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Increased Diagnosis of Eosinophilic Esophagitis in Young Children

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ABSTRACT

Objective: To investigate the patients with eosinophilic esophagitis that is diagnosed with an increasing frequency despite the still unknown etiology.

Materials and Methods: The data of patients diagnosed as eosinophilic esophagitis between 2012 and 2019 in our hospital were retrospectively reviewed from the medical records.

Results: A total of 21 patients (12 male) with eosinophilic esophagitis were included in this study. There was a significant increase in the number of patients in the last two years. The mean age at the onset of complaints was 3.42 + 2.47 years, and the mean age at diagnosis was 5.83 + 3.18 years. Vomiting, food impaction and food rejection were the most common presenting symptoms. The prick test was positive in 24% and the patch test was positive in 33% of the patients. Milk and egg were the most common positive food allergens in the patch test. Forty eight percent of the patients responded positively to proton pump inhibitor treatment. Forty eight percent of the patients had concomitant atopic disease, and 67% had a positive family history for atopic disease. Almost all of the cases were breastfed for more than six months and used antibiotics in the first year of life. Clinical remission was achieved in 8.33 + 5.61 (mean±SD) months. No side effects were observed related to topical steroids in any of the patients.

Conclusion: Eosinophilic esophagitis should be considered in the differential diagnosis of every patient with esophageal complaints. Endoscopic evaluation should be performed without delay, especially in young children with vomiting.

Keywords: Eosinophilic esophagitis, food allergy, child, vomiting

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic T-helper 2-associated inflammatory esophageal disease, the etiology of which has not yet been fully elucidated. It is diagnosed histopathologically in addition to detecting the clinical and endoscopic findings of eosinophilic infiltration in the esophagus. Clinical findings include dysphagia, failure-to-thrive, vomiting, food impaction, persistent reflux symptoms, food rejection, feeding difficulty, inability to proceed with complementary food, odynophagia, and abdominal pain, accompanied by supportive findings such as loss of vascularity in the esophagus, linear furrows, trachealization, narrowing of the lumen, exudation, and ulceration upon endoscopic evaluation. It is necessary that esophageal biopsies, which normally do not have eosinophils, contain ≥15 eosinophils in at least one high-power field for the diagnosis of EoE (1-3). Proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE), previously considered as a separate entity, is now considered to be a subtype of eosinophilic esophagitis (4-6).

A meta-analysis has demonstrated a significant increase in the incidence and prevalence of EoE in the last two decades (7). There is limited information with respect to the pathogenesis of eosinophilic esophagitis

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triggered by food allergens but genetic, environmental and host immune system factors are known to play a role. The pediatric cohort study determined that milk and eggs were the most common food allergens (8). Responsible allergenic food elimination, proton pump inhibitor and topical steroids are used for the treatment in order to reduce the eosinophilic inflammation and some histologic findings. The responsible allergenic food may not always be detected by food allergy tests. Topical steroids provide symptomatic recovery by reducing eosinophilic infiltration in the esophageal mucosa (9).

In this study, we aimed to retrospectively investigate the patients diagnosed with eosinophilic esophagitis, which is a recently recognized disease.

MATERIALS and METHODS

We retrospectively analyzed patients with eosinophilic esophagitis who were diagnosed between 2012 and 2019 and followed up jointly by the Department of Pediatric Gastroenterology, Hepatology and Nutrition and the Department of Pediatric Allergy at Erciyes University, Faculty of Medicine. The medical records were used to analyze demographic data, blood eosinophil counts, skin prick and/or patch testing results, endoscopic and histopathological findings, and background of treatment and response levels.

Diagnosis of EoE was confirmed by the presence of ≥15 eosinophils in one high-power field upon histopathological examination of esophageal biopsies. At least 5 biopsy specimens were taken from the distal and proximal mucosa of the esophagus. During upper gastrointestinal endoscopy, biopsies were also taken from the duodenum and gastric mucosa of the patients, thus excluding other eosinophilic gastrointestinal diseases. Histopathological examination was performed by a qualified pathologist. Successful EoE treatment was confirmed upon the presence of <15 eosinophils in esophageal biopsy specimens in a high-power field at follow-up endoscopies (1).

Eosinophilia was defined as a complete blood count greater than 400/mm^3 or a percentage greater than 4% of all cells. Atopic diseases were questioned in the patient and family history. Patients under two years of age underwent prick testing with milk, egg whites, egg yolk, wheat, soy, hazelnut, peanut, fish and house dust mites, whereas aeroallergens of molds, pollen species, cockroach, cat were additionally included for those older than two years of age. All patients underwent a 5-point patch test including milk, egg white, egg yolk, soy and wheat allergens. These allergens were placed in the wells in the Finn Chamber and adhered to the skin. The Finn Chamber was removed after 48 hours and the first reading was done, and the second reading was done after 72 hours. Allergens were used in 1/1 full concentration in five of the foods used in this test. Fish, nuts, and lentils were not routinely included in this patch test unless there was any suspicion about these nutrients depending on the history (10).

