

Clinical Communications

A prevalent exposure to male dog is a risk factor for exclusive allergic sensitization to Can f 5: An Italian multicenter study

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Clinical Implications

- A prevalent exposure to male dog seems to be an independent risk factor for Can f 5 monosensitization. In such patients, the correct prescription of allergen immunotherapy and the possibility to own a female dog should be considered.

Dog allergens are a common cause of allergic sensitization and respiratory symptoms worldwide, particularly in geographical areas characterized by a high level of pet ownership. Because the main dog allergens belong to different families of proteins (eg, lipocalins and albumins), diagnosis of dog allergy, and consequent prescription of allergen immunotherapy (AIT), can be more difficult than that for cat allergy, where a secretoglobulin (Fel d 1) is the main allergen involved.¹

Can f 5, a newly described dog allergen, is a prostatic kallikrein, an androgen-regulated protein expressed in the prostate and detectable only in male dogs.² Two recent studies have shown that the rate of a prevalent or exclusive allergic sensitization to Can f 5 is rather high, about 37% and 52%, respectively, in dog- or pet-sensitized individuals.² We also evaluated, by component-resolved diagnosis (CRD - ISAC 112, ThermoFisher Scientific, Uppsala, Sweden) the frequency of allergic sensitization to Can f 5, in North East Italy.³

In this study, within 1403 consecutive subjects, 520 (37 %) had a positive IgE response to at least 1 of available animal allergens. Among them, 268 (51.5%) showed at least 1 sensitization to any dog allergen. Among the dog-sensitized individuals, 183 (69.2%) had IgE against Can f 5, with 106 (57.9%) as single sensitization. The average titer of all 183 Can f 5 sensitizations is 8.810 ISU-E.³

The association between Can f 5 and other dog allergens in our study was as follows: Can f 5 + Can f 1 = 16.9%, Can f 5 + Can f 2 = 0%, Can f 5 + Can f 3 = 2.7%, Can f 5 + Can f 1 + Can f 2 = 14.2%, Can f 5 + Can f 1 + Can f 3 = 1.6%, Can f 5 + Can f 2 + Can f 3 = 0%, and Can f 5 + Can f 1 + Can f 2 + Can f 3 = 7.1%.³ The study also highlighted that the characteristics of Can f 5, in highly or exclusive sensitized patients, can suggest appropriate actions for allergists who manage such individuals.^{4,5} However, there is so far no data showing a clear relationship between the prevalent exposure to male dogs and monosensitization to Can f 5.

Based on the above-mentioned observations, the aim of our study was to evaluate whether monosensitization to Can f 5, as well as high levels of anti-Can f 5 IgE, is associated with a prevalent exposure to male dog in an Italian population. Fourteen Allergy Units, distributed over the Italian territory ("Italian Allergic Respiratory Diseases Task Force") participated in this cross-sectional study. Each center examined retrospectively all the CRD results saved in their databases from January 1, 2013, to December 31, 2018. Only patients with monosensitization to Can f 5 were selected and analyzed, regardless of the presence of IgE against other inhalant allergens. Therefore, patients sensitized to other dog allergens (Can f 1, Can f 2, and Can f 3) were excluded.

All selected Can f 5-monosensitized patients were contacted by e-mail or phone for information on their clinical symptoms at the time of blood sampling, on the modality of exposure to dogs according to our previously published criteria.⁶ In particular, we explored in detail the modality of dog exposure: (a) direct domestic contact (dog ownership), (b) direct contact elsewhere (no dog at home but dog contact outside), (c) previous ownership (dog no more present at home for at least 2 years), (d) indirect contact (through clothes or other items belonging to other dog owners), (e) no contact (any known direct or indirect exposure to dog).⁶ One question specifically addressed the sex of the dog when a prevailing contact was declared. The level of Can f 5 IgE at CRD analysis was categorized as low (0.3-0.9 ISU-E), medium (1-15 ISU-E), or high (>15 ISU-E).

Of 751 selected patients, 627 (83.5 %), 247 males and 380 females, with an age range of 6 to 90 years, responded to the email or accepted the telephone interview, and provided the requested information. In the case of children, information was obtained from their parents. All patients suffered from respiratory allergy (rhinitis and/or asthma), and symptoms associated with food allergy, if present, were also recorded.

In the group with low anti-Can f 5 IgE (n = 230), no dog contact (n = 44), male dog contact (n = 46), and female dog contact (n = 140) accounted for 19%, 20%, and 61%, respectively. In the group with medium levels of IgE (n = 346), no dog contact (n=23), male dog contact (n = 242), and female dog contact (n = 81) accounted for 7%, 70%, and 23%, respectively. Finally, in the group with high anti-Can f 5 IgE (n = 51), NDC (n = 1), MDC (n = 44), and FDC (n = 6) accounted for 25%, 86%, and 12%, respectively (Figure 1).

