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Intrinsic risk factors for alpha-gal syndrome in a case-control study, 2019 to 2020

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Abstract

Background: Alpha-gal syndrome (AGS) is an allergy to galactose-α−1,3-galactose (alpha-gal), a carbohydrate found in most mammals. Evidence indicates that AGS develops after a tick bite, and in the United States, AGS is most associated with bites from *Amblyomma americanum* (lone star tick); however, not all persons bitten by ticks develop clinical AGS.

Objective: To investigate intrinsic risk factors associated with the development of AGS.

Methods: We performed a case-control study among adults presenting for diagnosis or management of AGS at an allergy clinic in North Carolina during 2019 to 2020 and compared them with controls enrolled from 2 nearby internal medicine clinics. A questionnaire gathered epidemiologic and tick exposure data, and blood was obtained for alpha-gal−specific IgE and other testing.

Results: The 82 enrolled case patients and 191 controls did not differ significantly by age or sex. Case patients were more likely than controls to have A or O blood types (non B-antigen), have experienced childhood allergies, and have a family history of AGS and other food allergies. Case

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Supplementary Data

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patients were also more likely to report experiencing long healing times for insect bites or stings and a family history of allergy to stinging or biting insects.

Conclusion: This study suggested that intrinsic factors contribute to risk of developing AGS. Some traits are genetic, but common behaviors among households and family units likely also contribute. Identification of these risk factors can inform personal risk, aid health care providers in understanding susceptible populations, and contribute to ongoing understanding of AGS epidemiology.

Introduction

Alpha-gal syndrome (AGS) is an IgE-mediated hypersensitivity to the carbohydrate galactose-α−1,3-galactose, frequently referred to as alpha-gal.[1,2] Alpha-gal is found in New World monkeys and nonprimate mammals, such as cows or pigs, with exposures typically occurring through meat ingestion. Potential exposures to alpha-gal are ubiquitous, including hidden sources of mammalian derivatives (such as broths and fats), dairy products, some medications (cetuximab, horse- and sheep-derived antivenom), gelatin (Jell-O, marshmallows, or capsules), and vaccines with mammalian-derived excipients.[3,4] Alpha-gal is not found in avian, reptile, or fish sources. Notably, AGS is an emerging public health concern in the United States. Through laboratory testing-based surveillance, more than 110,000 suspected cases of AGS have been identified between 2010 and 2022, and case counts have increased annually during this time.[5,6] Suspected AGS cases in the United States have been predominantly identified in geographic areas that overlap with the known distribution of the lone star tick (*Amblyomma americanum*).[5–7]

A recent case-control study found a strong association of development of AGS with a history of tick bites.[8] Case patients were also more likely to live on larger and more wooded properties and to spend more time outside.[8] Although nearly all patients with AGS (98%) had specific IgE antibodies (sIgE+) to alpha-gal, the presence of alpha-gal sIgE antibodies in 33% of asymptomatic controls was also associated with tick bite.[8] There is a lack of understanding in what factors differentiate persons bitten by ticks who develop sIgE antibodies and remain symptom free from those who develop AGS. We analyzed additional data from that case-control study to ascertain intrinsic risk factors for developing AGS.

Methods

Study Design and Subject Enrollment

All participants were enrolled between 2019 and 2020 and were at least 18 years of age. Case patients were enrolled at a university-based allergy clinic in North Carolina, and controls were enrolled at 2 nearby internal medicine clinics. Case patients presented for diagnosis or management of AGS and were required to report clinical symptoms consistent with AGS (eg, urticaria, emesis, diarrhea, angioedema, and hypotension 3–6 hours after consuming mammalian meat or byproducts). Case patients were not required to have laboratory-confirmed AGS (alpha-gal sIgE ≥ 0.1 kU/L) before their study enrollment visit. Controls were required to report no AGS diagnosis and no symptoms after eating beef, pork, or lamb. Details of the study methods have been published previously.[8]

