Pediatr Allergy Immunol 2007: 18: 320–325
DOI: 10.1111/j.1399-3038.2006.00527.x

PEDIATRIC ALLERGY AND IMMUNOLOGY

Comparison of Der p1-specific antibody levels in children with allergic airway disease and healthy controls

Aydogan M, Mete N, Yazi D, Akkoc T, Ozdemir C, Blaser K, Akdis M, Akdis C, Bahceciler N, Barlan I. Comparison of Der p1-specific antibody levels in children with allergic airway disease and healthy controls.
Pediatr Allergy Immunol 2007: 18: 320–325.

Although children, with allergic airway disease, who are sensitized to house-dust mite (HDM) are known to have increased levels of allergen-specific IgE and IgG, the association between the quantity of those immunoglobulins and the clinical features of disease is not yet well established. The purpose of this study was (i) to evaluate Der p1-specific IgA, IgG1, IgG4, and IgE levels of children with HDM-allergic asthma and allergic rhinitis and to compare it with that of healthy controls (ii) to assess the association with disease duration. A total of 73 patients were included. Of those, 58 had asthma (M/F: 27/31, mean age 7.9 ± 2.7 yr) and 15 were diagnosed as allergic rhinitis (M/F: 8/7, mean age 10.1 ± 4.0 yr) without asthma. Twenty-five (M/F: 13/12, mean age 9.5 ± 4.2 yr) non-allergic children were included as healthy controls. Data on age at onset and duration of disease were recorded. Then, Der p1-specific IgA, IgG1, IgG4, IgE levels were measured in all of the 98 subjects by ELISA. Comparison of Der p1-specific antibody levels of patients and controls revealed that Der p1-specific IgG1, IgG4 and IgE levels of patients with asthma ($p = 0.012$, $p = 0.021$, $p = 0.004$, respectively) were significantly higher than healthy controls. Also, the ratio of Der p1-specific IgA/IgE was significantly lower in asthmatic children when compared with children with allergic rhinitis and controls ($p = 0.029$, $p < 0.001$, respectively). Der p1-specific IgG1, IgG4, IgE and IgA levels of asthmatic children with duration of disease of ≥4 yr were significantly higher than those with disease duration of <4 yr. IgA/IgE ratio was not significantly different in those two groups of asthmatics. We concluded that although all of the specific antibody levels increased with longer duration of asthma, IgA/IgE ratio remains to be low in asthmatic children allergic to HDM.

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Key words: asthma; children; Der p1-specific-antibody; house-dust-mite

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Accepted 28 October 2006

Allergic asthma is a chronic inflammatory disease of airways characterized by a Th2 cell-driven response and elevated serum IgE levels to inhaled allergens. The relationship between specific IgE responses and exposure to allergens has been established well whereas to date no such association had been demonstrated regarding the specific IgE response and the outcome of allergic airway disease. Recently, other allergen-specific antibodies such as IgG, IgG_4 and IgA have been reported to be involved during the course of allergic diseases (1–3). *Dermatophagoides pteronyssinus* (*D. pterronyssinus*) and *Dermatophagoides farinae* (*D. farinea)*, the major components of house-dust mites (HDM) are considered to be one of the major etiologic factors of allergic asthma (4).

Although children with allergic airway disease who are sensitized to HDM are known to have increased levels of HDM-specific IgE and IgG

antibodies, the association between the quantity of those antibodies, clinical manifestations, severity and duration of the diseases is not yet well established.

The purpose of this study was to evaluate Der p1-specific IgA, IgG_1, IgG_4 and IgE levels of children with HDM-allergic asthma and rhinitis and to compare it with that of healthy controls. Also, we evaluated the association of specific antibodies with clinical parameters such as age at onset and duration of disease.

Material and methods

Study population

Children with asthma and allergic rhinitis followed by the Pediatric Allergy and Immunology Unit of Marmara University, Istanbul who met the inclusion criteria listed below and a group of non-allergic healthy children were included into the study.

