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Original Article

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Nationwide Multicenter Study of Eosinophilic Esophagitis in Korean Children

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ABSTRACT

Purpose: In East Asian countries, there are only a few epidemiologic studies of eosinophilic esophagitis (EoE) and no studies in children. We investigated the incidence and compared the clinical characteristics of EoE and eosinophilic gastroenteritis involving the esophagus (EGEIE) in Korean children.
Methods: A total of 910 children, who had symptoms of esophageal dysfunction, from 10 hospitals in Korea were included. EoE was diagnosed according to diagnostic guidelines and EGEIE was diagnosed when there were >15 eosinophils in the esophagus per high power field (HPF) and >20 eosinophils per HPF deposited in the stomach and duodenum with abnormal endoscopic findings.
Results: Of the 910 subjects, 14 (1.5%) were diagnosed with EoE and 12 (1.3%) were diagnosed with EGEIE. Vomiting was the most common symptom in 57.1% and 66.7% of patients with EoE and EGEIE, respectively. Only diarrhea was significantly different between EoE and EGEIE (p=0.033). In total, 61.5% of patients had allergic diseases. Exudates were the most common endoscopic findings in EoE and there were no esophageal strictures in both groups. The median age of patients with normal endoscopic findings was significantly younger at 3.2 years, compared to the median age of 11.1 years in those with abnormal endoscopic findings (p=0.004).
Conclusion: The incidence of EoE in Korean children was lower than that of Western countries, while the incidence of EGEIE was similar to EoE. There were no clinical differences except for diarrhea and no differences in endoscopic findings between EoE and EGEIE.

Keywords: Eosinophilic esophagitis; Eosinophilic gastroenteritis; Incidence; Child

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

INTRODUCTION

Eosinophilic gastrointestinal diseases (EGIDs) are chronic inflammatory digestive diseases characterized by numerous eosinophils infiltrating the segments of the gastrointestinal (GI) tract [1]. EGIDs include eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC) [2]. EoE is the most common and has the most established guidelines of the EGIDs. Eosinophils can reside in all segments of the GI tract, but do not normally exist in the esophagus [3], which is why eosinophils in the esophagus are well recognized more than other eosinophil-related GI diseases. The first pediatric case of EoE was reported by Kelly et al. [4] in 1995. This study has become a fundamental study of EoE that is thought to be caused by an immune reaction induced by certain food antigens [4]. Since the first consensus on EoE was published by Furuta et al. [5] in 2007, a rapidly growing amount of literature on EoE has been published and several guidelines and consensus for the diagnosis and treatment of EoE have been developed [6-9].

EoE has been considered as a common cause of chronic and recurrent unexplained esophageal dysfunction, such as vomiting, nausea, and food refusal in children [10]. Clinical manifestation varies according to patient's age and ability to correctly express symptoms of esophageal dysfunction [11]. Infants and younger children are not able to report symptoms like dysphagia or heartburn, thus they present with food refusal, irritability, and vomiting similar to gastroesophageal reflux disease [12]. On the other hand, older children present symptomatic dysphagia and food impaction similar to adults [11]. As EoE is a progressive disease, it tends to change from an inflammatory phase in young children to a fibrostenotic phase in older children and adults [13]. In practice, endoscopic findings and phenotypes can reflect the degree of inflammation; however, up to 30% of children with EoE can have normal esophageal endoscopic findings [14].

Recently, studies and reports on EoE are rapidly increasing and those on the incidence and prevalence of EoE have mainly been conducted in North America and Europe. A meta-analysis showed the incidence and prevalence of EoE in population-based studies in children have increased to 5.1 and 19.1 per 100,000 persons, respectively [15]. EoE is also predominantly reported in Caucasians in both pediatrics and adults [11]. The reason for the difference in incidence between Western and Eastern populations has not been understood yet. Kinoshita et al. [16] reported that the prevalence of EoE in Asian countries was 20 per 100,000 persons, but this was neither a population-based study nor a study of only children. To date, there is no epidemiological multicenter study of EoE in children in Asian countries.

Therefore, this nationwide multicenter study was designed by the Korean Society of Pediatric Gastroenterology, Hepatology, and Nutrition (KSPGHAN) to evaluate the incidence of EoE and EGE involving the esophagus (EGEIE) in Korean children and analyze and compare the clinical features and endoscopic findings of EoE to those of Western countries.

