimen was allowed to clot at room temperature for 60–120 min. The specimen was centrifuged for 5 min at 600 g. Serum was collected and stored at –70°C until assay of specific IgE and total IgE.

Skin Testing

Allergen skin tests were carried out according to the prick technique [13], using eight allergens found to be

common in this geographical area. The allergens applied were *Dermatophagoides pteronyssinus* (house dust mite, HDM), cockroach, Bermuda grass, chenopodium, egg white, shrimp, peanut and *Aspergillus fumigatus*. A negative diluent control, 50% glycerine solution, and a positive control, histamine 1 mg/ml, were included in each series of tests. Twenty minutes after the tests were performed, the results were taken. A wheal of at least 3 mm in diameter after subtraction of the diameter size of the wheal of the negative control was taken as a positive reaction.

Table 1. Positive SPT encountered in different allergen extracts

SPT positive (n = 82)	Patients with positive SPT	% of total population
Chenopodium (goosefoot)	47	46.5
Mold mix	30	29.7
<i>D. pteronyssinus</i> (HDM)	28	28.7
Bermuda grass	27	26.7
Cockroach	25	24.7
Peanuts	23	22.7
Shrimps	15	14.85
Egg white	12	11.88

IgE Assay

The Pharmacia CAP-FEIA R test system comprising the CAP-RAST test was used for the allergen-specific IgE. Allergen-specific IgE was determined for the following allergens: *D. pteronyssinus*, pollen of Bermuda grass, goosefoot (*Chenopodium album*), cockroach (*Blatella germanica*), egg white, peanut and shrimp. This test system is a fluoroenzymatic modification of the conventional RAST test. The intensity of the resulting color was measured in a spectrometer. Results were expressed in kilounits per liter. These were obtained by reference to a standard curve derived with serial dilutions of human IgE which was calibrated against the World Health Organization standard for IgE (standard WHO 75/602). One kilounit per liter corresponds to 2.4 ng of IgE per liter. A value greater than 0.35 kU/l is defined as a positive CAP system result. The degree of positivity was classified into categories 0–6 according to Pharmacia CAP-RAST criteria.

Statistical Analysis

The Spearman rank correlation coefficient was estimated to quantify the correlation between skin test diameter size and serum concentration of allergen-specific IgE. The skin test sensitivity, specificity and diagnostic accuracy were calculated using the method advocated by Kirkwood [14].

Table 2. Degree of positive reaction to specific IgE in the four most common allergens isolated

Category of specific IgE positivity kU/l (class 0–6)	Chenopodium n	Cockroach n	Bermuda grass n	HDM n
(<0.35) 0 negative	75	82	82	90
(0.35–0.7) 1	6	2	2	1
(0.7–3.5) 2	10	12	8	6
(3.5–17.5) 3	10	5	8	3
(17.5–50) 4	–	–	–	–
(50–100) 5	–	–	1	1
(>100) 6	–	–	–	–
Total number of positive cases	26	19	19	11

n = Number of cases.

Results

One hundred and one adult patients were recruited for the study. There were 61 males and 40 females, giving a ratio of 3:2. Their ages ranged from 15 to 67 years with a mean of 30.34 ± 14.08 and a median of 29. The duration of asthma varied from 2 to 18 years. The skin prick test (SPT) was positive for at least one allergen in 82 (81%) of cases.

Table 1 shows the skin test results in the patients. Goosefoot (*C. album*) was the most frequently encountered allergen extract, being positive in 46% of cases, followed by mold mix and HDM (*D. pteronyssinus*) in 30 and 29% of cases, respectively. Positive skin test reactivity to cockroach was observed in 25% of cases. Positive specific IgE according to degree is illustrated in table 2 for the four common allergens in this environment.

Positive skin test reactions were compared with CAP specific IgE positivity in four common allergens found in this environment. While SPT was positive in 47 cases of chenopodium, it was observed that the specific IgE assay was positive in only 26 (55%) of the cases. In the cockroach antigen, 25 of the cases had positive SPT reaction while 19 were positive to specific IgE assay. The lowest positivity of specific IgE was recorded in the case of HDM, where only 11 (39%) of the 28 cases

of positive SPT also had a positive specific IgE result to HDM. The results are illustrated in table 3.

