

The Significance of Specific IgE and IgG to Dermatophagoides Farinae According to the Types of Asthmatic Reaction in House Dust Asthmatics

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To investigate the role of specific IgE and IgG in the various types of asthmatic reaction, we measured specific IgE and IgG levels to *Dermatophagoides farinae* (*D. farinae*) using the *D. farinae*-radioallergosorbent test (RAST) and Phadebas IgG-RAST in 39 house dust asthmatics (11 early responders, 21 dual responders and 7 isolated late responders) and 12 negative responders on house dust bronchoprovocation. There were significant differences in the *D. farinae*-specific IgE level and skin reactivity to *D. farinae* and house dust among the 4 groups ($p < 0.05$) and the specific IgE level of dual asthmatic responders was the highest and was significantly higher than that of early responders ($p < 0.05$). The specific IgG level showed no differences among the 4 groups. These results suggested that the types of asthmatic reaction in house dust asthmatics were closely related to specific IgE level to *D. farinae* and the specific IgG level seemed not to be related to an isolated late response.

Key Words: *D. farinae* specific IgE and IgG level, bronchoprovocation test.

It has been established that the pathogenesis of atopic asthma is multifactorial, involving both immunological and pharmacological responses to specific and nonspecific agents determined by genetic and nongenetic factors, and inherited individual susceptibility. When patients with atopic asthma were challenged with antigen inhalation, a large number of the patients showed late asthmatic reaction 6-12 hours after an immediate asthmatic reaction (Pepys *et al.* 1968). This late reaction has been thought to have more relevance to clinical asthma than the immediate response (Booij-Noord *et al.* 1971; Pepys and Hutchcroft 1975).

The immediate response can be explained by the reaction of IgE antibodies and allergens. However, the mechanism of the late reaction is not clear yet. It has been shown that chemical mediators, probably from mast cells, are increased by immediate and late reactions (Nagy *et al.* 1982; Durham *et al.* 1984). Ito *et al.* (1986) suggested that there was a close correla-

tion of the presence of high IgG₄ antibodies with a propensity to develop late asthmatic reaction. The relevance of IgG₄ antibodies to late reaction has been reported by Gwynn *et al.* (1982). There has been no evidence that late asthmatic reactions can be predicted from the knowledge of nonspecific reactivity or allergic hypersensitivity or any particular clinical feature.

The purpose of this study was to investigate if the types of asthmatic reaction in the house dust bronchoprovocation test can be predicted by that we simultaneously take into account nonspecific bronchial hyperreactivity, baseline airway caliber, *Dermatophagoides farinae* (*D. farinae*)-specific IgE and IgG levels and skin reactivity to *D. farinae*.

MATERIALS AND METHODS

Patients

We studied 51 asthmatics (20 males and 31 females, aged 15 to 52 years) sensitized to house dust and *D. farinae*, as proved by positivity to skin prick tests and the radioallergosorbent test (RAST). Beta 2-agonists, sodium cromoglycate, anti-histamine and theophylline, if any of these were taken, were stopped 12 hours before the study.

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Allergen

A crude lyophilized extract of *D. farinae* was generously donated by the Torri Co. (Tokyo, Japan). The protein content was measured by the Lowry method (1951) with 1 mg/ml of *D. farinae* extract containing 0.685 mg/ml of protein. Percent inhibition of *D. farinae*-RAST was 98.1% using 1 mg/ml of the crude extract incubated for 1 hour with an equal volume of a 1:40 diluted sera pool which represented *D. farinae*-RAST class 4 (Hong *et al.* 1987).

Serum

Sera of 51 asthmatic patients who showed positive or negative results on the house dust broncho-provocation test were obtained and stored at -20°C .

A sera pool obtained from 50 allergic patients who showed *D. farinae*-RAST 4 and had relatively high levels of IgE antibodies was used in making the standard solution by the elution technique which was used to construct a standard curve in measuring the absolute level of specific IgE to *D. farinae*.

