

Effect of Exposure and Sensitization to Indoor Allergens on Asthma Control Level

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ABSTRACT

Background: Reducing risk factors, such as exposure to allergens, and stepwise pharmacotherapy to achieve and maintain control of asthma are the mainstay of asthma care. The purpose of this study was to clarify the effect of exposure and sensitization to indoor allergens, including house dust mites, cats, and dogs, on the asthma control level.

Methods: Dust samples were collected from the mattresses of 101 adult asthma patient homes and the *Dermatophagoides* mite group 1 (Der 1), Fel d 1, and Can f 1 concentrations were measured using ELISA. Sensitization was determined by positive specific IgE antibodies. The Asthma Control Test (ACT), lowest peak expiratory flow (PEF) during 1 week expressed as a percentage of the highest PEF (Min%Max PEF), and spirometry were measured for the assessment of asthma control. Univariate and multivariate regression analyses were used to assess the relationships.

Results: Sixty-nine patients were exposed to high levels ($>10 \mu\text{g/g}$ dust for Der 1 and Can f 1 and $>8 \mu\text{g/g}$ dust for Fel d 1) of 1 or more allergens and 39 patients were sensitized to at least one allergen. Multivariate logistic regression analyses revealed that the FEV₁ (% of predicted value) was associated with low ACT scores (≤ 19) and that the number of highly exposed allergens and inhaled corticosteroid dose were associated with a low level of Min%Max PEF ($<80\%$).

Conclusions: The level of exposure to multiple indoor allergens, but not sensitization, is associated with the asthma control level determined by PEF variation.

KEY WORDS

asthma control, exposure, indoor allergen, peak expiratory flow variation, sensitization

ABBREVIATIONS

ACT, Asthma Control Test; Der 1, *Dermatophagoides* mite group 1; FVC, forced vital capacity; Min%Max PEF, lowest peak expiratory flow during 1 week expressed as a percentage of the highest peak expiratory flow; PEF, peak expiratory flow.

INTRODUCTION

The mainstay of asthma care includes reducing risk factors and a stepwise approach to pharmacologic treatment to achieve and maintain control of asthma.¹ Exposure and sensitization to indoor allergens, including house dust mites, cats, and dogs, are impor-

tant risk factors for asthma. Indoor allergen exposure in the development of allergic sensitization and asthma remains controversial; however, studies have shown that indoor allergens play a key role in triggering and exacerbating asthma symptoms.²⁻⁶

There are some differences in the role of exposure and sensitization in asthma. Several investigators

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have reported that sensitization and exposure to cat allergens were associated with asthma but not dust mite allergens,^{2,3} while others found a relationship between multiple indoor allergen exposure and asthma symptoms.^{4,6} Lack of an association between allergen sensitization and asthma morbidity has also been reported.⁷ Further, most studies focused mainly on asthma severity and only a few studies referred to asthma control levels.

The purpose of this study was to clarify the effect of exposure and sensitization to indoor allergens on the asthma control level in clinical practice. We measured the concentrations of dust mite, cat, and dog allergens in dust samples on bedding and specific IgE antibody positivity, and examined the relationships with asthma control variables, including the Asthma Control Test (ACT) and the lowest PEF during 1 week, expressed as a percentage of the highest PEF (Min%Max PEF) in adult patients with asthma.

