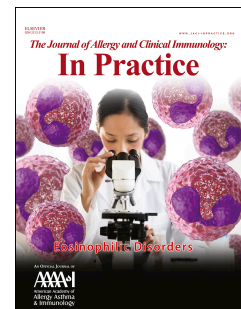


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Distinct clinical characteristics of boys and girls with eosinophilic esophagitis

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1 Figure/1 Table

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40 *Clinical Implications*

41 In adolescent males and females, frequency of specific symptoms and prevalence of new
42 diagnoses were different with 42% age ≥ 13 being girls. In a separate group of EoE patients, IgE
43 and IgG4 titers were similar among adolescent males and females.

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46 Keywords: eosinophilic esophagitis, pediatric, clinical features, sex-based differences

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TO THE EDITOR:

Consistently since early descriptions of eosinophilic esophagitis (EoE), an increased prevalence has been reported in males. A large cohort study spanning 14 years reported an overall 3:1 male to female ratio;¹ however, specific examination of separate cohorts studied in different decades suggests subtle, progressive increases in the proportion of females, from 19% in 2000 to over 30% at present.² This suggests recognition or prevalence of EoE in females may be increasing. Recent studies in adults, or mixed populations of adults and children, have shown that symptoms differ significantly in male and female EoE patients. Males more frequently reported dysphagia and food impactions and had more esophageal rings and strictures, and females were more likely to have abdominal pain, nausea, chest pain, and heartburn.^{3,4} We are not aware of any analysis of male and female differences performed in a purely pediatric EoE population. We analyzed clinical characteristics among EoE patients in a large pediatric cohort from our institution to examine evidence for male and female phenotypes.

Through a quality improvement initiative, all patients with ≥ 15 eosinophils/high power field (eos/hpf) and symptoms of esophageal dysfunction, who were diagnosed with EoE between January 2016 and May 2018, were included in a local registry. Clinical data including body mass index (BMI), esophageal eosinophil counts, other allergic diagnoses, and symptoms were obtained by review of the medical record. Because we anticipated age-related effects on symptoms, and we were interested in examining the association between any differences and puberty, we stratified patients into four groups before analysis: males $<$ and ≥ 13 years and females $<$ and ≥ 13 years. The chi square test of independence was used to compare categorical data, and the Kruskal Wallis test was used for comparison of continuous covariates. We collected

sera as part of a separate study of EoE patients having esophagogastroduodenoscopy. Serum analysis for specific IgE and IgG4 to milk proteins (Bos d 4, Bos d 5, and Bos d 8), wheat, and peanut was performed using ImmunoCAP. These studies were approved by the Institutional Review Board at Nationwide Children's Hospital.

There were 337 new EoE patients added to the local registry during 28 months. The majority were white (90%), and median peak esophageal eosinophils was 44 eos/hpf (range 15-150) (Table IA). In the whole group, females comprised 34%. However, the proportion of female patients was significantly greater at age ≥ 13 (42% female) compared with age < 13 (28% female) ($p=0.006$) (Fig 1, A).

Next, we looked at clinical features in separate patient groups. As a likely indicator of onset of puberty, age 13 was selected before analysis to delineate the groups. Percentile BMI at diagnosis for females age ≥ 13 (median 68 [range 0.50-99]) was significantly different from females age < 13 (median 51 [range 0.05-98]; $p=0.012$) (Table IA). There were also differences in the proportions of adolescent females and males presenting with specific symptoms. Abdominal pain was the most frequent symptom in females ≥ 13 (65%), and the proportion affected was greater than in the other groups ($p=0.014$) (Table IB). In contrast, food impactions were significantly more common in males ≥ 13 (39%, $p<0.001$), and vomiting was less common (31%, $p=0.048$). There were no significant differences in median baseline esophageal eosinophil counts (Table IA).

