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IgE recognition profile of aeroallergen components in young children sensitized to dogs

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Conflict of interest

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Author Contributions

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ABSTRACT

Background: Pet ownership is increasing rapidly and as growing numbers of dogs in household, clinicians are facing more allergic patients and so as in young children.

Objective: This study aims to profile the IgE recognition patterns to aeroallergen components in young children sensitized to dogs.

Methods: Through retrospective chart reviews, we evaluated the clinical, environmental, and laboratory findings of patients sensitized to dogs in early life. We further evaluated specific IgE to dog component allergens (Can f1, Can f2, and Can f3) and other aeroallergens using a microarray.

Results: The median age of 28 patients sensitized to dogs (dog-specific IgE \geq 0.35 kU/L; 0.38–101 kU/L) was 61 months and underlying diseases included doctor diagnosed atopic dermatitis (n = 17), asthma (n = 7), and allergic rhinitis (n = 5). Twenty patients (71.4%) had experienced self-reported dog allergy and 70.0% of them were symptomatic after exposed to dogs from others. Component-resolved diagnosis was performed on 18 patients. Can f1 positivity was the most common (77.8%) but had no value in symptom prediction. The most common cosensitized aeroallergen was house dust mites (44.5%). The symptomatic group tended to be poly-sensitized to Can f1, Can f2, and Can f3.

Conclusion: Can f1 was dominantly detected and poly-sensitized to Can f2 and/or Can f3 simultaneously tend to develop hypersensitivity to dogs in young children. Most of them were exposed to dogs not living with.

Keywords: Can f1; Microarray; Component-resolved diagnosis; Dog allergy; Child

INTRODUCTION

Studies demonstrating dog allergies have been limited to adolescence and adulthood as aeroallergen sensitization and symptom development tend to occur in late childhood [1, 2]. Thus, dog allergies in young children, and their clinical, environmental, and immunological manifestations, have rarely been evaluated. Particularly, although atopic eczema is one of the main allergic manifestations in this age group, the influence of household pets on such eczema is unclear and not well characterized [3].

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Pet ownership in Seoul has increased rapidly, with 20.4% of the population having pets in 2016, and the prevalence of dog ownership among pet owners (88.5%) being remarkably higher than that of cat ownership (26.6%) [4, 5]. Sensitization rates to dogs have not been reported among Korean children, but among adults, they are known to be 7.6% [6]. Even without having a pet in their own homes, children may be at risk of dog or cat allergies because animal allergens can be distributed in public places or at the homes of relatives [5, 7]. Previous studies have indicated that sensitization to pets from indirect exposure and a moderate dose of allergen concentration was more frequently observed in allergic patients compared to direct exposure and a high concentration of allergen [7, 8].

Recombinant technology now allows production of dog allergen components that can be used for component-resolved diagnosis (CRD) [9]. A component is defined as a molecule derived from a given allergen source that is identified by IgE antibodies, and distinct dog allergens including Can f 1, Can f 2, Can f 4, and Can f 6 (lipocalins); Can f 3 (serum albumin); Can f 5 (prostatic kallikrein); and Can f 7 (epididymal secretory protein) have been identified [10, 11]. Among these, commercially available CRD using microarray now allows examination of Can f 1, Can f 2, and Can f 3 with other aeroallergens.

Though it is not easy to confirm whether sensitization to dog allergen components is of clinical relevance but one recent study documented patients aged 10–18 years who were sensitized to at least one of all dog component proteins showed positive results for the nasal provocation test [12]. CRD may be useful to identify the most problematic allergens in patients and further help to make a better diagnosis and treatment [13, 14].

The purpose of this study was to investigate the clinical and immunological manifestations in young children sensitized to dogs. By using microarray, major-specific IgE antibodies to component dog allergens and cosensitization profiles to other aeroallergens were evaluated. Dog exposure patterns of the subjects were also examined.

MATERIALS AND METHODS

Based on a retrospective review of medical records of patients aged 14 years of younger who visited the Ajou University Hospital (Suwon, Korea) for their allergic diseases between January 2010 and June 2012, 28 patients were sensitized to dogs (dog-specific IgE \geq 0.35 kU/L, ImmunoCAP, Thermo Fisher Scientific Inc., Uppsala, Sweden) and clinical and environmental characteristics were well described to be enrolled. Demographic profile, clinical symptoms, and laboratory findings of the participants were evaluated. Detailed exposure patterns to dogs were also collected. Exposure patterns to dogs were defined as: direct (D), with previous and/or current own; and indirect (I), with occasional exposure to a relative's dog, perinatal exposure, and accidental exposure. For serologic analysis, dog-sIgE values $>$ 100 kUA/L were considered as 101 kUA/L.

