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Long-term Outcomes in Pediatric-Onset Esophageal Eosinophilia

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Abstract

Background—Pediatric eosinophilic esophagitis (EoE) is a newly recognized antigen-induced form of chronic esophagitis.

Objective—Characterization of long-term clinical outcomes in pediatric EoE patients is needed.

Methods—From histologic review of 3,817 pediatric esophageal biopsies from 1982–1999, we conducted a nested case-control study of patients with retrospectively-identified histologic eosinophilic esophagitis (rEoE) and chronic esophagitis (CE), as well as an age-matched control cohort. Participants were asked to complete validated health-related outcome questionnaires.

Results—After an average of 15 years following initial endoscopy, both cohorts, 42/198 rEoE and 67/468 CE patients (as well as 100 age-matched controls), completed questionnaires. Compared to control patients, quality of life was significantly decreased among rEoE patients ($P<0.001$) and CE patients ($P<0.001$). Rates of dysphagia (rEoE 49%; CE 37%; control 6%) and food impaction (rEoE 40%; CE 14%; control 3%) were significantly increased in the rEoE cohort compared to controls ($P<0.001$, $P<0.001$ respectively). Increased esophageal eosinophil counts (OR 1.6; 95% CI 1.1–2.5; $P<0.05$) during childhood were predictive of dysphagia during early adulthood. Food allergy (OR 2.7; CI 1.2, 6.0; $P<0.01$), allergic rhinitis (OR 3.5; CI 1.8, 6.8; $P<0.001$), and asthma (OR 2.1; CI 1.04, 4.3; $P=0.04$) were associated with dysphagia. Food impaction was more common among patients with reported food allergy than those without (OR 3.1; CI 1.2, 7.8; $P=0.02$).

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Conclusions—Esophageal eosinophilia is associated with reduced quality of life and persistent symptoms 15 years after presentation. Elevated esophageal eosinophil counts and the occurrence of food allergy and atopy in childhood increase the rate of dysphagia in young adulthood.

Keywords

eosinophilic esophagitis; pediatric; patient-reported outcomes; natural history; eosinophil

Introduction

Eosinophilic esophagitis (EoE) is an allergen-driven inflammatory disorder, presenting with chronic reflux-like symptoms that are refractory to acid suppressive therapy.¹ The incidence of EoE has increased dramatically over the past decade, mainly due to increased disease recognition and higher utilization of pediatric endoscopy; however, a bona-fide small increase in the annual incidence is also contributing.^{1–5}

To date, there are very limited data regarding the natural history of pediatric EoE, particularly in untreated patients. Specifically, there are no available data describing quality of life in children with EoE as they progress into adulthood. The peak eosinophil count on esophageal biopsies is used for diagnosis of EoE and is assumed to be a marker of disease severity, yet it is not known if the peak eosinophil count correlates with long-term clinical outcomes. Although EoE is now appreciated to be food antigen-driven in many patients, it is not known if long-term clinical outcomes differ among EoE patients with IgE-mediated food allergy versus patients without evidence of food allergy. Pediatric retrospective case series data suggest that a majority of pediatric EoE patients have persistent gastrointestinal symptoms and a waxing and waning clinical course,^{2,6,7,8} but these studies are limited by their relatively short follow-up intervals, lack of validated patient-reported outcomes, and a lack of appropriate control-cohorts. Data identifying EoE patients most at risk for poor outcomes could help guide clinical decision-making. Elucidating the frequency with which children with EoE experience adverse outcomes longitudinally through early adulthood will provide key information about the rationale for the magnitude of aggressive intervention, including the need for recurrent histologic follow up.

In our study, we aimed to characterize the long-term clinical outcomes of pediatric EoE patients as they enter early adulthood, using a nested case-control study design. We hypothesized that patients with EoE would report decreased quality of life, persistent upper gastrointestinal symptoms, and need for continual treatment. Finally, we aimed to determine if there were histologic or phenotypic characteristics that predicted adverse clinical outcomes, hypothesizing that esophageal eosinophilia in childhood would be a risk factor for adverse clinical outcomes in adulthood.