Serology

Blood was obtained for testing on the day of enrollment. Serum allergy testing and blood typing were performed at the university's research laboratory. Blood typing was performed using ABO reverse grouping reference cells (Immucor, Norcross, Georgia) and included type and Rh factor. Allergy testing included measurement of total serum IgE antibodies and measurement of sIgE antibodies to alpha-gal, cow's milk, stinging insects (fire ant, honey bee venom, paper wasp, white-faced hornet, or yellow jacket), mosquito, chicken, turkey, codfish, and cat serum albumin. Allergens for sIgE testing were chosen based on assessment of other possible meat allergies (chicken, turkey, or codfish), known cross-reactive allergens (cow's milk), potential confounding allergy syndromes (cat serum albumin), and assessment of stinging/biting insects (ant, bee, vespids, or mosquito). All antibody testing was conducted using commercially available ImmunoCAP assays (Thermo Fisher/Phadia, US, Portage, Michigan) performed with the ImmunoCAP 250 instrument. The results were expressed in kU/L. Testing for alpha-gal sIgE (ImmunoCAP # o215) was conducted per manufacturer instructions, and the cutoff for a positive test result was the limit of detection, at 0.1 kU/L.

Data Collection

Data were abstracted from questionnaire forms and entered into a Research Electronic Data Capture (REDCap) database. Data collected included demographic information, patient medical history (including diagnoses of hypertension, diabetes, heart disease, stroke, inflammatory bowel disease, and celiac disease), and reported history of any tick or chigger bites in the year before symptom onset for case patients and in the year before enrollment for controls. All participants were asked about non−alpha-gal allergy history (case patients were asked separately about alpha-gal), including history of food allergies, hives, anaphylaxis, and allergic reactions requiring medical attention. Participants were asked about dietary history and family history, including family history of allergies such as AGS. Case patients were asked additional questions regarding exposure to specific alpha-gal−containing products, including vaccines and medical products. Case patients were also asked about their AGS reactions, including symptoms experienced, the time from exposure to symptom onset, time of day symptoms typically occurred, and exacerbating factors for severity, such as exercise and alcohol.

Statistical Analysis

Comparisons of categorical variables between case patients, sIgE+ controls, and all controls were made with odds ratios (ORs) and 95% CI score; in these computations, one-half was added to table cell frequencies when there was a 0 cell.[9]

The exact binomial test was used to compare the distribution of blood types (B/AB vs A/O) for case patients and controls against the known US blood type distributions for each race category with sufficient data and for which population distribution information from the American Red Cross matched our race category specifications.[10,11] The distributions of blood types among case patients and controls were compared directly using ORs and 95% CI scores for these same race categories. Data management, analyses, and visualizations

were performed with R version 4.0.3 software (R Foundation, Vienna, Austria, https://r-project.org).

Ethics

This study was reviewed and approved by the University of North Carolina Institutional Review Board (#19–0938).

Results

Patient Demographic Characteristics

A total of 82 case patients and 191 controls were enrolled (Table 1). Patient characteristics have been previously published.[8] Case patients were older than controls, with median age of 58.5 years vs 54.0 years (Table 1). The case patient group was less racially diverse than the control group, with 88% White, 10% American Indian/Alaskan native, and 2% Black (Table 1). The control group was 79% White, 14% Black, and the remaining 7% either American Indian/Alaskan Native, Asian, other, or unknown (Table 1). Furthermore, 70% of the case patients lived in North Carolina, with out-of-state residency reported for 30%, compared with 100% North Carolina residence among the controls (Table 1). Case patients reported higher levels of education and income (Table 1).

Blood Type

Of the case patients tested, 96% had blood types A, O, or AB, compared with 4% for blood type B (Table 2). Furthermore, 11% of the controls had B blood type. Grouping blood types together by B-antigen presence (B/AB vs A/O), case patients (10%) were less likely than controls (22%) to have B-antigen blood types (B/AB) (OR, 0.40; 95% CI, 0.18–0.88) (Table 2).

There were sufficient data to analyze blood type distributions by race for 2 categories, White and Black. The blood type distribution of White and Black participants of our study did not significantly differ from the White and Black US population in any comparison. Neither White case patients nor White controls differed from the White US population ($P = .18$, $P = .07$, respectively). Neither Black case patients nor Black controls differed from the Black US population ($P = .41$, $P = 1.00$, respectively).