Inclusion criteria for patients were:

1 To have mild-to-moderate persistent asthma or rhinitis without asthma.
2 A positive skin prick test (SPT) to *D. farinae* and *D. pterronyssinus*, and a negative response to all other aeroallergens tested.
3 Need for anti-inflammatory treatment for control of asthma and allergic rhinitis symptoms.
4 No previous immunotherapy history.

The diagnosis of mild-moderate persistent asthma was based on the Global Initiative for Asthma (GINA) guidelines (5), and allergic rhinitis was diagnosed according to the criteria defined by The European Community Respiratory Healthy Survey (ECRHS) (6).

The study was approved by the Ethics Committee of Marmara University and parents of all patients signed informed consent forms.

Study design

Skin prick test was performed to all patients and healthy controls then, blood samples were drawn from all the participating children for determination of Der p1-specific IgE, IgG1, IgG4 and IgA. Data on age at onset and duration of disease were obtained from the records of the patients.

Skin prick tests

Skin prick test was done by employing a panel of allergen extracts (timothy, mugwort, dog, cat, *D. pteronyssinus*, *D. farinea*, *Cladosporium herbarum*, and *Alternaria alternata*), (Stallergenes, France) in addition to positive and negative controls (Histamine dihidrochloride and saline) on the volar surface of the forearm. A wheal size equal or larger than 3 mm was judged as positive.

Quantification of allergen-specific antibodies

The IgE, IgA, IgG1, and IgG4 anti-Der p1-specific antibody contents in serum were measured by ELISA (23). ELISA plates (Maxisorb, Roskilde, Denmark) were coated with 10 μg/ml Der p 1 overnight in phosphate buffered saline (PBS) at 4 °C. Uncoated parts were blocked with PBS, pH: 7.4 containing 3% Top BlockTM and 1% tween 20 (Sigma-Aldrich Co, Buchs, Switzerland). Standards and serum samples were added in eight steps 1:2 serial dilutions in duplicates and incubated 2 h at 4 °C. Biotinylated anti-IgE mAb 6–7 (Novartis, Basel, Switzerland) and peroxidase-labelled ExtrAvidine (Sigma Chem. Co., St Louis, MD, USA) were used to develop IgE anti-Der p 1. Anti-IgG4 mAb PJ4 (Oxoid Ltd., Basingstoke, UK) and peroxidase-labelled anti-mouse Ig antibodies (Tago AG, Burlingame, CA, USA) were used in IgG4 anti-Der p 1 ELISA. Mouse anti-human IgG1 mAb (Zymed, South San Francisco, CA, USA) and goat anti-human IgA (Chemicon, Hofheim, Germany) and appropriate peroxidase-labelled secondary antibodies were used to detect IgG1 and IgA anti-Der p 1 antibodies. Specific antibody binding to coated plates was controlled with hydrolyzed milk powder and human serum albumin (Sigma Chem. Co). Mouse and human mAbs to different antigens were used as negative controls. Uncoated parts were blocked with PBS pH: 7.4 containing 3% Top Block (Sigma Chem. Co) and 1% tween 20. A pooled serum from four Der p 1-allergic patients was used as a standard. High amounts of Der p 1-specific antibody containing serums were selected separately for each of the antibody isotype or subtype. Cut-off for allergen-specific antibodies was determined by mean + 3 s.d. of absorbance obtained in control wells (eight wells for each antibody), in which only dilution buffer (1% BSA in PBS) was added.

Statistical analysis

Statistical analysis was performed with the SPSS package program (Release 11.0; SPSS Inc. Chicago, IL, USA). Comparisons between groups

were made by using non-parametric Kruskal–Wallis test that was followed by *post hoc* Dunn's Multple Comparison test. The Pearson's rank correlation coefficient was calculated. The chi-squared test was used to study the association between qualitative variables. A p-value <0.05 was considered significant.