METHODS

SUBJECTS

One hundred one patients with asthma who attended outpatient clinics at Shizuoka General Hospital for routine check-ups between April 2008 and March 2009 were enrolled in this study. These patients were selected without prejudice by a coauthor (T. S.) who had not seen them or their medical records previously. All patients satisfied the definition of asthma of GINA 2006,¹ and were treated based on their asthma control level; that is, the patient's current level of asthma control and current treatment determined the selection of pharmacologic treatment. If asthma was not controlled using the current treatment regimen, treatment was stepped up until control was achieved. If control had been maintained for at least 3 months, treatment could be stepped down. Atopy was defined by positive specific IgE antibodies to at least one common inhalant allergen (CAP system; Pharmacia, Uppsala, Sweden). Inclusion criteria were as follows: (1) age between 20 and 80 years; (2) ability to perform an adequate forced expiratory maneuver; and (3) receiving inhaled corticosteroids with or without other medications for asthma, including long-acting β_2 -agonists, leukotriene receptor antagonists, or sustained release theophylline for at least 3 months. Patients were excluded from the study if they (1) had had any acute viral infections within at least 1 month before the study; (2) had a smoking history of >10 pack-years; (3) had chronic obstructive pulmonary disease; (4) had cardiovascular diseases; or (5) were pregnant. Peak expiratory flow (PEF) monitoring was performed in 81 patients using a Miniwright peak flow meter (Clement Clarke International Ltd., Harlow, UK). The protocols were approved by the local ethics committee and informed consent was obtained from all patients prior to the study.

EXPOSURE AND SENSITIZATION TO INDOOR ALLERGENS

Dust samples were collected for 2 min from a 1 m² area of the mattress using a hand-held vacuum cleaner (HC-V15; Panasonic, Osaka, Japan).⁸ All samples were assayed for the *Dermatophagoides mite* group 1 (Der 1), Fel d 1, and Can f 1 content using ELISA, as previously described.⁹ The results were expressed as micrograms of allergen per gram of dust ($\mu\text{g/g}$ dust). Subjects were classified as being exposed to high levels of domestic allergens if the concentration was >10 $\mu\text{g/g}$ dust for Der 1 and Can f 1 and >8 $\mu\text{g/g}$ dust for Fel d 1, respectively.^{4,6} The exposure score was defined as the number of highly exposed allergens ranging from 0 to 3.

Sensitization to dust mites, cats, and dogs was determined by positive specific IgE antibodies (CAP system; Pharmacia). Specific IgE titers ≥ 0.7 UA/ml were considered positive and the sensitization score was defined as the number of positive allergens ranging from 0 to 3.

STUDY DESIGN

On the examination day within 1 week from dust sampling, the patients completed the ACT questionnaire and underwent testing by spirometry. The ACT (Japanese version, supplied by GlaxoSmithKline Japan) questionnaire consists of 5 items assessing the impact of asthma on everyday functioning at school or work, shortness of breath, nocturnal asthma symptoms, use of rescue medication, and the patient's self-rating of asthma control during the previous 4 weeks.^{10,11} Spirometry was determined using computerized equipment (model CHESTAC-33; CHEST MI, Inc., Tokyo, Japan). FEV₁ was expressed as a percentage of predicted values according to the formula of the Japanese Respiratory Society,¹² and FEV₁/forced vital capacity (FVC) was also calculated. In patients who recorded their PEF values at home, the Min%Max PEF values¹³ during the 2-week period prior to examination were calculated.

STATISTICAL ANALYSIS

Categorical data are summarized as counts, and quantitative data are summarized as medians with ranges. The patients were classified into controlled or less controlled groups according to the following cut-off values: ≥ 20 versus ≤ 19 in ACT scores and $\geq 80\%$ versus $< 80\%$ in Min%Max PEF. Concerning PEF monitoring, no difference was found in quantitative and categorical data between the 81 patients with complete data and the remaining 20 patients with incomplete data by the t-test and chi-square test, respectively. Logistic regression analyses were performed to assess the relationships between exposure and sensitization and asthma control variables. After initial univariate analyses, variables that had $p < 0.05$ in the univariate models were included in the multi-

