Alpha-Gal Allergy as a Cause of Intestinal Symptoms in a Gastroenterology Community Practice

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Objectives: Immunoglobulin E (IgE) to galactose-α-1,3-galactose (alpha-gal) is a recently appreciated cause of allergic reactions to mammalian meat and dairy. In eastern North America Lone Star tick bites are the dominant mode of sensitization. Classically the alpha-gal syndrome manifests with urticaria, gastrointestinal symptoms, and/or anaphylaxis, but increasingly there are reports of isolated gastrointestinal symptoms without other common allergic manifestations. The objective of this retrospective study was to determine the frequency of IgE to alpha-gal in patients presenting with unexplained gastrointestinal symptoms to a community gastroenterology practice, and to evaluate the symptom response to the removal of mammalian products from the diet in alpha-gal–positive individuals.

Methods: An electronic medical record database was used to identify patients with alpha-gal IgE laboratory testing performed within the past 4 years. These charts were reviewed for alpha-gal test results, abdominal pain, diarrhea, nausea and vomiting, hives, bronchospasm, diagnosis of irritable bowel syndrome, postprandial exacerbation of symptoms, meat exacerbation of symptoms, patient recall of tick bite, other simultaneous gastrointestinal tract diagnoses, and clinical improvement with mammalian food product avoidance.

Results: A total of 1112 adult patients underwent alpha-gal IgE testing and 359 (32.3%) were positive. Gastrointestinal symptoms were similar in those positive and negative for alpha-gal seroreactivity. Of the 359 alpha-gal–positive patients, 122 had follow-up data available and 82.0% of these improved on a diet free of mammalian products. Few patients reported hives (3.9%) or bronchospasm (2.2%). Serum alpha-gal IgE titers ranged from 0.1 to >100 kU/L, with an average of 3.43 kU/L and a median of 0.94 kU/L.

Conclusions: Clinicians practicing in the region of the Lone Star tick habitat need to be aware that patients with IgE to alpha-gal can manifest with isolated abdominal pain and diarrhea, and these patients respond well to dietary exclusion of mammalian products.

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The authors did not report any financial relationships or conflicts of interest.
Accepted October 6, 2020.
0038-4348/0–2000/114-169

DOI: 10.14423/SMJ.0000000000001223

Key Words: abdominal pain, alpha-gal, unexplained diarrhea, gastrointestinal

During the past several years, it has been recognized that allergy to the galactose-α-1,3-galactose (alpha-gal) carbohydrate moiety on mammalian cells (alpha-gal allergy) causes significant allergic symptoms.[1,2] These symptoms include the usual allergic skin manifestations of itching and hives, as well as bronchospasm and anaphylaxis, but are also noted to frequently cause gastrointestinal (GI) symptoms. These symptoms usually do not develop until 3 to 6 hours after exposure to the mammalian product.[3–5] Also, patients may present with only GI symptoms, which may make this difficult to recognize as an allergic reaction to a food product.[5–8]

In North America alpha-gal sensitization is believed to be caused by the bite of the Lone Star tick (*Amblyomma americanum*); thus, the allergy is most common in areas of the southeast and coastal Atlantic, where the tick is the most abundant.[2,5,9] IgE sensitization to alpha-gal also has been linked to other arachnids on almost every continent.[9–16] In addition to being present in tick saliva, the alpha-gal antigen is expressed in all mammalian species except Old World primates.[3,17] As a consequence IgE to alpha-gal may lead to allergic reactions to mammalian food products and some pharmaceuticals that contain alpha-gal.[18]

This retrospective analysis reviewed 4 years of alpha-gal IgE test results in a Virginia community gastroenterology private

Key Points

- A total of 32.3% of patients with unexplained abdominal pain, diarrhea, nausea, and/or vomiting presenting to our community gastroenterology practice in central Virginia tested positive for immunoglobulin E to galactose-α-1,3-galactose (alpha-gal).
- A total 82.0% of patients with follow-up data available reported improvement in gastrointestinal (GI) symptoms with avoidance of mammalian food products.
- Immunoglobulin E to alpha-gal may be an underrecognized but frequent cause of GI tract symptoms in eastern North America in the habitat distribution of the Lone Star tick.
- Clinicians need to be aware that an alpha-gal food allergy can be a common cause of unexplained GI tract symptoms, and it responds well to clinical management.

practice, located in the epicenter of the Lone Star tick distribution. Our patients presented with intestinal tract symptoms, but usually without skin or respiratory manifestations of allergic reaction.