Because IgE and IgG4 antibodies are the only way to measure food specific responses in EoE, and we saw clinical differences in the adolescent groups, we were interested in studying those antibody levels in males and females > 13 years. Among 25 females and 23 males, low levels of specific IgE to milk proteins and wheat were common (Fig 1, B). In contrast, we

94 observed a subgroup of children with EoE who had high titer IgE to peanut. Similar to a pediatric
95 cohort that we previously studied,⁵ IgG4 Ab to milk proteins and wheat were measurable in most
96 EoE patients, and some of the levels were very high (Fig 1, C). There were no differences in
97 prevalence or titer of IgE or IgG4 between males and females ≥ 13 years.

98 Most pediatric EoE cohorts have been predominantly male and consisted of patients age 1
99 to 18. Analysis in this manner would reflect male characteristics and obscure changes that may
100 occur in childhood. We performed age and sex-based analysis of a large pediatric EoE cohort.
101 Although frequency of specific symptoms was different and proportion of new diagnoses shifted
102 in males and females in adolescence, eosinophil counts and food specific IgE and IgG4 titers were
103 similar. Our results are consistent with those found in adult EoE patients but extend the previous
104 findings to an all pediatric cohort. Furthermore, we show that those age dependent gender
105 differences, which are not related to measurable responses to food antigens, are evident around
106 the typical age of onset of puberty.

107 Similar to EoE, male predominance of 2:1 has been observed in young patients with
108 asthma. Increased prevalence of adolescent-onset asthma in females results in a shift so that the
109 male to female ratio is similar,^{6,7} and this was also seen to a lesser degree in our EoE cohort in
110 which the male to female ratio changed from 2.6:1 at age <13 to 1.4:1 at age ≥ 13 . Similarly in a
111 recently published large international, population-based study, an increased diagnosis of Crohn's
112 disease was found in females starting at age 10-14 years.⁸ It is important to note that unlike
113 asthma and Crohn's disease, EoE remains more common among males in adulthood (at 61-65%),
114 but the timing of the shift toward increased diagnosis in females occurs around the age of puberty
115 in each disease and this has been thought to be suggestive of a sex hormone effect.

Evidence from studies in mice and in vitro cellular immune responses, supports separate effects of androgens and estrogen on a variety of immune cell types. While androgens repress development of type 2 innate lymphoid cells (ILC2s) reducing Th2 responses, they may enhance IL-4-stimulated M2 macrophage polarization.⁶ Estrogen induces a proinflammatory response and in a Th2 cytokine environment also induces greater enhancement of M2 macrophage polarization.⁷ It is not yet known how sex hormones influence immune responses in EoE.

For a large proportion of EoE patients, milk and wheat are the primary triggers for eosinophilic inflammation and both low levels of IgE and high IgG4 are present in the blood which provides a measurable response to those antigens.⁹ Thus the finding that food specific IgE and IgG4 antibody titers are the same in adolescent patients in spite of clinical differences in age of presentation and frequency of specific symptoms can provide information about the nature and specificity of the immune response in patients with EoE.

A limitation of our study is that we did not assess pubertal status or hormone levels in our patients. Using a predetermined age cutoff dividing our cohorts into pre- and post-adolescent groups, we observed significant differences in patients diagnosed at different ages. In the future to evaluate the relationship between hormone levels and EoE, it will be helpful to consider Tanner Stage in the analysis. Additionally, we acknowledge that we used specific IgE and IgG4 to foods as a biomarker of the specific response to food antigens not for planning or monitoring clinical response to food elimination.

In conclusion, age of diagnosis and symptoms are different in male and female pediatric EoE patients. These results are consistent with some of the sex-based differences seen in asthma and Crohn's disease. Despite clinical differences, eosinophil counts and IgE and IgG4 Ab were similar in males and females with EoE. It seems paradoxical that females with the same

139 inflammation do not present until later. The striking difference in symptoms between girls and
140 boys despite similar levels of IgE and IgG4 ab raises more questions about the mechanisms of
141 inflammation and the causes of the increase in the disease.
142

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- 171

LEGENDS TO FIGURES

Fig 1. (A) Number of newly diagnosed EoE patients shown by age and sex (males represented by black shading and females by gray). (B) Titers of specific IgE and (C) specific IgG4 to milk proteins (Bos d 4, Bos d 5, and Bos d8), as well as wheat and peanut in males (black dots) and females (gray dots) ≥ 13 years. The numbers below the dotted line indicate negatives. Horizontal lines within the dot plot show the geometric mean titer to specific foods in males and females.