Sera of ten patients who showed negative results on the allergy skin test were obtained and used as the negative control in IgG-RAST to *D. farinae*.

Allergy Skin Test

Skin prick tests with Bencard's and Torii's commercial inhalant extracts were performed simultaneously. The results were read at 15 minutes after the prick. The wheal and erythema size were measured as maximum diameter and vertical length at the mid-portion of maximal length.

Methacholine Bronchial Challenge Test

Nonspecific bronchial hyperreactivity was determined by the previously described standard method (Chai *et al.* 1975). An aerosol of 0.9% NaCl followed by doubled concentrations of methacholine (0.075 to 25.0 mg/ml) was inhaled. The forced expiratory volume in one second (FEV_1) was measured 5 minutes after each inhalation and continued until the FEV_1 had fallen by 20% (calculated from the post-saline value). The provocative concentration of methacholine required for a 20% decrease in FEV_1 was obtained from the dose-response curve (PC_{20}).

Bronchoprovocation Test with House Dust

Bronchoprovocation tests were performed, using aqueous extracts of house dust (1:10 w/v, Torii Co.,

Japan) by the modified Chai's method (1975). The FEV_1 and forced mid-expiratory flow ($\text{FEF}_{25-75\%}$) were measured with a spirometer before inhalation and 10 minutes after inhalation. The test solutions were delivered by a Vaponefrine nebulizer (Meico Co., Japan) and compressed air source. The patients were asked to breathe the nebulized aerosol 5 times until their vital capacity was achieved. A 0.4% phenolized saline solution was inhaled for a baseline value and serial increments in antigen concentration (1:500, 1:100, 1:50, 1:10 w/v) were given at 10 min intervals until a 20% or greater decrease in FEV_1 from the baseline value was recorded. The FEV_1 and $\text{FEF}_{25-75\%}$ were measured frequently during the first hour and then the pulmonary function test was performed at hourly intervals for 7 hours after the challenge.

Measurement of Specific IgE Level to *D. farinae*

To determine the level of specific IgE and the ratio of specific IgE to total IgE, *D. farinae*-RAST was performed using the concentrated eluate (20 IU/ml) as a standard solution for *D. farinae*-specific IgE by the previously described method (Park and Hong 1989). One μl of 50 mg/ml *D. farinae* dissolved in 1% KOH was dotted on nitrocellulose paper (Millipore type HA, 0.45 μM , Cat No. HAWG 0.47) and blocked with 10% newborn calf serum. The paper was cut into suitable strips with 10 dots per strip and used as the solid phase. The strips were incubated with 10 ml of sera pool of *D. farinae*-RAST class 4 for 6 hours and washed 3 times with 50 mM Tris-200 mM NaCl solution (TBS, pH 7.5). Ten ml of alkali buffer (0.1M glycine/NaOH in 0.1 M NaCl, pH 11.0) was added to elute the *D. farinae* specific IgE bound to nitrocellulose paper. The samples were incubated for 1 hours on a rotator at room temperature. The supernatant was neutralized immediately with 0.5 M HCl solution. The strips were reincubated with sera pool of *D. farinae*-RAST class 4, eluted and neutralized as before. The replicates of the supernatant were pooled, concentrated 20-30 fold by vacuum dialysis, and dialyzed against TBS. When the absolute amount among the specific IgE to *D. farinae* was measured using a modified immunoabsorption technique as in the previous report (Park and Hong, 1989), it was estimated to be 20 IU per ml of the concentrated eluate. A standard dose-response curve was constructed with serial dilutions of this concentrated eluate with a known amount of specific IgE. Therefore, the results obtained from *D. farinae*-RAST were expressed as an international unit from this curve. All tests were run simultaneously and compared.

