

Esophageal Eosinophilia Is Common Among Relatives of Eosinophilic Esophagitis Patients

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BACKGROUND & AIMS:

Familial clustering of eosinophilic esophagitis (EoE) has been described, and we report on the biopsy-assessed prevalence of esophageal eosinophilia (EE) in first-degree family members. The aim was to determine the prevalence of EE in first-degree adult relatives (FDRs) of EoE patients. **METHODS:** Index EoE patients diagnosed by EE (>15 eosinophils per high-power field) and proton pump inhibitor nonresponsiveness were identified and family trees were constructed. Adult FDRs were invited to undergo upper endoscopy with esophageal biopsies and to complete reflux, dysphagia, and allergy/atopy questionnaires. Questionnaire information was gathered only for those who responded as per institutional review board purview. Records from other children and adult FDRs with prior EoE diagnoses also were obtained when permission was obtained. Simple and multivariable logistic regression models were used to evaluate the unadjusted and odds ratios of EoE for demographic and clinical variables.

RESULTS:

A total of 239 FDRs from 37 index EoE patients were identified. Seventy-one of 239 adult (age, >18 y) FDRs completed endoscopy and questionnaires and 18 of 71 FDRs had EE. An additional 17 FDRs were confirmed to have EE after external medical record retrieval, resulting in a total of 35 of 239 (14.6%) FDRs with EE. Significantly more male FDRs had EE compared with female FDRs ($P = .027$). Proton pump inhibitors, dysphagia, gastroesophageal reflux disease, asthma, and reflux symptoms predicted EE in FDRs. FDRs who had EE reported hay fever, allergic eye symptoms, and food allergy more frequently than those without EE ($P = .03$, $P = .001$, and $P = .02$, respectively). Specifically, younger age, higher serum eosinophils, being male, and having food allergies all were associated with higher odds of EoE ($P = .0211$, $P = .0031$, $P = .0362$, and $P = .0089$, respectively).

CONCLUSIONS:

The prevalence of esophageal eosinophilia is extremely high and male-predominant in first-degree relatives of EoE patients. Symptoms of hay fever, allergic eye symptoms, and food allergy were predictors of EE in FDRs. Dysphagia did not predict esophageal eosinophilia. Family members of EoE patients are at risk for EE, particularly those who have atopic symptoms.

Keywords: Familial Risk; Eosinophilic Esophagitis; Esophageal Eosinophilia; Dysphagia; First-Degree Family Members.

Eosinophilic esophagitis (EoE) is an emerging inflammatory and chronic immune-mediated esophageal disease characterized by atopy for the majority of cases and reduced quality of life because of the substantial impact the disease has on the ability to swallow. EoE affects all ages and costs up to \$1.4 billion in calculated medical expenses.¹⁻⁵ The exact mechanism of disease has yet to be elucidated but both environmental and genetic factors appear to play substantial roles. The risk of EoE in first-degree relatives (FDRs) has been observed to be 10- to 64-fold higher than in the general population, with males being at higher risk than females.⁶ We previously

observed an increased risk of EoE extending not only to FDRs, but also to first cousins also, suggesting a strong genetic contribution to EoE.⁷ We investigated the incidence of esophageal eosinophilia (EE) in FDRs of EoE patients. We hypothesized that first-degree

Abbreviations used in this paper: EE, esophageal eosinophilia; EGD, upper endoscopy; EoE, eosinophilic esophagitis; eos/hpf, eosinophils/high-power field; EREFS, eosinophilic esophagitis endoscopic reference scores; FDR, first-degree adult relative; OR, odds ratio; PPI, proton pump inhibitor.

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family members of EoE patients would have a very high prevalence of esophageal eosinophilia.

Methods

After Institutional Review Board approval from the University of Utah, patients with a diagnosis of EoE from 2011 to 2015 were identified via International Classification of Diseases, 9th revision, code 530.13, and International Classification of Diseases, 10th revision, code K20.0. Study participants were recruited and their EoE diagnosis was confirmed by standard criteria at the time of esophageal symptoms, EE (>15 eosinophils per high-power field [eos/hpf]) and proton pump inhibitor (PPI) nonresponsiveness (20–40 mg omeprazole or equivalent twice daily for 8 weeks).^{8–11} Letters were sent to index EoE patients asking them to invite their FDRs to participate in the study. Family trees were constructed of index EoE patients and their FDRs. For adult FDRs willing to participate in the study and who had a prior endoscopy, we requested medical record documentation of prior endoscopies, including pathology reports, to determine if EE was present. Validated questionnaires were administered to participants for dysphagia, heartburn, asthma, and food allergy at the time of endoscopy for all other FDRs willing to undergo endoscopy.^{12–15}

