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Demographic, Clinical, and Allergic Characteristics of Children with Eosinophilic Esophagitis in Isfahan, Iran

Tooba Momen[1], Hossein Saneian[2], and Niloufar Amini[3]

[1] Department of Asthma, Allergy and Clinical Immunology, Child Growth and Development Research Center, Research Institute of Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Department of Pediatric Gastroenterology, Child Growth and Development Research Center, Research Institute of Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
[3] Pediatric Ward, Child Growth and Development Research Center, Research Institute of Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease isolated to the esophagus Food allergy is thought to play an important role in the pathophysiology of EOE. The aim of this study is to evaluate demographic features and sensitivity of patients with reference to common food allergens.

Children with documented EoE were enlisted for this study. Skin prick test and patch test were done for all participants. Each test contained common food allergens. Other tests, such as evaluation of total IgE and eosinophil count, were also done.

A total of 30 patients (the mean age of participants was 3±6 years) with 6 months to 15 years documented EoE participated in this study. The mean duration of symptoms was 2 years. Association with other allergic disorders was seen in 16 (32%) patients [Asthma in 8 (26.7%), allergic rhinitis in 5 (16.7%) and eczema in 3 (10%)]. The mean level of total IgE was 413.5±505.5 (IU/ML): total IgE level was above normal range for age in 17 children. The mean level of eosinophil was 372.2±305.2, and eosinophilia was seen in 11 patients (36.7%). The skin prick test and patch test findings showed that 28 patients (93%) and 17 of 30 patients (56.6%) tested positive to foods respectively. The most common positive skin prick test was for sesame and walnut. Patch test showed that the most common positive test was for fish. Evaluating the symptoms indicated that vomiting (70%) is the most prevalent symptom in patients; the less prevalent symptom was dysphagia (3.3%). Other prevalent symptoms were subsequent abdominal pain (33.3%), gaining weight failure (33.3%), heartburn (16.6%), cough (10%), fecal impaction (10%), and constipation (6.66%).

Our series confirms the high degree of atopy in Iranian children with EoE. These patients seem to be polysensitized to several food allergens Because of different eating cultures in different countries, considering special food in selecting allergens for allergic tests is needed.

Keywords: Child; Esophagitis; Eosinophilic; Food

Corresponding Author: Niloufar Amini, MD:
Pediatric Ward, Child Growth and Development Research Center, Research Institute of Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran.
Tel: (+98 913) 4360412, E-mail: nilufar.amini66@gmail.com

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INTRODUCTION

Eosinophilic esophagitis (EoE) is an inflammatory esophageal disease. The histologic hallmark of this disorder is eosinophilic infiltration of esophagealmucosa.[1] The symptoms are variable, including gastroesophageal reflux like symptoms such as vomiting, regurgitation, growth failure, and, in older children, food impaction, constipation, abdominal pain, and dysphagia.[2] The most serious complication of this disease is the esophageal tightness which needs esophagus dilatation.[3-5]

Little is known about the incidence of EoE. It seems that the incidence of EoE has increased during the last decade: this might be due to early diagnosis.[6]The exact cause of EoE is unclear: it maybe because of hyper sensitivity to foods or aero allergens.[7]Although studies suggest high association of EoE patients with specific allergic sensitivities and other atopic diseases, the relationship between EoE and allergic sensitization is not straightforward.[8]

Several studies have confirmed the association of food allergy as a trigger in EoE. The role of food allergens is significant here, maybe due to the combination of IgE- and non-IgE mediated hypersensitivity responses.[9] A consensus statement published in 2007 recommended complete allergy evaluation for foods and inhalants in all eosinophilic esophagitis patients.[10]Since then, many studies have reported high rate of food sensitization in these patients, especially in children defined by skin prick test and specific IgE and atopy patch tests. There is no published data in Iran on this issue.

The present study sets to evaluate the demographic features and results of food allergy tests in children with EoE, including the skin prick test and the skin patch test. This is the first case series in Iranian pediatrics which evaluates the results of food allergic tests.