The allergen detected by prick and/or patch testing, if any, was first eliminated. Proton pump inhibitor therapy (Lansoprazole, 1 mg/kg/day) was initiated as soon as the patients were diagnosed with EoE. Clinical improvement within 6-8 weeks of proton pump inhibitor therapy was evaluated as a positive response. The relationship between food and symptoms was queried. In case of proton pump inhibitor unresponsiveness, a milk elimination diet was started if no different food allergy was detected in the tests. If there was no response to the milk elimination diet, the elimination diet was continued as 2-food (milk, wheat), 4-food (milk, wheat, egg, soy) and then 6-food (milk, wheat, egg, soy, peanut, fish) (11). Oral administration of budesonide nebule 1 mg/day was started as a topical steroid (1 mg/day in patients younger than 10 years and 2 mg/day in patients older than 10 years) and continued until histological improvement was achieved. The elimination diet was discontinued in the presence of remission both clinically and histopathologically. Disappearance of the symptoms, improvement of the endoscopic EoE findings, and less than 15 eosinophils in one high-power field in esophageal biopsy specimens were considered remission.

Ethics committee approval was obtained from Erciyes University Medical School for the study (Date: 07.11.2018, Decision Number: 2018/572). Written and verbal consent was obtained from the relatives of the patients.

Statistical Analysis

All data were analyzed by using SPSS for Windows version 22.0. Descriptive statistical methods were used for the evaluation of the data. Parametric statistics were presented as mean ± standard deviation and nonparametric statistics were expressed as median (minimum-maximum). Descriptive data were presented as frequencies and percentages.

RESULTS

We obtained the medical records of 21 patients diagnosed with EoE between 2010 and 2019. Twelve (57.1%) of the cases were male and nine (42.9%) were female. The mean age at onset of symptoms was 3.42 ± 2.47 years (6 months-8 years) and the mean age at diagnosis was 5.83 ± 3.18 years (2-12 years). The mean duration between the onset of complaints and the age of diagnosis was 2.77 ± 1.01 years (1-5 years). Thirteen patients (62%) were preschoolers and seven patients (33%) were younger than 3.5 years. The male to female ratio of our study was 1.3.

The mean duration of breastfeeding was 17.42 ± 7.45 months, while only only patient had never received breast milk. However, it was detected that 10 cases (47.6%) used formula along with breast milk. Of the cases with eosinophilic esophagitis, only one case had a pet. The investigation for antibiotic use in the first year of life revealed that all of them had a history of antibiotic use. Eighteen (85.7%) of the cases had lived in the city and three (14.3%) had lived in the village.

The admission complaints included 18 (86%) cases with vomiting, 12 (57%) with food impaction, six (29%) with food rejection, three (14%) with abdominal pain, one (5%) with difficulty swallowing and one (5%) with inability to gain weight. Figure 1 shows that the number of patients has increased in recent years. The prick test was positive in five (24%) patients and pollens were the most common allergens with positive results. Seven patients (33%) had a positive patch test in which the most frequent positivity was to milk and egg. One patient was thought to have lentil allergy according to the clinical history and that was later confirmed by the patch test. Remission was achieved with a three-month elimination diet and proton pump inhibitor treatment. Patients 10 and 21 were diagnosed as celiac disease in addition to EoE. Ten cases (48%) responded positively to proton pump inhibitor therapy. Ten cases (48%) had an accompanying atopic disease and 14 (67%) had a family history of atopic disease (Table I).

Table I. Demographic features and allergy test results of the patients.

Patients	Age at the time of diagnosis (years)	Prick test	Patch test	PPI response	Clinical remission time	Presence of atopic disease	Family history of asthma and allergic diseases
1	3.5	Neg	Milk	-	2 years	Neg	+
2	2.5	Neg	Neg	+	3 months	Neg	-
3	5.5	Neg	Milk, egg	-	1 year	AR	+
4	9	Neg	Egg	-	1 year	Drug allergy	+
5	4.5	Neg	Neg	+	6 months	Neg	-
6	9	Neg	Neg	+	6 months	Neg	+
7	10	Neg	Neg	-	1 year	Neg	-
8	5	Neg	Milk, egg, soy	+	1.5 years	Neg	+
9	12	Neg	Neg	+	1 year	Neg	-
10*	3	Neg	Milk	-	6 months	Asthma	+
11	9	Polen, cockroach	Neg	+	3 months	AR	-
12	2	Neg	Neg	-	3 months	FA	+
13	11	Egg	Neg	-	9 months	FA	+
14	6.5	Neg	Egg	-	6 months	Asthma, FA, AR	+
15	2	Neg	Lentil	+	3 months	FA	+
16	7.5	Polen, cockroach	Neg	-	6 months	AR	+
17	5	Neg	Neg	+	3 months	Neg	-
18	7	Cat, polen	Neg	-	6 months	AR, FA	+
19	2	Neg	Neg	-	Follow	Neg	-
20	4	Polen	Neg	+	Follow	Neg	+
21*	2.5	Neg	Neg	+	Follow	Neg	+