Table IA. Baseline demographic and clinical characteristics of the study patients.

Characteristic	All patients (n=337)	By Group				p value *
		Males <13 y (n=134)	Males ≥13 y (n=87)	Females <13 y (n=53)	Females ≥ 13 y (n=63)	
Median age, years (range)	12 (1.0-19)	8.0 (1.0-12)	16 (13-18)	6 (1.0-12)	15 (13-19)	nd
Race, n (%)						
White	302 (90 %)	120 (90 %)	83 (95 %)	42 (79 %)	58 (92 %)	p=0.025
Not white	35 [†] (10 %)	14 (10 %)	4 (5 %)	11 (21 %)	5 (8 %)	
BMI						
BMI-for-age, kg/m ²	18 (12-56)	16 (13-31)	21 (14-56)	16 (12-31)	22 (16-47)	p<0.001[‡] p=0.012[§]
BMI percentile	58 (0.01-178)	59 (0.41-99)	57 (0.01-178)	51 (0.05-98)	68 (0.50-99)	
Associated allergic problems						
Asthma	147 (44 %)	55 (41 %)	31 (36 %)	28 (53 %)	33 (52 %)	p=0.10
Rhinitis	195 (58 %)	75 (56 %)	54 (62 %)	26 (49 %)	40 (63 %)	p=0.34
Eczema	102 (30 %)	47 (35 %)	19 (22 %)	21 (40 %)	15 (24 %)	p=0.047
Food allergy	115 (34 %)	51 (38 %)	24 (28 %)	19 (36 %)	21 (33 %)	p=0.45
Median peak eos/hpf [†] (range)	44 (15-150)	45 (15-150)	40 (15-130)	38 (15-120)	45 (15-120)	p=0.87

Abbreviations: nd: not done, BMI: body mass index, eos/hpf: eosinophils/high power field

* p value by using the chi square test of independence comparing 4 age/sex groups, except as noted.

[†] Other races represented in the whole group included black or African American (n=31) and Asian (n=4).

[‡] p value by using the Kruskal Wallis Test to compare all 4 age/sex groups.

[§] p value by using the Mann Whitney Test to compare females <13 y and females ≥13 y.

Table IB. Symptom differences in pediatric EoE patients divided into 4 different groups based on age and sex.

Symptoms	Males <13y (n=134)	Males ≥13y (n=87)	Females <13y (n=53)	Females ≥13y (n=63)	p value*
Pain, n (%)	55 (41 %)	38 (44 %)	26 (49 %)	41 (65 %)†	p=0.014
Adjusted residual†	-1.9	-0.8	0.3	3.1	
Vomiting	66 (49 %)	27 (31 %)§	29 (55 %)	25 (39 %)	p=0.016
Adjusted residual	1.7	-2.7	1.8	-0.7	
Dysphagia	56 (42 %)	48 (55 %)	25 (47 %)	35 (56 %)	p=0.15
Adjusted residual	-2.1	1.4	-0.2	1.2	
Impactions	24 (18 %)	34 (39 %)¥	6 (11 %)	18 (29 %)	p<0.001
Adjusted residual	-2.2	3.7	-2.4	0.9	
Heartburn	37 (28 %)	26 (30 %)	15 (28 %)	26 (41 %)	p=0.26
Adjusted residual	-1.0	-0.2	-0.4	2.0	

* P value obtained by using the chi square test of independence.

† Adjusted standardized residuals show the contribution of each proportion to the value of the chi square (Sharpe). Numbers in bold show proportions making a significant contribution.

‡ More common in females ≥13y.

§ Less common in males ≥13y.

¥ More common in males ≥13y.