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Serum immunoglobulin E responses to aeroallergens in cats with naturally occurring airway eosinophilia compared to unaffected control cats

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Abstract

Background: Eosinophilic airway disease in cats is sometimes described as allergic in origin, but controversy exists in the documentation of allergy in cats and the utility of allergy testing for respiratory tract diseases.

Objective: To examine serum immunoglobulin E (IgE) response to aeroallergens in cats with airway eosinophilia.

Animals: Fifteen cats with idiopathic eosinophilic airway inflammation and 9 control cats.

Methods: Prospective, case-control study. Surplus serum from cats with airway eosinophilia documented by bronchoscopic bronchoalveolar lavage was submitted for IgE measurement using ELISA polyclonal antibody methodology. Responses for regional allergens (fungal organisms, weeds, grasses, trees, mites, insects) were assessed. Results were reported as ELISA absorbance units with scores 0 to 79 considered negative, scores between 80 and 300 considered intermediate, and scores >300 considered positive.

Results: Cats with airway eosinophilia had significantly more positive serum IgE responses (25/720) than did healthy controls (5/432, $P = .02$); however, the number of cats with positive IgE responses (5/15) did not differ from controls (1/9, $P = .35$). The allergen that most commonly resulted in positive serum IgE response in cats with airway eosinophilia was dust mite (n = 4) followed by 2 types of storage mites (n = 3 each). No control cat tested positive for these allergens.

Conclusions and Clinical Importance: Serum IgE production against aeroallergens was found in some cats with eosinophilic airway inflammation, but the number of affected cats with positive results did not differ from controls. Further investigation in cats with eosinophilic, mixed, and neutrophilic airway disease in comparison to control cats is warranted.

KEYWORDS
asthma, bronchitis, bronchoscopy, ELISA, immunology

Abbreviations: BAL, bronchoalveolar lavage; EAU, ELISA absorbance units; IDT, intradermal test; IgE, immunoglobulin E.

1 | INTRODUCTION

Cough in cats often is caused by inflammatory airway disease, which is a diagnosis of exclusion. Airway sampling plays an important role in the diagnostic evaluation of a coughing cat and inflammatory airway disease encompasses eosinophilic, neutrophilic, and mixed inflammation.[1,2] Eosinophilic airway inflammation can be induced experimentally in cats by parenteral or inhalational exposure to antigens or allergens.[3-6] Allergens play a role in the asthmatic syndrome in horses[7] and in approximately 50% of asthma cases in humans.[8]

In atopy in humans, diagnostic testing for an allergic response includes assessment of serum immunoglobulin E (IgE), skin prick tests, patch tests, and intradermal testing (IDT), with each methodology suffering from difficulties in completion or interpretation.[9] For example, manufacturer differences in the development of allergen extracts remains a challenge to standardized testing.[10] Testing methodologies differ and include quantification of IgE using FceR1a-based ELISA, polyclonal antibody testing, and enzyme immunometric methodology. A study in cats with experimentally induced disease found markedly disparate results between ELISA testing and enzyme immunometric assays,[11] raising questions about the validity of such testing to determine an allergenic response. Finally, in human medicine, serum IgE testing is considered only a part of allergy testing, with confirmation requiring more invasive skin testing methods. Skin testing is particularly problematic in cats because of the need for sedation or anesthesia to complete IDT and limited data on the use of patch testing or skin prick tests in cats.

Few studies report allergen-mediated responses in cats with cough. A pilot study described an increased number of positive responses to aeroallergens in cats with naturally occurring lower airway disease in comparison with controls, with significantly more positive results identified in serum analysis compared with IDT.[12] In experimentally induced airway disease in which response to 2 allergens was assessed, IDT had higher sensitivity but lower specificity than did serum IgE analysis in detection of allergen responses.[11] Finally, a recent noncontrolled retrospective study reported intermediate and positive serum IgE responses in a majority (78%) of cats with respiratory signs related to eosinophilic airway disease.[13]

We hypothesized that the number of cats with naturally occurring eosinophilic airway disease that produced allergen-specific IgE would be significantly higher than the number of control cats, which were matched for age and environment. We also hypothesized that the number of positive allergen reactions would be higher in affected as compared with control cats.