Methods

In a retrospective review, clinical data were collected from a community private gastroenterology practice consisting of 8 gastroenterologists and 8 advanced practice providers (7 nurse practitioners and 1 physician assistant).

Patients

We reviewed the charts of all of the patients who had an alpha-gal IgE antibody test drawn in an evaluation of their symptom complex from September 1, 2015 to September 1, 2019. Information extracted from the electronic medical record included sex; age; ethnicity; alpha-gal test results with IgE level; presence and location of abdominal pain; nausea and vomiting; diarrhea; and a charted diagnosis of irritable bowel syndrome (IBS) with diarrhea or constipation, if symptoms were exacerbated postprandially, if symptoms were exacerbated by meat, if symptoms improved not consuming mammalian products, and the follow-up interval of this improvement.

Alpha-Gal IgE Testing

Blood samples were analyzed for IgE antibodies against alpha-gal using a standardized test administered by Viracor-IBT. In October 2018 Viracor-IBT changed the positive reading for alpha-gal IgE from an assay reading of ≥0.35 kU/L to a value of ≥0.10 kU/L. We used this cutoff of ≥0.10 kU/L as the value for positive IgE to alpha-gal for our study.

Outcomes Review

For the alpha-gal–positive patients who had follow-up data available for response to avoidance of mammalian products, these charts were reviewed for preexisting GI diseases, for a new GI diagnosis made in addition to alpha-gal during this evaluation, and for individuals with only alpha-gal as a definite diagnosis determined for their symptoms. Alpha-gal IgE levels were compared across these subgroups.

Data Analysis

The χ^2 test was used for the analysis of demographic and symptom data using GraphPad software (GraphPad, San Diego, CA). The Fisher exact test was used for the analysis of bronchospasm. The Mann-Whitney *U* test was used on GraphPad to compare IgE levels between the responders and the nonresponders to a mammalian-free diet and between the subgroups defined above.

Results

Patient Data and Symptoms

Within the 4-year study period, the alpha-gal IgE blood test was drawn on 1112 patients (70.5% female, average age 51.1 years, range of 16–92 years, 86% White, 9% Black, 1% Asian, and 4% undefined); it was positive in 359 (32.3%) patients (Table 1). Data are listed in Table 2, showing that this percentage of positive tests remained relatively stable during the 4-year review, but that progressively more tests were drawn during this study interval, increasing from 108 4 years ago to 542 in the last year of the study. Our patients presented with GI symptoms (Table 3), but pain, diarrhea, nausea, and vomiting did not differentiate those who were positive from those who were negative for alpha-gal IgE antibody. Of the patients testing positive for alpha-gal, only 3.9% had a history on presentation of hives, and 2.2% had a history of bronchospasm or anaphylaxis. If present, these symptoms were significant predictors of positive IgE to alpha-gal. The other statistically significant predictors of alpha-gal seropositivity were postprandial exacerbation of symptoms and recall of a tick bite.

Of the 270 patients who were positive for IgE to alpha-gal and complained of abdominal pain, the pain was described as generalized in 34.4%, epigastric in 26.7%, left lower quadrant in 11.9%, right upper quadrant in 11.5%, right lower quadrant in 10.7%, periumbilical in 10%, left upper quadrant in 4.1%, and only 1.1% suprapubic.