Table 1 Characteristics of the study patients

Characteristics	Findings (n = 101)
Age, median (range), y	60 (22-77)
Male/female, No.	46/55
Non/ex/current smokers, No.	51/36/14
Atopic/non-atopic, No.	72/29
Current pet owners (cat/dog), No.	32 (14/19)
Coexisting nasal diseases, No.	55
Duration of asthma, median (range), y	10 (1-51)
FEV ₁ , median (range), % of predicted value	87.0 (29.6-145.7)
FEV ₁ /FVC, median (range), %	72.3 (25.2-100.0)
Allergen level, median (range), µg/g dust	
Der 1	14.9 (0.44-108.00)
Fel d 1	0.13 (0.00-5594.00)
Can f 1	0.36 (0.13-997.00)
Exposure to high levels of allergens [†]	
Dust mite/cat/dog, No.	57/15/13
Exposure scores 0/1/2/3, No.	32/54/15/0
Specific IgE titers, median (range), UA/ml	
Dust mite	0.34 (0.34-100.00)
Cat	0.34 (0.34-100.00)
Dog	0.34 (0.34-87.30)
Allergen sensitization (positive test results) [‡]	
Dust mite/cat/dog, No.	34/17/16
Sensitization scores 0/1/2/3	62/21/8/10
ACT scores, median (range)	24 (6-25)
≥20, No.	85
≤19, No.	16
Min%Max PEF, median (range) [§]	88.9 (60.0-100.0)
≥80, No.	67
<80, No.	14
Total IgE, median (range), U/ml	135.5 (8.4-12550.6)
Inhaled corticosteroids, No.	101
dose, median (range), µg/day [¶]	400 (200-1000)
Long-acting β ₂ -agonists, No.	52
Leukotriene receptor antagonists, No.	50
Sustained-release theophylline, No.	40
Prednisolone, No.	7
No. of medications, median (range)	2 (1-6)

Abbreviations: ACT, asthma control test; Der 1, *Dermatophagoides mite* group 1; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; Min%Max PEF, lowest peak expiratory flow during 1 week expressed as a percentage of the highest peak expiratory flow; PEF, peak expiratory flow.

[†] High level of exposure means >10 µg/g dust for Der 1 and Can f 1 and >8 µg/g dust for Fel d 1, respectively. Exposure score was defined as the number of highly exposed allergens ranging from 0 to 3.

[‡] Specific IgE levels ≥0.7 UA/ml were considered positive. Sensitization score was defined as the number of positive allergens ranging from 0 to 3.

[§] PEF monitoring was performed in 81 patients.

[¶] Fluticasone propionate or equivalent.

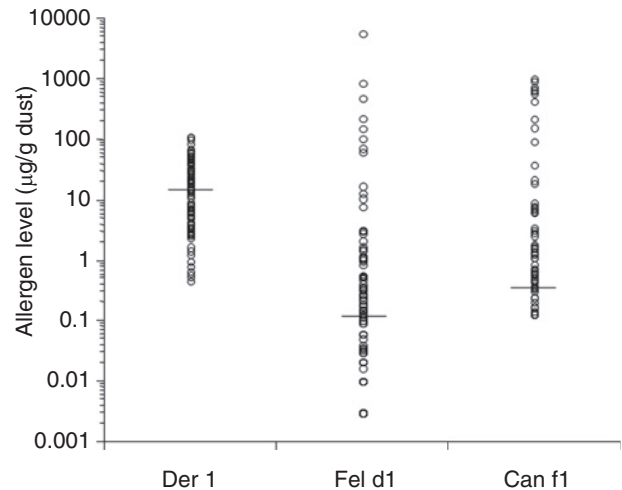


Fig. 1 Concentrations of Der 1, Fel d 1, and Can f 1 allergens in dust samples collected from bedding from 101 patient homes. Horizontal bars represent medians.

variate models together with variables concerning exposure and sensitization. Otherwise, variables deemed of clinical significance regardless of statistical significance were included in the model. Stat View Version 5.0 (SAS Institute, Cary, NC, USA) was used for statistical calculations. A *p* value of <0.05 was considered significant, and all tests were 2 sided.