2 | METHODS

Our case-control study used a convenience sample of cats diagnosed with idiopathic eosinophilic inflammatory airway disease at the William R. Pritchard Veterinary Medical Teaching Hospital at the University of California, Davis. Control samples were obtained from healthy cats presented for vaccination and wellness examinations during comparable seasons of the year. Residual serum remaining after completion of diagnostic testing was submitted for IgE analysis, and therefore owner consent and ethical approval were not required. Neither diseased nor control cats had a history or clinical signs of skin or gastrointestinal disease, and all were maintained on appropriate flea and parasite control, although heartworm prophylaxis was not in use for any cat because the disease is not endemic in our area. Clinical information abstracted from the medical record included duration of clinical signs in affected cats as well as date when signs were first noted, indoor/outdoor status, flea and internal parasite control, diet, and medication history. The date of sample collection was used for assessment of seasonality.

Bronchoscopy with bronchoalveolar lavage (BAL) was performed as previously described.[14] Briefly, cats were anesthetized and maintained with jet ventilation for bronchoscopy using either a 2.8 mm × 70 cm videoendoscope with a 1.2 mm channel (Karl Storz Flex XC, Goleta, California), or a 3.8 mm × 55 cm videoendoscope with a 1.2 mm channel (Olympus BF3C160, Center Valley, Pennsylvania). Bronchoalveolar lavage fluid from separate lung sites was submitted to the clinical pathology laboratory for cell counts and cytologic assessment and to the microbiology laboratory for aerobic and Mycoplasma culture.

Differential cell counts were performed on Wright-Giemsa stained cytospin preparations by counting 200 cells at high power (50×) examination, and cellular characteristics were evaluated by a board-certified clinical pathologist. Reference intervals for BAL cytology used by our laboratory for total cell counts are 300 to 400 cells/μL comprised of up to 7% neutrophils or lymphocytes, up to 18% eosinophils, and 65% to 85% macrophages.[15-17] Bronchoalveolar lavage fluid was characterized as eosinophilic if the differential count identified >20% eosinophils and neutrophil percentage was within reference limits or if eosinophils were >50%. Mixed inflammation was defined by an increase in eosinophils between 18% and 50% with neutrophils >7%, or by inflammation that was discordant between BAL sites.[2]

Tests results were evaluated for concordance with the diagnosis of idiopathic inflammatory airway disease, which was assigned to cats that lacked infectious or parasitic causes of cough and had positive responses to corticosteroid treatment.

Serum remaining after the cat had been discharged was submitted immediately for IgE analysis using the ELISA polyclonal antibody methodology (Greer Aller-g-complete) that evaluated allergen responses for 48 regional allergens including fungal organisms (n = 9), weeds (n = 12), grasses (n = 8), trees (n = 14), and mites or insects (n = 5, Table 1). Results were reported as ELISA absorbance units (EAU) with scores 0 to 79 reflecting lack of allergen-specific IgE considered negative, scores between 80 and 300 considered intermediate, and scores >300 considered positive.

3 | STATISTICS

Normality was assessed using the D'Agostino and Pearson omnibus test. Clinical characteristics were compared between groups using a *t* test for normally distributed results and Mann-Whitney *U* test for non-normally

TABLE 1 Regional aeroallergens evaluated in serum IgE analysis

Fungal	Weeds	Grasses	Trees	Insects/mites
Alternaria	Cockelbur	Bermuda	Acacia	Flea
Aspergillus	Dandelion	Johnson	Alder, red	Dust mite *Pteronyssus*
Cephalosporium	Dock/sorrel mix	Kentucky blue/June	Ash mix	Dust mite *farinae*
Cladosporium	English plantain	Meadow Fescue	Cedar, red juniper	Storage mite *Acarus*
Cuvularia	Goldenrod	Perennial rye	Cottonwood	Storage mite *tyrophagus*
Mucor	Kochia, Firebrush	Quack Grass	Eucalyptus	
Penicillium	Lamb's quarters	Red top	Maple mix	
Pullalaria	Pigweed mix	Timothy	Mulberrry, red	
Stemphylium	Ragweed Mix		Oak mix	
	Russian thistle		Olive	
	Sage mix		Orange	
	Scale Mix		Palm	
			Pine mix	
			Walnut, black	

Abbreviation: IgE, immunoglobulin E.

distributed results. The number of cats with negative, intermediate, and positive serum IgE results was compared between cats with airway eosinophilia and controls using Fisher's exact test with Freeman Halton extension, and the number of cats with negative vs combined intermediate and positive serum IgE was compared using Chi-squared analysis.