FA: Food allergy, **AR:** Allergic rhinitis, **Neg:** Negative, **PPI:** Proton pump inhibitor, *: Also diagnosed as celiac disease.

Table II shows the laboratory, endoscopic and esophageal eosinophil counts of the patients. An elimination diet was administered to eight (38%) patients whose prick and/or patch tests were positive. The mean duration of topical steroid use in these patients was 7.33 ± 2.86 (3-12) months. The mean clinical remission duration was 8.33 ± 5.61 months. The prognosis of the patients was good during the follow-up period and no relapse has developed so far under treatment or after discontinuation of treatment.

DISCUSSION

The prevalence of EoE, which has been reported more frequently in recent years, is reported to be 0.28% in America and Europe (12). A study from our country performed by Çakır et al. has noted an increase in the diagnosis of EoE in recent years, emphasizing EoE as the most common cause of esophageal eosinophilia (13). Similarly, our study has also demonstrated that the number of patients diagnosed with EoE has increased in recent years.

Hoofien et al. (8) reported the median age of diagnosis as 9 years for EoE. The mean duration from the onset of symptoms to diagnosis was 12 ± 33.5 months. In the same study, failure-to-thrive and diarrhea were mostly present in young children, whereas food impaction, abdominal pain and dysphagia were more prominent in the adolescent group. Ristic et al. reported that 35 children were diagnosed with EoE in seven years (12.45 ± 3.77 years) and dysphagia and food impaction were the primary symptoms (14). In Sağ et al.'s study, the main complaints of the patients were food impaction/dysphagia and chronic abdominal pain (15). Bakırtaş et al. reported that the most common symptoms of the patients were gastro esophageal reflux-like symptoms (16). The study carried out by Homan et al. revealed that the mean age at diagnosis was 9.5 years; vomiting, abdominal pain and growth retardation were more prominent in young children, whereas dysphagia and food impaction mostly appeared in older children (17). In a multicenter study, 15.7% of 108 pediatric patients with

Table II. Laboratory, endoscopic and histologic findings of the patients.

Patients	Blood eosinophil count/ mm^3 (% eosinophil)	Endoscopic findings of esophagus at three-month intervals (consecutive)	Esophageal eosinophil count/hpf (consecutive)
1	310 (5.4)	Linear furrows, erythema /edema/ N	84/27/0
2	330 (4.6)	Erythema/N	150/0
3	570 (5.7)	Linear furrows, erythema, edema	145
4	830 (11.4)	Stricture	138/67
5	380 (3.8)	Linear furrows, erythema/Linear furrows	163/60
6	340 (4.2)	Operated on for esophageal atresia	72
7	1260 (14.1)	Edema	54
8	740 (6.5)	Linear furrows, edema/ Linear furrows	190/50
9	300 (3.5)	Linear furrows, edema	104
10	360 (5)	Rings, linear furrows, LESR/Rings, linear furrows/N/N	80/72/15/1
11	510 (5.7)	N	42
12	670 (8)	Linear furrows/ N	112/0
13	480 (4.2)	Erythema, rings, linear furrows / Edema	110/27
14	270 (5.2)	Stricture, exudate/Rings, linear furrows, exudate	38/17
15	280 (3.5)	Erythema, LESR/ Erythema/N	88/40/0
16	400 (7.1)	Erythema, exudate/ N	65/0
17	410 (7.2)	Erythema, rings, linear furrows	107
18	720 (6.1)	Linear furrows, exudate	18
19	510 (4.8)	Erythema, linear furrows, LESR/N	61/0
20	340 (4.3)	Erythema, linear furrows, rings, LESR	218
21	520 (6.9)	Edema	5

LESR: Lower esophageal sphincter relaxation, **N:** Normal

EoE were preschoolers (18). In another study conducted in Saudi children, the mean age of 37 patients with EoE was 9.6 ± 2.3 years (19). In a study conducted in Minnesota, children diagnosed as EoE between 2005 and 2015 were compared to children diagnosed between 1995 and 2005, and the mean age at diagnosis was found to be reduced (7.5 years versus 12.8 years) (20). In our study, the mean age at diagnosis was 5.83. ± 3.18 years, which was younger than in previous studies. Sixty two percent of the cases were preschoolers and 33% of the cases were between 2 and 3.5 years old at the time of diagnosis. In addition, the majority of our cases presented with vomiting and food impaction at admission. According to our data, food impaction is more likely to be present in adolescents. However, our cases were mostly young children and 57% reported food impaction. These symptoms were thought to be associated with esophageal inflammation.

