

Clinical Communications

Precision allergy: Separate allergies to male and female dogs

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Clinical Implications

- Dog-allergic patients monosensitized to Can f 5 seem to tolerate female dogs. This particular type of dog allergy can be confirmed using skin prick test or ocular provocation test using male and female dog extract separately.

TO THE EDITOR:

Dog dander is one of the most common causes of respiratory allergy, and it consists of several allergenic molecules.¹ These allergens are present not only in the homes of dog owners (primary exposure) but also in public places, schools, and homes without dogs (secondary exposure), where they can cause allergic reactions such as rhinoconjunctivitis and asthma in sensitized people.^{2,3}

For the physician, it is often a challenge to definitively establish the disease-triggering allergen. Objective assessments are available in terms of specific IgE measurements against allergens in blood and skin prick tests (SPTs), but for both methods false-positive results are a well-known problem. This can have major social implications for families who must decide about keeping a pet on the basis of results of allergy testing.

The most well-known allergen components to cause dog allergy are the lipocalins Can f 1 and Can f 2, and the serum albumin Can f 3, that are present in dog hair and dander. In addition, the prostatic kallikrein Can f 5 has been identified as a major allergen component found mainly in the urine of dogs, as well as in extracts of dog hair and dander.⁴ Prostatic kallikrein Can f 5 is an androgen-regulated protein expressed in the prostate, and hence present only in male dogs,⁵ and there is no cross-reactivity between Can f 5 and the other major dog allergen components, Can f 1, 2, or 3.⁴ Can f 5 IgE antibodies are present in approximately 70% of patients sensitized to dogs, and in almost a third of the patients, this is the only allergen component that they are sensitized to. Because of the apparent monosensitization of some patients to Can f 5 produced only in male dogs, it is possible that patients may be differently sensitive to male and female dogs, depending on their sensitization pattern. The commercially available extracts used for both specific IgE and SPT are based on a mixture of male and female dogs of different breeds. The only way to identify a possible male-only dog allergy today is to use component-resolved diagnostics and verify that the patient is reacting only to the Can f 5 allergen component, and not Can f 1, 2, or 3.

In this case study, we present a patient with a history of reacting only when exposed to male dogs, and where the sensitization pattern confirmed the theory showing reactivity only to Can f 5. A preliminary experiment was performed in which proteins were extracted from the hair of male and female dogs, respectively, and for the first time, we performed SPT and ocular provocation tests using these extracts, to confirm that the patient reacted only to male dogs.

A 54-year-old woman presented with a longstanding history of dog allergy with asthma-like symptoms (wheezing and difficulty breathing) after exposure to dogs. She had noticed that her symptoms occurred only when exposed to male dogs, and she was now considering purchasing a female dog to fulfill the ongoing wish of her daughter to get a dog in the house.

The woman also had asthma and an established seasonal rhinoconjunctivitis caused by grass and birch pollen exposure. She used as-needed terbutalin inhalations (Bricanyl; Astra-Zeneca, Copenhagen, Denmark) for her asthma and fexofenadin tablets (Telfast; Sanofi, Hørsholm, Denmark) for her pollen allergy and before contact with male dogs. She recently completed subcutaneous immunotherapy for her grass and birch pollen allergy, which had significantly diminished her symptoms and subsequent use of antihistamine during the pollen season.

We first performed an SPT using standard allergen extract to dog (Soluprick SQ; ALK-Abello, Hørsholm, Denmark). Histamine dihydrochloride (10 mg/mL) and physiological sodium chloride (9 mg/mL) were used as positive and negative controls, respectively.

Total IgE and specific IgE levels to timothy grass, dust mite, birch pollen, and dog dander were determined using ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden).⁶ We included dust mite in the panel of tests to ensure that she was not sensitized to dust mite because there have been reports that some SPT extracts for dog can have traces of dust mite allergen.⁷ Because of the suspected allergy to only male dogs, we performed a more thorough investigation of her sensitization profile and included measurements of specific IgE levels to the dog components Can f 1 (lipocalin), Can f 2 (lipocalin), Can f 3 (albumin), and Can f 5 (arginine esterase, prostatic kallikrein) by ImmunoCAP.

