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Prevalence of alpha-gal sensitization among Kentucky timber harvesters and forestry and wildlife practitioners

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Clinical Implications

- This study shows that persons in occupations such as timber harvesting and forestry and wildlife practitioners who encounter frequent exposure to ticks may have a high prevalence of sensitization to the sugar molecule galactose-α-1,3-galactose. Clinicians who treat patients in occupations with frequent exposure to ticks, or with mild to severe gastrointestinal reactions when they eat red meat, should assess sensitization to galactose-α-1,3-galactose.

It has been discovered that people develop an allergy to an oligosaccharide galactose-α-1,3-galactose, also called alpha-gal, after experiencing tick bites.[1-3] Allergic reactions typically occur after eating meat from mammals that contain alpha-gal or are exposed to products made from mammals.[3,4] An association between tick bites and this allergy has been described in studies that detected serum IgE (sIgE) in antibodies to alpha-gal in persons reporting a history of tick bites.[3-5] US, European, and Australian studies have indicated that this disaccharide is not associated with just a single tick vector.[6,7]

Individuals with blood type B antigens have been found to be less likely to have an elevated sIgE response to the alpha-gal antigen compared with individuals with A or O blood types.[8,9] People who work in agriculture, forest-related agencies and industries, and hunting may have an increased risk encountering ticks and becoming sensitized to the alpha-gal antigen compared with the general population.[1,7] The purpose of this study was to evaluate the prevalence and risk factors for alpha-gal sensitization among timber harvesting professionals (loggers) and forestry and wildlife practitioners in Kentucky.

A cross-sectional study targeting workers in timber harvesting and aligned forestry and wildlife professionals was conducted in Kentucky. Participants were recruited during Kentucky Master Logger training workshops and regional Kentucky Department of Fish and Wildlife Resource meetings. Each participant completed a questionnaire describing allergy-associated symptoms, outdoor activities, and exposure to ticks. Following the interview, 7 mL of whole blood was collected via venous draw from the median cubital vein in the antecubital fossa by a licensed phlebotomist. Blood serum samples were shipped to the University of North Carolina, where they were analyzed through an alpha-gal–specific IgE ImmunoCAP assay. Total and specific IgE antibodies were measured using either commercially available ImmunoCAP reagents (Phadia US, Portage, Mich) or a modification of the assay with streptavidin on the solid phase. The assays were performed with the ImmunoCAP 100 instrument, and the results expressed in international units per milliliter (IU/mL), where the international unit both for specific and for total IgE is approximately 2.4 ng. For specific assays, the standard cutoff for a positive reaction is 0.10 IU/mL. Biotinylation was performed using sulfosuccinimidyl-6-(biotinamido) hexanoate (Enzotin; Enzo Biochemical Inc, New York, NY).[3,4] The streptavidin CAP technique was used to measure IgE antibodies to alpha-gal, where approximately 2 mg of biotinylated cetuximab antigen was added to each ImmunoCAP before adding 40 μL of undiluted serum. To demonstrate specificity, sera samples were tested with commercially available allergen extracts for cross-reactivity. Associations between the level of alpha-gal antibodies, self-reported symptoms, and tick exposure risks were evaluated using log-binomial regression to adjust for potential confounding variables.

A total of 46 loggers, applied forestry, and fish and wildlife practitioners enrolled in the study (Table I). The participants had a wide range of years of work experience in forest-related jobs (average 12 years). The participants reported spending an average of 4 days per week working outdoors. When asked to estimate their prior tick exposures, participants reported removing an attached tick on average about 20 ticks per year (ranging up to about 100).

The prevalence of sensitization based on the IgE analysis was estimated to be approximately 30% (sIgE $\geq$ 0.35 kUA/L) to 40% (sIgE $\geq$ 0.1 kUA/L), depending on which level of IgE antibody response was selected to indicate sensitization. These levels were selected to compare to results reported in other studies.[2,5-7] None of the participants reported being previously told they had red meat allergy (most participants had never heard of it). However, 59% of participants reported having heartburn, with most (15 of 27) reporting heartburn more than once per week. Approximately 25% (11 of 46) of the participants also reported using antacids for gastrointestinal symptoms.

The only variables significantly associated ($P < .05$) with being classified as sensitized were having a history of hives (chronic), having frequent heartburn, and frequent use of antacids (Table I). Other variables including older age, recreating outdoors more than 7 days per month, more frequently removing attached ticks, and having a strong reaction to ticks bites that last more than a week had elevated prevalence risk ratios. Participants with blood types B or AB had a lower prevalence of sensitization than participants with blood types A or O.

Table II presents the results of log-binomial modeling of variables for association with alpha-gal sensitization. Although statistical significance was not achieved with such a small number of participants, this analysis indicates that participants who reported a history of hives or a tick bite lesion lasting longer 1 week had elevated risk of being classified as sensitized and participants who were blood types B or AB had half the prevalence risk of being sensitized as participants with blood types A or O. These analyses indicate that a B blood type (B or AB) is protective for developing sensitization to the alpha-gal antigen while having a history of hives and long-lasting reaction to tick bites are associated with increased sensitization.