Adult FDRs without a prior diagnosis of EoE underwent an upper endoscopy (EGD) with biopsies of the proximal and distal esophagus. All EGDs were performed free of charge. FDRs were not required to undergo 8 weeks of high-dose PPI therapy before study EGD owing to medical and ethical considerations. Endoscopy was recorded as consistent with EoE if rings, furrows, or exudates were noted. Eosinophilic esophagitis endoscopic reference scores (EREFS) were not documented owing to initiation of the study before widespread utilization of EREFS.¹⁶ Four biopsies were performed within 5 cm of the esophagogastric junction and 4 additional biopsy specimens were taken approximately 15 cm proximal to the esophagogastric junction and submitted in formalin for routine histopathologic analysis. An additional 2 to 4 biopsy specimens were taken at each site for future RNA and DNA analysis when possible. Patients with more than 15 eos/hpf were diagnosed with EE.

Statistical Analysis

The aim of the study was to determine the prevalence of EE in adult FDRs of EoE patients. Frequencies and relative frequencies were used to describe categorical variables while means and SDs were used to describe continuous variables. Comparisons of proportions were made via the Fisher exact test or the chi-square test whereas comparisons of medians were made via the Mann–Whitney *U* test. To assess the odds of EE for demographic and clinical variables, simple and

What You Need to Know

Background

Familial clustering of eosinophilic esophagitis (EoE) has been described, but the biopsy-assessed prevalence of esophageal eosinophilia (EE) in first degree family members has never been reported.

Findings

We found that 14.6% of first-degree relatives (FDRs) of EoE index patients had EE (>15 eosinophils per high-power field). Younger age, higher serum eosinophils, being male, and having food allergies all were associated with higher odds of EE in FDRs

Implications for patient care

Adult FDRs of EoE patients are at risk for EE, particularly those who have atopic symptoms. This is important in counseling patients with EoE.

multivariable logistic regression models were used. The odds ratio (OR) and corresponding 95% CIs were used. Analyses were performed via SPSS and SAS. To maintain parsimonious models and avoid overfitting in the conducted multivariable logistic regression models, we kept only 3 predictors in each model at a time.

Results

First-Degree Relative Results From Endoscopy

A total of 37 index EoE patients agreed to participate in the study (Supplementary Table 1). Self-reported family trees resulted in a total of 239 adult and pediatric FDRs of the 37 index EoE patients. Seventy-one of these FDRs were enrolled and underwent endoscopy. There were no exclusions for endoscopy in the FDRs who consented and all underwent EGD without complications. Eighteen of 71 (25.4%) of enrolled FDRs had significant EE (>15 eos/hpf). Two additional FDRs had between 10 and 15 eos/hpf on biopsy examination. Sixteen of 71 (23.6%) FDRs undergoing endoscopy were taking proton pump inhibitors including 5 of 18 (22.2%) with EE. For the FDRs with EE, the mean proximal and distal number of eosinophils were 16.4 ± 13.0 and 28.6 ± 14.1 eos/hpf, respectively. All 18 FDRs with EE showed distal eosinophilia of 15 or more eos/HPF, while only 12 had concurrent 15 or more eos/HPF on proximal biopsy specimens. In comparison, FDRs without EE values were 0.7 ± 2.4 and 1.1 ± 2.3 eos/hpf, respectively ($P < .001$).

First-Degree Relative Data After Additional Outside Record Review

Seventeen FDRs were reported to have a prior diagnosis of EoE and therefore were not enrolled for

endoscopy. Outside record review confirmed esophageal eosinophilia using the standard criteria in all 17 FDRs. Therefore, a total of 35 of 239 (14.6%) FDRs (adults and children) of index EoE patients were diagnosed with EE (including the 18 diagnosed in performance of the study and the 17 diagnosed by outside record review).