The titer of anti-Can f 5 IgE, according to the prevalent exposure to dogs, is significantly higher in MDC (2.5, 1.3-6.8, median, lower and upper quartiles) than in NDC (0.7, 0.4-1.6)

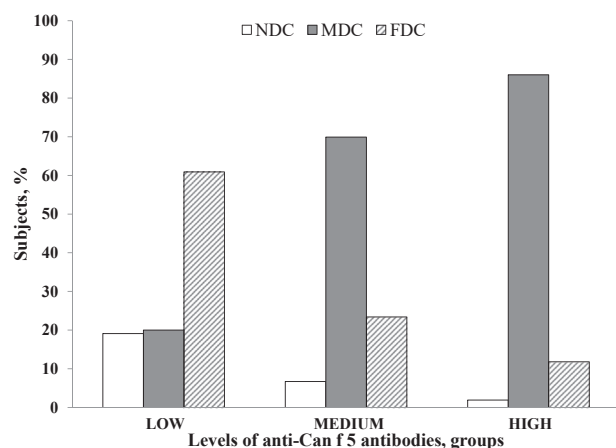


FIGURE 1. Distribution of no dog contact (NDC), male dog contact (MDC), and female dog contact (FDC) within the 3 groups defined by the anti-IgE Can f 5 level (low, medium, high).

and in FCD (0.7, 0.4-0.1), respectively ($P < .001$, Kruskal-Wallis test), with no difference between NDC and FDC (Figure 2).

Although in the real-life setting it is unlikely that a dog-lover/owner could be exposed “exclusively” to a male dog, our data show that a prevalent exposure to male dog (for ownership or direct contact elsewhere) is associated with a higher degree of IgE monosensitization to Can f 5. Exposure to female dog, with only “indirect or occasional” exposure to male dog, is associated with a lower degree of IgE levels, similar to the no dog exposure condition (with a likely “occasional” exposure to dogs of both sexes), which is associated with the lowest degree of anti-Can f 5 IgE. Therefore, the exposure to a female dog has no significant effect on Can f 5 titer.

This is the first report showing a significant relationship between a prevalent contact with a male dog and allergic monosensitization to Can f 5. Although some studies reported that this allergen is recognized by a high percentage of dog-sensitized patients (also exclusively), the real significance of Can f 5 in respiratory allergy remains controversial. In fact, Käck et al⁷ failed to find a role of Can f 5 in inducing allergic rhinitis in children, whereas Schoos et al⁸ described the case of a woman sensitized to Can f 5 who experienced worsening of respiratory symptoms after exposure to a male dog but not to a female dog. Recently, the latter authors showed, in children monosensitized to Can f 5, different reactions to male and female dog extract provocation using both skin prick test and conjunctival allergen provocation test, suggesting tolerance to female dogs.⁹ As previously mentioned, monosensitization to Can f 5 is an intriguing “puzzle” because it can potentially induce favorable effects such as a reduced risk of cross-reactivity, reduction of the occurrence of allergen “ubiquity,” possibility to own a female dog, and possible utility of neutering male dog. On the contrary, a likely negative effect could be a reduced efficacy of a standard AIT whereas an increased risk for allergic sensitization to human seminal fluids has been well established.^{3,5}

In conclusion, our multicenter study shows that a prevalent exposure to a male dog represents a risk factor for the presence of Can f 5 monosensitization in Italy. Further studies should be planned to confirm the significance of such sensitization in

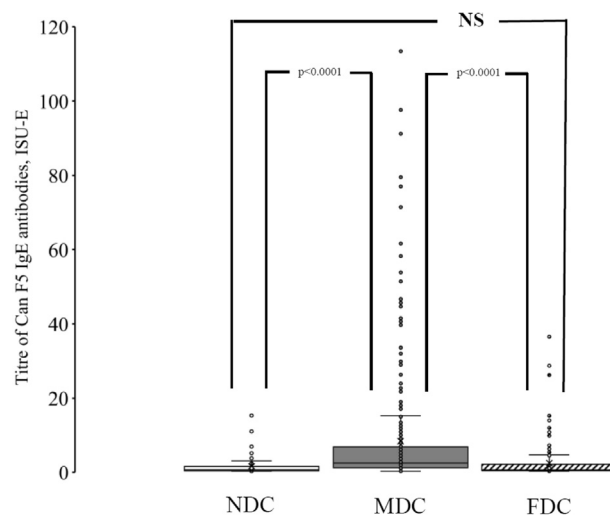


FIGURE 2. Comparisons of Can f 5 IgE antibody levels in subjects from groups with no dog contact (NDC), male dog contact (MDC), and female dog contact (FDC). In the box plots, the solid horizontal line and the cross represent the median and the mean, respectively; the box margins represent the interquartile (IQ) range; whisker lines extend for 1.5 times the IQ range and the individual observations are marked with circles. *NS*, Not significant.

respiratory allergy as well as in some previously described Can f 5-associated topics. Finally, the possible benefits of neutering male dogs in reducing the production of Can f 5 and, consequently, the necessity of getting rid of a male dog with or without substitution of a female dog remains to be established.

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