Measurement of Specific IgG to *D. Farinae*

IgG-RAST was performed by means of the standard Pharmacia technique (Pharmacia IgG RAST Kit, Uppsala, Sweden). Initially, 2.5 ml of washing solution was added to *D. farinae*-coated tubes and allowed to stand for 5 minutes. After complete aspiration, 100 μ l of 1:50 diluted serum of each patient and negative control, who showed negative results on the skin prick test to *D. farinae*, was incubated for 3 hours at room temperature. After washing 3 times with 2.5 ml of washing solution, 100 μ l of anti-human IgG radiolabelled with iodine-125 was added and incubated for 18 hours at room temperature. After further washing, the radioactivity was determined by a gamma counter and the results were expressed as a percent of reference response by calculating from the following formula:

$$\frac{\text{mean counts per minute unknown}}{\text{mean counts per minute reference}} \times 100 (\%)$$

Total IgE level by paper radioimmunosorbent test (PRIST) assay

According to the method presented in Phadebas IgE-PRIST, one anti-IgE disc was added to the bottom of each tube and incubated with 100 μ l of diluted serum at room temperature for 3 hours. The discs were washed 3 times with 2.5 ml of washing solution. One hundred μ l of 125 I-anti-IgE PRIST tracer was then added to each tube, incubated at room temperature for 18 hours and rinsed three times. The binding radioactivities were determined using a gamma counter and the absolute amounts of total IgE were determined using a standard curve.

Statistical Analysis

Analysis of variance (ANOVA) was used to examine the relationship between the types of asthmatic reaction and any of the skin reactivities and specific IgE or

IgG levels to *D. farinae*. The means of the two groups were compared by the student's t-test. P-values of <0.05 were considered significant. Logarithmic transformations were performed on PC₂₀ of methacholine, specific IgE, total IgE, and the specific IgE/total IgE ratio.

RESULTS

Baseline Pulmonary Function Test

After the house dust inhalation, 11 patients were single early asthmatic responders, 21 patients were dual asthmatic responders and 7 patients were

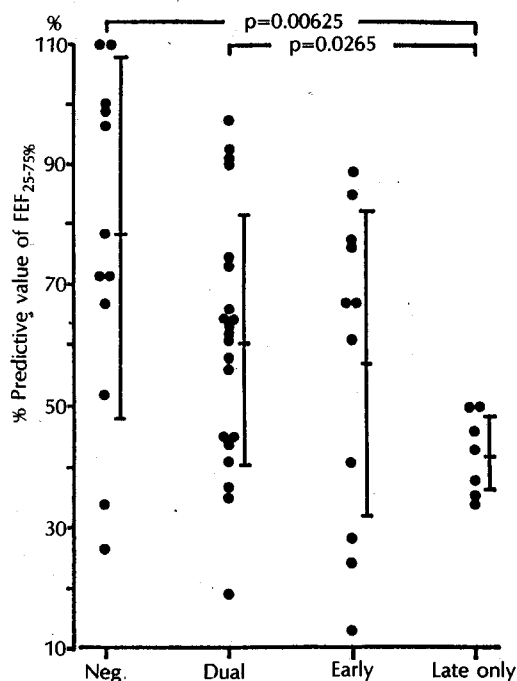


Fig. 1. Percent predictive value of baseline $FEF_{25-75\%}$ in various asthmatic responders.

Table 1. Baseline pulmonary function test in studied subjects

Pulmonary function test	Asthmatic responses			
	Negative (n=12)	Dual (n=21)	Early (n=11)	Isolated late (n=7)
FVC	82.6 \pm 15.3*	108.6 \pm 18.6	99.3 \pm 19.4	93.7 \pm 11.5
FEV ₁	82.8 \pm 16.4	82.5 \pm 12.7	79.6 \pm 23.2	74.3 \pm 7.8
FEF _{25-75%}	78.2 \pm 29.8	60.8 \pm 20.3	57.1 \pm 25.1	42.3 \pm 6.3

+: Mean \pm S.D. of percent of predictive value

isolated late asthmatic responders. Twelve patients showed negative responses. As shown in Table 1, there was no significant difference in baseline FEV₁ or functional vital capacity (FVC). Fig. 1 demonstrates that the baseline FEF_{25-75%} of the isolated late responders was significantly lower than that of negative responders ($p=0.006$) and dual asthmatic responders ($p=0.03$).

