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Relationship of Dog- and Cat-Specific IgE and IgG₄ Levels to Allergic Symptoms on Pet Exposure

Mary Burnett, MD^a, Ganesa Wegienka, PhD^b, Suzanne Havstad, MA^b, Haejin Kim, MD^a, Christine Cole Johnson, PhD^b, Dennis Ownby, MD^c, and Edward Zoratti, MD^a

^aDivision of Allergy and Clinical Immunology, Henry Ford Hospital, Detroit, Mich

^bDepartment of Public Health Sciences, Henry Ford Hospital, Detroit, Mich

^cDepartment of Pediatrics, Georgia Health Sciences University, Augusta, Ga

Abstract

BACKGROUND—Environmental allergens may induce the generation of allergen-specific IgE (sIgE) and IgG₄ (sIgG₄). Some studies report an association of sIgG₄ to protection against allergic symptoms after exposure to the relevant allergen.

OBJECTIVE—We examined the relationship of dog and cat sIgE and sIgG₄ levels to self-reported allergic symptoms on pet contact.

METHODS—Participants 18 years of age in the Detroit Childhood Allergy Study cohort were asked whether they experienced symptoms on exposure to cats and dogs. Serum was assayed for cat and dog sIgE and sIgG₄. Geometric means, ratios of cat and dog sIgE, sIgG₄, and ratios of sIgG₄/sIgE were compared between symptomatic and asymptomatic teens with the use of Wilcoxon rank sum tests. Ratios of sIgG₄/sIgE, adjusted for presence of sIgE (> 0.35 kU/ml) were analyzed with logistic regression.

RESULTS—Data on 500 participants were analyzed. Compared with asymptomatic teens, teens symptomatic with cat exposure had higher cat sIgE, sIgG₄, and lower ratio of sIgG₄/sIgE. Teens symptomatic after dog exposure had higher dog sIgE levels and lower sIgG₄/sIgE, but similar levels of sIgG₄ compared with asymptomatic participants. Increasing cat and dog sIgG₄/sIgE ratios were associated with lower likelihood of reporting allergic symptoms (cat: adjusted odds ratio, 0.8; 95% CI, 0.6–0.9; dog: adjusted odds ratio, 0.8; 95% CI, 0.7–1.0).

CONCLUSION—sIgG₄ levels to cat and dog allergens correlate with lower rates of pet-induced allergic symptoms when interpreted in the context of concomitant sIgE. However, sIgG₄ appears to have little utility as an isolated marker to indicate that pet exposure will be well tolerated.

Keywords

Tolerance; sIgG₄; sIgG₄/IgE ratio; Allergy; Protection sIgE antibody

Corresponding author: Mary Burnett, MD, Division of Allergy and Clinical Immunology, Henry Ford Hospital, One Ford Pl 4B, Detroit, MI 48202. mburnet1@hfhs.org.

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Multiple studies have shown that pet ownership is associated with protection against specific allergic sensitization for that pet.¹⁻⁸ Although the mechanism(s) leading to pet tolerance are unknown, multiple theories have been proposed. Platts-Mills et al² evaluated cat allergen (Fel d 1) specific IgG (sIgG) and IgG₄ (sIgG₄) and found that high cat allergen exposure is associated with increased serum Fel d 1 sIgG and sIgG₄. Prolonged cat exposure has been shown to produce progressive increases in sIgG and sIgG₄ antibodies without sensitization, and this has been classified as a “modified T_H2 immune response” and is also associated with tolerance.^{2,9,10} In 2003, Hesselmar et al⁹ found that sIgG₄ was highest in the group with the greatest cat exposure; however, sIgG₄ alone was not associated with decreased allergy. The current “gold standard” used to determine allergy is the presence of clinical symptoms while exposed to allergen and concomitant demonstration of elevated allergen-specific IgE antibody or positive skin prick testing.¹¹ However, allergen testing does have flaws, including a high number of false-positive tests. The role of using sIgG₄ in combination with IgE for allergy testing or for predicting tolerance to an allergen has not been well established, but it may be useful to improve current allergy testing strategies by clinicians and also to potentially inform clinicians as to the necessity of advising allergen avoidance strategies. Our aim was to determine whether allergen-specific IgG₄ modifies the association between sIgE and self-reported allergy symptoms on cat and dog exposure in a longitudinal birth cohort.

