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The Association of Skin Test Reactivity, Total Serum IgE Levels, and Peripheral Blood Eosinophilia with Asthma in Kuwait

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Key words: Asthma; Skin test; IgE blood eosinophil count

ABSTRACT

There is evidence that elevated serum immunoglobulin E (IgE) and eosinophilia correlate well with allergic skin test reactivity. These parameters have been used as alternative methods to characterize atopic subjects. Skin test reactivity is the only measure used routinely in clinical practice in Kuwait to reflect atopy in asthma patients. This study examines the usefulness of the two other param-

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ters of atopy in patients with asthma, and to determine the most common allergens involved in Kuwait. Between 1998 and 1999, 101 asthma patients and 33 healthy controls were recruited for this study. Skin sensitivity test, serum total and specific IgE, total blood eosinophil count (B-EOS), and eosinophil cationic protein (ECP) tests were performed in patients and controls. Nine allergens known to be prevalent in this environment were selected for the skin test and specific IgE test. Spirometry was also measured. These parameters were repeated after 4 weeks of therapy in the patients only. Skin test reaction was positive in 81% of the patients, while total IgE above 200 kU/L was obtained in 63% of cases. B-EOS above $300 \times 10^3/L$ was found in 75% of cases. House dust mite reactivity (positivity) was the most frequently encountered skin allergy, occurring in 28% of the patients. IgE correlated positively with B-EOS and ECP. B-EOS similarly correlated positively with ECP. There was a negative correlation between ECP and forced expiratory volume in 1 sec (FEV_1) (% predicted) as expected. At least one positive parameter of atopy was found in 95% of the patients. In 48% of the patients, all three parameters of atopy were found to be positive. Skin test reactivity and elevated IgE were found together in 62% of the cases. This study reveals a significant degree of allergy among patients with asthma in this environment. Skin testing was found to be the most effective measure of atopy in this environment, and correlates well with the other more sensitive newer tests.

INTRODUCTION

It is generally accepted that there are both allergic and nonallergic forms of asthma, the distinction of which is often based on the presence or absence of allergy skin test reactivity to one or more aeroallergens considered capable of inducing the disease (1). Experimental and clinical studies have provided evidence for the role played by allergy in the development of airway responsiveness. In a 4-year follow-up study (2) skin reactivity in early childhood was found to be a predictor of late appearance of bronchial hyperresponsiveness. After Ishizaka et al. (3) identified immunoglobulin E (IgE) as the antibody responsible for the immediate type of immune response, a number of authors observed a marked elevation of IgE in young patients with asthma, and some have attempted to distinguish extrinsic from intrinsic disease on the basis of the presence or absence of an elevated serum concentration of IgE (4–6). Evidence exists that there is a close relationship between skin test reactivity, serum IgE, and atopic symptoms in patients with asthma and other related diseases (7–10).

Similarly, eosinophilia and elevated serum

IgE correlate well with allergy skin test reactivity and have been used by many investigators as alternative methods to characterize atopic subjects (11). Skin test response, total serum IgE level, and number of peripheral blood eosinophils are independent features of a common underlying mechanism (12). It is unknown which of these atopy markers most strongly correlates with bronchial hyperresponsiveness.

Asthma is the most common respiratory disease in Kuwait. Patients are routinely treated according to internationally accepted guidelines. However, no comprehensive study has taken place concerning routine use of skin test reactivity, serum total IgE, or total eosinophil count in the investigation and management of asthma in this environment. Skin test reactivity, which is frequently performed in medical centers, is not even done routinely in most centers in Kuwait. Similarly, serum IgE is yet to be estimated routinely in the clinical investigation of asthma. This study therefore examines the relationship between these markers of atopy and asthma to determine which of these atopic measures best predicts bronchial hyperresponsiveness and could be adapted for use in the routine inves-

tigation and management of asthma in this region.

METHODS

Patients

This study was conducted at the chest clinic of Mubarak Hospital, Kuwait, between 1998 and 1999. Patients were adults aged between 15 and 67 years, who were diagnosed with bronchial asthma. Patients were only recruited to the study if they fulfilled the criteria for the diagnosis of asthma by the National Heart, Lung and Blood Institute (13). Some of the patients had previously taken bronchodilators, but no patient had taken oral corticosteroids in the last 12 months. A few of the patients were already taking inhaled corticosteroids prior to the study. Patients were randomly selected and were mostly Kuwaiti indigenes. All patients recruited were nonsmokers.

A comprehensive history from the patients, using a specially prepared protocol, was taken. This included history of cough, with or without sputum, shortness of breath, chest tightness, wheezing, duration of symptoms, frequency of acute attacks, history of allergy, and previous history of asthma and other chest diseases. Family and occupational history was also taken. History of previous and current drug therapy was taken as well. All patients were physically examined.