MATERIALS AND METHODS

Study protocol and subjects

This retrospective multicenter study was designed by KSPGHAN. The standardized study protocol was made and set to be applied to all study subjects. The subjects were children

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under 18 years of age who visited a hospital with symptoms of esophageal dysfunction and underwent upper GI endoscopy at 10 university hospitals in South Korea from August 1st, 2018 to July 31st, 2019. A total of 913 patients were initially included in the study. Tissue biopsies were taken from all subjects from the upper and lower esophagus, stomach, and duodenum during GI endoscopy. Three patients were excluded because one patient was a foreigner and two patients did not have duodenal biopsy results. Finally, 910 patients were enrolled in the study.

Clinical data including demographic data, clinical features, allergy histories, laboratory findings, as well as endoscopic and microscopic findings were reviewed retrospectively in all study subjects according to the standardized study protocol.

This study was approved by the Institutional Review Board of Seoul University Hospital (IRB No. B-1810-497-108) and Dankook University Hospital (IRB No. 2019-09-028).

Diagnosis of EoE

EoE was diagnosed when >15 eosinophils per high power field (HPF) were observed on microscopic examination in the upper or lower esophagus and normal endoscopic findings were observed in the stomach and duodenum with <20 eosinophils without any infections or other diseases that could cause eosinophil infiltration in the esophagus.

EGEIE was additionally diagnosed when there were >15 eosinophils per HPF in the upper or lower esophagus and >20 eosinophils deposited in the stomach and duodenum with abnormal endoscopic findings without any evidence of other diseases that could lead eosinophils to infiltrate the stomach and duodenum.

Data analysis and statistics

After collecting medical records from each hospital, the data was analyzed to find out the incidence of EoE and EGEIE and to compare clinical characteristics, endoscopic findings, and initial treatment protocols between the two groups.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Co., Armonk, NY, USA). A Mann-Whitney U-test and Fisher's exact test were used to compare continuous and categorical variables between the two groups, respectively. A p-value<0.05 was considered statistically significant.

RESULTS

Incidence of EoE and EGEIE

Of the 913 study subjects recruited, 14 (1.5%) were diagnosed with EoE and 12 (1.3%) were diagnosed with EGEIE (**Fig. 1**).

Clinical characteristics of EoE and EGEIE

In 14 EoE patients, the gender ratio was 1.33:1 with 8 boys (57.0%) and 6 girls (42.9%); while in 12 EGE patients, the gender ratio was 2:1 with 8 boys (66.7%) and 4 girls (33.3%). The median age at diagnosis of EoE and EGEIE was 6.7 years (range: 1.2–14.2 years) and 9.6 years (0.1–18.1 years), respectively (**Table 1**).

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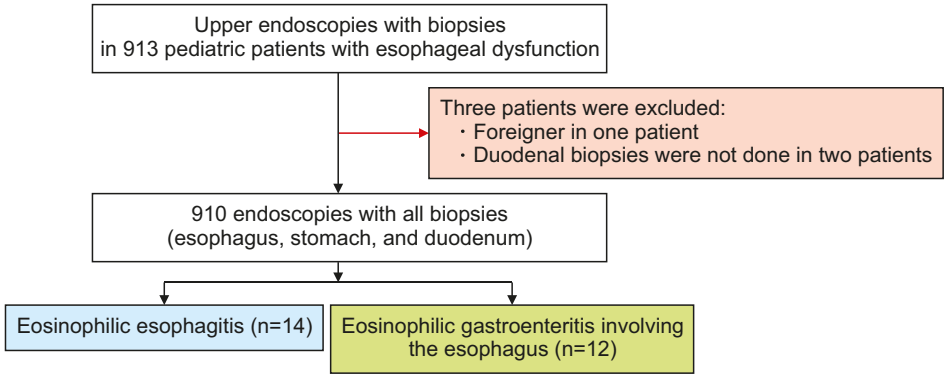

Fig. 1. Study design and the incidence of eosinophilic esophagitis and eosinophilic gastroenteritis involving the esophagus.