Methods

This study was performed with the approval of the Cincinnati Children's Hospital Medical Center's Institutional Review Board, and all participants gave written informed consent.

Patient Population

We have previously identified a cohort of 3,817 pediatric esophageal biopsies obtained at our institution between 1982 and 1999.⁴ To identify a natural history cohort of patients with retrospectively-identified pediatric histologic EoE (rEoE), the end of our study period was designated as the year in which the first diagnosis of EoE at our institution was made (1999). From this patient cohort, we designed a nested case-control study: based on the accepted histologic threshold for disease diagnosis, rEoE was defined as patients with histologic

evidence of EoE [≥ 15 eosinophils/high power field (eos/hpf)] and compared to a control group with chronic esophagitis (CE, < 15 eos/hpf).¹ A second control group (control) was recruited from a random sample of college students at the University of Cincinnati who were age matched to the current mean age of the rEoE and CE cohorts.

Once the rEoE and CE histologic cohorts were identified, initial addresses were obtained from a systematic review of paper and electronic medical records at Cincinnati Children's Hospital Medical Center. Updated addresses were obtained from a computerized database that combines several publicly available resources (Accurant, Lexis-Nexis), including: voter registration databases, commercial mailing lists, and updated death records from the federal government. Each identified subject was mailed an introductory letter, a consent form, and an envelope with pre-paid postage. To optimize recruitment, patients were contacted utilizing up to three letters, one reminder post card, and up to three telephone calls. For the control cohort, participants were recruited from the student union at the University of Cincinnati.

Study Questionnaires

Patients and age-matched controls who consented to participate in the study were asked to complete four study questionnaires: the validated SF-12 metric for quality of life, the validated Mayo Dysphagia Questionnaire (MDQ), the validated the Reflux Disease Questionnaire (RDQ), and a general medical questionnaire developed by the study authors.⁹⁻¹² The MDQ obtains specific information about the frequency and severity of dysphagia, in addition to historical information regarding esophageal dilation, fundoplication, food impaction, and allergic disease.¹³ The RDQ obtains information about current reflux symptoms and use of gastroesophageal reflux disease medication.¹⁴ The general medical questionnaire was also administered to obtain detailed information regarding patient self-reported personal and family history of allergic disease, co-morbid gastrointestinal disorders, and autoimmunity diagnosed by a physician

Subgroup Analyses

The data were initially analyzed utilizing a histologic cutoff of ≥ 15 eos/hpf (rEoE), in accordance with the EoE expert consensus guidelines.^{1,2} As histologic rEoE may represent both typical EoE and GERD patients, we conducted a subgroup analysis of patients with a self-reported diagnosis of EoE (DxEoE). Additional sub-group analyses that were conducted included: outcomes using a cutoff histologic peak esophageal eosinophilic count of ≥ 5 eosinophils/hpf (rEoE5), and outcomes among those with allergic disease. When a histologic cutoff of ≥ 5 eosinophils/hpf was utilized to define the rEoE5 cohort, patients with < 5 eos/hpf were assigned to the CE < 5 cohort.

Data Analysis

The data were entered into a secure database by a single investigator. Data quality analysis was performed by two independent investigators. Data were analyzed and displayed using JMP 8.0 and SigmaPlot 10.0 statistical software packages. Descriptive statistics were reported as means and standard deviations or medians, with interquartile ranges depending on the variable distributions. Data were compared using nonparametric Kruskal-Wallis tests and Pearson's Chi-squared tests or Fisher's Exact tests for dichotomous outcome variables. Logistic regression and ROC curves were utilized to investigate relationships among variables. All of the tests were considered significant if $P < 0.05$ and 95% confidence intervals (CI) were reported.

Results

Patient Population

From an initial cohort of 3,817 pediatric esophageal biopsies, 198 possible rEoE participants were identified (Figure 1). Of the CE patients, 60/468 (13%) were deceased, compared to 12/198 (6%) of the rEoE patients (OR 2.3; CI 1.2, 4.3; $P=0.01$). Basic demographics and descriptive statistics are shown in Table IA.