Patients with history and findings suggestive of cardiovascular, renal, or hepatic diseases were excluded from the study. Patients who had taken oral corticosteroids in the last 12 months were also excluded. To serve as controls, healthy adults, matched for age and sex, who had no history of cardiorespiratory, renal, hepatic, or allergic diseases, were chosen from medical students and members of the medical, nursing, laboratory, and secretarial staff. They were also confirmed to be nonsmokers.

All of the participants gave informed consent. The study was approved by the faculty of medicine ethical committee.

Blood Samples

Blood samples (7 mL) were drawn from patients and controls at first visit using a vacu-

tainer (Vacutainers SST-tubes, Becton Dickinson, Bedford, NJ) and were allowed to clot at room temperature for 60–120 min. The specimens were centrifuged for 5 min at $600 \times g$. Serum was collected and stored at -70°C until assay of total IgE, specific IgE, and eosinophilic cationic protein (ECP). Two milliliters of blood was also taken into a hematocrit bottle for complete blood count and total blood eosinophil count (B-EOS). Total blood count was done by one technician using a Neubauer counting chamber according to the method described by Dacie and Lewis (14).

IgE Assay

Total serum IgE was determined using the CAP-IgE test (Pharmacia and UpJohn, Uppsala, Sweden). The test, which is calibrated against the World Health Organization (WHO) IgE reference serum 75/502, has a detection range of 2–2000 kU/L. Samples were diluted if the values exceeded the upper limit. For samples with total IgE values below the detection limit, a nominal value of 1 kU/L was assigned for statistical purposes. In this test, serum samples and standards were incubated with anti-IgE caps and the bound antibody, after washing, was released with enzyme-labeled anti-IgE antibody. The release of the fluorescent product from the enzyme substrate was then measured fluorometrically.

Samples were initially analyzed in duplicate, but when the intra-assay coefficient of variation was consistently less than 10%, analysis was completed in single replicates. Serum ECP level was assayed in duplicate using the Pharmacia CAP FEIA test system, and the mean of the two was taken as the desired level.

Skin Testing

Allergy skin tests were carried out according to the prick technique (15), using eight allergens prevalent in this geographical region, glycerol negative control, and histamine HCl. The allergens applied were house dust mite, cockroach, Bermuda grass, eggwhite, *Chenopodium*, shrimp, peanuts, and *Aspergillus fumigatus*. The wheal reaction was read after 20 min. The size of the reaction was determined by measuring the largest diameter of

the wheal, at its perpendicular diameter. A wheal diameter of at least 3 mm, after subtraction of the diameter size of the negative control, was taken as a positive reaction.

The subjects were considered to have positive skin test reaction (ST) if one or more of the allergen applied gave a positive result.

Spirometry

Baseline measurement of the pulmonary function test (PFT) was performed on all the participants at first visit, using the Erich Jager Master Lab equipment. The parameters measured included forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV₁), peak expiratory flow (PEF), total lung capacity (TLC), residual volume (RV), and diffusion capacity (DLCO). Actual and percentage of predicted values were recorded.

Stools were examined for parasites and ova in all patients and controls. The blood samples, PFT, and symptom evaluation were repeated during the second visit, 4 weeks later in the patients' group.

Treatment

Treatment consisted, on average, of 600 µg/day of salbutamol aerosol and 800 µg/day of beclomethasone propionate aerosol.

Statistical Analysis

Descriptive statistics (mean, median, and standard deviation) were used to describe the data. Differences between two means were tested by *t*-test or by nonparametric test (Mann-Whitney). For a positively skewed distribution, the data were subjected to log transformation prior to *t*-test and findings were expressed as geometric mean. The mean differences with paired observation were tested either by paired *t*-test or by Wilcoxin paired test, depending on whether the data were consistent with Gaussian distribution. Spearman rank correlation coefficient was used to test the association between two continuous variables. The statistical significance level $p \leq 0.05$ is considered as the cut-off point for significance.

RESULTS

A total of 101 patients and 33 controls were admitted to the study; 61 males and 40 females, with a ratio of 3:2. The patients were aged 15–67 years with a mean of 30.34 ± 14.08 years and a median of 29 years, whereas the controls were aged 16–38 years with a mean of 27.49 ± 6.75 years and a median of 27 years, and with a male to female ratio of 1.5:1.0.

Skin test reaction was positive in 82 (81%) of the patients. Goose foot (*Chenopodium album*) was the most frequently encountered allergen, being found in 64% of cases, followed by house dust mite (*Dermatophagoides pteronyssinus*) 28%, Bermuda grass 27%, and cockroach 25%, respectively.