Within the study, White case patients were less likely than White controls to have B-antigen blood types (B/AB) (OR, 0.39; 95% CI, 0.15–0.90). There was no difference between Black case patients and Black controls (OR, 3.15; 95% CI, 0.29–38.29); however, confidence limits were wide because of small sample sizes.

Medical History

Case patients were less likely than controls to report hypertension (OR, 0.51; 95% CI, 0.29–0.88), type II diabetes (OR, 0.43; 95% CI, 0.18-, heart disease or heart attack (OR, 0.50; 95% CI, 0.16–1.33), and asthma (OR, 0.55; 95% CI, 0.22–1.37). Case patients were more likely than controls to report vitamin D deficiency (OR, 1.89; 95% CI, 1.02–3.51) (Table

3). Of both case patients and controls, 2% reported irritable bowel syndrome or ulcerative colitis. Additional medical history questions and dietary questions are available in eTable 1.

Allergy History

Case patients were more likely than controls to report particularly large marks or welts and/or longer healing times when stung or bitten by an insect (irrespective of tick bite reactions) (OR, 3.14; 95% CI, 1.81–5.47), experiencing allergies in childhood that they no longer had as an adult (OR, 1.99; 95% CI, 1.02–3.89), having food allergies other than red meat and associated products (OR, 1.88; 95% CI, 0.99–3.56), having an allergic reaction (independent of AGS reactions) that required medical care (urgent care, emergency department, or hospital) (OR, 1.93; 95% CI, 0.97–3.82), and having experienced anaphylaxis (independent of AGS reactions) (OR, 1.87; 95% CI, 0.96–3.64) (Table 3).

Approximately all case patients (98%) and 33% of controls had positive alpha-gal sIgE (sIgE+) result.[8] The sIgE+ control group allowed for comparison between persons with known reactions (case patients) and persons who reported meat tolerance, yet were alpha-gal sIgE+. Comparing all case patients with all controls, case patients were more likely to have sIgE reactive to the following allergens (all except chicken and turkey): cow's milk, yellow jacket, paper wasp, white-faced hornet, cat serum albumin, fire ant, mosquito, and codfish (Table 4). Comparing case patients with the alpha-gal sIgE+ controls, case patients were still more likely to test sIgE+ to cow's milk and paper wasp (Table 4).

Family History

Case patients were more likely to report a family history of food allergy (OR, 2.70; 95% CI, 1.47–4.98), allergy to stinging or biting insects (OR, 2.44; 95% CI, 1.35–4.42), and alpha-gal allergy to red meat (OR, 8.33; 95% CI, 2.99–27.38) (Table 5). The analysis for family history of alpha-gal allergy was modified to remove 2 individuals. A familial cluster among alpha-gal case patients was suspected when reviewing deidentified data that revealed a link among 3 case patients' responses. To limit the effect of these correlated responses, 2 of the 3 likely related people were removed from this comparison.

Case Patient Reaction Characteristics

The most common organ system reactions were gastrointestinal and mucocutaneous, with abdominal pain/cramping (74%) and hives (72%) as the most frequently reported symptoms (eTable 2). Among the case patients who reported drinking alcohol, 29% reported that drinking alcohol increased reaction severity (eTable 3). Among the case patients who reported exercising, 32% reported that exercising increased reaction severity (eTable 3). Consumption and tolerance of alpha-gal−containing foods varied widely. Some foods had been consumed by almost all case patients, with beef and dairy products at 95% and 96%, respectively. However, foods that most case patients reported having eaten were not necessarily the best tolerated. Beef caused a reaction for most case patients, with 97% reacting after ingestion (eTable 4). Dairy caused a reaction for 61% of those who reported consumption (eTable 4). Some alpha-gal−containing foods were less frequently consumed, with 91% of case patients reporting "never eat" for both goat and organ meat (tripe, scrapple, and sweet-bread) (eTable 4). Of the 9% of case patients who reported having eaten

organ meat, 100% reported having AGS symptoms after consumption (eTable 4). Goat was also consumed by only 9% of the case patients and was the best tolerated food, with only 29% of those who ate goat reacting (eTable 4). Among the case patients who had ingested gel caps, 31% had a reaction; similarly, marshmallows, Jell-O/gelatin, or gummies caused a reaction for 40% of the case patients who reported ingestion (eTable 4).