SF-12, MDQ, RDQ, and General Medical Questionnaire Analysis

Both rEoE and CE patients' quality of life scores were significantly lower than control patients ($P<0.001$ for both) (Figure 2A). Utilizing the validated MDQ metric, the presence of dysphagia was significantly more common in patients with rEoE (49%) and CE (37%) than control patients (6%; $P<0.001$ for both). Control patients reported significantly lower RDQ scores than rEoE patients and CE patients ($P<0.001$ for both) (Table IIA). Data from the MDQ and RDQ indicated that 73% rEoE and 74% of CE patients had experienced recent upper gastrointestinal symptoms, compared to just 37% of controls ($P<0.001$ for both). Data from general medical questionnaires demonstrated that the presence of physician-diagnosed food allergy (36% versus 13%; $P<0.01$), a history of food impaction (40% versus 14%; $P<0.001$), and the need for current care from a gastroenterologist (41% versus 18%; $P<0.01$) were reported more frequently in rEoE patients than in the CE group (Table IIA). There were no self-reported cases of Barrett's esophagus in the rEoE group, CE group, or controls. Esophageal cancer was identified in 1 rEoE patient at autopsy. This patient was on immunosuppressive therapy following lung transplantation and prior to the development of esophageal cancer. The patient ultimately died of respiratory failure.

Analysis of Initial Histologic Inflammation

A relationship was identified between increasing mucosal eosinophil counts at initial endoscopy and an increased odds ratio of dysphagia 15 years (mean value) later in rEoE patients ($P<0.05$) (Figure 3). Specifically, for every 10 eos/hpf identified on initial endoscopic biopsy, the odds of dysphagia was increased by 1.6 fold (CI 1.1, 2.5). Increasing eosinophil counts were also associated with increased odds of food impaction by 1.2 fold (CI 0.9, 1.7).

Subgroup Analysis: Self-reported Confirmed EoE (DxEoE)

Data were re-analyzed comparing patients who reported a history of EoE (DxEoE, $n=15$; 11 reclassified from rEoE, 4 reclassified from CE) to those with rEoE ($n=31$), CE ($n=63$), and controls ($n=100$) (Table IB and Figure 2B). DxEoE patients had poorer quality of life scores than controls (median: 53 versus 57, $p = 0.004$) and had significantly worse RDQ scores than controls (median: 7 versus 0, $p < 0.0001$). DxEoE patients also reported rates of dysphagia that were greater than controls (60% versus 6%; $p < 0.001$; OR 23.5; CI 6.3, 88.2; Figure 2). In the DxEoE cohort, rates of food impaction (27% versus 3%; $p < 0.05$) and esophageal endoscopic dilation (13% versus 1%; $p < 0.05$) were significantly higher compared to controls.

Subgroup Analysis: rEoE Diagnostic Cutoff of ≥ 5 eos/hpf (rEoE₅)

Compared to the analysis using a cutoff of ≥ 15 eos/hpf (rEoE) (Table IA), the rEoE₅ analysis was remarkably similar (Table IIB). As in the rEoE group, the median SF-12 score among rEoE₅ patients was lower than among controls ($P<0.001$). Food impaction was more frequently reported in the rEoE₅ group than in the control cohort (31% versus 3%; $P<0.0001$).

Subgroup Analysis: Allergic Disease

Among the combined rEoE and CE cohort patients, dysphagia was more likely to occur in patients with reported food allergies (41% versus 20%; OR 2.7; CI 1.2, 6.0; $P<0.01$), allergic rhinitis (38% versus 15%; OR 3.5; CI 1.8, 6.8; $P<0.001$), and asthma (37% versus 22%; OR 2.1; CI 1.04, 4.3; $P=0.04$). In addition, esophageal food impaction was more likely in patients with food allergy (27% versus 11%; OR 3.1; CI 1.2, 7.8; $P=0.02$). A similar, yet not statistically significant trend, was present among patients with asthma (20% versus 12%; OR 1.8; CI 0.75, 4.25; $P=0.2$). The presence of eczema was not associated with the outcomes of dysphagia or food impaction; however, eczema was associated with a history of esophageal dilation (15% versus 3%; OR 4.5; CI 1.3, 15.6; $P<0.05$).