Results for negative, intermediate, and positive serum IgE were compared between affected and control cats using Fisher's exact test. This analysis was repeated to compare negative to positive results and negative to combined intermediate plus positive tests. Positive and negative serum IgE responses for individual allergen groups (grass, weed, tree, fungus, and mite or insect) were compared between affected and control cats using Fisher's exact test.

Correlation analysis was performed using linear regression for duration of signs, number of positive and intermediate IgE results, and percentage of BAL eosinophils. Statistics were performed using commercially available software (GraphPad Prism v5.0f, San Diego, California) and for all tests $P < .05$ was considered significant.

4 | RESULTS

Cats with eosinophilic airway disease included 12 cats with eosinophilic inflammation, and 3 with mixed inflammation of similar age (Table 2) compared to 9 control cats. Mean age of cats with eosinophilic airway disease (5.6 ± 3.5 years) did not differ from that of control cats (8.0 ± 3.7 years; $P = .13$). Cough in affected cats was present for 352 ± 302 days.

The season for bronchoscopic evaluation and serum IgE analysis was available for all cats, but information regarding the onset of clinical signs was available in only 8/15 affected cats (Table 3). All seasons were represented with no difference compared to controls. Eight of 15 cats were primarily indoor compared to 2/9 control cats. Geographic location varied among mountainous regions, foothills, agrarian environments, rural, and suburban regions, with 83% of cats living within a 50 mile radius of the testing site. Dry food was consumed by 14/15 cats with eosinophilic airway disease and 6/8 controls (information not available in 1 cat).

One of 15 cats with eosinophilic airway disease had received an injection of methylprednisolone acetate 5 weeks before evaluation. The remaining 14/15 cats had not received corticosteroids within the previous 4 months. Heartworm testing was negative in 10/15 and Baermann fecal analysis was negative in 2/15 cats with airway eosinophilia.

Serum IgE analysis was positive (ie, >300 EAU) in 5/15 (33%) cats with airway eosinophilia compared to 1/9 (11%) control cats, with no significant difference between groups ($P = .35$). All cats with positive results also had intermediate responses (EAU 79-300) to various allergens, and all cats with positive results had eosinophilic rather than mixed airway inflammation. Overall, intermediate results were found in 13/15 (86%) of cats with airway eosinophilia and 6/9 (66%) controls ($P = .33$). The number of cats with only negative results (2 with airway eosinophilia and 3 controls) vs cats with combined intermediate plus positive results also did not differ between cats with airway eosinophilia and control cats ($P = .63$).

The allergen most commonly resulting in serum IgE production >300 EAU in cats with airway eosinophilia was dust mite (*Dermatophagoides farina*, n = 4) followed by 2 types of storage mites (*Acarus siro* and *Tyrophagus*, n = 3 each). No control cat tested positive for these allergens.

Two cats with airway eosinophilia were from the same household and were of similar age and lineage. One had 5 positive serum IgE results (to both dust mites and storage mites as well as to 1 tree pollen) and the other was negative to all allergens. The single control cat with positive results had 5 positive IgE results within the fungal category of allergens. A sibling from the same household had mostly negative IgE results, with intermediate results to 3 of 9 fungal allergens.

TABLE 2 Total nucleated cell count (TNCC) per μL, percent eosinophils, and percent neutrophils in BAL fluid from 15 cats with naturally occurring inflammatory airway disease

Inflammation	TNCC/μL	Percent eosinophils	Percent neutrophils	Age (y) (mean ± SD)
Eosinophilic (n = 12)	1920 ± 1391	62 ± 15	14 ± 12	5.2 ± 1.1
Mixed (n = 3)	2431 ± 656	42 ± 6	48 ± 16	7.1 ± 1.3

Note: Data are presented as mean ± SD. Age did not differ between cats with eosinophilic and mixed inflammation, $P = .51$.
Abbreviation: BAL, bronchoalveolar lavage.

TABLE 3 Samples for serum IgE analysis were submitted after discharge during multiple time frames for cats with eosinophilic airway disease and control cats, with no differences between groups

	Airway eosinophilia		Controls
Season	Serum analysis	Clinical signs	
January-March	4	0	1
April-June	3	0	3
July-September	3	5	3
October-December	5	3	2

Note: The time at which clinical signs were reported to start was available for only 8/15 cats and corresponded to the latter half of the year.
Abbreviation: IgE, immunoglobulin E.