METHODS

Population

The Detroit Childhood Allergy Study (CAS) is a longitudinal birth cohort that studied the natural history and environmental determinants of pediatric allergy. Pregnant women residing in metropolitan Detroit who were members of a health maintenance organization were invited to participate. Eligible pregnant women were 18 years or older, lived in a predefined geographic area, with an estimated date of confinement between April 15, 1987, and August 31, 1989. Only full-term infants (36 weeks of gestation) were included. Recruitment was not based on allergic history.

Of the 1194 eligible study participants, 953 women provided written consent to participate. Of the original 953 enrolled, 835 remained eligible to participate. Mothers of the remaining 835 children were asked to complete telephone interviews annually through the age of 6 to 7 years when children were invited to complete a clinic visit. In May 2005, the oldest children reached 18 years of age. After their 18th birthday, teens were contacted to obtain information about allergy symptoms, asthma, and other health and exposure histories through telephone interviews. Teens were then invited to provide blood samples for measurement of total IgE, sIgE, and sIgG₄ to several allergens, including cat and dog allergens. There were no exclusions for blood collection, such as concurrent medication use or viral illness, and samples were collected throughout the year at the convenience of the participants. All aspects of this research were approved by the institutional human subjects board of review of all participating institutions.

Symptoms

Participating CAS teens were asked at the 18-year visit whether they ever developed any of the following symptoms on exposure to cats or dogs: cough, wheeze, chest tightness, shortness of breath, runny or stuffy nose, sneezing, itchy or watery eyes, or hives/itchy red bumps on the skin. Teens were classified as symptomatic to the dog/cat if they reported at least one of the above symptoms. Current cat or dog exposure was defined as self-report of having a pet in the home in the past 12 months.

sIgE and sIgG₄ assessment

Venous blood was collected and stored at -80°C until assayed. Measurements of Fel d 1 and Can f 1 sIgE and sIgG₄ were performed according to the standard manufacturer's protocols with the use of the UniCAP system (ThermoFisher Scientific/Phadia AB US, Portage, Mich). sIgG₄ and sIgE values below the lower limit of detection (0.15 for sIgG₄ and 0.10 for sIgE) were set to half the lower limit. One percent of all sera were repeated in a different assay run on a different day to provide estimates of interassay reliability. The geometric mean (GM) coefficient of interassay variation was 5.9% for all allergens. sIgE was considered positive if 0.35 kU/mL.

Analysis

Both sIgE and sIgG₄ had skewed distributions and therefore log-transformations were performed before inclusion of these as continuous variables in regression models. GMs and 95% CIs for sIgG₄ and sIgE were calculated as descriptive statistics for the skewed data and compared between symptomatic and asymptomatic teens with the use of Wilcoxon rank sum tests. Ratios of sIgG₄/sIgE, adjusted for the presence of sIgE (> 0.35 kU/mL), were assessed for association with pet-specific symptoms (yes/no) with the use of logistic regression models. Models were run both on the entire sample and stratified by current pet exposure to assess potential modification of the effect by pet ownership.

RESULTS

Data on 500 teens who provided interview information and a blood sample were analyzed. Participant age ranged from 18 to 20.7 years with a mean age of 18.3 ± 0.6 years. The participants were mainly white (95.8%; $n = 479$) and with nearly equal sex distribution (men, 47.4%; women, 52.6%). Forty-nine subjects reported past immunotherapy. These 49 were not excluded from the study.

Of 147 teens (29.4%) who had symptoms when exposed to a cat, 46 (31.3%) reported owning a cat. Of 353 teens who were asymptomatic on cat exposure, 120 (34.0%) reported owning a cat (Table I). Teens experiencing allergic symptoms with cat exposure had significantly higher cat sIgE and higher cat sIgG₄, but a lower ratio of cat sIgG₄/sIgE (Table I) than teens who did not report symptoms. These relationships did not differ by current cat exposure (Table I).

Increasing cat sIgG₄/sIgE ratios were associated with lower odds of reporting cat-associated allergic symptoms, even after adjusting for sIgE positivity (adjusted odds ratio [aOR], 0.8;

95% CI, 0.6–0.9) (Table II). Results were similar when restricting the analyses to teens with sIgE <0.35 kU/mL (data not shown). Cat ownership was not an effect modifier. No statistical difference was observed when excluding those patients who reported previous immunotherapy. Several of the teens (20.4% [102/500]) had both dog(s) and cat(s) in their home environment; 10.4% (52/500) expressed concurrent symptoms to both cats and dogs. Adjusting for number of pet(s) made no difference in the results.

