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Original Article

Clinical Manifestations of Eosinophilic Esophagitis in Children and Adolescents: A Single-Center, Matched Case-Control Study

Ji Hyeon Roh, Eell Ryoo, and Hann Tchah

Department of Pediatrics, Gachon University Gil Medical Center, Incheon, Korea

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Correspondence to
Eell Ryoo
Department of Pediatrics, Gachon University Gil Medical Center, 21 Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Korea.
E-mail: ryoo518@gilhospital.com

ORCID iDs
Ji Hyeon Roh
https://orcid.org/0000-0002-1171-651X
Eell Ryoo
https://orcid.org/0000-0002-0785-5314
Hann Tchah
https://orcid.org/0000-0002-3386-4142

Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: To examine the prevalence and clinical manifestations of eosinophilic esophagitis (EoE) in Korea children.
Methods: The study was designed as a 1:2 matching case-control study. Using information from the endoscopic database of a tertiary center, we retrospectively reviewed the medical records of patients aged 18 years or younger who underwent upper gastrointestinal endoscopy between January 2014 and December 2017. A total of 21 patients were diagnosed with EoE based on current diagnostic criteria. In addition, 42 controls with normal esophageal biopsy findings matched to each EoE case by sex, age (±1 months), and season were randomly selected during the study period.
Results: The mean age of EoE diagnosis was 12.1±4.0 years and the male-to-female ratio was 2:1. The proportion of allergic diseases in patients with EoE (28.6%) was higher than that in the controls (6.8%) (p=0.04). Most EoE patients tested for allergy were positive for at least one antigen, which was significantly different to the controls (88.2% vs. 47.4%, p=0.01). Characteristic endoscopic findings of EoE were noted in 19 patients (90.5%), but 2 patients (9.5%) showed normal esophageal mucosa. The clinical symptoms of EoE were improved by a proton-pump inhibitor in 10 patients (50.0%), and by an H_2 blocker in 9 patients (45.0%). Only one patient (5.0%) required inhaled steroids.
Conclusion: While EoE is rare in the Korean pediatric population, the results of this study will improve our understanding of the clinical manifestations of the disease.

Keywords: Eosinophilic esophagitis; Child; Adolescent; Korea

INTRODUCTION

Eosinophilic esophagitis (EoE) is an immune-mediated esophageal disease that was first reported by Landres et al. [1] in 1978. There has been growing interest in EoE since its distinctive clinical manifestations and pathological findings were described by Attwood et al. [2] in 1993.

Following case reports and clinical studies, the first consensus report on the diagnosis and treatment of EoE was published in 2007 [3]. This report later revised by Dellon et al. [4] in

2018 to state that EoE is diagnosed only when there are clinical symptoms of esophageal dysfunction and at least 15 eosinophils/HPF on esophageal biopsy, and other diseases that can cause esophageal eosinophilia have been excluded.

Although EoE may occur across all age and race groups, it manifests more commonly among white males from childhood to age 50 years [5,6]. The clinical symptoms of EoE may vary depending on patient age. Children present with non-specific symptoms, such as failure to thrive, feeding difficulty, nausea and vomiting, abdominal pain, and heartburn, while teenagers and adults mostly present with dysphagia and food impaction [5,6].

EoE was previously considered a rare disease; however, a meta-analysis by Navarro et al. [7] in 2019 showed that the incidence and prevalence of EoE among children, adolescents, and adults is sharply increasing in Western countries. While there are few reports on the prevalence of EoE in Korea, Joo et al. [8] reported that the prevalence of EoE among Korean adult patients with esophageal or upper gastrointestinal symptoms was 6.6%. According to some studies, the reasons for the continued increase in the incidence and prevalence of EoE include environmental effects, such as cesarean section delivery, premature birth, antibiotic use during infancy, and a lack of breastfeeding [9,10].

EoE is highly associated with allergic diseases such as asthma, atopic dermatitis, and food allergy [11], while some studies have suggested that EoE is caused not only by food antigens, such as milk and flour, but also by aeroallergens, such as house dust mites, molds, and pollen [12-14].

Diagnosis and treatment are crucial since EoE is a chronic inflammatory disease that can progress to esophageal fibrosis and stenosis [11]. Hence, the present study aimed to examine the clinical manifestations of EoE in a Korean pediatric population who underwent upper gastrointestinal endoscopy, in order to assist with diagnosis and treatment.

