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Cross-reactivity of Can f 1 with Syrian hamster and Fel d 1 in children

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Abstract
Introduction and objectives: With increasing pet allergies among pediatric patients, the need for precise environmental care is increasing. We investigated the clinical, immunological, and environmental characteristics of pediatric patients sensitized to a dog to evaluate the cross-antigenicity of canine lipocalin Can f 1 with feline lipocalin Fel d 1 and Syrian hamster extract.
Materials and methods: The protein fractions of the processed and commercial Syrian hamster extracts were compared using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). An enzyme-linked immunosorbent assay (ELISA) inhibition test was performed on Can f 1, Fel d 1, and processed Syrian hamster extract, and the antigen-specific immunoglobulin E (IgE)-binding capacity for each antigen was analyzed using serum samples from patients.
Results: Twelve of 19 patients with a median age of 40.5 months were symptomatic when exposed to dogs. Eleven (91.7%) patients showed a positive IgE response to Can f 1. Two patients were positive for Fel d 1-specific IgE antibody, and one was positive for hamster-specific IgE antibody. SDS-PAGE confirmed the presence of different patterns of protein bands between the commercial and processed hamster extracts. There was no cross-antigenicity among Can f 1, Fel d 1, and processed Syrian hamster extract.
Conclusions: Since the standard commercial hamster extract did not contain Syrian hamster antigens that were diverse enough, caution should be taken when using it. In children allergic to cats and dogs, sensitization to isolated Can f 1 or Fel d 1 is unlikely to cause cross-reactivity to Syrian hamster hair and epithelium.

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Introduction

The number and diversity of pets in South Korea has increased over the past years.[1] Infants and young children are easily exposed and sensitized to indoor aeroallergens such as house dust mites or mold.[2] In addition, the rapid rise in the number of pets, especially dogs, consequently increases the chances of sensitization. While the exact incidence of sensitization has not been investigated, that of pediatric patients with dog allergy presenting with symptoms of immediate type allergy is increasing, indicating the need for research on this topic.

In the clinical settings of South Korea, serologic evaluation is preferred over the skin prick test for young children, where immunoglobulin E (IgE) specific to various animals, including dogs, is detected.[3] Allergens belong to a number of protein families and when sensitized to antigen with broad cross-reactivity, an immune-mediated phenomenon of IgE antibody in the epitopes of the homologous protein of allergens may develop. An example of such antigens is Can f 3, a canine albumin.[4,5] Since pet has become more diverse, including hamsters and cats, the presence of cross-reactivity among popular pets needs to be investigated.

Dogs show high antigen heterogeneity, which depends on breed, sampled area, and prepared batch, thus, hindering diagnosis and effective immunotherapy.[6,7] To date, seven antigens have been identified as major canine allergens.[7] One of them is Can f 1, a lipocalin protein. Although studies using recombinant Can f 1 have shown different results, it is one of the most important IgE-binding antigens, with sensitization confirmed in over 50% of patients with dog allergy, and a sensitization rate higher in children than in adults.[8] Similarly, Fel d 1 is a lipocalin protein and a major cat allergen, with sensitization in approximately 90% of patients.[4,7] Moreover, the Siberian hamster (*Phodopus sungorus*) is a dwarf hamster known to cause allergic symptoms in Europe and Japan.[9,10] Protein bands of approximately 18, 21, 23, and 32 kDa are known to be major hamster antigens.[10-13] These bands were identified using samples of extracts prepared from the saliva, epithelium, and hair of dwarf hamster. Apart from dwarf hamsters, the Syrian or golden hamster (*Mesocricetus auratus*) is also popularly used as a pet in South Korea. Lipocalin allergens of the Syrian hamster are known to be different from those of dwarf hamster allergens and to react differently in patients.[13,14]

In the present study, we aimed to examine the clinical, environmental, and immunological characteristics of young patients sensitized to a dog. With this aim, we examined the presence of specific IgE antibodies to one of the major canine lipocalin antigens, Can f 1, and evaluated its degree of cross-antigenicity with cat lipocalin Fel d 1 and Syrian hamster extracts from the hair and dander.