Table 1. Comparisons of the clinical features between children with EoE and those with EGEIE

Variable	EoE (n=14)	EGEIE (n=12)	Total (n=26)	*p*-value
Male	8 (57.1)	8 (66.7)	16 (61.5)	0.464
Age (yr)	6.7 (1.2–14.2)	9.6 (0.1–18.1)	8.9 (0.1–18.1)	0.198
Allergic diseases	8 (57.1)	8 (66.7)	16 (61.5)	0.464
Food allergy	5 (35.7)	5 (41.7)	10 (38.5)	0.536
Allergic rhinitis	5 (35.7)	3 (25.0)	8 (30.8)	0.437
Atopic dermatitis	3 (21.4)	4 (33.3)	7 (26.9)	0.404
Asthma	1 (7.1)	2 (16.7)	3 (11.5)	0.440
Duration of symptoms (mo)	4.5 (0.3–36.0)	0.7 (0.0–36.0)	1.5 (0.0–36.0)	0.054
Peripheral blood eosinophil count (/mm^3)	515.0 (46.0–3,308.0)	797.0 (41.0–5,250.0)		0.146
Total IgE (IU/mL)	372.2 (3.9–3,035.0)	674.6 (2.1–922.4)		0.303
Eosinophil infiltrates/HPF (upper esophagus)	7.50 (0–120)	1.00 (0–50)		0.432
Eosinophil infiltrates/HPF (lower esophagus)	43.0 (10–200)	38.0 (13–100)		0.267

Values are presented as number (%) or median (range).
EoE: eosinophilic esophagitis, EGEIE: eosinophilic gastroenteritis involving the esophagus, HPF: high power field.
p-value <0.05 is set to be statistically significant.

A total of 8 EoE patients (57.1%) and 8 EGEIE patients (66.7%) had allergic diseases (p=0.464) (**Table 1**). Among the allergic diseases, food allergy was the most common in both groups. In the next order, allergic rhinitis was the second most common in the EoE group and atopic dermatitis in the EGEIE group. When combining the two groups, the frequencies of allergic diseases were food allergies in 10 patients (38.5%), allergic rhinitis in 8 patients (30.8%), and atopic dermatitis in 7 patients (26.9%).

At diagnosis, vomiting was most commonly observed (57.1% and 66.7% in EoE and EGEIE patients, respectively), followed by abdominal pain and weight loss (both 42.9%) in EoE patients, and abdominal pain (58.3%) in EGEIE patients (**Fig. 2**). Dysphagia was observed in 14.3% of EoE patients. Only diarrhea was significantly different between EoE and EGEIE, and there was no difference in the frequency of other symptoms (p=0.033; **Fig. 2**). There was no diarrhea in EoE patients, while diarrhea was observed in 15.4% of EGEIE patients.

The sensitization rate of food allergens in both groups was 70.6%, 62.5%, and 50.0% for milk, eggs, and peanuts, respectively, followed by shrimp, soy, and wheat (**Fig. 3**).

Laboratory findings of EoE and EGEIE

The median peripheral eosinophil count in EoE and EGEIE patients was 515.0 mm^3 (46.0–3,308.0 mm^3) and 797.0 mm^3 (41.0–5,250.0 mm^3), respectively (**Table 1**), of which the

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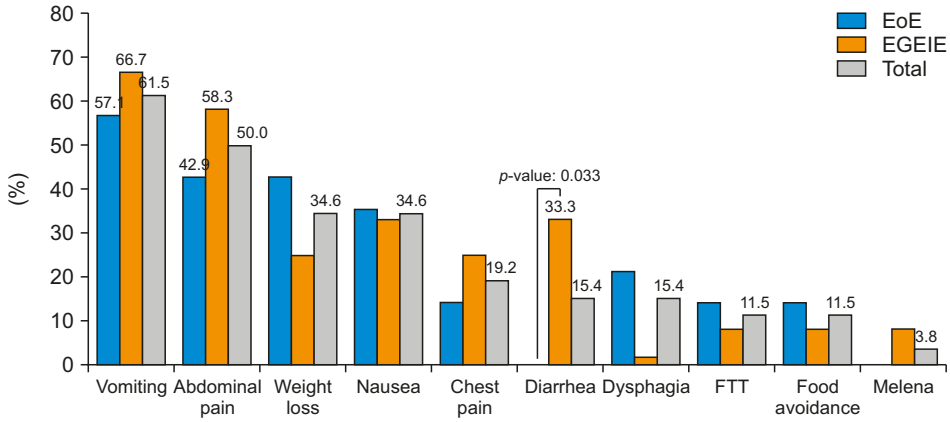

Fig. 2. Frequency of symptoms of EoE and EGEIE. Only diarrhea was significantly different between the two groups (p=0.033).
EoE: eosinophilic esophagitis, EGEIE: eosinophilic gastroenteritis involving the esophagus, FTT: failure to thrive.

