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High rate of galactose-alpha-1,3-galactose sensitization in both eosinophilic esophagitis and patients undergoing upper endoscopy

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Abstract

Eosinophilic esophagitis (EoE) is an antigen/allergy-mediated chronic inflammatory condition. The rapid rise in the number of cases of EoE suggests an as-yet discovered environmental trigger. This study tested the hypothesis that IgE to galactose-alpha-1,3-galactose (alpha-gal), a newly recognized sensitization induced by a tick bite that causes mammalian meat allergy, is a risk factor for eosinophilic esophagitis. We conducted a case-control study using prospectively collected and stored samples in the University of North Carolina EoE Patient Registry and Biobank. Serum from 50 subjects with a new diagnosis of EoE and 50 non-EoE subjects (either with gastroesophageal reflux disease or dysphagia from non-EoE etiologies) was tested for alpha-gal-specific IgE using an ImmunoCAP-based method. Specific IgE >0.35 kU_A/L was considered a positive result. Subjects with EoE were a mean of 35 years old, 68% where male, and 94% were white. Non-EoE controls were a mean of 42 years, 50% were male, and 78% were white. A total of 22 (22%) subjects overall had alpha-gal-specific IgE >0.35 kU_A/L. Of these, 12 (24%) were EoE cases and 10 (20%) were non-EoE controls (p=0.63). Neither the proportion sensitized nor the absolute values differed between EoE and non-EoE subjects. We found a similar but high rate of alpha-gal sensitization in patients with EoE as found in non-EoE controls who were undergoing endoscopy. While our data do not support alpha-gal sensitization as a risk factor for EoE, the high rates of

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sensitization observed in patients undergoing upper endoscopy for symptoms of esophageal dysfunction is a new finding.

Keywords

eosinophilic esophagitis; immunoglobulin E; galactose-alpha-1,3-galactose

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory condition estimated to affect approximately 57/100,000 persons in the United States.[1] The disease is characterized histologically by eosinophilic infiltration of the esophageal epithelium and clinically by symptoms of esophageal dysfunction.[2,3] The incidence and prevalence of EoE have increased remarkably over the last two decades,[4] transforming EoE from a case-reportable disease[5] to a major cause of upper GI morbidity with a continually rising incidence.[6,7] Of note, a recent epidemiological study reported a decrease in the prevalence of EoE after age 45,[1] potentially suggesting a cohort effect more likely relate to environmental causes rather than genetic influences. Accordingly, EoE is currently thought to be an immune- or antigen-mediated disease,[8] and food triggers can frequently be identified after dietary elimination.[9,10] However, the specific trigger that initiates the allergic response in EoE can rarely be identified.[11]

Galactose-alpha-1,3-galactose oligosaccharide (alpha-gal) is a carbohydrate found in non-primate mammalian meat, sensitization to which is newly recognized and thought to be precipitated by a bite from *Amblyomma americanum*, the lone star tick.[12] First reported in 2008,[13] alpha-gal allergy is estimated to affect thousands of Americans.[14] It is predominantly found in the Southeast, where the tick is common, and studies have shown a greater than 20-fold increase in alpha-gal-specific IgE following a tick bite.[12,14] Allergy to alpha-gal is atypical in that patients often suddenly present with allergic reactions after years of eating meat without problems,[15] and some alpha-gal allergic subjects can tolerate 2–3 bites of meat without symptoms.[16] It is possible that regular, but sub-threshold, meat ingestion may not cause traditional allergic symptoms, but instead mediate a chronic allergic condition, as can be the case in EoE. To our knowledge, alpha-gal sensitization has not yet been examined as a risk factor for or cause of EoE.

The aim of this study was to test whether sensitization to alpha-gal is a risk factor for eosinophilic esophagitis. We hypothesized that EoE patients would have a higher rate of alpha-gal sensitization as compared to non-EoE controls, and that alpha-gal sensitization could comprise a new mechanistic link between an environmental and food-allergen etiologies of EoE.

METHODS

Study design and population

We conducted a case-control study analyzing prospectively collected specimens stored in the University of North Carolina EoE Patient Registry and Biobank. The Registry and Biobank

was previously created during a prospective study of the prevalence of EoE and proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) in patients undergoing esophagogastroduodenoscopy (EGD) from 2009–2012.[17,18] In this study, patients undergoing endoscopy for either dysphagia or gastroesophageal reflux (GERD) symptoms (heartburn, regurgitation/vomiting, reflux, dyspepsia) were enrolled. Informed consent, including consent for future use of stored specimens, was obtained prior to the endoscopy. The study was approved by the UNC Institutional Review Board.