Alpha-Gal Serology

Of the 359 patients with a positive blood test for alpha-gal, IgE titers ranged 0.10 to >100 kU/L, with an average of 3.43 kU/L and a median of 0.94 kU/L, and an interquartile range (IQR) of 0.34 to 2.23 kU/L (Table 4). A total of 237 patients who had no follow-up data available regarding their response to mammalian-free diet had a median titer of 0.39 kU/L (0.20–1.34 IQR). Follow-up data were available for 122 patients, with 100 (82.0%) of these reporting symptomatic improvement on a diet free of mammalian products at an average interval of 2.9 months (range 1–36 months). The median IgE level was 1.05 kU/L (0.52–2.38 IQR) for the 100 responders versus a median of 1.41 kU/L (0.44–2.36 IQR) for the 22 nonresponders ($P = 0.50$). Of these

Table 1. Demographics

	Total patients	IgE positive for alpha-gal	χ^2 OR	*P*
Total no.	1112	359		
Age, y	51.5 (16–92)	53.9 (18–92)	—	—
Sex	70.5% female, 20.9% male	69.1% female, 30.1% male	0.26	0.61
Race/ethnicity				
White	86%	88%	0.73	0.39
Black	9%	8%	0.49	0.49
Asian American	1%	—	1.70	0.19
Unidentified	4%	4%	0.02	0.99

alpha-gal, galactose-α-1,3-galactose; IgE, immunoglobulin E; OR, odds ratio.

Table 2. Annual alpha-gal testing

Year (range)	Positive IgE alpha-gal	Total drawn	%
1 (9/15–8/16)	34	108	31.5
2 (9/16–8/17)	40	137	29.2
3 (9/17–8/18)	114	325	35.1
4 (9/18–8/19)	171	542	31.5
Total	359	1112	32.3

alpha-gal, galactose-α-1,3-galactose; IgE, immunoglobulin E.

122 patients, 37 had a preexisting GI disease diagnosis (19 IBS, 8 gastroesophageal reflux disease, 3 lactose intolerance, 2 cirrhosis, and 1 each of eosinophilic esophagitis, fructose intolerance, celiac disease, pancreatic exocrine insufficiency, lymphocytic colitis, collagenous colitis, ulcerative colitis, and diverticulitis), with a median alpha-gal IgE titer of 0.93 kU/L (0.50–1.72 IQR). A total of 78.4% of these patients responded to mammalian-free dietary change. Of the 19 patients with a preexisting diagnosis of IBS, 14 (73.7%) responded to a mammalian-free diet. Twenty-four patients had another GI disease diagnosed concurrently with the alpha-gal syndrome (6 lactose intolerance, 3 *Clostridium difficile*, 3 fructose intolerance, 2 eosinophilic esophagitis, 2 *Helicobacter pylori* gastritis, 2 gastritis without *H. pylori*, 2 lymphocytic colitis, 2 collagenous colitis, and 1 each of non-alcoholic fatty liver disease, pancreatic exocrine insufficiency, enteropathogenic *Escherichia coli*., and nephrolithiasis) with a median alpha-gal IgE titer of 0.83 kU/L (0.48–2.11 IQR). A total of 79.2% of these patients responded to a mammalian-free dietary change; 61 patients had only alpha-gal diagnosed as a culprit for their symptoms, with a median titer of 1.31 kU/L (0.47–2.88 IQR), and 86.9% of these patients responded to dietary change. None of these subgroups showed a significant difference in alpha-gal IgE levels between the responders and the nonresponders to a mammalian-free diet. Likewise, there was no significant difference in the alpha-gal IgE titers between the subgroups of preexisting GI disease, new diagnosis of concomitant GI disease, and alpha-gal diagnosis alone.

Discussion

We initiated this retrospective review to investigate the role that alpha-gal syndrome plays in patients presenting to our community-based gastroenterology practice with unexplained GI symptoms. Our patients presented with GI symptoms; some were self-referred, but most were sent to us from primary care providers and often had already undergone extensive testing and treatment trials. Further studies by the gastroenterology group were targeted to evaluate for specific diseases, and if no other etiology was found, then the patient moved closer to a diagnosis of a functional problem. This review showed that 32.3% of patients presenting with some combination of unexplained abdominal pain, diarrhea, and nausea or vomiting tested positive for IgE antibody to alpha-gal. These symptoms alone did not differentiate those testing positive or negative for IgE to alpha-gal (Table 3), but it is noteworthy that 82.0% of patients who tested positive and had follow-up data available improved on a diet free of mammalian products. This percentage was similar to the 80% to 90% of patients who allergists have reported with skin and airway symptoms of IgE to alpha-gal that will respond to a red meat–elimination diet.[4]