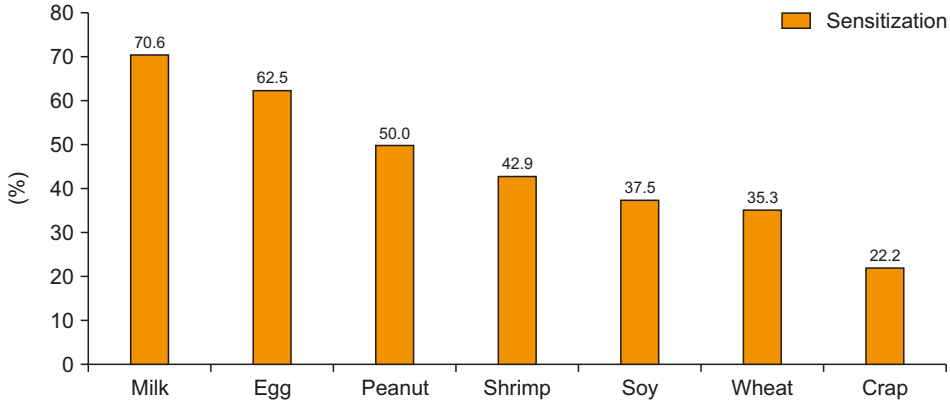

Fig. 3. Frequency of sensitized foods based on specific IgE tests (ImmunoCAP®) in both eosinophilic esophagitis and eosinophilic gastroenteritis involving the esophagus.

difference was not statistically significant. The median total IgE level was 674.6 (2.1–922.4) IU/mL in EGEIE patients, which was higher than 372.2 (3.9–3,035.0) IU/mL in EoE patients but was not statistically significant (**Table 1**).

Endoscopic findings of the esophagus and clinical features based on endoscopic abnormalities in EoE and EGEIE

At diagnosis, exudate in the esophageal endoscopic findings were the most frequent finding in EoE, followed by edema, furrows, and rings. Edema was the most frequent in EGEIE. When the two groups were combined, exudate, edema, furrows, and rings were found, in order of frequency, and 30.8% of patients showed normal endoscopic findings. There were no statistically significant differences in endoscopic findings between the two groups (p>0.05) (**Fig. 4**).

Comparisons of clinical features based on endoscopic findings of the esophagus in both EoE and EGEIE patients revealed significant differences in the median age between the abnormal and normal groups (median 11.1 years vs. 3.2 years, p=0.004; **Table 2**). However, there were no statistically significant differences in the median values of the duration of symptoms, peripheral eosinophil count, total IgE, and tissue eosinophil count. Out of the abnormal endoscopic findings, the median age and eosinophil infiltration in the lower esophagus were

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Table 2. Comparisons of the clinical features and laboratory findings based on endoscopic findings of the esophagus between EoE and EGEIE

Variable	Normal* (n=8)	Abnormal (n=18)	*p*-value	No furrow (n=18)	Furrow† (n=8)	*p*-value
Age (yr)	3.2 (1.2–9.0)	11.1 (0.1–18.1)	0.004	5.65 (0.1–18.1)	11.6 (4.3–15.7)	0.018
Duration of symptoms (mo)	1.5 (0.3–36.0)	3.0 (0–36)	0.387	1.5 (0.0–36.0)	3.0 (0.3–30.0)	0.484
Peripheral blood eosinophil count (/mm^3)	773.0 (41.0–5,250.0)	515.0 (46.0–4,301.0)	0.111	589.5 (41.0–5,250.0)	640.0 (250.0–1,440.0)	0.377
Total IgE (IU/mL)	97.4 (3.9–511.4)	593.3 (2.1–3,035.0)	0.052	189.0 (2.1–2,035.0)	512.0 (65.1–801.0)	0.268
Eosinophil infiltrates/HPF (upper esophagus)	0.5 (0.0–93)	10.0 (0–120)	0.075	3.0 (0–93)	20 (0–120)	0.078
Eosinophil infiltrates/HPF (lower esophagus)	35.0 (10–105)	43.5 (15–200)	0.172	35.0 (10–105)	99.0 (20–200)	0.026

Values are presented as median (range).
EoE: eosinophilic esophagitis, EGEIE: eosinophilic gastroenteritis involving the esophagus, HPF: high power field.
*Normal means the cases without any endoscopic lesions in the esophagus at diagnosis.
†Furrow means the cases with longitudinal lines to the esophageal axis at diagnosis.