Results

A total of 73 patients were included. Of those, 58 had asthma (M/F: 27/31, mean ± SD age 7.9 ± 2.7 yr) and 15 had allergic rhinitis (M/F: 8/7, mean ± SD age 10.1 ± 4.0 yr) without asthma. Twenty-five healthy children [(mean ± SD) aged 9.5 ± 4.2 yr, female to male ratio = 12/13] with a negative SPT to all allergens tested were included as controls. Patients and controls were not different with respect to age and gender (data not shown). Der p1-specific IgA, IgG1, IgG4 and IgE levels were measured in all 98 subjects (Table 1).

Comparison of patients and controls

Comparison of Der p1-specific antibody levels of patients and controls revealed that Der p1-specific IgG1, IgG4 and IgE levels of patients with asthma ($p = 0.012$, $p = 0.021$, $p = 0.004$, respectively) were significantly higher than healthy controls. While there was no significant difference in Der p1-specific IgA levels, the ratio of Der p1-specific IgA/IgE was found to be significantly lower in asthmatic children when compared with patients with allergic rhinitis and healthy controls ($p = 0.029$ and $p < 0.001$, respectively). The ratio of Der p1-specific IgG1/IgE of patients with allergic rhinitis was significantly higher than asthmatic children and healthy controls ($p = 0.043$ and $p = 0.001$, respectively) (Table 1).

Comparison of Der p1-specific antibody levels based on the duration of disease

Asthma. In order to evaluate whether an association exists between duration of asthma and specific antibody levels, patients with asthma were divided into two groups with regard to duration of their disease. Disease duration was defined as the period between the onsets of clinical symptoms until the time of the study. The median duration of asthma and allergic rhinitis was found to be 4 yr (range of 1.5–9.5 yr) and 3.95 yr (range of 1.5–15.8 yr), respectively. Based on this, patients with asthma and allergic rhinitis were subdivided into two groups, as less (<4 yr) and, equal or more than 4 yr (≥4 yr). There was no significant difference between the mean age and gender of those patients in either groups (data not shown).

Disease duration <4 yr. When compared with controls, the ratio of Der p1-specific IgA/E was significantly lower in children with a disease duration of <4 yr ($p = 0.003$) (Table 2).

Disease duration ≥4 yr. Comparison of asthmatic patients with a disease duration ≥4 yr with healthy controls revealed significantly higher values for IgA, IgG1, IgG4, IgE antibody levels ($p = 0.002$, $p < 0.001$, $p = 0.001$, $p < 0.001$, respectively) (Fig. 1). Furthermore, the ratio of Der p1-specific IgA/E was significantly lower than controls ($p = 0.046$) (Table 2).

Comparison of asthmatic patients with a disease duration of ≥4 yr with those of <4 yr revealed significantly higher values for IgA, IgG1, IgG4, IgE antibody levels in the first group ($p < 0.001$, $p < 0.001$, $p = 0.018$, $p = 0.014$, respectively) (Fig. 1), whereas ratio of IgA, IgG1 and IgG4 to IgE were not significantly

Table 1. Der p1-specific IgA, IgG1, IgG4, IgE in patients and controls

	Asthma (n = 58)	Allergic rhinitis (n = 15)	Controls (n = 25)	p*p-value
Der p1-sp IgA (U/ml)	4.4 (1.1–33.5)	5.9 (1.9–13.3)	3.6 (1.3–12.8)	0.119
Der p1-sp IgG1 (U/ml)	29.1 (3.6–498.6)†	33.7 (6.7–126.4)	4.6 (0.5–56.1)	<0.001
Der p1-sp IgG4 (U/ml)	60.1 (1.1–1533)†	12.2 (0.6–475)	1.9 (0.4–132.6)	<0.001
Der p1-sp IgE (U/ml)	24.1 (2.7–356.9)†	6 (0.7–118.4)	2.9 (0–7.6)	<0.001
Der p1-sp IgA/IgE	0.2 (0.01–1.9)†,‡	1.2 (0.1–10.4)	0.9 (0.2–14.2)	<0.001
Der p1-sp IgG1/IgE	1.3 (0.04–12.4)‡	5.5 (0.2–11.9)††	2 (0.1–15.3)	0.029
Der p1-sp IgG4/IgE	2.4 (0.1–30.6)	0.8 (0.2–97.9)	0.7 (0.2–30.8)	0.006