The background prevalence of alpha-gal seropositivity in our community had not been well studied, however it had been reported to range as high as 10% to 20%.[1,3,10] Of our patient group, 32% tested positive, suggesting either a higher prevalence in our area than previously recognized and/or a true association of this symptomatology with alpha-gal syndrome (Table 2). Alpha-gal syndrome typically presents with common allergic symptoms of urticaria, angioedema, or anaphylaxis.[3–5] Of the patients presenting to our gastroenterology practice, only 3.9% reported a history of hives, and 2.2% reported a history of bronchospasm or anaphylaxis. Even though these more classic allergy symptoms were highly associated with positive alpha-gal IgE, 94% of our patients with GI alpha-gal syndrome did not present with any classic allergy symptoms (Table 3). A postprandial exacerbation of symptoms was significantly associated, but the commonly noted 2- to 6-hour delay in symptoms after ingestion of mammalian products makes postprandial recognition more difficult and requires specific dietary questioning and patient recall. Also, a history of tick bite was significantly associated, but few patients had a specific history of tick bite. We suspect that many alpha-gal–positive patients experienced a bite by a larval "seed tick," which fell off after feeding and was never seen.[1,10]

Previous studies have shown that the alpha-gal syndrome presents with a spectrum of symptoms and symptom severity.[1] Likewise, patients may be alpha-gal seropositive and have no

Table 3. Symptoms in relation to alpha-gal IgE status

	IgE(+) (% of total 359)	IgE(−) (% of total 753)	χ^2 OR	*P*
Abdominal pain	270 (75.2)	576 (76.5)	0.93	0.64
Diarrhea	240 (66.8)	495 (65.7)	1.05	0.71
Nausea/vomiting	141 (39.3)	319 (42.3)	0.88	0.33
IBS-diarrhea diagnosis	64 (17.8)	135 (17.9)	0.99	0.97
IBS-constipation diagnosis	14 (3.9)	44 (5.8)	0.65	0.17
Meat exacerbation	55 (15.3)	103 (13.7)	1.14	0.41
Postprandial exacerbation	254 (70.8)	449 (59.6)	1.64	<0.001
Recall tick bite	10 (2.8)	8 (1.1)	2.67	0.03
Hives	14 (3.9)	7 (0.9)	4.32	<0.001
Bronchospasm	8 (2.2)	0 (0)	—	0.001[a]

alpha-gal, galactose-α-1,3-galactose; IgE, immunoglobulin E; IBS, irritable bowel syndrome; OR, odds ratio.

[a]*Fisher exact test.*

Table 4. Median alpha-gal IgE titers by patient group

	No. patients	Median alpha-gal IgE (IQR)	No. responders	Responder median alpha-gal IgE (IQR)	No. nonresponders	Noresponder median alpha-gal IgE (IQR)	*P*
All alpha-gal IgE positives	359	0.94 (0.34–2.23)					
Patients with no follow-up data available	237	0.39 (0.20–1.34)					
Patients with follow-up data available	122	1.05 (0.51–2.33)	100	1.05 (0.52–2.38)	22	1.41 (0.44–2.36)	0.5
Preexisting GI disease	37	0.93[a] (0.50–1.72)	29	0.93 (0.46–1.78)	8	1.02 (0.55–1.72)	0.41
Preexisting IBS subgroup	19	0.96[a] (0.57–2.09)	14	0.95 (0.46–1.78)	5	1.42 (0.50–2.82)	0.39
New diagnosis of concomitant GI disease	24	0.83[a] (0.48–2.11)	19	0.87 (0.51–2.14)	5	0.78 (0.43–3.06)	0.4
Alpha-gal alone	61	1.31[a] (0.47–2.88)	53	1.24 (0.50–2.99)	8	1.41 0.39–5.32)	0.39

alpha-gal, galactose-α-l,3-galactose; GI, gastrointestinal; IBS, irritable bowel syndrome; IQR, interquartile range.