Seventy-four participants (14.8%) reported allergic symptoms when exposed to dog, and 426 participants (85.2%) denied symptoms on dog exposure. Of the teens with symptoms with dog exposure, 41 (55.4%) reported owning a dog (Table III). Of the teens asymptomatic to dogs, 266 (62.4%) reported dog ownership (Table III). Teens experiencing allergic symptoms after dog exposure had significantly higher dog sIgE ($P < .001$) and lower sIgG₄/sIgE ($P < .001$). Similar levels of dog sIgG₄ were seen in symptomatic and asymptomatic teens. Increasing dog sIgG₄/sIgE ratios, even after adjusting for sIgE positivity, were associated with lower odds of reporting dog-specific symptoms (aOR, 0.8; 95% CI, 0.7–1.0) (Table IV). However, this relationship was attenuated within the group of teens without a current dog (aOR, 0.9; 95% CI, 0.7–1.2; $P = .56$), while remaining statistically significant within the teens with a current dog (aOR, 0.7; 95% CI, 0.5–0.9; $P = .007$). No statistical difference was seen when excluding patients who reported past immunotherapy.

DISCUSSION

Our data indicate that sIgG₄ alone is not associated with a protective effect for allergic symptoms on pet exposure. Increases in sIgG₄ in relation to pet exposure have been proposed to play a role in inducing tolerance to specific allergens.

Although the ratio of sIgG₄/sIgE was an independent predictor of protection against pet-related symptoms after adjusting for a positive sIgE test, levels of sIgG₄/sIgE were not better than sIgE alone. Furthermore, IgG₄ alone was not significantly associated with symptoms after adjusting for sIgE to cat or dog (data not shown). Thus, sIgG₄ appears to have little utility as an independent marker of whether allergen exposure will be well tolerated.

A strength of our study was that prospective data were collected among a large group of young adults that included participants with both high and general risk of atopy on the basis of family history. This minimizes bias that may be introduced by studying only a high-risk population as well as improves the generalizability of the results to the population at large. The study also has several limitations. Self-reported symptoms in response to an interviewer's directed questions about pet-related symptoms are unlikely to exactly replicate an evaluation in a clinician's office where a patient specifically is seeking evaluation. In addition, the most recent date of symptom—pet exposure episode was not collected or analyzed; thus, the timing of reported symptoms in relation to sIgE and sIgG₄ measurements are not known. Provocative challenges to cat or dog would have been preferable for confirming clinical hypersensitivity. However, provocative challenge is unrealistic for a large cohort study, and the combination of symptom reports and measures of IgE sensitization approximates clinical practice. Finally, the study population was not diverse for geographic

location, age group, or ethnicity, which may affect whether these results are reflective of populations from other groups (racial, geography, age, etc).

In conclusion, although cat and dog ownership may decrease allergy to these pets later in life, our results do not confirm that sIgG₄ is a strong predictor of tolerance. The higher ratios of sIgG₄/sIgE seen in participants without allergic symptoms suggest that IgG₄ may be associated with tolerance to some degree, but it does not appear to act independently of sIgE. We currently cannot recommend measuring sIgG₄ in addition to IgE as providing additional value about the likelihood of having clinical tolerance to pet allergens.

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Abbreviations used

aOR	Adjusted odds ratio
CAS	Detroit Childhood Allergy Study
GM	Geometric mean
sIgG₄	Specific IgG ₄
sIgE	Specific IgE

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What is already known about this topic?

Previous studies have suggested that increases in sIgG₄ may be linked to the development of tolerance, but currently the mechanism and exact role is unclear.

What does this article add to our knowledge?

sIgG₄ does not add substantial accuracy to sIgE as a predictor of clinical response to allergen exposure.

How does this study impact current management guidelines?

The data do not support the addition of sIgG₄ to sIgE as a substantial clinical indicator of allergen tolerance. This is consistent with current management guidelines where this marker is not routinely recommended for diagnostic or prognostic purposes.