RESULTS

The clinical characteristics of the study population are shown in Table 1. Der 1, Fel d 1, and Can f 1 levels in the samples from bedding surfaces are presented in Figure 1. It was found that the median Der 1 level was higher than 10 µg/g dust, that 69 patients were exposed to high levels of at least one domestic allergen, and 39 patients were sensitized to at least one allergen. There were 32 current pet owners. Eleven non-cat owners and 11 non-dog owners were sensitized to cats and dogs, respectively, while 9 cat owners and 13 dog owners were not sensitized to cats and dogs, respectively.

In the univariate models (Table 2), the FEV₁ and inhaled corticosteroid dose were associated with low ACT scores, but no other factor was associated, including allergen concentrations, allergen-specific IgE titers, and exposure and sensitization scores. Unlike ACT scores, no factor was associated with low levels of Min%Max PEF (Table 3).

Multivariate logistic regression analysis was performed by including the duration of asthma, FEV₁, inhaled corticosteroid dose, and variables concerning exposure and sensitization. As shown in Table 4, the FEV₁ was negatively associated with low ACT scores, whereas exposure scores and the inhaled corticosteroid dose were positively associated, but did not reach statistical significance (Table 4). The results from the

Table 2 Univariate analysis for factors associated with low ACT scores (≤ 19)

Characteristics	OR	95% CI	p Value
Age	0.990	0.956-1.026	0.598
Female sex	1.090	0.372-3.197	0.875
Current smoking	1.364	0.290-6.416	0.695
Atopy	1.155	0.363-3.678	0.807
Current pet owners	1.253	0.378-4.156	0.713
Absence of nasal diseases	0.917	0.313-2.691	0.875
Duration of asthma ($\times 10$), y	0.914	0.554-1.508	0.725
FEV ₁ , % of predicted value	0.961	0.936-0.988	0.004
FEV ₁ /FVC, %	0.974	0.938-1.013	0.185
Der 1, $\mu\text{g/g}$ dust	1.001	0.979-1.023	0.926
Fel d 1, $\mu\text{g/g}$ dust	1.000	0.998-1.001	0.786
Can f 1, $\mu\text{g/g}$ dust	1.000	0.996-1.003	0.779
Exposure scores	1.124	0.503-2.515	0.775
Dust mite-specific IgE titers, UA/ml	1.001	0.980-1.023	0.909
Cat-specific IgE titers, UA/ml	0.978	0.890-1.076	0.648
Dog-specific IgE titers, UA/ml	0.974	0.842-1.127	0.724
Sensitization scores	0.865	0.484-1.548	0.625
Log (Total IgE), U/ml	1.061	0.444-2.539	0.894
Inhaled corticosteroids, dose ($\times 100$), $\mu\text{g/day}^\dagger$	1.248	1.032-1.510	0.022

Abbreviations: CI, confidence interval, Der 1.

 † Fluticasone propionate or equivalent.**Table 3** Univariate analysis for factors associated with low levels of Min%Max PEF ($< 80\%$)

Characteristics	OR	95% CI	p Value
Age	1.005	0.962-1.050	0.806
Female sex	1.219	0.381-3.897	0.738
Current smoking	0.550	0.055-5.457	0.610
Atopy	1.404	0.416-4.733	0.585
Current pet owners	0.822	0.245-2.753	0.750
Absence of nasal diseases	1.393	0.439-4.420	0.574
Duration of asthma ($\times 10$), y	0.894	0.522-1.534	0.685
FEV ₁ , % of predicted value	0.980	0.955-1.006	0.128
FEV ₁ /FVC, %	0.976	0.936-1.018	0.185
Der 1, $\mu\text{g/g}$ dust	0.991	0.962-1.021	0.559
Fel d 1, $\mu\text{g/g}$ dust	0.997	0.985-1.009	0.620
Can f 1, $\mu\text{g/g}$ dust	1.002	0.999-1.004	0.180
Exposure scores	1.335	0.580-3.070	0.497
Dust mite-specific IgE titers, UA/ml	0.984	0.948-1.021	0.383
Cat-specific IgE titers, UA/ml	0.763	0.337-1.726	0.516
Dog-specific IgE titers, UA/ml	0.092	0.054-28.883	0.416
Sensitization scores	0.555	0.236-1.305	0.177
Log (Total IgE), U/ml	0.914	0.355-2.351	0.852
Inhaled corticosteroids, dose ($\times 100$), $\mu\text{g/day}^\dagger$	1.191	0.962-1.476	0.109

Abbreviations: CI, confidence interval.