Correlation between Specific IgE/total IgE Ratio and Wheal Size to *D. farinae*

The results in Fig. 2 show that a correlation was found between the Log₁₀ specific IgE/total IgE ratio and wheal size (mm) to *D. farinae*, with a correlation coefficient of 0.73 ($p<0.05$).

Specific IgE Level to *D. farinae*

Fig. 3 demonstrates the *D. farinae*-specific IgE level in various asthmatic responders. An ANOVA test revealed that there was a significant difference in the specific IgE level among the 4 groups. The highest specific IgE level was found in the dual asthmatic responder group, and the early responder group was next. A similar level of specific IgE was noted in the isolated late responder group and negative responder group. There were significant differences between the dual asthmatic responder group and the early

asthmatic responder group ($p<0.05$).

Specific IgG Level to *D. Farinae*

Fig. 4 shows the specific IgG level to *D. farinae* in

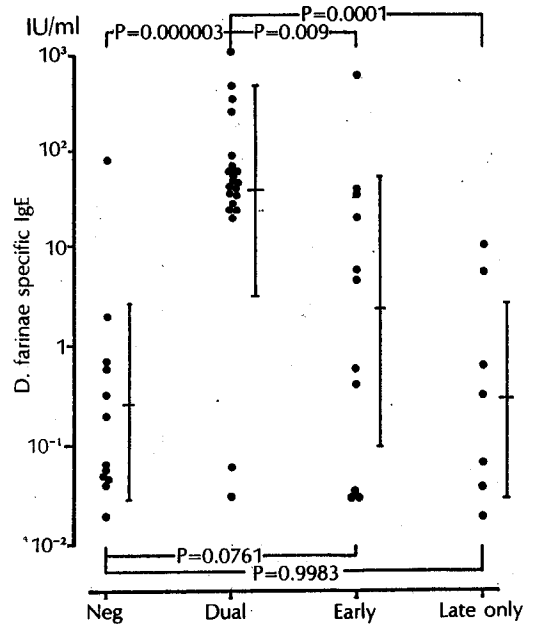


Fig. 3. The level of specific IgE to *D. farinae* in various asthmatic responders.

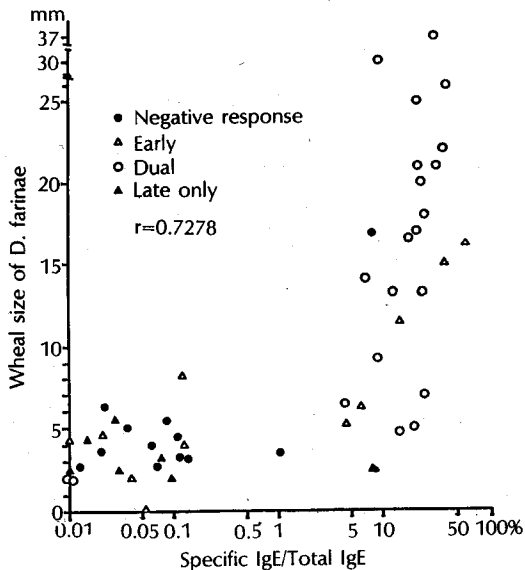


Fig. 2. The correlation between the percent ratio of *D. farinae*-specific IgE to total IgE and the wheal size to *D. farinae* on skin prick test.

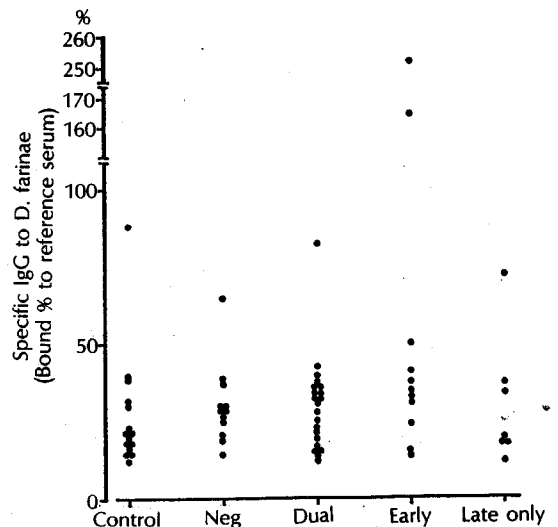


Fig. 4. The level of specific IgG(%) to *D. farinae* in various asthmatic responders.

various asthmatic responders. There was no difference among the 4 groups ($p>0.05$).