TABLE I. Characteristics of Kentucky loggers and forestry and wildlife practitioners in cross-sectional prevalence survey of alpha-gal sensitization

Characteristic	sIgE ≥ 0.1 kUA/L, n (%)*	Risk ratio	*P* value	sIgE ≥0.35 kUA/L, n (%)*	Risk ratio	*P* value
All study participants (n = 46)	18 (39.1)	—	—	14 (30.4)	—	—
Job						
Logger (n = 27)	10 (37.0)	1.14	.727	9 (33.3)	0.790	.615
Forest-related workers (n = 19)	8 (42.1)	Reference	—	5 (26.3)	Reference	—
Age (y)						
≤32 (n = 15)	5 (33.3)	Reference	—	5 (33.3)	Reference	—
33-45 (n = 14)	5 (35.7)	1.07	.893	3 (21.4)	0.64	.482
≥46 (n = 17)	8 (47.1)	1.41	.440	6 (35.3)	1.06	.907
Sex						
Male (n = 39)	15 (38.5)	Reference	—	11 (28.2)	Reference	—
Female (n = 7)	3 (42.9)	0.90	.822	3 (42.9)	0.66	.408
Blood type						
Non−B blood type (n = 37)	16 (43.2)	Reference	—	13 (35.1)	Reference	—
Blood type B (n = 9)	2 (22.2)	0.51	.307	1 (11.1)	0.32	.235
History of hives						
Yes (n = 8)	6 (75.0)	2.38	.006	5 (62.5)	2.64	.015
No (n = 38)	12 (31.6)	Reference	—	9 (23.7)	Reference	—
Years work						
≤5 (n = 15)	6 (40.0)	Reference	—	6 (40.0)	Reference	—
6-14 (n = 15)	7 (46.70)	1.17	.713	6 (40.0)	1.00	.999
≥15 (n = 16)	5 (31.3)	0.78	.613	2 (12.5)	0.31	.113
Days per week work outside						
Fewer than 5 d (n = 22)	10 (45.5)	Reference	—	7 (31.8)	Reference	—
More than 5 d (n = 24)	8 (33.3)	0.73	.404	7 (29.2)	0.92	.845
Days per month spend outside						
7 or fewer days per month (n = 23)	7 (30.4)	Reference	—	5 (21.7)	Reference	—
More than 7 d per month (n = 23)	11 (47.8)	1.57	.238	9 (39.1)	1.80	.214
Tick removed past 2 wk						
Yes (n = 5)	2 (40.0)	1.03	.966	2 (40.0)	1.37	.602
No (n = 41)	16 (39.0)	Reference	—	12 (29.3)	Reference	—
Embedded ticks removed/y						
≤5 (n = 20)	6 (30.0)	Reference	—	3 (15.0)	Reference	—
More than 5 (n = 26)	12 (46.2)	1.54	.284	11 (42.3)	2.82	.074
Embedded ticks removed in life						
<100 (n = 21)	7 (33.3)	Reference	—	4 (19.1)	Reference	—
100 or more (n = 25)	11 (44.0)	1.32	.468	10 (40.0)	2.10	.148
Reaction to tick bites						
Yes (n = 30)	13 (43.3)	1.39	.442	11 (36.7)	1.96	.242
No (n = 16)	5 (31.3)	Reference	—	3 (18.8)	Reference	—
Tick bite reaction duration						
No reaction to tick bites (n = 16)	5 (31.2)	Reference	—	3 (18.8)	Reference	—
Reaction <1 wk (n = 17)	5 (29.4)	0.94	.909	4 (23.5)	1.25	.738
Reaction >1 wk (n = 13)	8 (61.5)	1.97	.116	7 (53.9)	2.87	.069
Use insect repellent when work						
Yes (n = 36)	13 (36.1)	0.72	.399	9 (25.0)	0.50	.106
No (n = 10)	5 (50.0)	Reference	—	5 (50.0)	Reference	—
Ever eat red meat						
Yes (n = 45)	18 (40.0)	—	—	14 (31.1)	—	—
No (n = 1)	0 (0.00)	—	—	0 (0.0)	—	—
Frequency eat red meat						
Less than 5 times per week (n = 28)	11 (39.3)	Reference	—	7 (25.0)	Reference	—
Five or more times per week (n = 18)	7 (38.9)	0.99	.979	7 (38.9)	1.56	.316
Have heartburn						

(continued)