 † Fluticasone propionate or equivalent.**Table 4** Multivariate analysis for factors associated with low ACT scores (≤ 19)

Characteristics	Adjusted OR	95% CI	p Value
Duration of asthma ($\times 10$), y	0.760	0.381-1.514	0.435
FEV ₁ , % of predicted value	0.960	0.926-0.996	0.028
Der 1, $\mu\text{g/g}$ dust	0.979	0.939-1.020	0.315
Fel d 1, $\mu\text{g/g}$ dust	0.998	0.992-1.004	0.573
Can f 1, $\mu\text{g/g}$ dust	0.709	0.417-1.205	0.204
Exposure scores	3.984	0.806-19.687	0.090
Dust mite-specific IgE titers, UA/ml	0.996	0.966-1.027	0.801
Cat-specific IgE titers, UA/ml	0.920	0.512-1.653	0.779
Dog-specific IgE titers, UA/ml	1.110	0.575-2.141	0.756
Inhaled corticosteroids, dose ($\times 100$), $\mu\text{g/day}^\dagger$	1.293	0.970-1.732	0.079

Abbreviations: CI, confidence interval.

 † Fluticasone propionate or equivalent.**Table 5** Multivariate analysis of factors associated with low levels of Min%Max PEF ($< 80\%$)

Characteristics	Adjusted OR	95% CI	p Value
Duration of asthma ($\times 10$), y	0.672	0.285-1.586	0.365
FEV ₁ , % of predicted value	0.991	0.956-1.026	0.596
Der 1, $\mu\text{g/g}$ dust	0.931	0.858-1.011	0.088
Fel d 1, $\mu\text{g/g}$ dust	0.968	0.896-1.046	0.413
Can f 1, $\mu\text{g/g}$ dust	0.997	0.992-1.002	0.174
Exposure scores	15.850	1.369-183.563	0.027
Dust mite-specific IgE titers, UA/ml	1.001	0.998-1.005	0.344
Cat-specific IgE titers, UA/ml	0.985	0.937-1.036	0.565
Dog-specific IgE titers, UA/ml	0.868	0.686-1.099	0.241
Sensitization scores	0.498	0.030-8.257	0.626
Inhaled corticosteroids, dose ($\times 100$), $\mu\text{g/day}^\dagger$	1.429	1.013-2.017	0.042

Abbreviations: CI, confidence interval.

 † Fluticasone propionate or equivalent.

multivariate models for Min%Max PEF differed from the univariate models in that exposure scores and the inhaled corticosteroid dose were significantly associated, while other variables were not (Table 5).

DISCUSSION

Bedding is the most important source of mite allergens in indoor environments and exposure to mite allergens in daily life occurs predominantly while sleeping at night.⁹ The Der 1 level (median, 14.9 $\mu\text{g/g}$ dust) and the percentage of patients with a high level of exposure (56%) in this study were higher than those reported from the USA¹⁴ and Europe¹⁵ but lower than from Australia,² although these were general population studies. Our hospital lies 200 km west

of Tokyo and all patients live in a typical South East Asian climate of high temperature and high humidity. It is suggested that the living conditions and traditional Japanese lifestyle are associated with high dust mite concentrations in dust samples. In contrast, the Fel d 1 and Can f 1 levels in this study were lower than those reported from other countries,^{2,4,16,17} possibly reflecting the lower frequency of pet ownership of the patients (32%) and the communities where they live.

The sensitization rates to dust mites, cats, and dogs in this study were 34%, 17%, and 16%, respectively, which were lower than those of 60%, 49%, and 40%, respectively, in 462 asthmatic patients reported by Langley *et al.*⁴ Possible explanations for the differences include older age (60 versus 42 years) and frequency of pet ownership (32% versus 43%).