Further, the parents of 18 patients agreed to participate additional serologic analysis and provided serum samples. Sera of the patients were taken simultaneously at diagnosis and stored at -20°C . CRD was performed using the commercially available immune solid-phase allergen chip (ISAC) immunoassay ImmunoCAP ISAC (CRD 113; Thermo Fisher Scientific Inc.) according to the manufacturer's guidelines and as reported previously [9]. Data are expressed as ISAC standardized units (ISU/L, ISU), and the decision threshold was set at 0.

Statistical analyses were performed using R ver. 3.0.2 software (R Foundation for Statistical Computing, Vienna, Austria). Normality was tested, and p values for continuous variables were calculated using a Wilcoxon rank-sum test. A Fisher exact test was performed to compare categorical variables. A value of $p < 0.05$ was considered statistically significant.

The study protocol was approved by the Institutional Review Board of Ajou University Medical Center (MED-OBS-13-335), and informed consent was obtained from the parents of all participants.

RESULTS

The median age of 28 patients sensitized to dogs (dog-sIgE ≥ 0.35 kU/L) was 61 months (4–165 months). The sex ratio was the same for 14 girls and 14 boys. The range of dog-sIgE concentration was 0.38–101 kU/L. Twenty-five patients (89.3%) had underlying allergic diseases. The most common comorbidity was atopic dermatitis (AD), which affected 17 patients, followed by bronchial asthma (As, $n = 7$) and allergic rhinitis (AR, $n = 5$). Twenty patients (71.4%) reported repeated immediate-typed allergic symptoms upon contact with dogs and 8 patients were tolerant.

The median age of symptomatic patients (11 boys and 9 girls) was 61 months. The range of dog-sIgE concentration was 0.38–101 kU/L. Hypersensitivity reactions were charted as anaphylaxis ($n = 1$), itching ($n = 4$), eczema aggravation ($n = 4$), and respiratory symptoms such as coughing and runny nose (R, $n = 4$). Among 4 patients who took antihistamines due to worsening of itching, 3 had underlying AD. An environmental survey revealed that 6 patients were directly (D) exposed to a dog, whereas 14 (70.0%) experienced hypersensitivity reactions from indirect (I) exposure. Among 6 D-patients, 3 (50.0%) had owned a dog in the past but not currently.

The median age of tolerant patients (3 boys and 5 girls) was 57.5 months. Dog-sIgE concentration ranged from 0.68 kU/L to 101 kU/L. Underlying diseases were AD ($n = 5$), As ($n = 3$), and AR ($n = 2$). Environmental survey revealed that 3 children were D-exposed to a dog, and all of them currently had a dog at home. Among 5 I-exposed patients, 2 were exposed perinatally and at their grandparents' houses after birth. Three children were exposed accidentally (**Table 1**).

CRD was performed on 18 patients after obtaining an additional consent form, and the results are shown in **Fig. 1** and **Table 2**. Fourteen children (77.8%) showed Can f 1 positivity and 8 (57.1%) among them showed Can f 1 mono-sensitization. Nine children (50.0%) showed Can f 3 positivity and only 2 (22.9%) showed Can f 3 mono-sensitization (KDE; dog-sIgE 14.2 kU/L, PJM; dog-sIgE 0.92 kU/L) (**Table 2**). The mean dog-sIgE concentration of patients who poly-sensitized to 2 or more antigens ($n = 7$) was 44.4 ± 36.1 kU/L, which was higher than that of patients who mono-sensitized to certain antigen ($n = 10$) (11.6 ± 17.1 kU/L) ($p = 0.06$) (**Table 3**). **Table 4** shows comparison of clinical and immunological characteristics of patients in the symptomatic and tolerant groups. The tolerant group was predominantly female, had a higher dog-sIgE concentration and higher rate of mono-sensitization to Can f 1 and its concentration, but the difference was not statistically significant. In both groups, the percentage of children with I-exposure to dogs was higher.