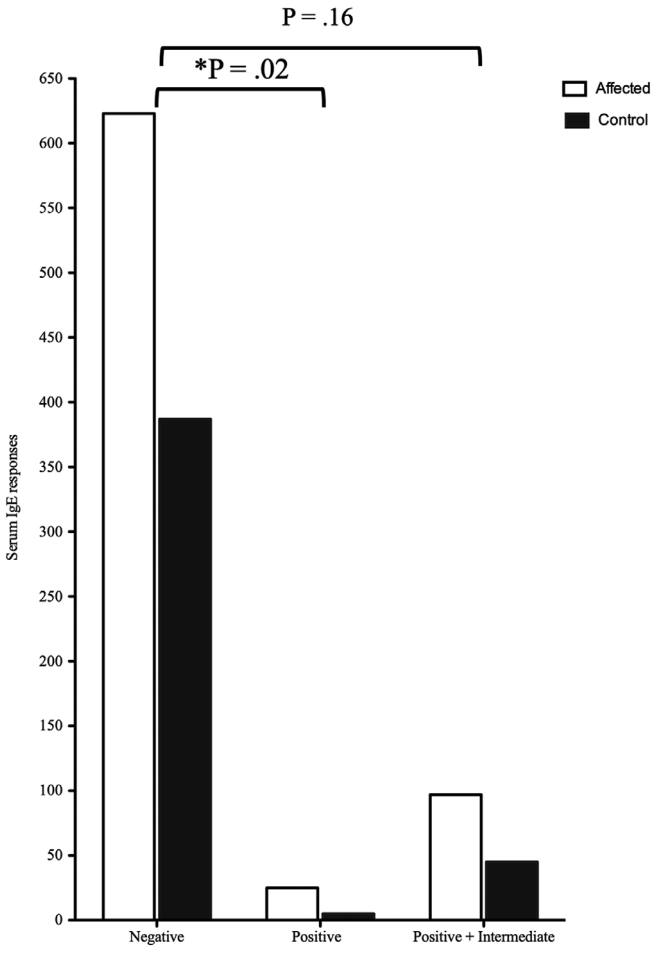

FIGURE 1 Number of negative (<79 EAU), positive (>300 EAU), and intermediate (80-300 EAU) + positive IgE response in affected and control cats. EAU, ELISA absorbance units; IgE, immunoglobulin E

TABLE 4 Positive allergen-specific serum IgE results (>300 EAU) in 5 cats with airway eosinophilia compared to the 1 control cat with positive serum IgE results

	Airway eosinophilia (n = 5)	Control (n = 1)
Fungal	1	5
Grasses	7	0
Trees	1	0
Weeds	4	0
Insects/mites	12	0

Abbreviations: EAU, ELISA absorbance units; IgE, immunoglobulin E.

In cats with airway eosinophilia, 25/720 (3.5%) allergen-induced serum IgE results were positive compared with 5/432 (1.2%) in control cats ($P = .02$; Figure 1). The number of negative IgE results was not significantly different from the number of combined intermediate and positive allergen-induced responses when comparing control cats to cats with airway eosinophilia ($P = .16$; Figure 1). The allergens responsible for induction of serum IgE were significantly different in cats with airway eosinophilia compared to controls ($P < .001$; Table 4). One cat with eosinophilic airway disease developed 14 positive serum IgE results to grasses, weeds, and 4 mites and accounted for 56% of all positive IgE responses. One cat had 5 positive results to 4 mites and 1 tree accounting for 20% of all responses, 1 cat had 4 positive results to 3 mites and to fleas, and the remaining 2 cats developed IgE in response to *Aspergillus* or *D farina* allergens.

No correlation was found between duration of cough and IgE positivity or between percentage of BAL eosinophils and IgE positivity ($P = .47$ and $P = .5$, respectively).

5 | DISCUSSION

We found that positive serum IgE results were more common in cats with eosinophilic airway inflammation than in clinically unaffected cats, and affected cats responded to different allergen groups than did control cats. However, no significant difference was found between the number of cats in each group that developed positive serum responses. This finding is similar to results of a pilot study[12] that reported increased prevalence of both serum IgE reactions and IDT responses in cats with lower airway disease compared with controls. Our study had a power of only 20%, and therefore although the number of allergen responses was significantly different between groups, recruitment of additional cats would be required to detect differences in the number of affected cats. Assuming an incidence of positive allergen responses 3-fold higher in affected cats compared to controls, over 55 cats per groups would be needed.