Materials and Methods

Patients and sera

The study used a retrospective chart review of patients aged ≤6 years and selected the patients who satisfied the following criteria for inclusion in the study: (1) clinical history showing the repetitive and consistent presentation of allergic symptoms when exposed to a dog; (2) immunoCAP results confirming sensitization to a dog with specific IgE ≥ 0.35 kU/L; and (3) informed consent obtained for the use of serum from blood samples collected at the time of diagnosis and stored at −20°C. Serum samples from six pediatric patients with a dog- or cat-specific IgE antibody level <0.35 kU/L were used as the control group for comparison. The study protocol was approved by the Institutional Review Board of Ajou University Medical Center (AJIRB-MED-OBS-13-335), and informed consent was obtained from the parents of all participants. All methods were performed following the relevant guidelines and regulations.

Preparation of antigens

Standard commercial golden hamster extract was purchased from Allergopharma (Diagnostic Allergen Extracts; Hamburg, Germany) and Can f 1 and Fel d 1 from Biotechnologies Inc (Charlottesville, USA). The processed Syrian hamster extract was prepared using the following method. Hair and dander samples were collected twice from seven hamsters for a total of 6 g. The samples were then added to phosphate-buffered saline (PBS, pH 7.4; 1:1 w/v) and stirred for 7 days at 4°C. The extracts were centrifuged at 10,000 rpm for 1 h. The resulting supernatant was dialyzed in deionized water for 48 h (pore size cut-off: 3.5 kDa). Subsequently, the samples were freeze-dried at −70°C and protein concentrations were then measured via a Bradford assay (Bio-Rad, Hercules, CA, USA) using a microplate reader.

Identification of hamster proteins by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE)

For SDS-PAGE, processed Syrian hamster extracts were prepared at concentrations of 10, 50, and 100 mg/mL, and mixed with loading buffer (0.5 M Tris-HCl, pH 6.8, glycerol, 10% SDS, 0.5% bromophenol blue, and 2.5% β-mercaptoethanol). The mixture was heated for 10 min at 100°C and electrophoresed in 4–20% Tris-glycine gradient gel (Invitrogen) at 120 V for 2 h, together with the marker (SeeBlue®plus2, Invitrogen, San Diego, CA, USA). To compare the results, the commercial Syrian hamster extract (Diagnostic Allergen Extracts; Hamburg, Germany) was electrophoresed using the same method.

Analysis of IgE binding capacity to Can f 1, Fel d 1, and Syrian hamster extract using enzyme-linked immunosorbent assay (ELISA)

Syrian hamster, Can f 1, and Fel d 1 diluted to 5 μg/mL with coating buffer (0.1 M carbonate buffer, pH 9.6, Sigma, St. Louis, MO, USA) were dispensed to each well of an immuneELISA plate (Nunc, Roskilde, Denmark) and allowed to adhere to the well for 16 h at 4°C, followed

by five washes with washing solution (0.05% Tween-20 in PBS, pH 7.0). The samples were incubated for 2 h at room temperature in blocking solution (10% fetal bovine serum in PBS) to inhibit unspecific interactions and then washed five times. Subsequently, 100 µL of patient serum diluted 1:10 in blocking solution was added to each well, and the plate was incubated for 16 h at 4°C. After five washes, biotinylated human anti-IgE (Vector Laboratories, Burlingame, CA, USA) was diluted 1:1,000 in blocking solution and then it was diluted 1:250 with streptavidin-HRP (BD PharMigen, San Jose, CA, USA). The reaction was carried out for 1 h at room temperature, followed by seven washes. Then, 3,3′,5,5′-tetramethylbenzidine (BD PharMigen, San Jose, CA, USA) was added for 10 min in a dark room, after which 100 µL 2 N H_2SO_4 was added to stop the reaction. Optical density (OD) was measured at 450 nm, and the value was multiplied by 1,000 to derive the log value from which the relative concentrations of specific IgE were derived. The cut-off value for a positive result was set as mean + 2 standard deviation (2SD) of the negative control log(OD × 1,000).