Discussion

Our current study analyzes the largest pediatric EoE natural history cohort, has the longest follow-up period (over fifteen years), and is the only case control study of its kind for pediatric EoE.^{2,6,7,15,16} We have identified several key findings. First, 73% of the rEoE cohort had persistent symptoms as adults, and symptoms were reported more frequently than in both CE patients and in age-matched controls. In fact, the majority of the pediatric rEoE cohort required subspecialty care as adults, with 40% reporting esophageal food impaction and 14% reporting an esophageal stricture requiring endoscopic dilation. Second, we report that rEoE patients have a persistently worse quality of life than control patients. Third, the important clinical outcomes of food impaction and dysphagia were both related to peak esophageal eosinophil counts and increased among patients with food allergies. These results suggest that patients with elevated esophageal eosinophil counts and food allergy should be treated and monitored more aggressively for the development of EoE-associated sequelae. Last, we report that patients who had peak eosinophil counts as low as 5 eos/hpf have greater symptoms and decreased quality of life as adults compared to controls.

It is notable that only 27% of patients in the rEoE cohort ultimately received a current diagnosis of EoE. Thus, up to 70% of rEoE patients previously classified as gastroesophageal reflux disease-related esophagitis may still be unrecognized EoE patients in the general population. This group of patients may remain unrecognized due to lack of physician awareness of EoE. It is also possible that a proportion of patients with rEoE had severe gastroesophageal reflux disease. However, consistent with a recent report indicating that food allergy differentiates EoE from gastroesophageal reflux disease,¹⁷ the high rates of food allergy and dysphagia present in our population strongly suggest that the majority of rEoE patients would warrant a clinical diagnosis of EoE.

Our study benefited from an approach that is comparatively unique from other published studies. We utilized validated patient-reported outcome metrics (SF-12, MDQ, and RDQ) to assess the respective outcomes of quality of life, dysphagia, and gastroesophageal reflux disease.^{12–14} These data were combined with prior work, including a re-analysis of a natural history cohort of patient biopsies, allowing us to make novel observations regarding eosinophil count and disease outcomes.⁴ Notably, the majority of our patients did not receive adequate treatment for EoE at initial presentation, providing the opportunity to make truly conclusive observations about the natural history of esophageal eosinophilia.

Because our data set included eosinophil counts for all rEoE and CE patients, it allowed us to analyze our data utilizing difference thresholds for the diagnosis of rEoE. When diagnostic cutoff was lowered to ≥ 5 eos/hpf, subjects with rEoE₅ continued to display significantly higher rates of food impaction, dysphagia, and esophageal dilation compared with control individuals. Decreased quality of life scores among rEoE₅ patients was also evident. These observations concur with our previously published data demonstrating that

the histologic manifestations of EoE emerge at a threshold of ≥ 5 eos/hpf.⁴ Taken together, these histologic and clinical observations suggest that the diagnostic criteria for EoE may need to be re-examined, because the recommended threshold for clinical diagnosis is now 15 eos/hpf.¹

Despite the many strengths of our analysis, our study had limitations. Our study was a patient self-reported questionnaire-based analysis; therefore, reporting and recall bias for the presence of co-morbid diseases such as food allergy are possible, because individuals with a lower quality of life and more severe symptoms may be more likely to participate. Thus, the outcomes reported in our cohort may be higher than those experienced by a more homogenous population of EoE patients. However, it is also possible the CE group represents a high systemic disease severity cohort. This is supported by both the higher death rates in the CE cohort than the rEoE cohort and by recent studies indicating a selection bias towards patients with higher disease severity in the 1980s and 1990s among pediatric patients undergoing endoscopy.⁴ Franciosi and colleagues have described that pediatric endoscopy in the early years was performed for patients with high disease severity with an increased likelihood of mortality such as portal hypertension–associated variceal bleeding that has been significantly reduced with the advent of pediatric liver transplantation.⁵ Given that disease severity was high among our CE group, this would bias our findings towards the null hypothesis and make our study's findings of significant differences even more notable. The inclusion of both CE and control groups further strengthens our results and minimizes the impact of bias, because any bias should also be present in these two control cohorts.