Table 4 shows the distribution of sensitivity, specificity and diagnostic accuracy of SPT, using the CAP specific IgE as a reference standard. For the four common allergens, the SPT

Table 4. Sensitivity and specificity of SPT using CAP specific IgE for four common allergens

	CAP specific IgE positive	CAP specific IgE negative	Total
<i>Chenopodium</i> ¹			
SPT positive	26	21	47
SPT negative	13	41	54
Total	39	62	101
<i>HDM</i> ²			
SPT positive	11	17	28
SPT negative	10	63	73
Total	21	80	101
<i>Bermuda grass</i> ³			
SPT positive	19	8	27
SPT negative	20	54	74
Total	39	62	101
<i>Cockroach</i> ⁴			
SPT positive	19	6	25
SPT negative	17	57	74
Total	36	63	99

¹ SPT sensitivity = $26/39 \times 100 = 66\%$;
SPT specificity = $41/62 \times 100 = 66\%$;
diagnostic accuracy = 66.3%.

² SPT sensitivity = $11/21 \times 100 = 52.4\%$;
SPT specificity = $63/80 \times 100 = 78.5\%$;
diagnostic accuracy = 77.3%.

³ SPT sensitivity = $19/20 \times 100 = 48.7\%$;
SPT specificity = $54/62 \times 100 = 87\%$;
diagnostic accuracy = 72.3%.

⁴ SPT sensitivity = $16/36 \times 100 = 52.8\%$;
SPT specificity = $57/63 \times 100 = 90.5\%$;
diagnostic accuracy = 76.5%.

Table 3. Number of patients with positive SPT and positive allergen-specific IgE using four common allergens in Kuwait

Allergen	SPT positive	CAP specific Ig positive
Chenopodium	47	26
<i>D. pteronyssinus</i> (HDM)	28	11
Bermuda grass	27	19
Cockroach	25	19

Table 5. Correlation between SPT wheal diameter and CAP specific IgE concentration (kU/l)

Variable	HDM	Bermuda grass	Cockroach	Chenopodium
HDM (<i>D. pteronyssinus</i>)	0.165			
Bermuda grass		0.376***		
Cockroach			0.255**	
Chenopodium				0.254**
Spearman's correlation coefficient; ** $p \leq 0.01$, *** $p \leq 0.001$.				

sensitivity was generally low. It was only in the case of chenopodium that it was above 60%, and that was only 66%. However, SPT specificity was much higher; the highest was observed in Bermuda grass and cockroach with 87 and 90%, respectively. The diagnostic accuracy of SPT was above 70% in all except that of chenopodium.

The wheal size diameter of SPT was correlated with the concentration of specific IgE for the four allergens. The findings are shown in table 5. There was a positive correlation with Bermuda grass ($r = 0.376$, $p \leq 0.001$), cockroach ($r = 0.255$, $p \leq 0.01$), and chenopodium ($r = 0.254$, $p \leq 0.01$). No correlation was observed with HDM.

Discussion

Allergen-specific IgE determination is widely used in the diagnosis of IgE-mediated allergic diseases, but the relative merits of in vitro measurement of IgE antibody in comparison to in vivo skin tests are still debated [15].

In this study, allergen sensitivity was high, being found in 81% of the cases in this environment. A similar finding was recorded for inhalant-allergens among blood donors in an earlier study from the same environment [16]. A high sensitivity had also been observed

among the asthma population in Europe and United States of America (USA). Kang et al. [17] recorded a prevalence of 85% among patients in an inner city study of asthma in Chicago, while Hendrix et al. [18] reported a figure of 88% in London and Burrows et al. [19] had a figure of 72% among adults in Tucson, Arizona, USA.

Chenopodium was the most commonly identified allergen among the adult population. This is a weed found to be growing in gardens of houses in the city. HDM the allergen most commonly found in Europe, was the third commonly recognized allergen in this study; this finding being similar to that of Ezeamuzie et al. [20] in their recent study in the same environment. In their study, in which a large number of patients was enrolled, 70% of their patients gave a positive reaction to chenopodium, while HDM reactivity was only observed in 48% of cases, being the sixth most common allergen. However, the findings in these two studies were in contrast to those obtained in Europe and USA [21–23] where HDM was the most commonly found allergen. In Indonesia, a tropical country in Asia, HDM predominated among the allergens found after skin testing, the reason probably being the fact that Indonesia has high humidity, high rainfall and moderate temperature compared with Kuwait. HDM is known to thrive in an environment of high

humidity and moderate temperature [24]. The reason for a low prevalence of HDM in Kuwait may be related to the environmental and geographical condition of Kuwait, where the climate is dry and hot, with low humidity of 15–30% and very little rainfall.