MATERIALS AND METHODS

Participants and methods

This study was designed as a 1:2 matching case-control study. We retrospectively reviewed the medical records from patients aged 18 years or younger who had upper gastrointestinal endoscopy between January 2014 and December 2017 at the Department of Pediatrics of Gachon University Gil Hospital. A total of 994 cases out of 1,241 cases had endoscopic esophageal mucosal biopsies at two or more sites. Among these, 230 cases were excluded as eosinophil infiltration was not confirmed from the esophageal mucosal biopsies, and 38 cases were excluded as duplicate patients who received more than one endoscopy during the study period.

EoE was diagnosed according to the diagnostic criteria revised by Dellon et al. [4] in 2018, as follows [4]: (i) Presence of the clinical symptoms of esophageal dysfunction; (ii) histological findings of ≥15 eosinophils/HPF on biopsy; and (iii) exclusion of other conditions that could cause esophageal eosinophilia, such as Crohn's disease, infections, and eosinophilic gastroenteritis.

Of the 726 cases in which eosinophil infiltration was confirmed from esophageal mucosal biopsies, 23 cases had ≥15 eosinophils/HPF on biopsy. One patient was excluded for

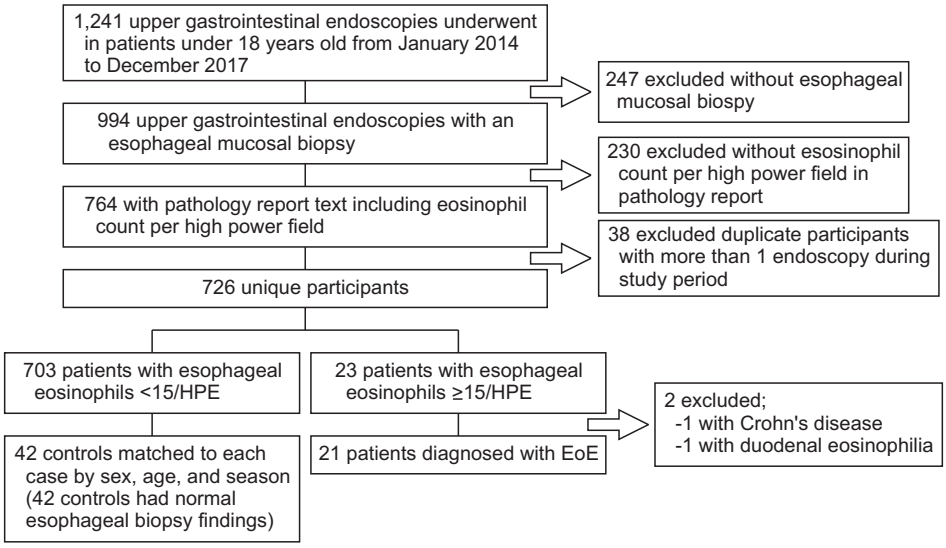

Fig. 1. Selection algorithm for patients with eosinophilic esophagitis (EoE) and controls.

Crohn's disease and one patient was excluded for eosinophil infiltration extending to other gastrointestinal sites. Therefore, 21 patients were finally diagnosed with EoE, and 42 controls with normal esophageal biopsy findings matched to each EoE case by sex, age (±1 months), and season were randomly selected during the study period (**Fig. 1**).

The patient medical records (EoE patients and controls) were retrospectively reviewed to compare age, sex, height, weight, body mass index (BMI), season, personal history of allergic disease, clinical symptoms, endoscopic findings, esophageal biopsy findings, laboratory data, and treatment. Laboratory data included allergy specific immunoglobulin E (IgE) blood test, skin allergy prick test, serum total IgE, and peripheral blood eosinophil count to confirm the association with allergic diseases. In addition, therapeutic efficacy was determined by improvements in eosinophilic infiltration based on the findings of the esophageal mucosal biopsy and clinical symptoms.

This study got an exemption and was approved by the Institutional Review Board of the Gachon University Gil Medical Center (IRB No. GBIRB2018-356).

Statistical analysis

Continuous variables are expressed as means and standard deviations or median with interquartile range, while categorical variables are expressed as numbers and percentages. Among the epidemiological and clinical characteristics of patients, continuous variables were compared using Student's *t*-test or Mann-Whitney U-test, while categorical variables were compared using chi-square test or Fisher's exact test. IBM SPSS Statistics for Windows, Version 24.0 (IBM Co., Armonk, NY, USA), was used for analysis, and *p*-values <0.05 were considered statistically significant.