The case patients were asked whether they had received the following vaccines within the last 5 years: measles/mumps/rubella, rabies, shingles (Zostavax), chicken pox (varicella), and yellow fever. Of the 82 case patients, 20 (24%) reported receiving 1 of these vaccines (eTable 5). One case patient received 2 vaccines, shingles and yellow fever, for 21 total doses administered. Of these 21 administrations, 1 case patient reported having anaphylaxis after receipt of a vaccine (Zostavax) (eTable 5). Risk of reaction to Zostavax among patients with AGS has been previously documented because of hydrolyzed porcine gelatin.[12] As of November 2020, Zostavax is no longer available for use in the United States.[13]

Discussion

Tick bites are not unusual in many parts of the United States, but what determines if a person develops alpha-gal sIgE or clinical AGS after a tick bite is likely complex, involving environmental and intrinsic risk factors. Although environmental risk factors associated with AGS have previously been identified, our case-control study identified individual and familial risk factors for AGS.[8] AGS case patients were more likely to have atopy than controls, indicated by a history of childhood allergies, allergies to foods other than red meat, increased cutaneous reactions to insect bites, and sIgE antibodies to a broad array of allergens. Case patients were also more likely than controls to report related family members (parents, siblings, and children) with food allergies and allergies to insect bites. Of note, case patients were approximately 8 times as likely to report related family members with AGS.

The strong association of AGS case patients having a family history of allergies further suggests that genetic factors may influence AGS susceptibility. However, observed familial effects may be partially attributable to common household or lifestyle traits rather than inherited risk. Peridomestic exposure to arthropods, which could include gardening, yardwork, or children playing outside contributes to household risk of vector-associated conditions. Independent of residence, family groups could have lifestyle risks for tick exposure, including spending more time outdoors, or hobbies such as fishing or hunting. Additional studies are required to understand how genetic and lifestyle factors contribute to family risk of AGS.

In addition to genetic predispositions and common environmental exposures to tick bites, increased awareness of AGS among family members may contribute to the effect of familial association. AGS diagnosis is known to be patient driven, with a 2016 study (N=28) identifying that only 21% of patients were diagnosed with having AGS within a year of symptom onset.[14] A 2022 health care provider survey revealed that of 1500 respondents, only 5% felt very confident in their ability to diagnose or manage patients with AGS, and 42% had not heard of AGS.[15] Persons with a family member with AGS may be more likely to suspect their own diagnosis, seek health care, locate an informed provider, request

appropriate testing, and ultimately reach a diagnosis of AGS compared with persons without a family member with AGS.

A previous study indicated that persons with blood type B were approximately one-fifth as likely to have AGS than persons with blood type O.[16] Our study found a similar effect of similar magnitude, with persons with blood group B approximately one-fourth as likely to have AGS. Our study supports existing literature suggesting that B-antigen blood types may be protective against elevated alpha-gal IgE and development of AGS, thought to be due to a structural similarity between alpha-gal and the B-antigen.[16,17]

African Americans are approximately twice as likely to have blood type B than Whites (19% vs 10%), which would increase the prevalence of B-antigen blood type in the controls in our study and amplify the protective impact of B-antigen blood type.[11] We compared the study population to the American Red Cross's published blood type distributions by race because of well-established racial variation. There was not an apparent difference between the control group's blood type distribution and that of the US population, which provides assurance that the control group provides a distribution adequately similar to the US population to draw meaningful comparisons to the case patient group. White case patients were significantly less likely to have B-antigen blood types (B/AB) than White controls; this difference was not found in the Black participants, though this could have been due to low power caused by the small sample size.