Nonspecific Bronchial Hyperreactivity

Fig. 5 shows the PC_{20} of methacholine in various asthmatic responders. The lowest PC_{20} was found in the isolated late responder group and it was

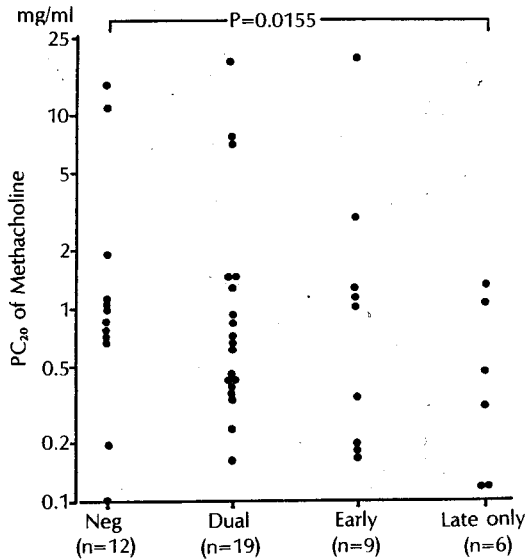


Fig. 5. The PC_{20} of methacholine in various asthmatic responders.

significantly lower than that of the negative responder group ($p<0.05$).

Comparison of Allergic Responses

As shown in Table 2, there were significant differences in wheal size of *D. farinae* and house dust among the 4 groups ($p<0.05$). No differences were found in total IgE level and the ratio of specific IgE to total IgE of dual asthmatic responders was significantly higher than that of early asthmatic responders.

DISCUSSION

The mechanisms responsible for the various types of asthmatic reactions are not completely understood. The intensity of the immediate reaction has been shown to depend on both the nonspecific reactivity of the airway and the degree of the patient's allergic hypersensitivity as measured by skin testing (Killian *et al.* 1976; Nathan *et al.* 1979). Hill *et al.* (1982) were able to predict the immediate reaction from a combination of skin test results and exercise testing in children.

Late asthmatic reactions have been reported to occur in 47% to 67% of adult patients who exhibited an early asthmatic reaction after the inhalation of house dust allergen (Killian *et al.* 1976; MacIntyre and Boyd 1984; Hong *et al.* 1987). It has been found that patients with dual asthmatic reaction tended to have higher serum concentrations of IgE than patients with

Table 2. The comparison of allergic responses in house dust asthmatics

	Asthmatic responses			
	Negative (n=12)	Early (n=11)	Dual (n=21)	Late (n=7)
Wheal size of <i>D. farinae</i> (mm) ^c	4.54±3.97@	6.93±5.39*	15.35±9.61*	3.14±1.09
Wheal size of house dust (mm) ^c	2.54±1.17	4.68±3.06	6.50±2.29	2.55±1.39
Log ₁₀ PC_{20} (mg/ml)	0.02±0.18*	-0.07±0.18	-0.06±0.11	-0.36±0.16*
Log ₁₀ tIgE (IU/ml)	2.42±0.16	2.46±0.16	2.66±0.11	2.37±0.28
Log ₁₀ sIgE (IU/ml) ^c	-0.55±0.28	0.36±0.41**	1.59±0.24**	-0.52±0.37
Log ₁₀ sIgE/tIgE (%)	-0.91±0.23	-0.11±0.41**	0.90±0.23**	-1.19±0.38
Specific IgG (%)	29.8±3.7	63.2±22.8	29.8±3.4	30.2±7.9