TABLE IIgG₄ and sIgE to cat by teen symptomatic to cat

	Teen report of symptoms to cat		<i>P</i> value [*]
	Yes (n = 147) GM (95% CI)	No (n = 353) GM (95% CI)	
Cat-specific levels			
sIgE	0.52 (0.36–0.76)	0.06 (0.05–0.07)	<.001
sIgG ₄	0.32 (0.26–0.39)	0.21 (0.19–0.23)	.001
sIgG ₄ /sIgE	0.61 (0.42–2.87)	3.41 (2.93–3.98)	<.001
Stratified by current cat as pet exposure			
Current cat, yes	(n = 46)	(n = 120)	
sIgE	0.39 (0.19–0.80)	0.06 (0.05–0.08)	<.001
sIgG ₄	0.47 (0.32–0.68)	0.25 (0.21–0.31)	.003
sIgG ₄ /sIgE	1.18 (0.66–2.12)	4.05 (3.11–5.29)	<.001
Current cat, no	(n = 101)	(n = 233)	
sIgE	0.59 (0.37–0.94)	0.06 (0.05–0.07)	<.001
sIgG ₄	0.27 (0.21–0.33)	0.19 (0.17–0.22)	.022
sIgG ₄ /sIgE	0.45 (0.29–0.70)	3.12 (2.59–3.77)	<.001

* Determined by Wilcoxon rank sum test.

TABLE II

Logistic regression models, overall and by current cat exposure, of cat-specific sIgG₄/sIgE ratio on cat symptom(s)

Strata [*]	Cat-specific allergen variables in model simultaneously	aOR (95% CI)	P value
All	sIgG ₄ /sIgE [†]	0.8 (0.6–0.9)	.004
	sIgE positive [‡]	4.5 (2.2–9.4)	<.001
Current cat, yes	sIgG ₄ /sIgE [†]	0.8 (0.6–1.0)	.079
	sIgE positive [‡]	2.9 (1.0–8.7)	.056
Current cat, no	sIgG ₄ /sIgE [†]	0.8 (0.6–1.0)	.060
	sIgE positive [‡]	6.5 (2.3–17.9)	<.001

* Each strata represents one logistic regression model.

[†] Ratio log-transformed before inclusion in model because of skewness.

[‡] sIgE positive defined as ≥ 0.35 kU/mL.

TABLE IIIIgG₄ and sIgE to dog by teen symptomatic to dog

	Teen report of symptoms to dog		<i>P</i> value [*]
	Yes (n = 74) GM (95% CI)	No (n = 426) GM (95% CI)	
Dog-specific levels			
sIgE	0.36 (0.21–0.59)	0.10 (0.09–0.11)	<.001
sIgG ₄	0.88 (0.65–1.19)	0.78 (0.70–0.87)	.45
sIgG4/sIgE	2.45 (1.51–4.00)	7.97 (6.84–9.28)	<.001
Stratified by current dog as pet exposure			
Current dog, yes	(n = 41)	(n = 266)	
sIgE	0.55 (0.27–1.16)	0.09 (0.08–0.11)	<.001
sIgG ₄	1.04 (0.74–1.49)	0.85 (0.74–0.97)	.28
sIgG ₄ /sIgE	1.89 (0.93–3.87)	9.04 (7.56–10.81)	<.001
Current dog, no	(n = 33)	(n = 160)	
sIgE	0.21 (0.11–0.41)	0.11 (0.09–0.13)	.087
sIgG ₄	0.70 (0.42–1.19)	0.69 (0.58–0.82)	.93
sIgG ₄ /sIgE	3.40 (1.75–6.61)	6.45 (4.90–8.51)	.047

* Determined by Wilcoxon rank sum test.

TABLE IV

Logistic regression models, overall and by current dog exposure, of dog-specific sIgG₄/sIgE ratio on dog symptom(s)

Strata [*]	Dog specific allergen variables in model simultaneously	aOR (95% CI)	P value
All	sIgG ₄ /sIgE [†]	0.8 (0.7–1.0)	.015
	sIgE positive [‡]	2.1 (1.0–4.5)	.054
Current dog, yes	sIgG ₄ /sIgE [†]	0.7 (0.5–0.9)	.007
	sIgE positive [‡]	2.2 (0.8–5.9)	.12
Current dog, no	sIgG ₄ /sIgE [†]	0.9 (0.7–1.2)	.56
	sIgE positive [‡]	1.9 (0.6–6.2)	.27

^{*} Each strata represents one logistic regression model.

[†] Ratio log-transformed before inclusion in model because of skewness.

[‡] sIgE positive defined as ≥ 0.35 kU/mL