Cases of EoE were defined as per consensus guidelines,[2,3] and all EoE patients were newly diagnosed. They were required to have at least one symptom of esophageal dysfunction, ≥15 eos/hpf on esophageal biopsy after an 8 week PPI trial (20–40 mg twice daily of any of the available agents, selected and prescribed at the discretion of the clinician); and other causes of esophageal eosinophilia excluded.

Control subjects were those who underwent endoscopy but did not meet clinical or histologic criteria for EoE. Patients with PPI-REE were excluded from the present study.

Demographics, symptoms, and endoscopy findings were recorded on a standardized case report form. Concurrent atopic disorders were self-reported on a questionnaire which asked patients if they had ever been told that they had eczema, asthma, seasonal allergies, or food allergies. Atopic diagnoses were also confirmed by chart review when possible. For histologic analysis, the study pathologists utilized our validated protocol to assess maximum eosinophil counts.[19]

Measurement of specific IgE

Serum samples from consecutive EoE cases and non-EoE control patients were selected from the Registry and Biobank. Blood samples were previously obtained prior to endoscopy and centrifuged after collection. Serum was placed in 200–400 uL aliquots and stored at −80°C. For this analysis, all aliquots were removed from the freezer at the same time, none had previously been thawed, and all were analyzed together in a single batch.

Galactose-alpha-1,3-galactose-specific IgE was measured using a commercially available ImmunoCAP-based test (Viracor-IBT, Lee's Summit, MO). The range of the test was 0.10 – 100 kU_A/L. Specific IgE >0.35 kU_A/L was considered a positive result, in accordance with the standard allergy practice.[15,20] For the purposes of analysis, results <0.10 kU_A/L were considered to be 0 and results over >100 kU_A/L were considered to be 100.

Data analysis

Statistical analysis was performed using Stata version 9 (College Station, TX). Summary statistics were used to describe the clinical and endoscopic characteristics of the cases and controls. For bivariate analysis, means were compared with two-sample t-tests and proportions were compared with chi square. For variables that were not normally distributed, medians were compared with non-parametric tests. In addition to the primary analysis, stratified analysis by atopic disease status was also performed.

For the sample size, we assumed that few patients in the control group would be sensitized to alpha-gal (given the non-allergic nature of their presenting symptoms and diseases). We calculated that with 50 subjects in each group, we would be able to detect as little as a 20% difference in alpha-gal sensitization rates between the two groups with a power of 0.8 at an alpha of 0.05.

RESULTS

Characteristics of the study group

A total of 100 subjects were included for analysis in this study, 50 EoE cases and 50 non-EoE controls. Overall, the majority were male (59%), white (86%), and had symptoms of dysphagia (82%) (Table 1). A high proportion had asthma (35%), allergic rhinitis/sinusitis (65%) and/or known food allergies (35%), and the median IgE level was elevated (98 kU_A/L). Few (12%) had a normal upper endoscopy.

Comparison of the characteristics of EoE and control subjects

The EoE and control subjects differed in many clinical, endoscopic, and histological findings (Table 2). Compared to non-EoE controls, EoE cases were younger (35 vs 42 years, p=0.001), were more likely to be white (94 vs 78%, p=0.02), and were more likely to have dysphagia (100 vs 64%, p<0.001). EoE subjects were less likely to have heartburn (6 vs 32%, p=0.001) or abdominal pain (6 vs 28%, p=0.003), and were less likely to have a normal EGD (0 vs 24%, p<0.001), EGD findings of erosive esophagitis (0 vs 18%, p=0.002) or a hiatal hernia (12 vs 38%, p=0.003). EoE subjects were more likely to have EoE-associated EGD findings of rings, narrowing, furrows, crêpe-paper mucosa, white plaques, and decreased vascularity. As expected by the case definition, EoE subjects also had higher maximum eosinophil counts (132 vs 9 eos/hpf, p<0.001). Both groups had high rates of atopic disorders, including asthma (32 and 38%), allergic rhinitis/sinusitis (68 and 62%), and food allergies (32 and 32%) (p=ns for all), though there was trend toward higher median IgE levels in the EoE group (129 vs 67 kU_A/L, p=0.06).