RESULTS

The mean age of patients diagnosed with EoE was 12.1±4.0 years and there were more males (n=13, 68.4%) than females. Regarding seasonal distribution, there were more patients in the

winter (n=8) and spring (n=6). There was no significant difference between EoE patients and control groups with regards to height, weight, or BMI (**Table 1**).

Six of the 21 patients with EoE had a history of allergic diseases, including food allergy (n=3, 14.3%), asthma (n=1, 4.8%), allergic rhinitis (n=1, 4.8%), and allergic dermatitis (n=1, 4.8%) which was significantly different to the percentage of patients in the control group with a history of allergic diseases (p=0.01). The chief clinical symptoms of EoE patients included abdominal pain (n=11, 52.4%), nausea and vomiting (n=6, 28.6%), heartburn (n=2, 9.5%), and weight loss (n=1, 4.8%). These symptoms did not differ significantly from those in the control group (p=0.66). The duration of symptoms, which lasted until EoE was diagnosed, was 8 weeks or longer in 15 patients (78.9%), a significant difference from that of the control group (p=0.01) (**Table 2**). The mean eosinophil counts on esophageal mucosal biopsies in EoE patients was 24/HPF (interquartile range, 20–31).

The median peripheral blood eosinophil count in EoE patients was 344.0/mm^3 (interquartile range, 238.0–500.0), which was higher than that in the control group (p=0.01). The median serum IgE level of the 11 patients who received this test was 383.0 U/mL (interquartile range,

Table 1. Baseline characteristics of patients with EoE and controls

Characteristic	EoE patients (n=21)	Controls (n=42)	p-value
Sex			1.00
Male	14 (66.7)	28 (66.7)	
Female	7 (33.3)	14 (33.3)	
Age at diagnosis (yr)	12.1±4.0	12.1±4.0	1.00
Seasonal distribution			1.00
March to May	6 (28.6)	12 (28.6)	
June to August	4 (19.0)	8 (19.0)	
September to November	3 (14.3)	6 (14.3)	
December to February	8 (38.1)	16 (38.1)	
Height (m)	1.5±0.2	1.5±0.2	0.83
Weight (kg)	46.3±20.4	45.0±17.9	0.80
BMI (kg/m^2)	19.9±4.9	19.1±3.5	0.45

Values are presented as number (%) or mean±standard deviation.
EoE: eosinophilic esophagitis, BMI: body mass index.

Table 2. Comparisons of associated allergic diseases and clinical symptoms between patients with EoE and controls

Variable	EoE patients (n=21)	Controls (n=42)	p-value
Allergic disease			0.01*
None	15 (71.4)	40 (95.2)	
Asthma	1 (4.8)	0 (0.0)	
Allergic rhinitis	1 (4.8)	0 (0.0)	
Allergic dermatitis	1 (4.8)	2 (4.8)	
Food allergy	3 (14.3)	0 (0.0)	
Presenting symptoms			0.66*
No symptoms	0 (0.0)	2 (4.8)	
Weight loss	1 (4.8)	1 (2.4)	
Nausea and vomiting	6 (28.6)	11 (26.2)	
Abdominal pain	11 (52.4)	24 (57.1)	
Heartburn	2 (9.5)	2 (4.8)	
Chest pain	0 (0.0)	2 (4.8)	
Others	1 (4.8)	0 (0.0)	
Duration of symptoms (wk)			<0.001
<8	6 (28.6)	29 (69.0)	
≥8	15 (71.4)	13 (31.0)	

Values are presented as number (%).
EoE: eosinophilic esophagitis.
*p-value from Fisher's exact test.

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212.0–618.5), which was significantly higher than that of the control group (p=0.04). In total, 17 of the 21 patients with EoE were tested for allergy; 16 had a specific IgE blood test and one had a skin allergy prick test. Of the 42 controls, 14 patients were tested for allergy, and all had a specific IgE blood test. Fifteen of the 17 patients with EoE tested for allergy were positive for at least one antigen, which was significantly different from the control group (p=0.01) (**Table 3**). Among the specific IgE blood test findings, the most commonly detected antigen among EoE patients was house dust mites (n=13), followed by house dust (n=9). Five patients showed positive results for food antigens, such as shrimp, garlic, onions, walnuts, peanuts, egg white, rice, mugwort, and potatoes. One patient who underwent a skin allergy prick test showed positive results for oat flour, barley flour, flour, and strawberries (**Table 4**).

Characteristic endoscopic findings of EoE were noted in 19 patients (90.5%) and included white mucosal plaques (exudates) in 14 cases (66.7%), furrowing in 4 cases (19.0%), and mucosal fragility in 1 case (4.8%). No patient showed mucosal fragility with crepe paper esophagus (transient ring) or trachealization (fixed ring). The esophageal mucosa was completely normal in two patients (9.5%) (**Table 5**).