The impact of alpha-gal sIgE positive status (a state referred to as sensitization) on individual dietary tolerance and physical health is unclear. A cohort of patients undergoing colonoscopy in North Carolina found that 31.4% of participants were sensitized (sIgE+), though they reported being able to tolerate mammalian meat, cheese, and milk at similar levels as their alpha-gal sIgE-negative counterparts.[18] Other studies have suggested negative cardiovascular impacts of alpha-gal sensitization; however, it is unknown whether those study participants had clinical AGS or were able to tolerate mammalian meat.[19,20] In our study, case patients were more likely than sensitized controls to have reactive sIgE to cow's milk and paper wasps. Reactivity to these antigens is unsurprising, as cow's milk ImmunoCAP contains alpha-gal and cross-reactivity has been documented between wasp and tick proteins.[21] The greater reactivity against these antigens in patients with AGS compared with sensitized controls could reflect higher levels of alpha-gal sIgE in the cases. In addition, cow's milk may not be a substantial source of alpha-gal as only 61% of the case patients who consumed dairy reported experiencing AGS symptoms after exposure. Clinicians diagnosing people with AGS should rely on a careful clinical history and results of alpha-gal sIgE testing.

Several factors must be considered when interpreting our findings. Patients were not asked whether they knew their biological parents' medical history or whether they had blood relatives in the study. This may affect the strength of the family history findings in our study; however, potentially related participants were identified during the analysis, and adjustments were made accordingly. Case patient and control populations were enrolled from different sites and differed demographically, which may explain differences in medical history. Case patients may have less reported hypertension because of lifestyle factors, such as exclusion

of mammalian meat from diet. Case patients reported spending more time outside each week; although this put them at higher risk for tick bites and development of AGS, it could have reduced their burden of hypertension.[8] Alternatively, controls may have presented to the internal medicine clinics to receive treatment for chronic conditions such a hypertension and type II diabetes. Furthermore, interpretation of differences in hypertension, vitamin D deficiency, and blood type is limited because of established variation between racial groups.

The burden of AGS is increasing, with approximately 15,000 new suspect cases identified in the United States each year between 2017 and 2021.[6] A 2023 Centers for Disease Control and Prevention report estimated that the number of persons in the United States affected by AGS since 2010 could be as many as 450,000.[6] Low health care provider knowledge of AGS is concerning and contributes to underdiagnosis.[15] Health care providers should suspect the syndrome in persons with adult-onset atopy, particularly in those with other allergies, sensitivity to insect bites, a history of childhood allergies, or with a family history of food allergies including AGS. Persons with A or O blood types may be at higher risk of developing AGS than those with AB or B blood types. Health care providers should be aware of the geographic distribution of AGS, recognize its clinical presentation, and appreciate the environmental, behavioral, and intrinsic factors that influence AGS risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Number of Case and Control Patients, by Demographic Characteristics

Demographic Characteristics	Case patients, n (%) N = 82	Control patients, n (%) N = 191	OR	LCL	UCL
State of residence					
North Carolina	57 (70)	191 (100)	–	–	–
Other state	25 (30)	0 (0)	–	–	–
Sex					
Female	45 (55)	118 (62)	0.76	0.45	1.29
Male	36 (44)	72 (38)	Ref	–	–
Median age, IQR	58.5 (45.5–69.8)	54.0 (43.0–65.5)			
Race					
American Indian/Alaskan Native	8 (10)	6 (3)	2.80	0.97	8.04
Asian	0 (0)	3 (2)	0.30	0.00	2.75
Black	2 (2)	26 (14)	0.20	0.04	0.63
Native Hawaiian/Pacific Islander	0 (0)	2 (1)	0.42	0.00	4.12
White	72 (88)	151 (79)	Ref	–	–
Other	0 (0)	1 (1)	–	–	–
Unknown	0 (0)	1 (1)	–	–	–
Ethnicity					
Hispanic	1 (1)	6 (3)	0.52	0.06	2.44
Non-Hispanic	81 (99)	183 (96)	Ref	–	–
Unknown	0 (0)	2 (1)	–	–	–
Education					
College or technical school graduate and/or completed graduate school	57 (70)	111 (58)	3.95	1.01	31.15
HS diploma and /or some college or technical school	23 (28)	64 (34)	2.79	0.61	25.00
Less than HS diploma	1 (1)	11 (6)	Ref	–	–
Unknown	1 (1)	5 (3)	–	–	–
Income					
Prefer not to say	16 (20)	34 (18)	2.49	1.02	6.07
>$100,000	36 (44)	47 (25)	4.06	1.83	8.97
$50,000-$100,000	20 (24)	57 (30)	1.86	0.81	4.28