ELISA inhibition test

ELISA inhibition test on Can f 1 was performed using pooled sera from patients positive in ELISA for Can f 1-specific IgE. Processed Syrian hamster extract and Fel d 1 were used as inhibitors. The concentrations of the inhibitors used were 0.1, 1, 10, and 100 µg/mL. Diluted inhibitors and pooled patient sera were left to react for 2 h at room temperature. The degree of IgE inhibition for Can f 1 was calculated with the following equation: % inhibition = [(uninhibited OD − inhibited OD)/uninhibited OD] × 100. Measured values were compared as mean ± SD, and t-tests were performed for statistical analyses using the R program version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) with the significance level set to $p < 0.05$.

Results

Clinical and immunological characteristics of subjects

There were seven (Patient #13–19) asymptomatic patients and 12 (Patient #1–12) symptomatic patients with repeated acute hyperreactivity by exposure to dogs. The median age of symptomatic patients was 40.5 months (range: 4–72 months), and their median dog-sIgE concentration was 15.1 kU/L (range: 0.63–101 kU/L). The median age of asymptomatic patients was 24 months (range: 6–51 months), which was much lower than that of symptomatic patients, and their median dog-sIgE concentration was 24.9 kU/L (range: 4.98–101 kU/L), which was higher than that of symptomatic patients. In the environmental survey, 10 out of 12 symptomatic patients reported being repeatedly exposed to dogs in places other than their homes. Among symptomatic patients, eight (66.7%) showed skin reactions to exposure, which was the symptom with the highest frequency. Among these eight patients, four were diagnosed with urticaria. Of the four patients, two had underlying atopic dermatitis and the other two (#10 and #12) had asthma. Patient #2 was unable to visit the maternal grandparents owing to severe atopic dermatitis. The mother of patient #3 was a veterinarian, and the patient lived with a dog and had atopic dermatitis. The patient got rid of the dog and received a combination of drug therapy and environmental management, whereby the subjective symptoms of atopic dermatitis improved. Both patients with non-specific itchiness (#6 and #11) had underlying atopic dermatitis. There were two patients (16.7%) with anaphylaxis. Patient #1 had underlying egg allergy and atopic dermatitis. The maternal grandmother, who the patient visited often, had a dog, and the patient experienced itchy eyes, sneezing, urticaria, and coughing. The dog-sIgE concentration was >100 kU/L in this patient. Patient #5 had no underlying allergies. This patient was also exposed only at the maternal grandparents' home and showed symptoms of urticaria and sneezing. The dog-sIgE concentration was 27.7 kU/L. Among the 11 patients who co-sensitized to cats (cat-sIgE > 0.35 kU/L), three (#2, #6, and #17) had a confirmed history of exposure and were asymptomatic when exposed to cats (Table 1).

Identification of proteins in hamster extract using SDS-PAGE

The concentration of proteins in Syrian hamster extract processed from collected hair and dander samples was 6.4 mg/mL. SDS-PAGE revealed six distinct protein bands with molecular weights of 6, 11, 20, 24, 68, and 108 kDa (Figure 1). Meanwhile, when the same SDS-PAGE technique was used on standard commercial hamster extract (Allergopharma, Golden hamster epithelium), the results showed protein bands of 6, 11, and 68 kDa (Figure 2).

ELISA detection of Can f 1-, Fel d 1-, and hamster-specific IgE in patients

Can f 1-specific IgE binding was found in 11 out of 12 symptomatic patients and in all seven asymptomatic patients, showing no difference in positive rate according to the presence of symptoms. The geometric mean of Can f 1-specific IgE antibody concentration was 2.66 ± 0.55 in symptomatic patients and 2.71 ± 0.26 in asymptomatic patients, showing no significant difference. The geometric mean of Fel d 1-specific IgE antibody concentration was higher than the mean + 2SD in two out of 11 cat-specific IgE sensitized (>0.35 kU/L) children. One of them was symptomatic to dogs, while the other was asymptomatic, and both had no history of exposure to cats. Only one patient tested positive for hamster-specific IgE, and the patient had no history of exposure (Table 2).