In the earlier pilot study, cats with respiratory disease most commonly developed serum IgE responses to grasses, weeds, and trees,[12] whereas in our study, cats with airway eosinophilia had significantly more serum reactions to allergens in the mite category, followed by grasses. Most cats in our study were kept primarily indoors, which could increase exposure to house dust mites. Most cats in our study ate dry food, which could be expected to result in equal exposure to storage mites in each group,[18] but cats with eosinophilic airway disease had more serum reactions to these mites. In contrast to the previous pilot study,[12] we experienced no difficulty identifying cats with respiratory disease that lacked dermatologic disease. This might reflect differences in geography, climate, or population dynamics (including genetics and epigenetic factors) between the 2 studies. These potential differences also might explain results of a retrospective study that reported positive and intermediate serum allergen responses in 78% of cats with respiratory disease,[13] although no comparisons were made to unaffected cats. The previous retrospective study reported a median of 17 (range, 3-68) combined intermediate and positive responses per cat, which exceeds those found in our study (median = 4; range, 1-17). Similar to that report,[13] the most common serum IgE response in our study also was to indoor allergens. This finding might be anticipated given that risk factors for developing allergic asthma in humans are related to increased exposure to fungi and the degree of bacterial richness in the home environment,[19] but these associations have not been evaluated in the cat.

Several factors could have impacted or confounded our results. Atopic asthmatic humans have seasonal intrasubject variability in total serum IgE concentrations throughout the year,[20,21] which could lead to false-negatives, false-positives, or intermediate IgE reactivity at certain times in any given patient. This phenomenon has not been evaluated in veterinary medicine but is likely to exist. Allergen-specific IgE in cats can correlate with age, absence of parasite control, and outdoor living status,[22] although these features would likely have affected both groups of cats in our study. Also, IgE might not be the only relevant immunoglobulin in the asthmatic phenotype. Eosinophil degranulation via IgG has been shown in vitro,[23] and experimentally induced asthmatic cats have increases in allergen-specific IgG and IgA concentrations in both serum and BAL samples.[24] Local production of antibodies, including IgE, also occurs in respiratory mucosa, which might not be reflected by serum IgE analysis, thus hindering the diagnosis of allergic disease.[25,26] Different laboratories performing allergy testing can report variable results for the same patient.[27] Finally, manufacturer differences in allergens can lead to variable serum reactivity,[10] and although the tests used in our study have been validated in dogs,[28,29] they have not been evaluated in cats.

Development of asthma not only includes environmental allergen exposure and genetic predisposition, but the complex interactions between these.[30] Interestingly, 2 of the control cats were siblings from the same household, 1 of which had positive IgE responses to multiple fungi whereas the other had mostly negative and some intermediate responses to the same fungi. Additionally, in the affected group, 2 cats were from the same household, with 1 cat having multiple positive IgE responses and the other having only negative responses. Finally, 1 cat in our study accounted for 56% of all positive IgE responses in cats with airway eosinophilia. Although the goal of our study was not to evaluate genetic predisposition and environmental factors in the development of allergic disease, these finding emphasize the complex pathophysiology involved in inflammatory airway disease in cats, and indicate that diagnosis of allergic disease cannot be made based on airway eosinophilia or serum IgE responses alone.

In conclusion, we found significantly more positive serum IgE responses in cats with airway eosinophilia in comparison with healthy controls. This finding could indicate that some cats with airway eosinophilia have an IgE-mediated allergic etiology and that serum allergen IgE responses should be further studied. However, as in the previous study,[12] the number of cats with positive serum IgE responses did not differ between cats with airway eosinophilia and controls, which could indicate that other factors are involved in the production of airway eosinophilia. A recent study in humans reported that severe asthmatics often have concurrent neutrophilic inflammation and that the neutrophil count in BAL samples is positively correlated with serum IgE.[31] Assessment of serum IgE responses in more cats with mixed inflammation and in those with idiopathic neutrophilic airway inflammation could contribute to our understanding of the etiopathogenesis of naturally occurring inflammatory lower airway disease in cats.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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