Serum total IgE values varied from 9.5 to 547 kU/L with a geometric mean value of 229.7 kU/L. Serum IgE was above 200 kU/L in 64 (63%) of cases. The reference value for upper limit of normal for total IgE in this environment is 200 kU/L (16). Total blood eosinophil count (B-EOS) ranged from 20 to $1200 \times 10^3/L$. The reference value for increased total eosinophil count in this environment is $300 \times 10^3/L$. B-EOS above $300 \times 10^3/L$ was found in 34 cases (75%) of the 45 cases in which it was estimated.

Serum ECP (S-ECP) was estimated in 101 patients. The values varied from 4 to 256 µg/L, with a geometric mean of 31.7 µg/L.

The mean percentage predicted FEV₁ was 71%, whereas the mean PEF value was 298 L/min.

Table 1 shows the summary of variables between controls and the patients. There was a statistically significant difference with total IgE ($p < 0.05$), B-EOS ($p < 0.01$), FEV₁ % predicted ($p < 0.001$), and PEF ($p < 0.001$).

Using Spearman's rank correlation (Table 2), total serum IgE correlated significantly with B-EOS and S-ECP. B-EOS correlated, as expected, with ECP. ECP had a negative correlation with FEV₁ (% predicted). There was also a correlation between FEV₁ (% predicted) and PEF, which is expected as well.

Table 3 shows comparison of variables before and after treatment with beclomethasone (weeks 0 and 4) in the patients. There was a significant difference in the levels of IgE, ECP, and PEF.

Table 1. Summary of Parameters Between Patients and Controls

VARIABLES	CONTROLS			PATIENTS			p VALUE
	NO.	MEAN (SD)	MEDIAN	NO.	MEAN (SD)	MEDIAN	
Age (years)	33	27.49 (6.75)	29.00	101	30.34 (14.08)	27.00	—
IgE (kU/L) ^a	33	142.52 (3.8)	132.00	101	299.74 (4.2)	347.50	0.010*
B-EOS ($\times 10^3/L$) ^a	20	164.00 (2.8)	170.00	45	317.0 (2.0)	333	0.003**
S-ECP ($\mu g/L$) ^a	8	51.0 (3.50)	78.10	95	31.74 (2.4)	30.0	0.374
FEV ₁ (% predicted)	33	91.4 (23.1)	87.90	101	71.1 (21.3)	74.05	0.000***
PEF (L/min)	33	474.5 (143.1)	433.0	101	298.3 (125.6)	278	0.000***

^aData expressed as geometric mean after logarithmic transformation.*** $p \leq 0.001$; ** $p \leq 0.01$; * $p \leq 0.05$.**Table 2.** Correlation Between Pretreatment Variables

VARIABLES	IgE	B-EOS	S-ECP	FEV ₁ (% PREDICTED)	PEF
IgE	1.000	0.349	0.395**	-0.174	-0.024
B-EOS	0.349*	1.000	0.506**	-0.195	-0.141
S-ECP	0.395**	0.506**	1.000	-0.287**	-0.079
FEV ₁ (% predicted)	-0.174	-0.195	-0.287**	1.000	0.662**
PEF	-0.024	-0.141	-0.079	0.662***	1.000

*** $p \leq 0.001$; ** $p \leq 0.01$; * $p \leq 0.05$.

Data were generated using Spearman's rank correlation.

Table 3. Comparison Between the Variables at Week 0 (Before) and Week 4 (After) Inhaled Corticosteroids Therapy in the Asthmatic Patients

VARIABLE	NUMBER OF PATIENTS	MEAN (SD)	MEDIAN	p VALUE
Total IgE ^a				
Week 0	78	287.21 (4.42)	347.5	0.033*
Week 4	78	270.75 (4.49)	298.0	
B-EOS ^a ($\times 10^3/L$)				
Week 0	25	315 (2.18)	333	0.263
Week 4	25	313 (1.77)	340	
S-ECP ^a				
Week 0	78	32.33 (2.35)	30.0	0.023*
Week 4	78	23.83 (2.59)	23.8	
PEF				
Week 0	78	298.29 (125.59)	278	0.01*
Week 4	78	339.04 (130.63)	331	

^aData expressed as geometric mean after logarithmic transformation.* $p \leq 0.05$.