Demographic Characteristics	Case patients, n (%) N = 82	Control patients, n (%) N = 191	OR	LCL	UCL
<$50,000	10 (12)	53 (28)	Ref	–	–

Abbreviations: HS, high school; LCL, lower confidence limit; OR, odds ratio; Ref, reference; UCL, upper confidence limit.

Table 2

Number of Case and Control Patients, by Blood Type

Blood Type	Case patients, n (%)	Control patients, n (%)	OR	LCL	UCL
ABO blood group					
B	3 (4)	21 (11)	0.27	0.08	0.91
AB	5 (6)	21 (11)	0.45	0.17	1.26
A	29 (37)	68 (36)	0.81	0.46	1.44
O	42 (53)	80 (42)	Ref	—	—
B-antigen					
B/AB	8 (10)	42 (22)	0.4	0.18	0.88
A/O	71 (90)	148 (78)	Ref	—	—

Abbreviations: LCL, lower 95% confidence limit; OR, odds ratio; Ref, reference; UCL, upper 95% confidence limit.

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Table 3

Number of Case and Control Patients, by Medical History

Medical History	Case patients, n (%)	Control patients, n (%)	sIgE+ controls, n (%)	Cases vs controls			Cases vs sIgE+ controls		
				OR	LCL	UCL	OR[c]	LCL	UCL
Medical conditions: Have you ever been told by a doctor, nurse, or other health professional that you have the following?									
Hypertension/high blood pressure	23 (28)	84 (44)	33 (52)	0.51	0.29	0.88	0.36	0.18	0.72
Diabetes, type II	6 (7)	30 (16)	13 (21)	0.43	0.18	1.06	0.31	0.11	0.85
Heart disease/heart attack	4 (5)	19 (10)	7 (11)	0.50	0.16	1.33	0.42	0.12	1.37
Inflammatory bowel disease	4 (5)	7 (4)	2 (3)	1.41	0.41	4.46	1.41	0.32	7.57
If you have any additional medical conditions that I did not ask about, please list them (5 most frequently reported):									
Vitamin D deficiency	22 (27)	31 (16)	7 (11)	1.89	1.02	3.51	3.51	1.43	8.59
Gastroesophageal reflux disease	15 (18)	28 (15)	11 (18)	1.30	0.66	2.58	1.06	0.45	2.47
Asthma	6 (7)	24 (13)	12 (19)	0.55	0.22	1.37	0.34	0.12	0.93
Irritable bowel syndrome or ulcerative colitis	2 (2)	4 (2)	1 (2)	1.29	0.24	5.60	—	—	—
Eczema	2 (2)	4 (2)	0 (0)	1.29	0.24	5.60	—	—	—
Evidence of atopy:									
Have you ever experienced hives?	38 (46)	86 (45)	30 (48)	1.04	0.62	1.76	0.92	0.48	1.78
Have you ever experienced anaphylaxis[a]?	18 (22)	25 (13)	9 (14)	1.87	0.96	3.64	1.69	0.71	4
Are you allergic to any foods other than red meat and associated products?	20 (24)	28 (15)	8 (13)	1.88	0.99	3.56	2.22	0.92	5.35
Have you ever had to go to the urgent care, emergency department, or hospital for an allergic reaction?	17 (21)	23 (12)	7 (11)	1.93	0.97	3.82	2.09	0.82	5.28
When stung or bitten by an insect (other than a tick), do you get a particularly large mark or welt, or does it take a long time to heal?	58 (71)	83 (44)	27 (43)	3.14	1.81	5.47	3.22	1.62	6.42
Did you have any allergies that you experienced as a child that you no longer have as an adult?	18 (22)	24 (13)	3 (5)	1.99	1.02	3.89	5.71	1.69	19.1
Are you currently taking any medications[b] to manage or alleviate your non−alpha-gal allergies?	26 (32)	60 (31)	24 (38)	1.01	0.58	1.76	0.75	0.38	1.49