In the total group, EE was significantly more common in male FDRs (25 of 128; 19.5%) than in female FDRs (10 of 111; 9.9%) ($P < .03$). In addition, we found that younger age, higher serum eosinophils, being male, and having food allergies all were associated significantly with a higher odds of having EoE (Table 4). In particular, a 1-year increase in age was associated with a 7.3% decrease in the likelihood of EoE (OR, 0.927; 95% CI, 0.870–0.989; $P = .0211$). A 1-unit increase in serum eosinophils was associated significantly with a 131% increase in the odds of EoE (OR, 2.308; 95% CI, 1.327–4.015; $P = .0031$). Males were 4.9 times more likely than females to have EoE (OR, 4.896; 95% CI, 1.107–21.650; $P = .0362$). In addition, those with food allergies were 5.7 times more likely to have EoE compared with those without (OR, 5.688; 95% CI, 1.546–20.927; $P = .0089$).

Endoscopic Findings in First-Degree Relatives

Endoscopy showed abnormal findings in 31 of 71 (43.7%) FDRs. As noted earlier, EREFS was not performed routinely in the study endoscopies because the study was designed before widespread EREFS adoption. Endoscopy was reported as consistent with EoE if furrows, exudates, or rings were present. Nineteen of 71 (26.8%) FDRs undergoing endoscopy had endoscopy findings consistent with EoE (1 of whom did not have >15 eos/hpf on biopsy). All FDRs with esophageal eosinophilia had findings consistent with EoE.^{17–20} The majority showed either rings or furrows. Additional

Table 1. Endoscopic Findings in All FDRs Undergoing Endoscopy

Endoscopic findings in FDRs	Prevalence
Sex	Men, 34; women, 37
Average age, y	Men, 41.9 (22–85); women, 42.1 (22–69)
Normal	40/71 (56.3%)
Consistent with eosinophilic esophagitis	19/71 (26.8%)
Schatzki ring	4/71 (5.6%)
Barrett's esophagus	1/71 (1.4%)
Reflux esophagitis	6/71 (8.5%)
Candida esophagitis	1/71 (1.4%)

FDR, first-degree relative.

Table 2. Endoscopic Findings of FDRs Diagnosed With Esophageal Eosinophilia

Endoscopic documentation	Participants, n	%
Edema	1	6.7
Rings	11	73.3
Exudates	4	26.7
Furrows	11	73.3
Stricture	1	6.7
Normal	2	13.3

NOTE. Specific endoscopic findings were documented for only 15 of 18 FDRs diagnosed with esophageal eosinophilia. Three of 18 participants diagnosed with esophageal eosinophilia did not have findings described on endoscopy reports.

FDR, first-degree relative.

abnormalities included erosive esophagitis, Schatzki ring, and Barrett's esophagus. A normal esophagus was found in 56.3% of FDRs (Tables 1 and 2).

Questionnaire Results

Dysphagia and heartburn did not predict whether esophageal eosinophilia would be present on biopsy specimens. Dysphagia complaints ranged from daily to every 3 months. Dysphagia scores were not significantly different between FDRs with EE and without EE (3.5 ± 3.0 vs 2 ± 2.2 , respectively; $P = .21$). We choose to look at the prevalence of EE in patients who had more frequent dysphagia, which may have increased the likelihood of EE. Twenty of 71 (28.2%) of all FDRs who

Table 3. Characteristics of FDRs With More Than 15 Eosinophils/HPF (EE) on Esophageal Biopsy Specimens Compared With Those Without Increased Eosinophils (no EE)

Characteristic	EE (%)	No EE	P value
Age, y	38.0 (SD, 15.4)	44.7 (SD, 15.6)	.11
Male	11/18 (61.1)	24/53 (45.3)	.28
Proximal eosinophils/HPF*	16.4 (13.0)	0.7 (2.4)	.01
Distal eosinophils/HPF*	28.6 (14.0)	1.1 (2.3)	.01
Dysphagia score	2 (2.2)	3.5 (3.0)	.21
Reported heartburn	10/18 (55.65)	33/53 (62.3)	1.0
Asthma	5/18 (27.8)	19/53 (35.8)	.56
Hay fever*	13/15 (86.7)	25/47 (53.2)	.03
Allergic rhinitis	7/15 (46.7)	11/44 (25.0)	.19
Allergic eye symptoms*	13/14 (92.8)	20/47 (42.6)	.001
Reported food allergy*	9/18 (50)	14/53 (26.4)	.02

EE, esophageal eosinophils; FDR, first-degree relative; HPF, high-power field.