TABLE I. *(Continued)*

Characteristic	sIgE ≥ 0.1 kUA/L, n (%)*	Risk ratio	*P* value	sIgE ≥0.35 kUA/L, n (%)*	Risk ratio	*P* value
Yes (n = 27)	13 (48.2)	1.83	.163	10 (37.0)	1.76	.268
No (n = 19)	5 (26.3)	Reference	—	4 (21.1)	Reference	—
Heartburn frequency						
Never (n = 19)	5 (26.3)	Reference	—	4 (21.1)	Reference	—
≤One time per week (n = 12)	3 (25.0)	0.95	.935	3 (25.0)	1.19	.797
>One time per week (n = 15)	10 (66.7)	2.53	.029	7 (46.7)	2.22	.128
History of food allergy						
Yes (n = 8)	4 (50.0)	1.36	.459	2 (25.0)	0.79	.722
No (n = 38)	14 (36.8)	Reference	—	12 (31.6)	Reference	—
Frequency use of gastrointestinal antacids						
Never (n = 23)	6 (26.1)	Reference	—	5 (21.7)	Reference	—
≤One time per week (n = 12)	5 (41.7)	1.60	.339	5 (41.7)	1.92	.213
>One time per week (n = 11)	7 (63.6)	2.43	.033	4 (36.4)	1.67	.360

Log-binomial regression was used to calculate prevalence risk ratios and tests for significance using SAS 9.4.
*Kilo units of antigen per liter.

TABLE II. Major risk factors for sensitization to alpha-gal epitope among loggers and forestry and wildlife practitioners

Variable comparison	Prevalence risk ratio	95% CI	*P* value
sIgE ≥ 0.1 kUA/L			
Blood type B or AB/blood type A or O	0.59	0.22-1.55	.285
History of hives/no history of hives	1.72	0.77-3.82	.184
Tickbite reaction >1 wk/tickbite reaction <1 wk	1.53	0.77-3.04	.226
sIgE ≥ 0.35 kUA/L			
Blood type B or AB/blood type A or O	0.32	0.05-2.05	.232
History of hives/no history of hives	1.79	0.71-4.53	.217
Tickbite reaction >1 wk/tickbite reaction <1 wk	1.95	0.74-5.10	.174

Log-binomial regression was used to calculate adjusted prevalence risk ratios and tests for significance using SAS 9.4.

A major limitation of this study was the small sample size and limited power to detect associations with immunoglobulin levels. However, this study showed a high prevalence of immune reaction to alpha-gal in a population with frequent exposure to tick bites. This finding is comparable to the prevalence observed in a population of forest wardens, lumbermen, and private hunters in Germany.[7] It is unknown how many of the participants in our study may have had alpha-gal syndrome, if any. As other researchers have found, the strongest risk factors for being classified as sensitized were being prone to hives, having a reaction to a tick bite that lasted longer than 1 week, and spending time outdoors in recreational activities and having exposure to a high number of ticks.[1,2,7,9] The high prevalence of sensitivity to alpha-gal observed in this occupational sample, paired with the expressed symptomology, indicates evidence of a concern among timber harvesting, forestry, and fish and wildlife workers. Employers and physicians should be educated of this emerging disease to allow for proper prevention, diagnosis, and treatment of alpha-gal syndrome.

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REFERENCES

1. Mitchell C, Lin FC, Vaughn M, Apperson C, Meshnick S, Commins S. Association between lone star tick bites and increased alpha-gal sensitization: evidence from a prospective cohort of outdoor workers. Parasit Vectors 2020;13:470-3.
2. Wilson J, Keshavarz B, Retterer M, Workman L, Schuyler A, McGowan E, et al. A dynamic relationship between two regional causes of IgE-mediated anaphylaxis: α-gal syndrome and imported fire ant. J Allergy Clin Immunol 2021;147:643-52.e7.
3. Commins S, James H, Kelly L, Pochan S, Workman L, Perzanowski M, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. J Allergy Clin Immunol 2011;127:1286-1293.e6.
4. Mabalane T, Basera W, Botha M, Thomas H, Ramjith J, Levin M. Predictive values of alpha-gal IgE levels and alpha-gal IgE: total IgE ratio and oral food

challenge-proven meat allergy in a population with a high prevalence of reported red meat allergy. Pediatr Allergy Immunol 2018;29:841-9.
5. Fischer J, Huynh HN, Hebsaker J, Forchhammer S, Yazdi A. Prevalence and impact of type I sensitization to alpha-gal in patients consulting an allergy unit. Int Arch Allergy Immunol 2020;181:119-27.
6. Gonzalez-Quintela A, Laursen ASD, Vidal C, Skaaby T, Gude F, Linneberg A. IgE antibodies to alpha-gal in the general adult population: relationship with tick bites, atopy, and cat ownership. Clin Experiment Allergy 2014;44:1061-8.
7. Fischer J, Lupberger E, Hebsaker J, Blumenstock G, Aichinger E, Yazdi A, et al. Prevalence of type I sensitization to alpha-gal in forest service employees and hunters. Allergy 2017;72:1540-7.
8. Hamsten C, Tran T, Starkhammar M, Brauner A, Commins S, Platts-Mills T, et al. Red meat allergy in Sweden: association with tick sensitization and B-negative blood groups. J Allergy Clin Immunol 2013;132:1431-4.
9. Cabezas-Cruz A, Mateos-Hernández L, Alberdi P, Villar M, Riveau G, Hermann E, et al. Effect of blood type on anti-α-gal immunity and the incidence of infectious diseases. Exp Mol Med 2017;49:e301.