The most common cosensitized aeroallergen was house dust mite, with Der p 1 and Der f 1 positivity of 44.5% ($n = 8$) and 5 children having AR or bronchial asthma. Cat Fel d 2 positivity

Microarray in dog sensitized children

Table 1. Clinical, environmental, and immunological characteristics of patients

ID	Sex	Age (mo)	Total IgE	Dog-sIgE (kU/L)	Underlying diseases	Symptoms on dog exposure	Exposure patterns to dogs			
							At home - previously	At home - current	Perinatal	Occasional
PHS	F	117	123	0.38	None	Itching	0	0	0	1
KSY	M	92	362	0.46	AR, As	R	0	0	1	1
HSW	M	60	346	0.63	AR, As	Urticaria	0	0	0	0
NHW	F	18	31	0.79	FA	Urticaria	0	0	0	1
SJW	M	136	941	1.29	None	Urticaria	0	0	0	0
BJH	M	95	193	1.51	AR, As	R	0	0	1	1
JSH	M	126	257	1.76	AD	Anaphylaxis	0	0	1	1
JHN	F	36	100	2.10	AD	Itching	1	0	1	1
KJY	F	121	910	3.46	AD	Itching	0	0	0	0
HJA	F	72	ND	4.33	AD	Urticaria	0	0	0	1
GSW	F	26	108	4.69	AD	Eczema agg	0	0	1	1
YSH	F	109	271	5.57	AD	Eczema agg	0	1	0	0
KSY	M	30	71	7.57	AD	Urticaria	1	0	1	0
YCJ	M	4	42	11.3	AD	Eczema agg	1	1	1	0
KDE	F	38	848	14.2	AD	Urticaria	1	0	1	1
JYE	F	43	590	16	AD	Itching	0	0	0	1
JMJ	M	36	207	27.7	None	Urticaria	0	0	0	1
LJH	M	82	1,831	65	As	R	0	0	1	1
LSJ	M	4	2,607	69.8	AD	Eczema agg	0	1	1	1
YWC	M	62	1,115	101	AD	R	0	0	0	1
LHJ	F	77	ND	0.68	AD	Negative	0	1	0	0
PJM	M	64	3,255	0.92	AD	Negative	0	0	0	0
KMS	F	37	110	5.40	AR, As	Negative	0	0	0	0
YTH	M	23	844	7.71	AD	Negative	0	0	1	1
KSH	F	51	529	24.90	AR, As	Negative	1	1	1	1
LJM	F	82	963	41.6	AD	Negative	1	1	0	0
JSH	M	19	821	55	AD	Negative	0	0	1	1
KBM	F	165	2,345	101	As	Negative	0	0	0	0

AD, atopic dermatitis; agg, aggravation; Ana, anaphylaxis; AR, allergic rhinitis; As, bronchial asthma; FA, food allergy; IgE, immunoglobulin E; ND, not done; R, respiratory symptoms.