Table 4. The Unadjusted and Adjusted Odds of EE in FDRs of EoE Patients for Demographic and Clinical Variables From Simple and Multivariable Logistic Regression Modeling

Variables	Unadjusted OR	P value	Adjusted OR	P value
Age	0.950 (0.905–0.997)	.0356	0.927 (0.870–0.989)^a	.0211
Serum eosinophils	1.806 (1.225–2.663)	.0028	2.308 (1.327–4.015)^a	.0031
Sex		.0372		.0362
Male	3.491 (1.077–11.316)		4.896 (1.107–21.650)^a	
Female	Ref = 1		Ref = 1	
PPI		.4812		
Yes	0.655 (0.202–2.127)			
No	Ref = 1			
Dysphagia		.5670		
Yes	1.412 (0.434–4.596)			
No	Ref = 1			
GERD		.6460		
Yes	0.773 (0.258–2.315)			
No	Ref = 1			
Asthma		.5670		
Yes	0.708 (0.218–2.306)			
No	Ref = 1			
Food allergies		.0083		.0089
Yes	4.767 (1.495–15.195)		5.688 (1.546–20.927)^b	
No	Ref = 1		Ref = 1	

EE, esophageal eosinophils; EoE, eosinophilic esophagitis; FDR, first-degree relative; GERD, gastroesophageal reflux disease; OR, odds ratio; PPI, proton pump inhibitor.

^aThe adjusted ORs for age, serum eosinophils, and sex were obtained from the same model.

^bThe adjusted ORs for food allergies were obtained from a model that adjusted for age and sex.

underwent endoscopy complained of dysphagia at a weekly frequency, but only 9 of these (45%) had EE. Two of 20 had endoscopic esophagitis, while the remaining 9 of 20 had normal endoscopies. There was no evidence of lymphocytic infiltration identified in the esophagi of the remaining FDRs.

Fifteen of 18 of the FDRs who had esophageal eosinophilia complained of some form of esophageal symptoms (trouble swallowing or heartburn). In contrast to esophageal symptoms, allergic or atopic symptoms including hay fever, allergic eye symptoms, and reported food allergy were associated with EE. Thirteen of 15 EE patients noted hay fever (vs 25 of 47 without EE), 13 of 14 with EE noted allergic eye symptoms (vs 20 of 47 without EE), and 9 of 18 EE patients noted food allergies (vs 14 of 53 without EE) ($P < .05$ for all comparisons).

However, reported allergic rhinitis and asthma were not associated with EE (Table 3).^{21–24}

Discussion

This was a systematic, prospective, histologic assessment of EE in adult (age, >18 y) FDRs of patients with EoE. We found the prevalence of EE was 7.5% in FDRs of EoE patients including just the subjects endoscoped during the study. However, after adding additional FDRs who previously had been endoscoped

outside the study, we found the overall prevalence of EE in FDRs was 14.6%, with a large attributable risk to male relatives (20%). Our final calculation of prevalence conservatively assumed all FDRs not scoped previously or in this study did not have EE. Thus, this intention-to-treat analysis resulted in conservative measurement of the prevalence of EE in FDRs. Interestingly, esophageal symptoms were not helpful in identifying whether a FDR would have eosinophilia on esophageal biopsy. We found that a diagnosis of asthma, reported heartburn, or dysphagia did not predict whether EE was found. As might be expected, male sex increased the risk of EE within FDRs. In addition, on univariate analysis of our questionnaire data, the presence of hay fever, allergic eye symptoms, and food allergy also predicted EE in FDRs.

Prior twin and familial studies have suggested that EoE is increased within families. A previous pedigree analysis at our institution suggested that the risk for EoE extends even beyond second-degree relatives. In our prior study using the Utah Population Database, we reported that FDRs showed an increased odds of EoE that was 7 times that of FDRs from non-EoE probands.⁷ The present study shows an even higher association than that found through our previous study. This may be a result of 2 factors: issues with documentation of the code for EoE, which results in under-reporting; and increased participation for diagnosis in our study. We previously

identified under-reporting in the pediatric population in our state.²⁵ We offered upper endoscopy free of charge after notifying FDRs of EoE patients in our study investigating familiarity of EoE. In addition, many of our FDRs who participated in the study had dysphagia but had not undergone a previous endoscopy. Both of these factors may have increased participation in our study. All of these issues may have contributed to our finding of a greater prevalence of EE in FDRs in our study than we detected via medical coding through database study (Utah Population Database). In the present study, we found a very high prevalence of EE in FDRs, rivaling the risk seen for celiac sprue seen in families of patients with celiac disease.^{26,27} Thus, current prevalence estimates of EoE may be grossly underestimated. Population prevalence estimates currently hold that 10 to 12 per 10,000 population may have EoE.²⁸ Recent data from Utah have suggested that population incidence in children is greater than previously reported.²⁹ Based on our data, the true prevalence of EE could be at least twice that currently reported, although a significant proportion may be minimally or completely asymptomatic.