Abbreviations: LCL, lower confidence limit; OR, odds ratio; sIgE, specific IgE; UCL, upper confidence limit.

[a]Involvement of 2 or more organ systems; including symptoms such as severe difficulty breathing, swelling of tongue or throat, and drop in blood pressure.

[b] Over the counter or prescription.

[c] ORs suppressed if less than or equal to 5 total patients.

Table 4

Number of Case and Control Patients, by sIgE Testing Results

Allergen				Cases vs controls			Cases vs sIgE+ controls		
	Case patients, n (%)	Control patients, n (%)	sIgE+ controls, n (%)	OR	LCL	UCL	OR	LCL	UCL
Fire ant sIgE	36 (44)	55 (29)	25 (40)	1.94	1.13	3.31	1.19	0.61	2.32
Chicken sIgE	6 (7)	5 (3)	4 (6)	2.94	0.92	9.38	1.12	0.33	4.04
Codfish sIgE	4 (5)	2 (1)	2 (3)	4.35	1.01	23.12	1.41	0.32	7.57
Cow milk sIgE	67 (82)	47 (25)	33 (52)	13.69	7.17	26.08	4.06	1.93	8.54
Mosquito sIgE	15 (18)	17 (9)	12 (19)	2.29	1.09	4.8	0.95	0.41	2.18
Cat serum albumin sIgE	7 (9)	4 (2)	1 (2)	4.14	1.32	14.4	4.14	0.89	37
Turkey sIgE	4 (5)	6 (3)	5 (8)	1.64	0.47	5.39	0.61	0.16	2.16
Honey bee venom sIgE	23 (28)	32 (17)	22 (35)	1.94	1.05	3.57	0.73	0.36	1.47
Paper wasp sIgE	58 (71)	63 (33)	34 (54)	4.91	2.80	8.61	2.06	1.04	4.09
White-faced hornet sIgE	49 (60)	56 (29)	34 (54)	3.58	2.09	6.14	1.27	0.65	2.46
Yellow jacket sIgE	59 (72)	64 (34)	38 (60)	5.09	2.89	8.97	1.69	0.84	3.38

Abbreviations: LCL, lower 95% confidence limit; OR, odds ratio; sIgE, specific IgE; UCL, upper 95% confidence limit.

Table 5

Number of Case and Control Patients, by Family History

Family History				Cases vs controls			Cases vs sIgE+ controls		
Do any of your family members[a] have the following?	**Case patients, n (%)**	**Control patients, n (%)**	**sIgE+ controls, n (%)**	**OR**	**LCL**	**UCL**	**OR**	**LCL**	**UCL**
Food allergy	26 (32)	28 (15)	10 (16)	2.70	1.47	4.98	2.46	1.09	5.53
Allergy to stinging or biting insects	27 (33)	32 (17)	11 (18)	2.44	1.35	4.42	2.32	1.05	5.1
Alpha-gal allergy to red meat	13[b] (16)	4 (2)	1 (2)	8.33	2.99	27.38	8.33	1.93	73.76
Celiac disease	3 (4)	5 (3)	2 (3)	1.49	0.36	5.51	1.08	0.22	6
Inflammatory bowel disease	8 (10)	12 (6)	4 (6)	1.61	0.65	4.02	1.59	0.48	5.25

Abbreviations: LCL, lower 95% confidence limit; OR, odds ratio; sIgE, specific IgE; UCL, upper 95% confidence limit.

[a] Parents, siblings, and children related by blood.

[b] 2 of 3 family members removed due to correlated responses.