Cockroach is assuming an increasing importance in allergen sensitivity in Kuwait. Skin reactivity to cockroach was found in 25% of the cases. In a recent study using a larger sample size, a prevalence as high as 58% was observed [20] in the same environment. It was observed that cockroach was the most prevalent sensitizing indoor allergen, much more than HDM. A high prevalence of cockroach allergen sensitivity has been reported in several studies in Europe and America, especially among patients from the low socioeconomic class [25–29].

Kang et al. [17], in their study of aeroallergen sensitivity in Chicago, found 45% of all cases to be sensitive to cockroach, second only to HDM. The asthma population of Chicago is representative of the low socioeconomic class of the inner city. A similar observation was made by Mendoza and Snyder [25] in New York City: cockroach sensitivity was reported in 44% of the atopic asthma population. Cockroach sensitization has also been reported in Spain [30, 31], and a recent study [32] also reported that cockroach sensitivity was the most important indoor allergen in Madrid [32].

The reason for the increasingly high cockroach reactivity in asthma in Kuwait is not clear, as Kuwait is an oil-rich country with a low population, whereas reports of high prevalence have emanated from the low socioeconomic class of patients in crowded urban areas. It is conceivable that some of the patients included in the study, though of Arab ethnic origin, might have come from the crowded area of the city where the nonindigenous migrant workers also live. Furthermore,

although the majority of Kuwaiti patients (80%) included in the study come from the upper and middle social classes, it is recognized that in this study virtually all households keep maids and other domestic helpers who are from a low socioeconomic class originating from some Asian countries where studies have shown a high prevalence of cockroach infestation. These helpers interact freely with members of the Kuwaiti household, and they could easily transmit cockroach allergens to them, resulting in sensitization after prolonged exposure.

It was observed from this study that only a proportion of patients with a positive SPT also had a positive CAP specific IgE to the same allergen at the same time. Only 39% of patients who had positive skin test reactions to HDM also showed positive specific IgE to the same allergen. The corresponding figures for Bermuda grass and cockroach were 70 and 76%, respectively. This finding has demonstrated that the CAP specific IgE test is less sensitive than the skin test, as has previously been reported in similar studies [32–34]. A recent study by Ezeamuzie et al. [35] also confirmed that specific IgE positivity is much lower than SPT positivity. They also found that in the normal Kuwaiti population the specific IgE positivity is, however, much lower than the asthmatic population, with a figure of 5.8%.

The sensitivity, specificity and diagnostic accuracy of the skin test were examined using CAP specific IgE as a reference standard. The low sensitivity recorded may be due to geographical and sociocultural differences when compared with the results obtained from studies done in Europe, where high sensitivity and specificity were generally recorded [36]. Santoso [37], however, in his own study using the HDM allergen alone, recorded a high sensitivity but a low specificity.

An interesting correlation between the size of the wheal of the SPT and the concentration of specific IgE in the four common allergens was observed. There was a significant correlation with Bermuda grass, cockroach and chenopodium, while none was obtained with HDM. On the contrary, in the study of Santoso [37] in Indonesia, there was a positive correlation between wheal size and RAST scores to HDM. In that study, HDM was the most prevalent allergen, but in this study, the prevalence of HDM was low. This might have been responsible for the absence of a significant correlation.

Conclusion

This study has revealed that SPT is the most convenient and cost-effective method for detecting allergen sensitivity. It may, however, be necessary to confirm the positive reaction of SPT with the CAP-RAST system

for the evaluation of allergens in patients with allergic asthma. This study has shown the upward trend of cockroach as an allergen of significance in asthma in this environment. Finally, the study has shown that the sensitivity of SPT is higher than that of the CAP-RAST system in the four common allergens examined.

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