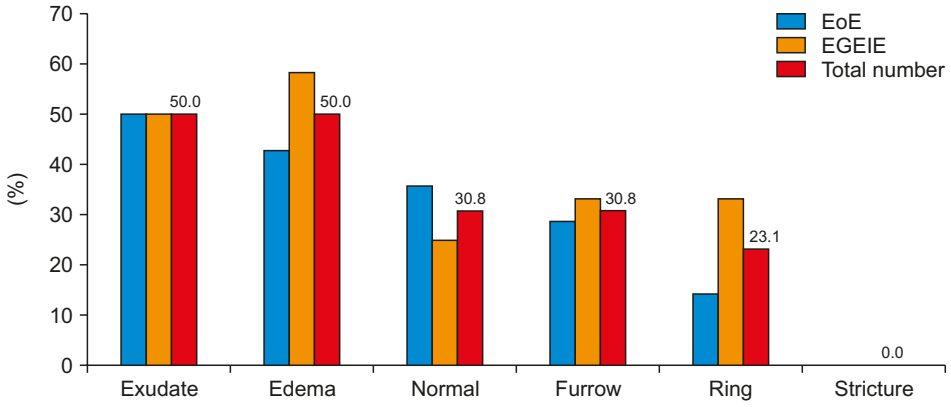

Fig. 4. Comparison of endoscopic findings of the esophagus between EoE and EGEIE at diagnosis. There were no significant differences between the two groups (All $p>0.05$).
EoE: eosinophilic esophagitis, EGEIE: eosinophilic gastroenteritis involving the esophagus.

significantly higher in the furrow group than in the no furrow group ($p=0.018$ and 0.026, respectively; **Table 2**).

Initial treatment for EoE and EGEIE

The most commonly used initial treatment for EoE was proton pump inhibitors (n=22, 84.6%), followed by a targeted elimination diet based on the results of allergen tests (n=11, 42.3%). The frequency of six-foods elimination diets (n=4, 15.4%) and swallowed topical steroids (n=3, 11.5%) were relatively low (**Fig. 5**).

DISCUSSION

The prevalence of EoE has been rapidly increasing and this phenomena is observable regardless of the study design including prospective, population-based studies, and studies using institutional electronic medical records or databases [6,17]. This increase in incidence is explained by both an increased awareness and incidence rate of the disease [17].

Of the EGIDs, only EoE has diagnostic criteria, hence the exact incidence and prevalence of EGE, EG, and EC are not clearly known. Recently, some researchers called for a distinction between EoE and non-esophageal EGIDs [18]. Mansoor et al. [19] reported that the overall prevalence rate of EGE in the US was 5.1 per 100,000 persons in 2017 and EoE was the most common disease of EGIDs, followed by EGE [19,20]. A study was performed in Utah

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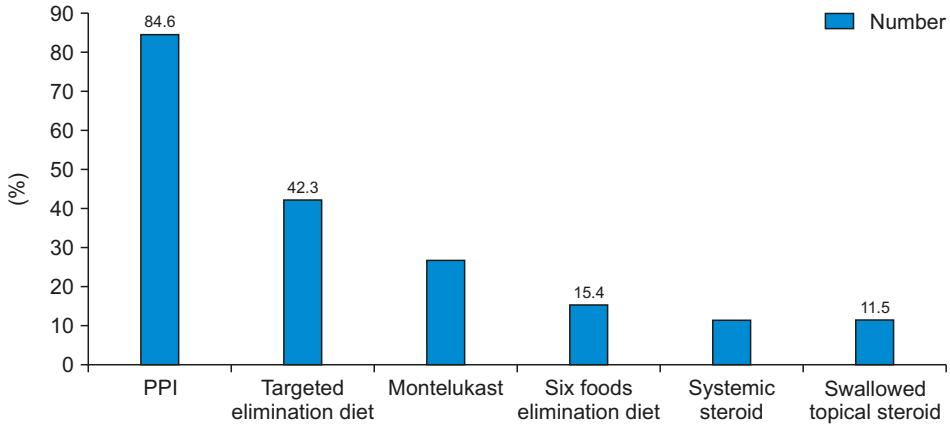