Alpha-gal-specific IgE

In the overall study population, 22 (22%) of the subjects had alpha-gal-specific IgE >0.35 kU_A/L and were considered sensitized. There was no difference in sensitization rates between the EoE cases and non-EoE controls (24 vs 20%, p=0.63) and the median specific IgE level was 0 for both groups (Table 2). Looking only at the positive subjects in each group, the median specific IgE levels were not significantly different (2.44 vs 1.36 kU_A/L, p=0.55). In addition, after stratifying the study population by atopic status, there were still no clear trends in rates of alpha-gal positivity between EoE cases and controls (Table 3).

DISCUSSION

Eosinophilic esophagitis is currently thought to be an immune/antigen-mediated disease, associated with food allergy but the exact trigger that initiates this response is unknown. Sensitization to alpha-gal has never been examined in relation to eosinophilic esophagitis, but this new food sensitization triggered by an environmental event was an appealing

hypothetical candidate as a trigger of EoE. In this study, we conducted a case-control analysis of IgE specific to alpha-gal in prospectively collected serum samples from subjects with EoE and non-EoE controls. In contrast to our hypothesis, we found that while a high proportion (24%) of our EoE subjects was sensitized to alpha-gal, a similarly high proportion (20%) of our control subjects was also sensitized.

These high rates are somewhat surprising, but in a previous study in North Carolina (where tick bites are common), 15/75 (20%) hospitalized patients were sensitized to alpha-gal, with 9 patients (12%) having alpha-gal-specific IgE >3.5 kU_A/L.[12] A similar study screening outpatients in Virginia found that 36/243 (15%) were sensitized to alpha-gal, with 15 patients (6%) with alpha-gal-specific IgE >1.0 kU_A/L.[15] Here, we found that 22/100 study subjects (22%) undergoing endoscopy at University of North Carolina were sensitized to alpha-gal, with 7 subjects (7%) with specific IgE >3.5 kU_A/L, and 14 (14%) subjects with specific IgE >1.0 kU_A/L. Because there were no differences between the EoE cases and controls, we cannot conclude that alpha-gal sensitization is a risk factor for EoE. Further, the rates of sensitization observed were on the same order of magnitude with the other studies of non-EoE patients. It is notable, however that we had a high prevalence of atopy in the control group compared to the EoE group. Ascertainment of atopic status may have been increased by relying on patient self-report, and in the case of food allergies rates may reflect both food allergies and food sensitizations. However, the non-EoE control group did have an elevated serum IgE, at a level that was similar to the EoE group, which lends support to the high rates of atopy noted. While this may have impacted the results, the stratified analysis by atopic status did not support this. In addition, all patients in the study were from the southeastern United States, and the high rates of sensitization reported in this geographical area[12–15] may mask any association of alpha-gal-specific IgE and EoE in our patient population.

There are some limitations of the current study, including lack of functional studies such as skin testing. Additionally, there was lack of detailed information regarding tick bite history or overt reactions to ingestion of mammalian meat, as these variables were not included in the original parent study. Because of this, we are not able to easily correlate clinical symptoms of food allergies with alpha-gal sensitization on serum testing. However, there are also a number of strengths of this study design, including the prospective design and sample collection, and large sample size, which lend validity to the results.

In conclusion, we found a similar but high rate of alpha-gal sensitization in patients with EoE as well as non-EoE controls. While our data do not support the hypothesis that alpha-gal sensitization is a risk factor for EoE, the high rates of sensitization observed in patients undergoing upper endoscopy for symptoms of esophageal dysfunction is a new finding. This suggests that in areas with high rates of tick bites or endemic tick-borne illnesses, it makes sense to take a thorough food allergy and tick bite history in atopic patients undergoing endoscopy. Additionally, there is still a question of whether alpha-gal sensitization may contribute to EoE in certain individuals. Red meat is not one of the foods eliminated in the standard six food elimination diet (milk, egg, wheat, soy, peanuts/treenuts, and fish/shellfish), so future studies may examine whether patients who do not improve on this

regimen could have persistent symptoms due to alpha-gal sensitization and intolerance to mammalian meat.