All values on table are presented as median (range).
*Analysis by medians of Kruskal–Wallis and Dunn's Multiple Comparision tests.
†Asthma vs. controls IgG1 $p = 0.012$, IgG4 $p = 0.021$, IgE $p = 0.004$, IgA/IgE $p < 0.001$.
‡ Asthma vs. allergic rhinitis IgA/IgE $p = 0.029$, IgG1/IgE $p = 0.001$.
††Allergic rhinitis vs. controls IgG1/IgE $p = 0.043$.
Der p1-specific: Der p1-sp.

Table 2. Der p1-specific IgA/IgE, IgG1/IgE, IgG4/IgE in asthmatic patients with duration of asthma <4 yr vs. ≥4 yr and controls

	Asthma			
	<4 yr (n = 36)	≥4 yr (n = 22)	Controls (n = 25)	p*p-value
Der p1-sp IgA/IgE	0.20 (0.01–1.7)†	0.29 (0.01–1.85)‡	0.91 (0.24–14.23)	<0.001
Der p1-sp IgG1/IgE	1.11 (0.11–9.59)	2.27 (0.04–12.36)	2 (0.12–15.26)	0.24
Der p1-sp IgG4/IgE	2.39 (0.14–30.57)	2.93 (0.41–22.17)	0.72 (0.21–30.84)	0.009

All values on table are presented as median (range).
*Analysis by medians of Kruskal–Wallis and Dunn's Multiple Comparison tests.
†Duration of asthma <4 yr vs. controls, IgA/IgE p = 0.003.
‡Duration of asthma ≥4 yr vs. controls, IgA/IgE p = 0.046.
Duration of asthma <4 yr vs. ≥4 yr no significant difference.
Der p1-specific: Der p1-sp.

