RESEARCH LETTERS

Family History of Eosinophilic Esophagitis or Other Eosinophilic Gastrointestinal Disease Is Not Associated With Response to Topical Steroids in Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic antigen-mediated inflammatory disease that clinically presents as esophageal dysfunction with histological eosinophilic predominance.[1] Swallowed topical steroids (topical corticosteroid [tCS]; budesonide or fluticasone) are a first-line treatment for EoE.[2] If left untreated, EoE can lead to esophageal fibrosis, strictures, and food impactions, significantly impacting quality of life.[2] Eosinophilic gastrointestinal diseases (EGIDs) are defined by gastrointestinal symptoms in the setting of gastrointestinaltract eosinophil infiltration without secondary causes of eosinophilia and include eosinophilic gastritis, eosinophilic enteritis, and eosinophilic colitis.[3] Given genetics and environmental exposures are significant risk factors and contributors to the development of EoE and EGID,[4,5] we aimed to investigate the impact of family history of EoE and EGID on EoE presentation and treatment response.

We conducted a retrospective cohort study utilizing the University of North Carolina EoE Clinicopathologic database, details of which have previously been reported.[6] Participants included in this study were patients of all ages who received a new diagnosis of EoE per consensus guidelines.[3] Variables of the database included family history of EoE/EGID, demographics, atopic comorbidities, symptom length before diagnosis, symptoms, baseline endoscopic findings, and symptom and endoscopic findings posttreatment. The data for a subset of patients with at least one follow-up endoscopy post-steroid treatment were extracted. Treatment in our center typically involved an 8–12 week initial course of swallowed budesonide or fluticasone based on clinical judgment followed by endoscopy to evaluate treatment response.

Our primary outcome of interest was histological response, defined as peak eosinophil count on esophageal biopsy <15 eosinophils per high-power field (eos/hpf), with additional assessment of ≤ 6 eos/hpf and <1 eos/hpf.[7] Global endoscopic response as reported by the endoscopist was also assessed. EoE Endoscopic Reference Score (EREFS) was used when available, and Endoscopic Severity Score (ESS) was used otherwise.[8] ESS is a sum of scores (presence $=$ 1, absence $=$ 0) of 5 features identified on endoscopy: exudates, rings, edema, furrows, and stricture, with a maximum score of 5.[8]

Summary statistics described the demographics and baseline characteristics of participants with and without a positive family history of EoE/EGID. Chi-squared tests and 2-sample t tests were used to assess the difference between participants with and without a positive family history of EoE/EGID for categorical variables and continuous variables, respectively. Multivariable logistic regression was used to assess the independent association between participants with and without a positive family history of EoE/EGID while including covariates of interest and those with $P < .1$ in bivariate analysis. Statistical analysis was conducted via Stata version 12 (StataCorp, College Station, TX). This study was approved by University of North Carolina Institutional Review Board.

Of the 1305 patients identified, 49 (4%) had a positive family history of EoE/EGID (Table 1). Among the 49 patients, 47 (96%) participants had a family history of EoE and 2 (4%) participants had a family history of EGID. On average, 1.1 $\pm$ 0.5 family members were affected. Additionally, 42 patients had details about which family member was affected: 7 mothers, 11 fathers, 15 brothers, 3 sisters, 5 uncles or aunts, and 1 niece or nephew. Patients with a family history of EoE/EGID were more likely to be younger (21.5 years $\pm$ 17.0 vs 28.5 years $\pm$ 19.0, $P = .01$), be insured (96% vs 82%, $P = .02$), have lower body mass index (21.3 $\pm$ 5.6 vs 24.6 $\pm$ 7.1, $P = .004$), have atopic conditions (76% vs 57%, $P = .02$), and present with vomiting (41% vs 24%, $P = .009$). On endoscopy, those with a family history of EoE/EGID were more likely to have furrows (82% vs 31%, $P = .03$) and lower total EREFS (2.8 $\pm$ 1.7 vs 3.6 $\pm$ 1.9, $P = .02$). However, multivariable analysis revealed none of the above risk factors was independently associated with a positive family history of EoE/EGID.

For patients treated with tCS, the type of tCS used (fluticasone: 22% vs 32%, budesonide: 78% vs 68%, $P = .49$) and the mean steroid dose (1473 $\pm$ 519 mcg vs 1671 $\pm$ 732 mcg, $P = .26$) were similar between patients with and without a family history of EoE/EGID (Table 2). Patients with a family history of EoE/EGID were more likely to have normal endoscopic findings (44% vs 22%, $P = .02$), and less likely to have esophageal rings (17% vs 44%, $P = .02$) post-tCS treatment than those without. Overall, patients with a family history of EoE/EGID had a similar level of histologic response, endoscopic response, as well as posttreatment endoscopic severity (EREFS and ESS scores) as those without a family history of EoE/EGID (Table 2).