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Table 1

Characteristics of the overall study population

	All patients (n = 100)
Age at diagnosis (mean years ± SD)	38.1±10.6
Male, *n* (%)	59 (59)
White, *n* (%)	86 (86)
Symptoms, *n* (%)	
Dysphagia	82 (82)
Heartburn	19 (19)
Abdominal pain	17 (17)
Nausea/vomiting	3 (3)
Atopic disorders, *n* (%)	
Asthma	35 (35)
Atopic dermatitis	9 (9)
Allergic rhinitis/sinusitis	65 (65)
Food allergies	32 (32)
EGD findings, *n* (%)	
Normal	12 (12)
Rings	54 (54)
Stricture	27 (27)
Narrowing	25 (25)
Furrows	53 (53)
Crêpe-paper mucosa	5 (5)
White plaques/exudates	26 (26)
Decreased vascularity	23 (23)
Erosive esophagitis	9 (9)
Schatzki's ring	9 (9)
Hiatal hernia	25 (25)
Dilation performed	24 (24)
Maximum eosinophil count (mean eos/hpf ± SD)	72.0±111.4
Peripheral eosinophils (mean cells × 10^9/L ± SD)	0.27±0.21
Total IgE levels (median kU_A/L; IQR)	98 (37–242)

Table 2

Comparison between EoE cases and controls

	EoE cases (n = 50)	Controls (n = 50)	p
Age at diagnosis (mean years ± SD)	34.7±8.9	41.5±11.1	0.001
Male, *n* (%)	34 (68)	25 (50)	0.07
White, *n* (%)	47 (94)	39 (78)	0.02
Symptoms, n (%)			
Dysphagia	50 (100)	32 (64)	<0.001
Heartburn	3 (6)	16 (32)	0.001
Abdominal pain	3 (6)	14 (28)	0.003
Nausea/vomiting	2 (4)	1 (2)	0.56
Atopic disorders			
Asthma	16 (32)	19 (38)	0.53
Atopic dermatitis	4 (8)	5 (10)	0.73
Allergic rhinitis/sinusitis	34 (68)	31 (62)	0.53
Food allergies	16 (32)	16 (32)	1
EGD findings, *n* (%)			
Normal	0 (0)	12 (24)	<0.001
Rings	44 (88)	10 (20)	<0.001
Stricture	15 (30)	12 (24)	0.50
Narrowing	24 (48)	1 (2)	<0.001
Furrows	47 (94)	6 (12)	<0.001
Crêpe-paper mucosa	5 (10)	0 (0)	0.02
White plaques/exudates	23 (46)	3 (6)	<0.001
Decreased vascularity	21 (42)	2 (4)	<0.001
Erosive esophagitis	0 (0)	9 (18)	0.002
Schatzki's ring	3 (6)	6 (12)	0.30
Hiatal hernia	6 (12)	19 (38)	0.003
Dilation performed	10 (20)	14 (28)	0.54
Maximum eosinophil count (mean eos/hpf ± SD)	132.3±128.9	9.2±19.8	<0.001
Peripheral eosinophils (mean cells × 10^9/L ± SD)	0.37±0.24	0.19±0.14	<0.001
Total IgE levels (median kU_A/L; IQR)	129 (60–296)	67 (14–224)	0.06
Alpha-gal testing			
Positive (0.35 cut-off), *n* (%)	12 (24)	10 (20)	0.63
Median (IQR)	0 (0–0.12)	0 (0–0.31)	0.90
Median (IQR) of positive patients	2.44 (0.74–6.78)	1.36 (0.56–2.57)	0.55

Table 3

Stratified analysis of EoE cases and controls by atopic status

	Alpha gal positive (n, %)		
	EoE cases	**Controls**	**p**
Any atopy (n = 72)	11 (29)	5 (15)	0.15
No atopy (n = 28)	1 (8)	5 (31)	0.14
Asthma (n = 35)	6 (38)	2 (11)	0.06
No asthma (n = 65)	6 (18)	8 (26)	0.42
Eczema (n = 9)	3 (75)	0 (0)	0.02
No eczema (n = 91)	9 (20)	10 (22)	0.76
Rhinitis (n = 65)	9 (26)	5 (16)	0.31
No rhinitis (n = 35)	3 (19)	5 (26)	0.60
Food allergy (n=32)	6 (38)	3 (19)	0.24
No food allergy (n = 68)	6 (18)	7 (21)	0.76