Analysis of cross-reactivity among Can f 1, Fel d 1, and hamster extract

Inhibition ELISA showed that pre-incubation of sera with Fel d 1 or hamster extract did not decrease IgE binding to Can f 1, indicating no allergenic cross-reactivity (Figure 3).

Table 1 Clinical characteristics of subjects.

Patient no.	Sex	Age (months)	Dog-IgE (kU/L)	Cat-IgE (kU/L)	Clinical symptoms to dog	Clinical symptoms to cat
1	M	62	>100	N.D.	Anaphylaxis	Unknown
2	M	58	>100	7.55	AD aggravation	Asymptomatic
3	M	4	69.8	94.7	AD aggravation	Unknown
4	F	49	63.1	4.87	Cough, rhinorrhea	Unknown
5	M	36	27.7	1.87	Anaphylaxis	Unknown
6	F	43	16.0	1.69	Itchy	Asymptomatic
7	F	38	14.2	1.34	Urticaria	Unknown
8	M	36	14.0	1.06	Rhinorrhea Eye swelling	Unknown
9	F	72	4.33	N.D.	Urticaria	Unknown
10	M	36	2.65	0.10	Urticaria	Unknown
11	F	36	2.10	0.20	Itchy	Unknown
12	M	60	0.63	0.09	Urticaria	Unknown
13	M	24	>100	18.1	Asymptomatic	Unknown
14	F	49	63.1	4.89	Asymptomatic	Unknown
15	M	19	55.0	N.D.	Asymptomatic	Unknown
16	F	51	24.9	3.18	Asymptomatic	Unknown
17	M	23	7.71	1.17	Asymptomatic	Asymptomatic
18	F	37	5.40	<0.35	Asymptomatic	Unknown
19	M	6	4.98	N.D.	Asymptomatic	Unknown

IgE: immunoglobulin E, kU/L; N.D.: not done; AD: atopic dermatitis.

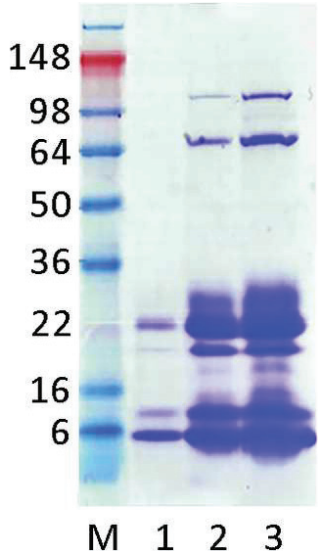

Figure 1 Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis of processed Syrian hamster extract. Protein bands identified: 6, 11, 20, 24, 68, and 108 kDa. M: marker, 1: 10 mg/mL, 2: 50 mg/mL, 3: 100 mg/mL.

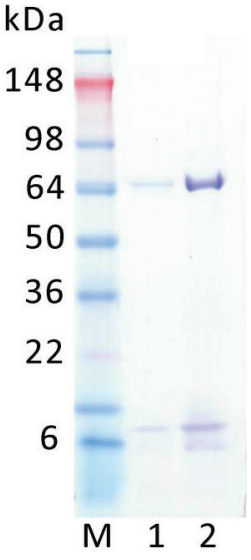

Figure 2 Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis of the standard commercial hamster extract for skin prick test. Protein bands identified: 6, 11, and 68 kDa. M: marker, 1: 5 mg/mL, 2: 7 mg/mL.

Discussion

With the increasing number of pets, many cases of dog allergies among infants and young children are being reported.[15] Lipocalins are major animal allergens that show a high frequency of sensitization in patients and constitute the highest content in subcutaneous immunotherapy extract used in clinical practice.[7] Can f 1 is a typical dog lipocalin, while Fel d 1 is a typical cat lipocalin. The co-sensitization rate to hamster among people who have previously raised a cat or a dog remains unknown, but allergy presentation has been reported in studies of adults.[11,16] Children are rarely exposed directly to hamsters and, thus, as far as we know, hamster allergy in young children has not yet been reported. However, a common question posed to pediatric professionals is whether children can be exposed to hamsters despite being diagnosed as allergic to dogs or cats.