An additional consideration for potential bias would be regarding socioeconomic status. Data was not available regarding the socioeconomic status of the patient groups. However, the potential bias that is being discussed would not apply to the comparisons between the rEoE and CE cohorts that also demonstrate significant differences. The potential socioeconomic bias would be that the rEoE cohort would have a low socioeconomic status, and the University of Cincinnati control group would have a higher socioeconomic status. Given that prior studies have suggested that typical EoE cohorts may have a higher socioeconomic status, the direction of the potential bias between the rEoE and control cohort would be towards the null.¹⁸ Therefore, the differences described may be an underestimation of the true differences. For all the potential biases mentioned, the inclusion of both CE and control groups further strengthens our results and minimizes the impact of bias, because any bias should also be present in these two control cohorts.

Another limitation of our study is that our rEoE cohort is based solely on histopathology; it is not restricted to patients pretreated with proton pump inhibitor medication or with negative pH probe testing. Therefore, the rEoE cohort likely represents both typical EoE patients and GERD patients. However, it is important to emphasize that the current clinical definitions of EoE were proposed in 2007 as the first consensus guidelines and that proton pump inhibitor medication was not routinely used in pediatric gastroenterology in the 1980s and early 1990s.^{2,19–28}

In summary, our data demonstrate that pediatric rEoE patients are at risk for adverse quality of life and clinical outcomes in early adulthood. Patients with food allergy and atopy (eczema, asthma, and allergic rhinitis) and those with elevated esophageal eosinophil counts are at increased risk for developing food impactions and persistent gastrointestinal symptoms. Importantly, our data substantiates that the magnitude of esophageal eosinophilia is directly proportional to the degree of future dysphagia. As such, we have identified the natural history of pediatric EoE and relevant biomarkers with predictive value for disease progression into adulthood.

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Abbreviations

CE	Chronic Esophagitis
DxEoE	self-reported diagnosis of eosinophilic esophagitis
EoE	eosinophilic esophagitis
MDQ	Mayo Dysphagia Questionnaire
RDQ	Reflux Disease Questionnaire

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Figure 1. Identification and Recruitment of Study Participants

Following histologic review of esophageal biopsies obtained between 1982 and 1999, patients were categorized as retrospectively-identified histologic eosinophilic esophagitis (rEoE, ≥ 15 eos/hpf) or chronic esophagitis (CE, < 15 eos/hpf). A healthy control group was also identified. Patients were then invited to complete validated outcome metrics.

Figure 2. Clinical Features of Control, CE, rEoE, and DxEOE Cohorts
 Patients completed metrics for dysphagia (MDQ), food allergy, and quality of life (SF-12). The percentage of control, CE, and rEoE patients reporting dysphagia and food allergy, as well as median quality of life were calculated (Panel A). Data were re-analyzed with the subgroup of DxEOE removed from the rEoE and CE cohorts and classified independently (Panel B).

Figure 3. Reported Rates of Dysphagia and Peak Esophageal Eosinophil Count
 Logistic regression analysis and ROC curves were generated to identify the relationship between dysphagia and peak esophageal eosinophil count. The blue line represents the relationship between eosinophil count and the probability of developing dysphagia.

Table IA

Demographics of Control, CE and rEoE Cohorts

	Control	CE	rEoE
Number of Subjects	100	67	42
Mean Age (years)	21 (18–37)	24 (12–49)	22 (11–35)
Male (%)	50	48	69
Caucasian (%)	78	97	95
Follow-Up (years)	N/A	16 (10–27)	15 (9–23)

Table IBDemographics of Control, CE, rEoE_{Minus DxEOE}, and DxEOE Cohorts.