Although genetic, environmental and immunological features have not been fully elucidated, the association between EoE and other allergic diseases such as atopic dermatitis, IgE-mediated food allergies, asthma and allergic rhinitis is well known (21). Hill et al. carried out a study which supported the notion that EoE was a late finding of allergic diseases (22). Slae et al. reported that food and pollen allergies were common in children with EoE, but they did not find any association between EoE, breast-feeding, antibiotic exposure and a furry pet in infancy (23). In the case-control study of Witmer et al., it was stated that the use of antibiotics and acid-blocking medications in the early infantile period was a significant risk factor that increased the occurrence of EoE in the long-term due to the negative effects on the gut microbiome and immunity development (24). Jensen et al. reported that maternal fever during pregnancy, preterm labor, cesarean delivery, and antibiotic or acid suppressant therapy in infancy increased the risk of EoE but they found no relationship between breastfeeding and EoE (25). Atopic disease, especially food allergy and allergic rhinitis, accompanied EoE at the time of diagnosis in half of our cases. However, almost all our patients with EoE had been breastfed for more than six months and had used antibiotics in the first year of their lives. The fact that the majority of the cases had lived in the city was a factor that increased allergen exposure.

It is known that food allergens play a role in the pathogenesis of eosinophilic esophagitis. Food allergy tests are performed to detect potential allergens in these patients. Early hypersensitivity reaction is evaluated by skin prick testing and delayed hypersensitivity reaction by patch testing. In the study by Spergel et al., milk, egg, wheat and soy were the most common food allergens, and allergy to at least one food allergen was detected in approximately 70% of children with skin prick testing (26). A pediatric cohort study performed in Europe has revealed that milk and egg were the most common allergens that triggered EoE (8). In our study, pollen was the most common cause of sensitivity in prick testing, whereas milk and egg were the most common ones detected in patch testing.

The term PPI-REE, defined as a separate entity in the previous guidelines, has been abandoned and referred to in the current guidelines under the heading of EoE. Proton pump inhibitors are included in the treatment of EoE in addition to diet and steroids. In addition to the acid-suppressive effects, proton pump inhibitors exhibit anti-inflammatory effects by down-regulating Th2 in allergic esophageal inflammation (27). Our study demonstrated that half of the patients with EoE were responsive to proton pump inhibitor therapy.

There are studies showing that the incidence of EoE is increased in patients with celiac disease. Th1-related immune responses play a role in Celiac disease, whereas Th2-related immunological processes occur in EoE. However, the fact that EoE is also triggered by wheat, which is held responsible for celiac disease, also suggests a possible association between them. The association between celiac disease and EoE is not very clear yet (28). Patton et al. examined 350 pediatric patients with celiac disease retrospectively and reported that 6% of them had EoE (29). In the current study, EoE and celiac disease were detected simultaneously in two patients upon histopathological evaluation. These patients were started on a gluten-free diet for the celiac disease, in addition to proton pump inhibitor therapy for EoE, to which they responded positively.

Treatment of EoE includes an elimination diet, acid suppression and topical glucocorticoid therapy. The mainstay of treatment is to remove the food allergen from the diet. However, it is not always possible to detect allergens with allergy tests. In the presence of a clinical response to proton pump inhibitor therapy, treatment is maintained at the optimal dose for symptom control. Oral administration of budesonide or fluticasone is preferred as topical glucocorticoid treatment. Topical glucocorticoids are continued until histological remission is achieved (9).

In the current study, an elimination diet was used with respect to the allergens detected by allergy tests in patients with EoE, and those who did not respond to proton pump inhibitor therapy were treated with budesonide. A patient who did not respond to proton pump inhibitor therapy was started on a milk elimination diet after which clinical and histological remission was achieved. Milk and egg were the most common responsible allergens in our patients, which was consistent with the literature. The patients, except for the three patients who had not completed treatment yet, were kept on an elimination diet for 13.5 months and administered topical steroids for 7.3 months. No patients developed side effects associated with topical steroids.

CONCLUSION

In conclusion, EoE should be taken into consideration in the differential diagnosis of all patients with esophageal dysfunction. EoE should be considered in the differential diagnosis, in addition to gastroesophageal reflux disease, especially in young children who present with vomiting.

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