Table 1. Comparison of Baseline Characteristics Between Patients With EoE Without and With a Family History of EoE/EGID

Patient characteristic	No family history (n = 1256)	Family history of EoE or EGID (n = 49)	*P*
Age at diagnosis (mean y ± SD)	28.5 ± 19.0	21.5 ± 17.0	.01
Children <18 y (n, %)	488 (39)	26 (53)	.05
Male (n, %)	843 (67)	36 (73)	.35
White (n, %)	1057 (84)	46 (94)	.10
Insurance (n, %)	1033 (82)	47 (96)	.02
BMI (mean kg/m^2 ± SD)	24.6 ± 7.1	21.3 ± 5.6	.004
Any atopic condition (n, %)	721 (57)	37 (76)	.02
Allergic rhinitis	520 (41)	31 (63)	.004
Asthma	313 (25)	19 (39)	.04
Eczema	191 (15)	17 (35)	<.001
Food allergy	323 (26)	24 (49)	.001
Symptom length prior to diagnosis (mean y ± SD)	6.9 ± 8.3	5.6 ± 5.7	.29
Children <18 y only	3.0 ± 3.2	2.8 ± 3.3	.79
Adults 18+ y	9.4 ± 9.4	8.9 ± 1.5	.82
Symptoms (n, %)			
Dysphagia	952 (76)	35 (71)	.44
Food impaction	412 (33)	15 (31)	.69
Heartburn	440 (35)	13 (27)	.19
Chest pain	129 (10)	4 (8)	.61
Abdominal pain	226 (18)	6 (12)	.28
Nausea	122 (10)	2 (4)	.18
Vomiting	300 (24)	20 (41)	.009
Endoscopic findings (n, %)			
Exudates	524 (42)	23 (47)	.49
Rings	622 (50)	19 (39)	.13
Edema	544 (43)	21 (43)	.92
Furrows	388 (31)	40 (82)	.03
Stricture	355 (28)	11 (22)	.36
Narrowing	186 (15)	7 (14)	.91
Crepe-paper mucosa	47 (4)	1 (2)	.53
Dilation	356 (28)	13 (27)	.76
Total EREFS (mean ± SD)[a]	3.6 ± 1.9	2.8 ± 1.7	.02
Total ESS (mean ± SD)[a]	2.3 ± 1.5	2.3 ± 1.5	.94
Peak eosinophil count (mean eos/hpf ± SD)	65.1 ± 45.9	74.1 ± 46.6	.18

SD, standard deviation.
[a]EREFS, data available for n = 660; ESS, for which all data available.

Our study investigated whether family history of EoE/EGID was associated with differences in EoE presentation and tCS treatment response. We are among the few studies that investigated this topic in EoE and EGID.[9] We found that family history of EoE/EGID is not a risk factor for symptoms and treatment nonresponse to tCS. Alexander et al found that the recurrence risk ratio of EoE among first-degree relatives of a proband is increased 1064-fold compared to the general population.[4] Our study showed 4% of the cohort had a positive family history of EoE/EGID, which would be in range with that prior paper. This finding is also supported by Allen-Brady et al where first-degree relatives have increased EoE risk (odds ratio 7.19, 95% confidence interval 5.65–9.14).[10] Alexander et al found that recurrence risk ratio was higher in brothers (64, $P = .04$), fathers (42.9, $P = .004$), and males (50.7, $P < .001$) compared to female counterparts. This finding is consistent with our study where more male family members (fathers, brothers) were found to have EoE history compared to female family members (sisters, mothers). Limitations of our study include potential incomplete family history data based on patient recollection or documentation, nonstandardized family history definitions, and a relatively small sample size with positive family history of EoE/EGID. Strengths include the relatively large sample size of the cohort, standardized data collection ensuring accuracy of data, and clear and stringent criteria for newly diagnosed EoE cases. In summary, patients with EoE with a positive family history of EoE/EGID have similar presentations and topical steroid treatment responses compared to those without family history.

Table 2. Topical Steroids Treatment and Response Data Between Patients With EoE Without and With Family History of EoE/EGID

Treatment and outcomes	No family history (n = 505)	Family history of EoE or EGID (n = 18)	*P*
Type of steroid used (n, %)			.49
Fluticasone	160 (32)	4 (22)	
Budesonide	345 (68)	14 (78)	
Mean steroid dose (mcg ± SD)	1671 ± 732	1473 ± 519	.26
Symptom response (n, %)[a]	138 (78)	5 (56)	.13
Posttreatment peak eosinophil count (mean eos/hpf ± SD)	24.9 ± 37.3	12.1 ± 19.3	.14
P value vs baseline	<0.001	<0.001	
Histologic response (n, %)			
<15 eos/hpf	586 (57)	13 (72)	.19
≤6 eos/hpf	253 (50)	10 (56)	.65
<1 eos/hpf	150 (30)	6 (33)	.74
Posttreatment endoscopic findings (n, %)			
Normal	109 (22)	8 (44)	.02
Exudates	125 (25)	3 (17)	.39
Rings	220 (44)	3 (17)	.02
Edema	149 (30)	5 (28)	.85
Furrows	229 (47)	6 (33)	.27
Stricture	156 (31)	3 (17)	.18
Narrowing	82 (16)	2 (11)	.53
Crepe-paper mucosa	4 (1)	0 (0)	.70
Dilation	153 (30)	2 (11)	.07
Candida	33 (7)	1 (6)	.84
Endoscopic response (n, %)	358 (71)	14 (78)	.55
Posttreatment endoscopic severity (mean scores ± SD)			
EREFS[b]	2.3 ± 1.9	1.7 ± 2.1	.29
P value vs baseline	<0.001	0.06	
ESS	1.8 ± 1.5	1.1 ± 1.5	.06
P value vs baseline	<0.001	0.001	

[a]Available for n = 178 and 9.
[b]Available for n = 282 and 13.

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Abbreviations used in this paper: **EGID, eosinophilic gastrointestinal disease; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; EREFS, EoE endoscopy reference score; ESS, endoscopic severity score; tCS, topical corticosteroid**

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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data, analytic methods, and study materials may be made available for other researchers for reasonable requests and if permissions are in place.

Reporting Guidelines:
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