To definitively establish whether this patient reacted only to male dogs, an experiment was performed in which dog dander was collected separately from female and male golden retrievers according to standard extraction procedures for dander. Thereafter, we made a dilution of the extracts to perform SPT with a concentration of 25 mg/mL.

Last, we made a series of dilutions, decreasing in strength, to perform ocular provocation testing using the female and male dog extracts in the right eye and the left eye accordingly. Initially, we applied a droplet of extract with a concentration of 0.25 µg/mL, and every 10 minutes increased the concentration till a final concentration of 25 mg/mL. The reaction was evaluated according to the Total Ocular Symptom Score, based on 4 objective symptoms observed, red, itchy, tearing, or swelling of the eyes, maximum score 4, as we did not have the timely aspect of the symptoms.⁸

TABLE I. Specific IgE and total levels in serum

Allergen	kU _A /L	Cutoff levels
Dog dander (e5)	0.27	0.35
Cat dander (e1)	0.30	0.35
<i>D Pteronyssinus</i> (d1)	<0.1	0.35
Timothy grass (g6)	8.36	0.35
Birch (t3)	4.35	0.35
rCan f 1 (e101)	<0.1	0.35
rCan f 2 (e102)	<0.1	0.35
nCan f 3 (e221)	<0.1	0.35
rCan f 5 (e226)	0.31	0.35
Total IgE (kU/L)	50.4	150

The results of the IgE testing including allergen components are presented in Table I. The woman was sensitized to dog dander just above the detection limit (0.27 kU_A/L), cat dander (0.30 kU_A/L), timothy grass (8.36 kU_A/L), and birch pollen (4.35 kU_A/L). Total IgE level was 50.4 kU/L. Among the dog components, she was monosensitized to Can f 5 (0.31 kU_A/L).

The clinical history suggested that the patient was sensitized only to male dogs, and for the first time ever, we performed an SPT and an ocular provocation test using extracts from female and male dogs separately. The SPT showed a positive reaction to the male dog only: male dog (4 mm), female dog (0 mm), positive control (3.5 mm), and negative control (0 mm), respectively. SPT reaction to dog dander e5 was 3.5 mm.

The ocular provocation test showed no reaction to the female dog extracts, whereas for the male extracts, the patient reacted with immediate itchy, red, and tearing eye (Total Ocular Symptom Score 3) at the highest concentration of 25 mg/mL, in agreement with the relatively low level of specific IgE antibodies against Can f 5.

The theory of allergic sensitization to male dogs only has been hypothesized previously, but this is the first time a clinical allergic reaction to male dogs has been demonstrated in a patient. This was performed by using separate allergen extracts from male and female dogs to perform SPTs and ocular provocation tests. Because this is the first time the clinical relevance of Can f 5 monosensitization is being demonstrated, there is a lack of information regarding prevalence, sensitivity, and specificity of Can f 5 monosensitization for male dog-only clinical reactivity, which cannot be answered by a case report alone.

Previous studies of the Can f 5 allergen have primarily focused on its cross-reactivity with human seminal plasma^{9,10} to resolve the rare cases of suspected semen allergy. It appears far more clinically relevant to focus Can f 5 research on the large group of patients globally who suffer from dog allergy. It has previously been reported that up to a third of dog-allergic patients are monosensitized to the Can f 5 allergen component,⁴ which may implicate male-only dog allergy and thus tolerance to female dogs.

To date commercially available dog dander extracts used to perform SPT consist of a mixture based on male and female dogs of different breeds. In addition, the percentage of male and female dog content in these extracts may vary, and extracts from different batches can therefore give contradicting results in the same patient, if the patient is sensitized only to Can f 5. Our case report suggests that patients with male-only dog allergy can be

distinguished by using SPT extracts made exclusively from male and female dogs or by using component-resolved diagnostics. For the patients, such precision medical care means that they may not have to deprive their families of owning a dog or getting rid of their dog because of an allergic family member.

In this case report, we suggest that dog-allergic patients monosensitized to Can f 5 are allergic only to male dogs, with no reaction to either SPT or ocular provocation test using female dog extract and thereby not allergic to female dogs. Questions regarding this clinical phenotype, such as prevalence, sensitivity, and specificity of monosensitization to Can f 5 in predicting clinical reactivity to male dogs only, should be answered in future studies.

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