Table 3. Laboratory test and allergy test results in patients with EoE and controls

Laboratory test and allergy test	EoE patients	Controls	p-value
Serum eosinophil count (/mm^3)	344.0 (238.0–500.0)	127.5 (88.8–181.8)	0.01
Serum eosinophil ≥500/mm^3	6 (28.6)	0 (0.0)	<0.001*
Total	21	42	
Serum IgE count (U/mL)	383.0 (212.0–618.5)	60.5 (37.5–330.0)	0.04
Serum IgE ≥100 U/mL	10 (90.9)	6 (42.9)	0.03*
Total	11	14	
Negative allergy tests†	2 (11.8)	10 (52.6)	0.01
Positive allergy tests	15 (88.2)	9 (47.4)	
Total	17	19	

Values are presented as median (interquartile range), number (%), or number only.
EoE: eosinophilic esophagitis, Ig: immunoglobulin.
*p-value from Fisher's exact test. †Allergy tests included IgE-specific blood tests or skin allergy prick tests.

Table 4. Specific results of allergy test in patients with EoE

Patient number*	Specific-IgE blood test	Skin allergic prick test
1	House dust mites, house dust, cockroach	-
2	Neg	-
3	-	Barley flour, oat flour, wheat flour, strawberry
4	House dust mites	-
5	House dust mites, house dust, shrimp, crab	-
6	House dust mites, garlic, onion	-
7	House dust mites, fungus	-
8	House dust mites, house dust, dog	-
9	House dust mites, house dust, molds, cat, garlic, peanut, rye grass, egg whites, rice, tomato	-
10	House dust mites, house dust	-
11	House dust mites, house dust	-
12	Neg	-
13	House dust mites	-
14	Mugwort, rye grass, potato, oak trees	-
15	House dust mites, house dust	-
16	House dust mites, house dust, cat	-
17	House dust mites, house dust, walnut, cat, egg white, fungus, kiwi, peanuts, cheese	-

EoE: eosinophilic esophagitis, Ig: immunoglobulin, Neg: the result of the test was negative, -: the test was not performed.
*17 of the 21 patients with EoE were tested for allergy.

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Table 5. Endoscopic findings in patients with esophageal esophagitis

Endoscopic findings	No. patients (n=21)
Normal	2 (9.5)
Furrowing	4 (19.0)
White mucosal plaques (exudates)	14 (66.7)
Mucosal fragility	1 (4.8)
Mucosal fragility with crepe paper esophagus (transient ring)	0 (0.0)
Trachealization (fixed ring)	0 (0.0)

Values are presented as number (%).

Table 6. Medications used by 20 patients with esophageal esophagitis followed-up for at least 12 months

Medications	No. patients (n=20)
H_2 blocker	9 (45.0)
Proton pump inhibitor	10 (50.0)
Leukotriene receptor antagonist	0 (0.0)
Inhaled steroid	1 (5.0)

Values are presented as number (%).

One patient out of 21 diagnosed with EoE was not followed-up after diagnosis, and the remaining 20 patients were followed-up for at least 12 months. The median treatment duration was 3 weeks (interquartile range, 2–5). Clinical symptoms were improved by a proton-pump inhibitor in 10 patients (50.0%) and by an H_2 blocker in 9 patients (45.0%). Only one patient (5.0%) required inhaled steroids (**Table 6**).

DISCUSSION

In the present study, EoE was rare in children and adolescents; an esophageal mucosal biopsy was required for diagnosis of EoE due to the presence of non-specific symptoms. Similar to recent studies of EoE patients responsive to acid-suppressive drugs [15-18], the majority of EoE patients in the present study had improved clinical symptoms with acid-suppressive drugs. To date, the underlying pathogenic mechanism of acid-suppressive drugs in EoE patients remains poorly understood, and further studies are necessary to clarify their mechanisms.

Although the prevalence of EoE in Western countries, including the USA and Europe, differs across regions, the common trend is an increasing annual prevalence [7,19]. In a population-based study on the prevalence of EoE among children and adolescents in Utah, Robson et al. [20] found a high prevalence in the past 5 years in the USA of 118 cases per 100,000. According to the demographic statistics reported for Incheon, the estimated prevalence in the last 4 years was around 4 cases per 100,000 among 525,591 children and adolescents in Incheon as of the end of December 2017 [21]. Compared to the aforementioned study in the West, the prevalence in this study is relatively lower, which suggests a limited number of EoE cases in a pediatric population in Korea.