Table 2 Specific immunoglobulin (IgE) binding to Can f 1, Fel d 1, and Syrian hamster according to enzyme-linked immunosorbent assay test using sera from subjects. Negative controls (N) are patients with IgE antibodies to dog and cat under 0.35 kU/L, as detected using ImmunoCAP.

Patient No.	Can f 1		Fel d 1		Syrian hamster	
	Log (OD×1000)	>Mean+2SD (1.681)	Log (OD×1000)	>Mean+2SD (1.655)	Log (OD×1000)	>Mean+2SD (1.897)
1	3.139	+	1.638	–	1.686	–
2	3.143	+	1.550	–	1.580	–
3	3.136	+	3.195	+	2.157	+
4	2.695	+	1.531	–	1.663	–
5	2.672	+	1.562	–	1.623	–
6	2.796	+	1.574	–	1.724	–
7	1.538	–	1.525	–	1.681	–
8	2.911	+	1.602	–	1.869	–
9	2.420	+	1.585	–	1.613	–
10	2.234	+	1.525	–	1.613	–
11	1.699	+	1.699	–	1.597	–
12	3.149	+	1.574	–	1.690	–
13	3.059	+	1.597	–	1.712	–
14	2.695	+	1.531	–	1.663	–
15	3.207	+	1.580	–	1.833	–
16	2.601	+	1.607	–	0.053	–
17	2.741	+	1.860	+	1.648	–
18	2.485	+	1.562	–	0.041	–
19	2.539	+	1.477	–	1.653	–
N1	1.519	–	1.491	–	1.712	–
N2	1.532	–	1.477	–	1.690	–
N3	1.638	–	1.597	–	1.703	–
N4	1.638	–	1.597	–	1.892	–
N5	1.562	–	1.562	–	1.748	–
N6	1.597	–	1.574	–	1.748	–

OD: optical density.

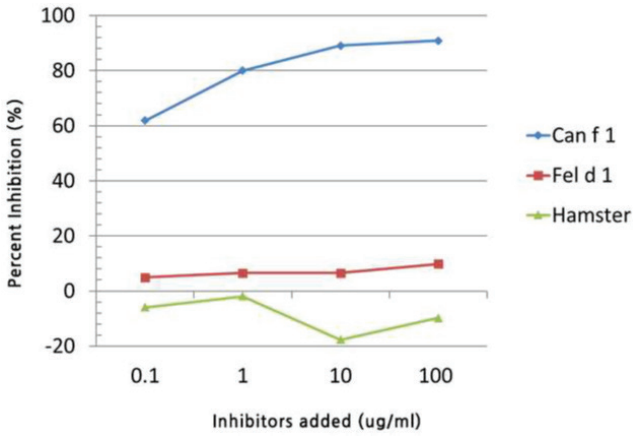

Figure 3 Inhibition degree (%) of IgE to Can f 1 immunoglobulin E (IgE) extract. Enzyme-linked immunosorbent assay inhibition test using Fel d 1 and crude Syrian hamster extract as inhibitors.

This study was conducted to investigate cross-reactivity among Can f 1, Fel d 1, and processed Syrian hamster extract from hair and dander. We did not use dog and cat crude antigens because albumin is already known to contribute to cross-reactivity between animals. Also, it would be cumbersome to prepare an extract including all antigens of dogs since characteristic dog antigens are diverse among species and are not fully discovered. The frequency of co-sensitization to lipocalin and albumin is common among pediatric patients, while sensitization to albumin alone is relatively rare. Therefore, when only crude antigens are used for diagnosing allergies, the patient may be asymptomatic, if attributed to cross-antigenicity, while showing co-sensitization, and may lead to unnecessary avoidance. In addition, the Syrian hamster hair sampled in the present study came from a breed commonly raised at home as a pet in South Korea.