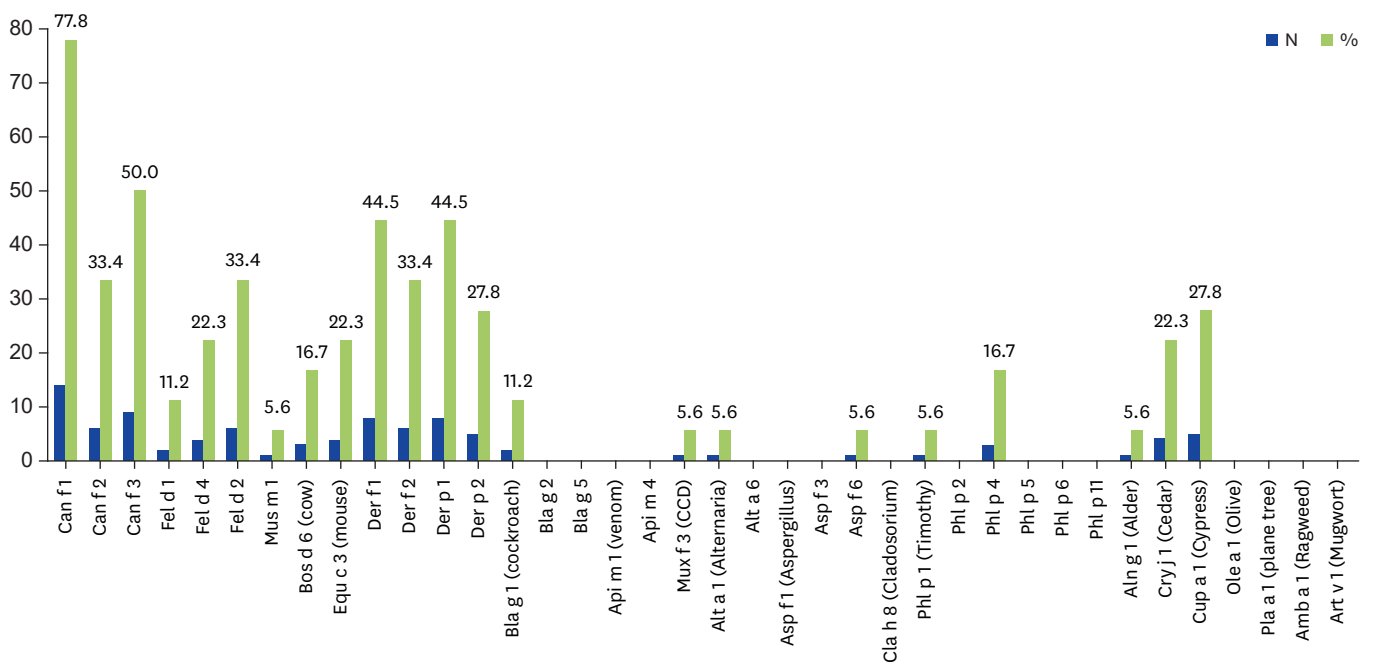


Fig. 1. Analysis of IgE recognition of aeroallergen components using ImmunoCAP ISAC (CRD 113) in 18 children sensitized to dogs (dog-specific IgE ≥ 0.35 kU/L, ImmunoCAP).

Table 2. Characteristics of children included in the component-resolved diagnosis microarray

ID	Sex	Age (mo)	Total IgE (kU/L)	Dog-sIgE (kU/L)	Symptoms on dog exposure	ISAC (ISU/L)		
						Can f 1	Can f 2	Can f 3
PHS	F	117	123	0.38	Itching	1.79	0	0
HSW	M	60	346	0.63	Urticaria	1.14	0	0
NHW	F	18	31	0.79	Urticaria	0.32	0	0
JHN	F	36	100	2.1	Itching	1.41	0	1.41
GSW	F	26	108	4.69	Eczema agg	0	1.73	2.01
YSH	F	109	271	5.57	Eczema agg	1.92	0	0
YCJ	M	4	42	11.3	Eczema agg	0	0	0
KDE	F	38	848	14.2	Urticaria	0	0	1.37
JMJ	M	36	207	27.7	Urticaria	19.5	10.8	7.16
LJH	M	82	1,831	65	R	63.9	46.7	39
LSJ	M	4	2,607	69.8	Eczema agg	29	11.4	5.6
YWC	M	62	1,115	101	R	63.7	63.9	61.9
PJM	M	64	3,255	0.92	Negative	0	0	0.45
KMS	F	37	110	5.4	Negative	7.49	0	0
YTH	M	23	844	7.71	Negative	12.7	0	0
KSH	F	51	529	24.9	Negative	6.64	0	0
LJM	F	82	963	41.6	Negative	10.9	6.01	31.1
JSH	M	19	821	55	Negative	11.4	0	0

ISAC, ImmunoCAP ISAC; IgE, immunoglobulin E; Dog-sIgE, dog-specific IgE; R, respiratory symptoms; agg, aggravation.

Table 3. The mean dog-sIgE concentration in patients according to the numbers of sensitized antigens

	No.	Dog-sIgE (kU/L), mean \pm SD	<i>p</i> value
Mono-sensitized to dog components	7	11.6 \pm 17.1	0.06
Poly-sensitized to dog components	10	44.4 \pm 36.1	

Dog-sIgE, dog-specific immunoglobulin E; SD, standard deviation.

Table 4. Comparison of clinical and immunological characteristics of patients in the symptomatic and tolerant groups

Variable	Symptomatic (n = 20)	Tolerant (n = 8)	<i>p</i> value
Age (mo)	65.3 \pm 42.2	64.8 \pm 46.7	0.974
Sex, male:female	11:9	3:5	0.676
Disease			0.500
AD	12 (60.0)	5 (62.5)	
AR or As	4 (20.0)	3 (37.5)	
Exposure			1.000
Direct	6 (30.0)	3 (37.5)	
Indirect	14 (70.0)	5 (62.5)	
Dog-sIgE (kU/L)	4.5 (1.4–15.1)	16.3 (3.2–48.3)	0.309
	Patients included in the component-resolved diagnosis microarray		<i>p</i> value
	Symptomatic (n = 12)	Tolerant (n = 6)	
Total IgE (kU/L)	239.0 (104.0–981.5)	832.5 (529.0–963.0)	0.250
Dog-sIgE (kU/L)	8.4 (1.4–46.4)	16.3 (5.4–41.6)	0.750
Can f 1 (ISUL)	1.6 (0.2–24.2)	9.2 (6.6–11.4)	0.638
Can f 1+	4 (33.3)	4 (66.7)	0.402
Can f 1+ 2+ 3+	4 (33.3)	1 (16.7)	0.852

Values are presented as mean \pm standard deviation, number (%), or median (interquartile range).