In most studies, the sex ratio of patients with EoE was 3:1, with the disease being more prevalent among men [6,22]. In the present study, the ratio of male to female EoE patients was 2:1, which is similar to previous studies. While EoE can occur in any age or race group, EoE is more commonly found among white males [10], which may be attributable to genetic factors associated with its onset [23].

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By comparing patients diagnosed with EoE and the control group, we determined elevated peripheral blood eosinophil count and serum IgE levels among EoE patients. Furthermore, the majority of EoE patients showed positive results in a specific-IgE blood test or skin allergy prick test. These results are similar to those obtained by Homan et al. [24] in which most EoE patients showed elevated serum IgE counts and positive allergy test results. These findings suggest an association between allergic diseases and EoE. In addition, the present study showed that more patients had positive aeroallergen tests, such as house dust, than positive food antigen tests, which shows that EoE was not only associated with food antigens but also aeroallergens.

Previous studies have reported seasonal differences in EoE distributions due to aeroallergens, including pollen, with the incidence of patients with EoE rising in the spring and summer [25]. In the present study, there were more EoE patients in the spring and winter however, since the number of patients investigated was small, additional studies including more patients are needed to fully assess the seasonal distribution of EoE.

In the present study, the most common endoscopic finding among patients with EoE was white mucosal plaques (exudates), followed by furrowing; this finding is similar to those of multiple studies on children [26,27]. Unlike pediatric EoE patients, esophageal ring and stricture are prevalent in adult patients [27,28]. The reason for this difference may be that, while exudate and furrowing appear due to acute allergic inflammation of esophageal mucosa in the early stage of EoE, untreated inflammation progresses to fibrosis-dysmotility in the later stages [11]. In the current study, two of the patients with EoE (9.5%) showed normal esophageal mucosa, similar to other studies that showed no EoE-specific endoscopic findings in some EoE patients [24,27,29].

Similar to the findings of other studies [5,6], most pediatric EoE patients in our study showed non-specific symptoms, such as abdominal pain, nausea, and vomiting. In pediatrics, it is difficult to suspect EoE with clinical symptoms only. Indeed, in the current study, the duration of symptoms, which lasted until EoE was diagnosed, was longer in EoE patients than in the controls. This implies that that the possibility of rare diseases, such as EoE, should also be considered if non-specific symptoms continue for an extended period. Even if a child does not have specific symptoms that are suspicious of EoE, an esophageal mucosal biopsy may be required to detect EoE for earlier diagnosis.

As proton pump inhibitors (PPIs) have been shown to not only inhibit the secretion of gastric acids but also reduce esophageal eosinophilia through their anti-inflammatory effects, some studies report that PPIs are effective for the treatment of EoE [15,16]. In the present study, all EoE patients showed improvement in clinical symptoms with PPIs or H_2 blockers, with the exception of one patient who required inhaled steroids. Although the role of other non-PPI acid-suppressive drugs is not clear, several reports describe their treatment effect on EoE, and a case report of a patient with typical features of EoE responsive to H_2 blockers was published recently [17]. Moreover, the first report on vonoprazan, a new potassium-competitive acid blocker, demonstrated it's ability to resolve both symptoms and eosinophilic infiltration in three patients with EoE [18]. These findings suggest that gastroesophageal reflux disease (GERD) and EoE are not exclusive disorders, and that GERD may contribute to the pathogenesis of EoE [30,31]. Further studies are necessary to clarify the role of acid-suppressive drugs in the pathogenesis of EoE.

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To the best of our knowledge, this study is the first retrospective study in Korea aimed at evaluating the prevalence and clinical manifestations of EoE in a pediatric population. There are several limitations to this study. First, it was a retrospective study conducted at a single location for a short time, as such, there was a limitation of available data. Second, the study sample was small. Third, we could not perform other tests such as 24-hour pH monitoring or esophageal manometry to identify GERD which may be accompanied by EoE. Therefore, a population-based multi-center study with long-term follow-up is warranted to confirm the prevalence and clinical manifestations of EoE.

In conclusion, although EoE is rare in a Korean pediatric population and difficult to diagnose, most patients in this study showed good clinical progress. Acid-suppressive drugs induced clinical and histological remission in a proportion of EoE patients, and these drugs can be considered as treatment for EoE. Further studies are necessary to clarify the role of acid-suppressive drugs in the pathogenesis of EoE.

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