Certainly, some patients may have been co-sensitized to other lipocalins besides Can f 1 and Fel d 1 and might show IgE responses to an unknown antigen alone or in combination with others. Patient #7 in this study may have been such a case. However, all patients, except Patient #7, were positive to Can f 1-specific IgE antibody, whereas no specific IgE antibody binding to the processed hamster extract was observed. Moreover, our analysis using recombinant antigens Can f 1 and Fel d 1, and the processed hamster extract, showed no cross-reactivity among them. Based on such findings, it can be concluded that pediatric patients with dog allergy show a high frequency of IgE sensitization to Can f 1, and in the case of monosensitization to Can f 1, an IgE-mediated allergic reaction to Syrian hamster will not be present. Besides, patients who have been monosensitized to Fel d 1 would be asymptomatic to Syrian hamster.

However, simply because there was no cross-allergenicity between Can f 1 and Fel d 1 in the present study, it would not be prudent to inform patients with dog allergies that they can raise a cat, since they may have been sensitized to dog allergens other than Can f 1. Cross-allergenicity between other lipocalins from cat and dog has indeed been reported, such as Can f 1 cross-allergenicity with Fel d 6, which is a feline component antigen.[17] Moreover, it is important to explain that even if there is no risk of cross-allergenicity at this time, atopic patients may develop an allergy in the future if they raise a hamster. This is because studies on adult patients with allergy to dwarf hamsters have shown the occurrence of allergic reactions 1–2 months after exposure.[16,18] In addition, unlike dog and cat antigens, the major allergenic components of hamsters have not been identified and are not commercially available. Thus, we inevitably used a crude extract of hamsters. Though such limitations exist, we think that this study has provided the basis for an explanation of the cross-antigenicity with hamster antigens in dog hair allergy patients who are mono-sensitized to Can f 1.

Currently, the methods primarily used for the diagnosis of hamster allergy are skin prick test or serological diagnosis using a standard commercial extract. Whether the preparations contain a variety of antigens in sufficient amount and whether the immunotherapy agents contain enough allergens to cause allergic symptoms in the patients are issues that have been studied for a long time, and among such studies on pets, dogs are the most studied.[6,7] In dogs, the composition of antigens varies depending on what part of the body the sample is collected from, but commercially available allergen preparations often do not contain a sufficient amount of problematic allergen components, which could lead to misdiagnosis. In this study, six protein bands were identified in the in-house processed Syrian hamster extract, including three additional bands not found in the standard commercial preparation. When six adult patients were diagnosed with dwarf (Siberian) hamster allergy, they tested negative in the skin prick test preparation, but IgE responses to proteins (18, 21, and 32 kDa) in the hamster hair and saliva samples were identified.[9,11] As shown in the present study, differences in allergenic potency and composition may be owing to a number of factors, including the difference in sampling sites used to obtain the crude extracts. Considering that dwarf hamster allergens have been reported to be present not only in hair but also in urine, prostate, and saliva,[13] a limitation of the present study is that we only sampled hair and dander, which do not represent all possible cross-antigenicity. Another limitation was that the study population did not include any patient with hamster allergy, and as a result, a significant protein showing specific IgE binding could not be identified among the protein bands that differed between the commercial and manufactured hamster extracts. Nevertheless, our results provide valuable information regarding Syrian hamster allergy, since to date, the existing information has been limited to dwarf hamsters.

In summary, when a patient suspected of having a hamster allergy is studied for diagnosis, it is important to identify the breed of the pet. If it is a dwarf breed, a false-negative serological or skin prick test result may be obtained depending on the type of preparation used. Moreover, if the pet hamster is a Syrian hamster breed, using only the commercially available standard extract could show a false-negative result. Thus, it should be kept in mind that the diagnosis of an allergy begins and ends with the patients' clinical history and physical examination. Moreover, in children allergic to cats and dogs, sensitization to isolated Can f 1 or Fel d 1 is unlikely to cause cross-reactivity to Syrian hamster hair and dander.

Author contributions

Substantial contributions to conception and design: SL and JL; acquisition of data, or analysis and interpretation of data: JL and SJ; drafting the article or revising it critically for important intellectual content: JL; final approval of the version to be published: SL.

Conflict of interest

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