Importantly, more than 50% of the cases we detected were found only through familial recruitment into this study. Although symptoms often were present, these relatives had not previously undergone medical evaluation. Possible reasons for this lack of medical evaluation included financial costs of endoscopy, minimal symptoms, or a lack of awareness that such esophageal symptoms required medical attention. However, we did not formally study the causes for lack of previous medical evaluation.

Our high prevalence rates may be reflective of our primarily Caucasian population in Utah or other environmental or genetic factors specific to our population studied. Some of the FDRs in our study with EE denied dysphagia on questionnaire. However, we did not ask about lifestyle modifications (ie, mastication patterns or drinking water with swallows), which may have modified the symptoms of dysphagia. It also is not clear whether such patients would have presented later with esophageal symptoms, as has been reported, or would remain relatively asymptomatic.³⁰ Interestingly, esophageal symptoms were not predictive of esophageal eosinophilia, and dysphagia was common among relatives whether or not they had any esophageal inflammation. The association with atopic symptoms we found suggests that comorbid atopic disease may be better at predicting EE in FDRs of EoE patients and that atopic mechanisms may be more involved in the pathogenesis of familial risk of esophageal eosinophilia.

Limitations

Because our study was not designed to be prospective we were not able to follow up FDRs to determine if any of those who had minimal or no symptoms became

symptomatic or if FDRs with dysphagia but no EE eventually were diagnosed with other causes for their dysphagia. In addition, we were not able to capture whether those with minimal eosinophilia that did not qualify for EE went on to develop more robust EE. We had very limited data on FDRs who did not take part in the study so were unable to determine if there were any significant differences between FDRs who took part in the study vs those who did not. Finally, our probands were diagnosed with EoE based on the standard criteria at the time, which included PPI nonresponsiveness, which subsequently has been removed from the present diagnostic criteria.⁸ This may have altered the degree of EE in FDRs if the prevalence is different in those with and without PPI nonresponsiveness, but likely does not change the significance of our overall findings.

This study has identified a gap in medical recognition and diagnosis of potentially life-altering disease. Only approximately half of the affected FDRs studied were diagnosed before this study. In this study, all endoscopies were performed without cost to relatives and thus we were able to identify EE that otherwise would have gone undetected.

Importantly, we identified other significant esophageal pathology in an additional 7 (13.2%) relatives without EE (1 with Barrett's and 6 with endoscopic esophagitis).

In summary, EE occurs frequently in FDRs of patients with EoE. In this study, esophageal symptoms were not predictive of EE in FDRs. However, a high prevalence of other esophageal conditions (ie, esophagitis) were found on endoscopy. Because of the high prevalence of eosinophilia and reflux esophagitis in adult FDRs of EoE patients, endoscopic assessment including esophageal biopsy specimens of patients who present with esophageal symptoms who have a family history of EoE should be considered. Expedited diagnosis of disease will enable patients and providers to manage inflammation without delay, potentially preventing complications of EoE including fibrostenotic disease and food impactions.

Conclusions

The prevalence of EE is high and male-predominant in FDRs of EoE patients. Allergic complaints, but not esophageal symptoms, may increase the risk of EE in relatives of EoE patients. These results suggest there is a genetic and/or shared environmental component to EoE.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2020.11.023>.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.

Supplementary Table 1. Disease Characteristics of Index Patients With EoE

EoE characteristic	Index patients with characteristic
Average age, y	Men, 42.6 (22–85); women, 40.1 (22–69)
Sex	Men, 19; women, 16
GERD	23/35 (65.7%)
Dysphagia	30/35 (85.7%)
Asthma	6/35 (17.1%)
Food allergies	11/35 (31.4%)
Seasonal allergies	19/35 (54.3%)

EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease.

*Data from 35 of 37 index patients who had information available were included.