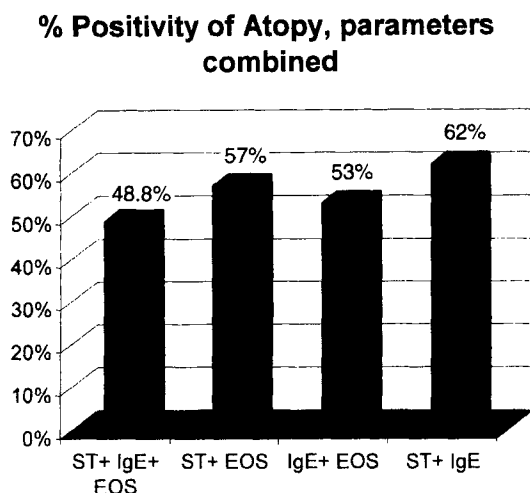


Figure 1. Percent positivity of atopy when parameters are combined. ST: skin test; IgE: total immunoglobulin E; EOS: blood eosinophils.

Stool examinations for ova and parasites were negative in all of the patients and controls. We further re-examined the relationship between skin test reactivity (positivity), elevated total IgE, and eosinophilia (Fig. 1). At least one positive measure of atopy was found in 97 (95%) of the patients. Skin test was positive alone in 81% of cases, whereas IgE alone was above normal range in 63% of cases, and elevated total eosinophil count alone was found in 75% of cases. Fourteen (73%) of the 19 patients with negative skin test had elevated total IgE. Further analysis of the three measures of atopy was done in 45 patients who had all three tests. Twenty-two (48%) of the patients had positive results in the three parameters combined (ST + IgE + B-EOS). Positive ST and IgE were found in 28 (62%) of the patients, whereas positive ST and B-EOS were found in 26 (57%) of the cases. The results revealed that skin test reaction is the most common measure of atopy in this study, whereas a combination of skin test and total IgE is the next frequently encountered measure of atopy.

DISCUSSION

Studies involving respiratory diseases and allergy traditionally apply skin test reactivity,

serum IgE level, and peripheral blood eosinophilia to identify atopic subjects. Several studies have also established that asthma is associated with an increase in blood eosinophils and IgE levels, and that a correlation exists between the severity of asthma and the degree of eosinophilia and IgE (7,17–19).

In this study, an attempt was made to examine the usefulness of three parameters in defining atopy in this region. This study revealed a high prevalence of allergy among patients with asthma. At least one positive parameter of atopy was found in 95% of the patients, whereas skin test alone was positive in 81% of the patients. In 48% of cases, skin test positivity, elevated IgE level, and increase in blood eosinophils were found at the same time in the patients. This finding is in sharp contrast to the findings in the recent study by Jansen et al. (12), where the three measures of atopy were found in the same patient in only 1.5% of cases. The high prevalence of allergy in this study is not surprising, because a previous study in this environment (16) observed that the normal total IgE values in the young adult Kuwaiti population are generally high, hence the cut-off point for an elevated total IgE was fixed at 200 kU/L. They also recorded a similarly high level among patients with asthma. Studies on skin sensitivity tests in asthmatics in this environment also revealed a high prevalence of atopy (20). In a similar study in Indonesia (21), which is a developing country similar to Kuwait, a significant number of children with asthma were found to have high levels of IgE and marked eosinophilia.

The role of parasites as a contributory factor to high levels of IgE and eosinophilia is unclear, because neither parasites nor ova were found in the stools of patients and controls in this study. In a recent editorial (22), the association of parasite infection with the risk of asthma and atopy was further examined. Although there is a general consensus that IgE antibody is an important component of the immune resistance to helminthiasis, conflicting results have been obtained concerning the role of parasites in atopy (23,24). In the study by Kartasamita et al. (21) in Indonesian children who had no parasites in their stool, the total

IgE level and total eosinophil count were still high. Similarly, Santoso et al. (25) demonstrated that more than 50% of children with no ascaris organisms in the stool sample had a positive radioallergosorbent test result for ascaris species, thus indicating a persisting immunologic reaction after a past infection. In developing countries, the "normal" IgE levels reported in children are generally higher (17). Johansson et al. (26) found that total IgE values were five times higher in Ethiopian children with a stool sample negative for ascaris lumbricoides.

This study demonstrated a correlation between IgE and S-ECP levels. This is of interest because ECP is a product of eosinophil activation. Any of these three parameters (ST, IgE, and B-EOS) and possibly ECP can then be employed in the evaluation and monitoring of asthmatic patients in this environment, in addition to the traditional lung function parameters. They could even aid in the management of asthma by identifying the allergen.

In this study, 73% of patients with negative skin test had an elevated serum total IgE level. A similar observation was made in other studies in children and young adults (27,28). It has thus been shown that no single parameter of atopy is adequate to determine atopy in the evaluation of the patients. However, skin test reaction was found to be the most useful measure of atopy in this study. This was also the observation in some previous studies (28,29).

This study also revealed that a combination of two parameters of atopy, positive skin test and elevated IgE level, will detect allergy in the vast majority of patients with asthma.

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