Fig. 5. Frequency of initial treatment for eosinophilic esophagitis and eosinophilic gastroenteritis involving the esophagus in Korean children.
PPI: proton pump inhibitor.

that revealed the number of pediatric EoE and EGEIE cases among 10,619 children who underwent upper endoscopies with biopsies were 1,060 (10.0%) and 59 (0.6%), respectively [21]. In another Western study on pediatric EoE over 7 years (2010–2017) also showed a higher incidence of 15.3% [22]. Although our study is not a population-based study and not intended to diagnose EGE, our results revealed that Korean children had a relatively lower incidence of EoE compared to Western children and the incidence of EGE was similar to that of EoE. The incidence of EGE was also relatively low in Korean children but the percentage of EGE among EGIDs was higher than that in Western children.

As for the data from Asian countries, 2 (0.8%) out of 244 pediatric patients in Japan who underwent endoscopy from 2009 to 2011 were diagnosed with EoE [23]. Our study shows a slightly higher incidence of EoE (1.5%) compared to the study in Japan; however, the incidence of pediatric EoE in the East was lower than in the West. The prevalence of EoE is also different between Western (higher incidence) and Eastern (lower incidence) countries [12]. The reason for geographical differences in the incidence and prevalence of EoE has not been identified yet. Further studies should be conducted to elucidate the etiological epidemiologic features.

According to previous studies, vomiting, abdominal pain, failure to thrive, and dysphagia are the most common clinical symptoms in pediatric EoE patients with a mean age at diagnosis between 5.4 and 9.6 years [24]. Our study revealed that vomiting was the most common symptom of EoE (57.1%), followed by abdominal pain and weight loss (42.9%). Dysphagia and chest pain were noted in 14.3% of patients. The frequency of EoE symptoms was similar to that in Western studies, while the frequency of dysphagia was relatively lower; however, this may vary depending on the age of study subjects. In our study, the median age at the time of diagnosis was 6.7 years (range, 1.2–14.2 years). As for EGEIE, vomiting was also the most common symptom and there was no difference in symptoms except diarrhea, which was only observed in EGEIE patients.

According to Western studies, there can be a difference in the gender ratio in pediatric patients with EoE as boys are known to have a three times higher prevalence than girls [25]. However, in our study, the gender ratio of males to females was 1.33:1, which was not much

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more noticeable than in the West. Nevertheless, there is a limitation to acknowledge that this difference may be due to the small sample size.

Both pediatric and adult patients with EoE tend to have allergic diseases, such as asthma, allergic rhinitis, food allergies, and atopic dermatitis [11]. Some studies reported that atopic ailments have been found in up to 80% of EoE cases [11]. Hill et al. [26], reported that 68% of pediatric EoE patients had IgE-mediated food allergies and the most common food allergens in EoE patients were peanuts, eggs, tree nuts, milk, and shellfish. In our study, 57.1% of EoE patients had concomitant allergic diseases and when combining EoE and EGEIE patients, 61.5% had allergic diseases. When the two groups were combined, the highest frequency of sensitization to food antigens was milk (70.6%), followed by eggs (62.5%), and peanuts (50.0%). This result is similar to previous Western studies. A meta-analysis study reported that allergic rhinitis was significantly the most common concomitant allergic diseases in EoE patients of all ages [27]. Our study also showed that food allergies and allergic rhinitis were the most common among allergic diseases, as noted in 35.7% of EoE patients. In previous studies on the atopic features of EoE, children had a higher rate of asthma and positive rate for patch tests to foods compared with adults, and there were racial differences of the co-morbid atopic disease rate between Caucasian and African American children [28,29]. Caucasian and African American children accounted for about more than 80% of allergic diseases and only atopic dermatitis was significantly more frequent in African American EoE patients than Caucasian children (57% vs. 9%, respectively) [28]. Both Caucasian and African American children had a 40% and 30% prevalence of asthma and food allergies, respectively. In the present study, the proportion of children who had food allergies was similar to Western countries, but asthma was relatively uncommon in Korean children.