PC_{20} : Methacholine PC_{20} , tIgE: total IgE, sIgE: Specific IgE, IgG(%): Bound radioactivity to reference serum,

sIgE/tIgE: The ratio of specific IgE to total IgE,

@: Mean ± S.E., ^c: $p<0.05$, compared among four groups,

++ **: $p<0.05$, compared between two groups.

early reaction only (Robertson *et al.* 1974; Boulet *et al.* 1983; Boulet *et al.* 1984). MacIntyre and Boyd (1984) and Price *et al.* (1983) observed that late asthmatic reactions are more likely to occur in patients who develop an early asthmatic reaction with a small dose of allergen. In the present study, there were no differences in the methacholine PC₂₀ and baseline pulmonary function test between dual asthmatic responders and early asthmatic responders. The *D. farinae*-specific IgE level was highest in the dual asthmatic responder group and a significant difference was noted between dual asthmatic responders and early asthmatic responders. We can speculate that patients with a high specific IgE level are more susceptible of developing dual asthmatic reactions. Also, the results of this study provided good evidence that the type of asthmatic responses after inhalation of house dust can be predicted from the *D. farinae*-specific IgE level and skin reactivity to *D. farinae* and house dust.

The possible role of IgG in bronchial asthma, especially in late asthmatic response, is not clear. The IgG and possibly also the IgM antibodies are presumed to play a major role in the forming of immune complexes after their interaction with antigens (Hall *et al.* 1979; Kay 1982; Hensen 1982). They also directly activate eosinophils through their membrane IgG receptors (Hensen 1982; Kay 1983; Walsh and Kay 1984), and stimulate macrophages (Huber and Fudenberg 1968), neutrophils (Henson 1972; Kay and Walsh 1984) and platelets (Hensen and Ginsberg 1981; Hensen 1982). Such an assumption was supported by Pelikan and Palikan-Filipek (1986) who demonstrated an increase in the serum concentration of IgG in 66%, and of IgM in 49% of late asthmatic reaction cases. With respect to the IgG subclass, they found that there was a significant increase in serum concentration of IgG₄ during 52%, of IgG₃ during 25%, and of IgG₁ during 8% of late asthmatic reactions. In the present study, there was no significant difference in the specific IgG level among the 4 groups and negative controls. Two cases of early asthmatic responders showed high levels of *D. farinae*-specific IgG and their specific IgE level was lower than that of the other early responders. In these two patients, any type of IgG subclass antibodies might be associated with their early asthmatic reactions. Further studies are still needed to evaluate the potential role of IgG or IgG subclasses in the late asthmatic reaction.

The occurrence of a late asthmatic reaction without an early asthmatic reaction is considered a very rare event in adults, affecting only about 1% according to Orie *et al.* (1963). Hills (1984) noted a high incidence of isolated late asthmatic reactions to the

house dust mite in the patients less sensitive to it and conversion of an early asthmatic reaction to an isolated late asthmatic reaction when the concentration of inhaled allergen was reduced. In the present study, an isolated late reaction was observed in 7 cases (13.7%) of asthmatic patients sensitized to house dust and *D. farinae*. Their specific IgE levels to *D. farinae* were very low and similar to those of negative responders. Moreover, the methacholine PC₂₀ and baseline FEF_{20-75%} of this group were lowest among the 4 groups and significantly lower than those of negative responders. The results of our study suggest that nonspecific bronchial hyperreactivity and baseline caliber might be important factors in determining an isolated late reaction. This group of patients seems to be clinically indistinguishable from those with intrinsic asthma. The isolated late reaction was not fully investigated in our study, because all patients inhaled an increasing dose of allergen until an early asthmatic reaction was elicited or a maximum concentration of the allergen was reached (1:10 w/v). Extended studies, such as bronchoprovocation tests with a constant dose of inhaled mite allergen, are needed to clarify the relationship among various asthmatic responses.

We could conclude that the types of asthmatic reactions to house dust were closely related to the specific IgE level to *D. farinae* and the specific IgG level seemed not to be related to an isolated late response.

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