AD, atopic dermatitis; AR, allergic rhinitis; As, bronchial asthma; IgE, immunoglobulin E; dog-sIgE, dog-specific IgE; Can f 1+, number of patients with positive IgE to Can f 1 (ImmunoCAP ISAC, ISU/L > 0.0); Can f 1+2+3+, number of patients with positive IgE to all 3 dog components, i.e. Can f 1, Can f 2, Can f 3 (ImmunoCAP ISAC, ISU/L > 0.0).

was the second most common (n = 6, 33.4%), followed by tree pollen positivity, with 27.8% (n = 5) sensitized to cypress and 22.3% (n = 4) sensitized to cedar. Equ c 3, a horse antigen, also showed 22.3% positivity (n = 4). Next, positivity to Bos d 6, a cow antigen, and Phl p 4, a timothy grass antigen, was 16.7% (n = 3), respectively. Meanwhile, 8 children were sensitized to more than one food antigen, 6 of whom had AD. Antigens included egg white (n = 7), milk (n = 5), soybean (n = 5), nuts (n = 3), peanuts (n = 3), wheat (n = 2), and fish (n = 1). One child had PR-10 sensitization, and none had sensitization to lipid transfer proteins (Fig. 1).

DISCUSSION

The microarray chip used in this study allows semi-quantitative measurement of IgE antibodies to various components simultaneously. Although sensitization profile for dog allergy varies across studies, in the present study, we found that Can f 1 positivity was higher than those of previous reports, with no cases of Can f 2 positivity. The mono-sensitization rate to Can f 1 was 57.1% in our subjects which were higher than the 32% mono-sensitization rate reported among adults [10]. Such a difference may be attributable to differences in age, distribution of underlying diseases caused by age difference, and regions. The major underlying disease among the age group of our participants was AD, which affected about 60.7% of the participants. This is in contrast with the findings of previous studies on children above the age of 10 or in adults, where many patients had respiratory allergic diseases [10, 12, 15]. The prominent symptoms that participants had upon exposure to a dog also differed from those in previous studies. Patients may be in a subclinical state or symptoms that are exhibited upon exposure at early stage may change to respiratory symptoms later on. However, at the time of assessment, skin symptoms were the most common (16 out of 20, 80.0%).

Although not statistically significant, poly-sensitized patients (sensitized to Can f 1, Can f 2, and Can f 3) with relatively lower dog-sIgE concentration tended to be more reactive upon exposure. The association between a specific lipocalin antigen and severity has not been established yet, but it has been reported that poly-sensitization 3 or more component antigens is associated with severity, particularly in asthma [14, 15].

Meanwhile, many children sensitized to dogs regardless of reactions have not lived with dogs and exposed to them indirectly. This is similar to the findings of some previous studies. They have reported that Can f 1 is detected in about one-third of houses that do not own a dog [5, 8, 16]. Members of such houses were found to frequently visit a relative who owns a dog, and our findings supported previous results. It is widely known that indirect exposure results in a significantly lower Can f 1 concentration compared to that obtained from direct exposure [8]. It is supposed that our findings, indirect exposure to dog allergens at low concentrations, might be disadvantageous to obtaining tolerance, in line with previous reports [7]. However, additional studies are needed to substantiate the specific range in which the risk for sensitization increases and tolerance decreases.

One shortcoming of our study is that we only examined sensitization distributions because of the difficulty in clinically applying a method to confirm the diagnosis of dog allergy in very young children. Furthermore, the types of components analyzed with CRD were limited at the time of assessment, and we could not analyze the sensitization distributions for Can f 4, Can f 5, Can f 6, and Can f 7, which were only added to the list recently. Also, this study has major limitations in a very small number of subjects. Therefore, the results of the study are considered to be preliminary data that require further study in the future. Nevertheless, our report could be still beneficial as it is the first report on very young patients, who have not attracted much research interest. The median age of our participants was 61 months, which was far lower than that in the recent report on dog allergy among adults around the age of 20 years; none of the previous studies has studied dog allergy in such a low age group.

We expect our study findings to be helpful for clinicians, as they assist in understanding therapeutic targets and aeroallergens that need to be assessed with priority in young children generally suffering from allergic skin diseases and suggest factors that need to be assessed in patients' living environments.

In conclusion, Can f1 was positive in 77.8% of young children sensitized to dogs and cosensitization to house dust mite was the most common. The symptomatic group tended to be poly-sensitized to Can f1, Can f2, and Can f3. Most of patients have been exposed to dogs not living with.

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