[a]*Comparison of alpha-gal titers between subgroups does not demonstrate statistical significance.*

GI symptoms,[5] they may have another GI problem as the cause for their symptoms, or alpha-gal syndrome may contribute to or be the entire explanation for their GI problems. Our 122 patients with follow-up diet data available included 37 patients with preexisting GI disease, 24 patients with a concomitant new diagnosis of GI disease, and 61 patients with only alpha-gal syndrome diagnosed as the culprit for their symptoms (Table 4). Alpha-gal IgE titers did not differentiate these groups. Certainly, other GI diseases may have contributed to symptoms, but the favorable response to dietary changes in 78.4% with preexisting GI disease, 79.2% in those with a concomitant diagnosis of another GI disease, and 86.9% in those with alpha-gal diagnosis alone suggested that alpha-gal was playing a role in all of these groups. Because there was no control for completeness of removal of mammalian product exposure from the diet, other alpha-gal–containing products such as dairy and gelatin-containing capsules may have continued to contribute to symptoms.[1] Despite this, overall, 82.0% of these seropositive patients with follow-up data available improved with dietary change. Further prospective studies are needed that control for other GI diseases, evaluate for the completeness of dietary intervention, and confirm these observations and determine whether there is a significant difference in titers between patients who do and do not respond to mammalian-free diets. It is of interest to note that many patients with only GI symptoms have significantly elevated titers, even up to >100 kU/L, without other common allergy symptoms. Future studies will be needed to determine whether the level of alpha-gal IgE titers, or the percentage of total IgE that this represents, correlates with symptom severity or overall allergic risk.[1]

This study was limited in that it was retrospective and not designed to control for other confounding GI diseases or for strict dietary control. It was also limited in that only 122 of the 359 patients testing positive for alpha-gal had follow-up data available. Future prospective studies will be necessary to better define the relationship between alpha-gal titers, symptom severity, and response to treatment.

This study confirms our clinical experience that patients presenting with symptoms of IBS such as diarrhea and/or unexplained abdominal pain and who have a positive IgE to alpha-gal improve 82% of the time on a diet free of mammalian products. In prospective evaluation of patients, this may reduce the number coming to a functional diagnosis. As noted above, 14 of 19 patients (73.7%) with a prior diagnosis of IBS and are now found to be alpha-gal IgE positive reported symptomatic improvement after avoidance of mammalian products. As the clinical awareness of this allergic symptom complex has developed within our group, we have tested and treated progressively more patients each year; from 34 patients testing positive in year 1 to 171 patients testing positive in year 4. An important consequence of the recognition of alpha-gal syndrome is that testing is being performed much earlier in our diagnostic pathway, often at the beginning of our evaluation. We are in the epicenter of the Lone Star tick distribution and alpha-gal syndrome in eastern North America, but it is important to remember that this is a worldwide disease, with tick vectors carrying alpha-gal on nearly every continent.[2,9–16] In this age of increasing mobility and international travel, it is important for gastroenterologists, allergists, primary care physicians, emergency department physicians, general surgeons, and other physicians to be aware that

IgE to alpha-gal often presents with only GI symptoms and without other classic skin and airway symptoms of allergic reaction.

Conclusions

A total of 32.3% of our patients presenting with abdominal pain and diarrhea tested positive for IgE to alpha-gal, and a substantial proportion of these patients have improved with the avoidance of mammalian products. The alpha-gal GI syndrome can develop in people without prior intestinal symptoms or be superimposed upon other preexisting GI diseases. Our practice is in the epicenter of the Lone Star tick distribution, and it is important that practitioners in our region and elsewhere recognize IgE to alpha-gal as a possible cause for GI symptoms, even in the absence of skin and respiratory symptoms of allergy. Further research is needed to clarify the molecular pathology that is causing isolated GI symptoms in alpha-gal syndrome. Future prospective studies are needed to define whether there is a clear pattern of GI symptoms that can more specifically suggest IgE to alpha-gal as the culprit, and clarify short- and long-term treatment beyond simple avoidance of alpha-gal–containing food and pharmaceutical products.

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