Multivariate analyses revealed that exposure scores, the number of highly exposed allergens, were associated with Min%Max PEF, an asthma control variable. Min%Max PEF is the most common method of calculating between-day PEF variability, which increases as PEF variation decreases.¹⁸ Since dust samples were collected from bedding in this study, the exposure level to indoor allergens predominantly means that while sleeping at night. In view of the lack of association between Min%Max PEF and FEV₁ in the multivariate model, variation in lung function appears to represent a different aspect of asthma control from static lung functions and is suitable for assessing the association with exposure levels. The importance of reducing allergen exposure in asthma care was suggested in this study.

There was no association between each allergen concentration and Min%Max PEF or ACT scores, indicating that the effect of indoor allergens on asthma control should be assessed not as single allergens but as multiple allergens. Few studies have examined the role of multiple allergen exposure in relation to asthma. The National Survey of Lead and Allergens in Housing in the USA reported that a high multiple allergen burden increased the odds of having asthma symptoms (OR = 1.81),⁶ but the effect on lung function was not studied. Langley *et al.* reported that asthmatic patients both sensitized and exposed to high levels of sensitizing allergen had lower FEV₁, higher exhaled nitric oxide, and more severe airway reactivity than patients not sensitized and exposed.⁴ Unfortunately, we found no association between the sensitization-related variables and Min%Max PEF or ACT scores, suggesting that exposure rather than sensitization to indoor allergens may affect the asthma control level.

The FEV₁ was associated with a low ACT level but variables concerning allergen exposure were not. The low but significant correlation between ACT scores and FEV₁ values has been reported previously.¹¹ This finding suggests that the ACT, a vali-

dated questionnaire for asthma control, is not suitable for the assessment of allergen exposure effects and that ACT may reflect the different aspects of asthma control from Min%Max PEF.

Since this study was a small cross-sectional one, it is difficult to assess the cause-and-effect relationship between exposure and sensitization to indoor allergens in the studied population. There are conflicting reports in this regard. Custovic *et al.* investigated the relationship between current exposure to dust mite, cat, and dog allergens with sensitization to inhalant allergens using a dust sampling and skin prick tests in a large sample of 2502 adults.¹⁹ They found that sensitization to dust mites increased with the increasing exposure, whereas cat ownership was associated with a lower prevalence of sensitization to cat and dog. Dharmage *et al.* also assessed the influence of current indoor levels of house dust mite allergen and cat allergen on sensitization in a follow up study with 485 adults.² They found that people exposed to high Der p 1 levels in dust were less likely to be sensitized to house dust mites and high Fel d 1 levels were found to increase the risk of being sensitized to cats. These findings suggest that depending on the studied population, the study design, and statistical methods, results may be changeable. A large scale, longitudinal study will be at least partly required to assess the cause-and-effect relationship between exposure and sensitization to indoor allergens.

Recently, there are some reports in support of the hygiene hypothesis.²⁰ Campo *et al.* assessed the relationships between early pet ownership and endotoxin exposure with atopy and wheezing during infancy. They found that high endotoxin exposure in the presence of multiple dogs were associated with reduced wheezing.²¹ This hypothesis is attractive, but there are difficulties in accepting it since preventive effect of pet-keeping on atopy or asthma has not been proven. The present study does not negate the hygiene hypothesis but does not recommend pet-keeping for patients with asthma, either.

Although the limitations of this study include a small sample size, a study population of old age, and a high percentage of controlled patients, we believe that we have demonstrated the importance of reducing allergen exposure in clinical practice.

In conclusion, this study shows that exposure, but not sensitization, to multiple indoor allergens, including house dust mites, cats, and dogs, is associated with the asthma control level determined by PEF variation. We should keep in mind the importance of indoor allergen exposure as well as pharmacotherapy in asthma care.

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CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

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