Although there are no pathognomonic endoscopic findings in EoE, typical endoscopic findings in EoE patients include exudate, furrowing, concentric rings, and esophageal strictures [30]. According to previous studies, normal endoscopic findings of the esophageal mucosa were reported between 10% and 30% of children diagnosed with EoE [30]. EoE has the clinical characteristic of progression from the development of inflammation to fibrostenosis in endoscopy and histology [12]. This nature of disease progression in EoE can lead to the difference in symptoms and endoscopic findings between children and adults. In the early stage of EoE, children may have symptoms of inflammation, such as vomiting, food refusal, and abdominal pain and endoscopic features like edema, furrowing, and exudates. On the other hand, adolescents and adults can show symptoms like dysphagia and food impaction and endoscopic findings like stricture and fixed rings [11]. Fibrotic changes of the esophagus in EoE, called esophageal remodeling, increases with every 10-year increase in age and disease duration without treatment [11].

A large retrospective pediatric study on EoE showed a 41%, 15%, and 12% prevalence of furrowing, exudate, and rings but no patients with strictures [30]. In our study, the most common endoscopic finding was exudate (50.0%), followed by edema (42.9%), furrowing (28.6%), and rings (14.3%). No strictures were also found in our study. When we investigated the endoscopic findings in both EoE and EGEIE together, 30.8% of patients showed normal endoscopic features, which was similar to those of Western studies. Therefore, when a child is suspected of EoE, physicians should take biopsies in the esophagus despite normal endoscopic findings.

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When we analyzed the clinical features of EoE based on gross endoscopic findings of the esophagus in both EoE and EGEIE groups, the median age of patients with normal endoscopic findings was younger than the median age of those with abnormal findings. These results enabled us to figure out that the disease entity of EoE is progressive. When the patients are young, the progression of EoE is slow and thus the endoscopic findings can be normal. However, as the patient ages, EoE tends to progress so that endoscopic abnormalities may also develop.

Collins et al. [31] reported that endoscopic severity was correlated with esophageal tissue eosinophilia as a long-term course in children with EoE. According to this study, female sex and initial response to medications were good prognosis factors for long-term control of esophageal eosinophilia [31]. Our data also showed that patients with furrows had more eosinophilic infiltration in the esophagus.

In a previous study on EoE, generalized eosinophilic infiltration to other GI parts did not develop in EoE patients [12]. On the other hand, non-esophageal EGIDs were noted in 20 to 88% of patients with eosinophilic inflammation at multiple GI sites [18]. According to a study by Pesek et al. [18], 41% of patients with EGIDs had eosinophilic involvement at multiple sites other than the primary GI site. Of those with multiple site involvement, 75% had esophageal involvement and the most common combination of multi-site involvement was the esophagus and stomach/small intestine [18]. In a study by Caldwell et al. [32] 87% of EG patients had eosinophilic inflammation in multiple GI segments. The esophagus was the most common site of eosinophil involvement except for the primary involvement site [32]. In addition, the gastric transcriptome of EG and the esophageal transcriptome of EoE were clearly different from each other, thus the two disease entities were fundamentally different. Through these studies, we have identified the esophagus as a common involvement site in EG and EGE of non-esophageal EGIDs. When physicians correctly diagnose EoE, they should examine and take biopsies of the stomach and duodenum in addition, instead of taking a biopsy in just the esophagus. Since we only focused on the incidence of EoE in this study, further research on EGIDs are needed to find out the true incidence and esophageal involvement rate of EGIDs in Korean children.

Our study has some limitations. We could not confirm the accurate incidence of EoE because our study was not a population-based study but a well-designed prospective multicenter study in Korean children. In addition, we could not diagnose EGIDs definitively because there is no consensus for diagnosing EGIDs using tissue eosinophil counts. Diagnosis of EGIDs was made only if there were GI symptoms, abnormal endoscopic findings, and >20 eosinophils infiltrating the stomach and duodenum. Finally, there is lack of statistical power due to the small number of cases of EoE and EGEIE. Therefore, prospective multicenter studies based on a well-designed diagnostic protocol in order to identify the exact incidence of EoE and EGEIE in Korean children is needed. Nevertheless, our study is still meaningful since this multicenter study was the first study on pediatric EoE not only in South Korea but also East Asia.

In conclusion, we determined that the incidence of EoE in Korean children was less than that in Western countries, while the incidence of EGE out of all EGIDs was higher than that of Western children. Clinical characteristics of symptoms and endoscopic findings, and co-morbid allergic diseases were similar to those of Western studies. In the future, further research should be conducted to elucidate the reasons for epidemiologic differences

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between Western and Eastern EoE patients and differences in the pathophysiology of EoE and EGIDs.

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