	Control	CE	rEoE (minus DxEOE)	DxEOE
Number of Subjects	100	63	31	15
Mean Age (years)	21 (18–37)	24 (12–49)	23 (11–33)	18 (11–35)
Male (%)	50	44	61	93
Caucasian (%)	78	97	94	100
Follow-Up (years)	N/A	16 (10–27)	15 (10–23)	14 (9–21_)

Table IIA

Clinical Outcomes in Control, CE, and rEoE Cohorts.

	Control	CE	rEoE	rEoE vs. Control (OR, 95% CI)	rEoE vs. CE (OR, 95% CI)	CE vs. Control (OR, 95% CI)
Dysphagia (%)	6	37	49	14.9 (5.3, 41.7) #	1.6 (0.7, 3.5)	9.3 (3.6, 24.4) #
Impaction (%)	3	14	40	21.6 (5.8, 80.0) #	4.1 (1.6, 10.5) #	5.2 (1.4, 20.4) #
Dilation (%)	1	8	14	16.3 (1.8, 145.3) #	1.9 (0.51, 7.1)	8.6 (0.98, 75.4)
GERD (%)	23	76	81	14.1 (5.7, 34.9) #	1.3 (0.52, 3.5)	10.4 (5.0, 21.7) #
Food Allergy (%)	13	13	36	3.9 (1.6, 9.4) #	3.8 (1.4, 10.4) #	1.0 (0.39, 2.6)
GI care (%)	1	18	41	67.3 (8.5, 530.3) #	3.1 (1.3, 7.5) #	21.6 (2.7, 170.6) #
Allergic Rhinitis (%)	30	48	46	2.0 (0.95, 4.3)	0.95 (0.43, 2.1)	2.1 (1.1, 4.1) #
PPI Use (%)	3	32	41	22.7 (6.1, 83.7) #	1.5 (0.68, 3.4)	14.9 (4.2, 52.7) #
SF-12 Score	57 (54–59)	53 (43–57)	53 (44–58)	p = 0.002	p = 0.91	p < 0.001
RDQ Score	0 (0–2)	2 (0–11)	4 (0–17)	p < 0.001	p = 0.41	p < 0.001

Table IIB

Clinical Outcomes in Control, CE_{<5}, and rEoE₅ Cohorts.

	Control	CE _{<5}	rEoE ₅	rEoE ₅ vs. Control (OR, 95% CI)	rEoE ₅ vs. CE _{<5} (OR, 95% CI)	CE _{<5} vs. Control (OR, 95% CI)
Dysphagia (%)	6	36	46	13.4 (5.0, 36.1) #	1.5 (0.7, 3.2)	8.9 (3.3, 24.1)
Impaction (%)	3	15	31	14.8 (4.1, 53.8) #	2.5 (0.96, 6.6)	5.8 (1.5, 23.2)
Dilation (%)	1	10	11	12.0 (1.4, 105.5) #	1.1 (0.30, 4.1)	10.9 (1.2, 95.9)
GERD (%)	23	74	81	14.3 (6.2, 33.0) #	1.5 (0.60, 3.8)	9.5 (4.4, 20.5)
Food Allergy	13	14	30	3.0 (1.2, 7.0) #	2.7 (0.99, 7.3)	1.1 (0.4, 3.0)
GI care (%)	1	16	38	60 (7.8, 464.5) #	3.1 (1.2, 7.7)	19.4 (2.4, 157.4) #
Allergic Rhinitis (%)	30	49	44	1.9 (0.92, 3.7)	0.83 (0.38, 1.8) #	2.2 (1.1, 4.6) #
PPI Use (%)	3	31	40	21.7 (6.1, 77.6) #	1.5 (0.66, 3.3)	14.7 (4.1, 53.1)
SF-12 Score	57 (54–59)	50 (48–53)	53 (35–57)	p < 0.001	p = 0.43	p < 0.001
RDQ Score	0 (0–2)	0 (0–8)	9.5 (3.2, 32.2)	p < 0.001	p = 0.16	p < 0.001

p < .05