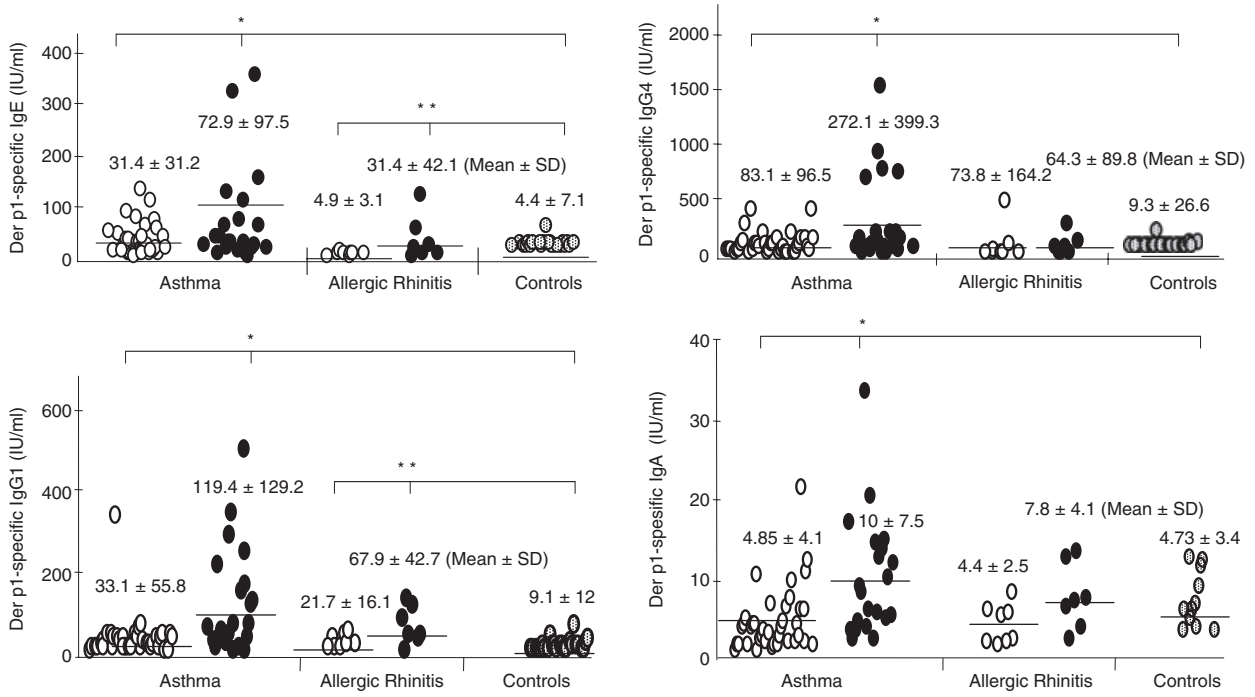

Fig. 1. Specific IgE values with respect to duration of disease: <4 yr (open circles), ≥4 yr (solid circles), controls (dotted circles). Analysis by means of Kruskal–Wallis and Dunn's Multiple Comparison tests. *For asthmatic patients: ≥4 yr vs. <4 yr duration of disease p = 0.014, ≥4 yr duration of disease vs. controls p < 0.001. **For patients with allergic rhinitis ≥4 yr vs. <4 yr duration of disease p = 0.021, ≥4 yr duration of disease vs. controls p = 0.004. Specific IgG4 values with respect to duration of disease: <4 yr (open circles), ≥4 yr (solid circles), controls (dotted circles). Analysis by means of Kruskal–Wallis and Dunn's Multiple Comparison tests. *For asthmatic patients: ≥4 yr vs. <4 yr duration of disease p = 0.018, ≥4 yr duration of disease vs. controls p < 0.001. Specific IgG1 values with respect to duration of disease: <4 yr (open circles), ≥4 yr (solid circles), controls (dotted circles). Analysis by means of Kruskal–Wallis and Dunn's Multiple Comparison tests. *For asthmatic patients ≥4 yr duration of disease vs. <4 yr duration of disease and controls p < 0.001, respectively. **For patients with allergic rhinitis ≥4 yr duration of disease vs. <4 yr duration of disease and controls p < 0.001, respectively. Specific IgA values with respect to duration of disease: <4 yr (open circles), ≥4 yr (solid circles), controls (dotted circles). Analysis by means of Kruskal–Wallis and Dunn's Multiple Comparison tests. *For asthmatic patients: ≥4 yr vs. <4 yr duration of disease p < 0.001, ≥4 yr duration of disease vs. controls p = 0.002.

different in the comparison of those two groups (<4 yr and ≥4 yr).

The individual and mean values of specific antibody levels according to duration of disease of patients with asthma and allergic rhinitis are presented in Fig. 1. Furthermore, Der p1-specific IgA, IgG1, IgG4 and IgE values were positively correlated with duration of asthma [(p = 0.011, r = 0.35), (p ≤ 0.001, r = 0.48), (p ≤ 0.001, r = 0.52), (p ≤ 0.001, r = 0.48), respectively]. On the other hand, there was no correlation between current age of patients and Der p1-specific Ig A, IgG1 and IgG4 values [(p = 0.36, r = −0.23), (p = 0.66, r = 0.11), (p = 0.65,

r = −0.11), respectively]. Only specific IgE levels were positively correlated with increasing age (p = 0.014, r = 0.32).

Allergic rhinitis. In the comparison of subjects with a disease duration of <4 and ≥4 yr with healthy controls, only Der p1-specific IgG1 and IgE levels revealed statistically significant differences. Der p1-specific IgG1 and IgE antibodies were significantly higher in those with a disease duration of ≥4 yr when compared with controls. The comparison of ratios of IgA, IgG1 and IgG4 to IgE was not significantly different in any of the groups (data not shown). The results of correlation analyses revealed no significant association between duration of allergic rhinitis and Der p1-specific antibody levels except for Der p1-specific IgA (r = 0.63, p = 0.015). In addition, current age was not found to be correlated with specific antibody levels in patients with allergic rhinitis.

Relation with age at onset and duration of disease at referral

Der p1-specific IgA and IgG1 antibody levels demonstrated a significantly negative correlation with age at onset of asthma (r = −0.4, p = 0.004, r = −0.32, p = 0.03, respectively), whereas there was no such correlation in children with allergic rhinitis.

Discussion

In the present study, we have demonstrated that levels of Der p1-specific IgE, IgG1 and IgG4 were significantly higher in children with asthma sensitized to HDM when compared with non-sensitized healthy children. On the other hand, the ratio of Der p1-specific IgA/IgE was significantly lower in asthmatic children when compared with children with allergic rhinitis and controls. Furthermore, specific antibody levels tended to increase with longer disease duration of asthma and allergic rhinitis.

Children with allergic asthma and rhinitis included in the current study were sensitized both to *D. pteronyssinus* and *D. farinae*. It is well known that there is an important cross-reaction between *D. pteronyssinus* and *D. farinae* and human sensitivity to both mites is frequently observed (7). Although only Der p1-specific antibody levels were evaluated in this study, we suggest that this had no influence on our results regarding this strong cross-reactivity.

Aeroallergens such as pollens and HDM all play an important role in the development and the triggering of allergic rhinitis and asthma. Atopic infants have an earlier and steeper rise in serum IgE levels during their early years of life when compared with non-atopic controls (8). In some studies, elevation of allergen-specific IgE antibodies in patients with asthma was reported to coincide with high levels of IgG antibodies with the same specificity (9, 10). A number of studies reported good correlations between the IgE and IgG4 antibody level after natural exposure to purified allergens in patients with asthma (11–13). Mukoyama et al. (14) demonstrated that elevated HDM specific-IgG antibodies in children with asthma and atopic dermatitis correlated to specific IgE antibody levels. Similarly, in the current study, levels of Der p1-specific IgE, IgG1 and IgG4 were significantly higher in children with atopic airway diseases when compared with healthy children.

Kitani et al. (15) demonstrated that IgA antibodies to mite in sputa were significantly higher in mite-sensitive patients than in normal controls and mite-insensitive asthmatic patients. Additionally, IgG and IgA antibodies in sera were significantly higher in mite-sensitive patients than in the other two groups. Schwarze et al. presented a murine model of airway sensitization to allergen in which the effect of pre-treatment with allergen-specific IgA prior to inhalation of an airborne allergen was evaluated. This intervention was able to prevent the development of airway hyper-responsiveness, pulmonary eosinophilic inflammation, allergen-specific IgE, and local Th2 cytokine production, while at the same time inducing the production of allergen-specific IgG2a antibodies. They concluded that allergen-specific IgA can modify the respiratory and immunologic consequences of airway challenge in sensitized mice (16). One limitation of our study is that only serum levels of Der p1 specific IgA, but not secretory-specific IgA was studied.

Recently, Jutel et al. studied specific IgA, IgG1, IgG4 and IgE levels of individuals allergic to HDM and compared with a group of non-atopic healthy individuals. Healthy individuals demonstrated increased Der p1-specific IgA and IgG4 antibody production in serum, but did not show IgE or IgG1 antibodies to Der p1. The increases in specific IgA and IgG4 in serum coincided with increased TGF-beta and IL-10, respectively. They suggested that this may account for the role of IgA and TGF-beta as well as IgG4 and IL-10 in peripheral mucosal immune responses to allergens in healthy individuals (17).

In the current study, although Der p1-specific IgA levels of asthmatic children were not significantly different than children with allergic

rhinitis and controls, it tended to increase in time, showing statistically significant elevations in those with a disease duration of ≥4 yr. On the other hand, when the ratio of IgA/IgE was investigated, it was found to be significantly lower in children with asthma regardless of disease duration, but not in children with allergic rhinitis. We concluded that although all of the specific antibody levels increased with longer duration of asthma, IgA/IgE ratio remains to be low in asthmatic children allergic to HDM.

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