MATERIALS AND METHODS

This current cross-sectional study was performed from 2014 and 2016 in the Pediatric Imam Hussein Hospital of the Isfahan University of Medical Science. All participants were children aged 6 months to 15 years old, who referred to pediatric gastroenterologist and suffered from upper gastrointestinal symptoms including vomiting, eating problems, chest or epigastric pain and drooling, and poor response to at least 4 weeks' treatment by proton pump inhibitor medications (Omeprazol, Abidi Pharmacutical company, Iran) with appropriate dose (1 mg/kg/day). EoE diagnosis was confirmed through biopsy and histology. To reach this goal, all patients underwent esophagogastroduodenoscopy. At least, three individual biopsy specimens were obtained from the esophagus. Two biopsies were taken from the distal esophagus and one from the mid esophagus; biopsy from duodenum and stomach were given to rule out eosinophilic gastroenteritis. Cases with more than 15 eosinophils in high-power field (HPF) in microscopy were strongly diagnosed as EOE, especially in the presence of endoscopic findings such as severe epithelial hyperplasia, esophageal ring, or involvement of the distal part. The exclusion criteria were gastroesophageal reflux treated with proton pump inhibitors or other local or systemic gastrointestinal disorders.

The inclusion criteria for the study were a definitive diagnosis of EOE. Demographic variables, chief complaint, and the history and physical examination of patients were recorded in the appropriate files, and parental consent was obtained. This study was approved by Ethics Committee of Isfahan University of Medical Sciences (N. IR.mui.rec.1394.3.131).

Skin prick test was done for all participants, and they were all asked not to use anti histamines for at least a week before the test. In this evaluation, Histamine-HCl and NaCl were used as positive and negative controls. After 10–15 minutes, wheal size of 3millimetergreater than negative control was reported as 'positive test'. Each test contained common food allergens, including cow's milk, egg, soy, wheat, peanut, walnut, fish, and shrimp. They also included sesame and corn: these are common in Isfahan. Skin patch test included cow's milk, egg, soy, wheat, peanut, walnut, and fish.

In all participants, eosinophil level was measured by complete blood cell count (CBC), and eosinophil levels of more than 450/ µL and 1500/ µL were defined as eosinophilia and hyper eosinophilic Syndrome respectively. Also, serum total IgE was measured by ELIZA method in all patients. The IgE level was considered elevated when it exceeded the age-adjusted reference range for the laboratory. (Normal range for 0-5 year<60, 6-9 year<90 and for 10-15<200)

All patients with positive tests were supposed to use elimination diet therapy for at least 6 weeks, and clinical response was evaluated. For quantitative variables and qualitative variables, mean±standard deviation and proportion in percentage are expressed respectively. Skin test results, level of total IgE, and association with other allergic diseases are also presented. The association between demographic variables and other variables were analyzed by x^2 t-test. A two-sided α level of 0.05 was used to assess statistical significance.

RESUTLS

Thirty patients with EoE were evaluated. Demographic data and results of allergic tests are shown in Table1.The mean age of participants was 6±3 years (range 6-12): 36.7% were younger than 4 years. 76.7% of patients were boys and 23.3% were girls.

Association with other allergic disorders was seen in 16(32%) patients. Asthma was seen in 8(26.7%) patients and allergic rhinitis and eczema in 5(16.7%) and 3(10%) patients respectively. Allergic rhinitis was more prevalent in patients less than four years of age (*p* value= 0.028).

Evaluating these symptoms indicated that vomiting (70%) is the most prevalent symptom in patients; the less prevalent symptom was dysphagia (3.3%). Other prevalent symptoms were subsequent abdominal pain (33.3%), gaining weight failure (33.3%), heartburn (16.6%), cough (10%), fecal impaction (10%), and constipation (6.66%). The mean duration of symptoms was 2 years.

The mean level of total IgE was 413.5±505.5, and about 17 (34%) children had total IgE level above the normal range. The mean level of eosinophil was 372.2±305.2: though eosinophilia was seen in 11 patients (36.7%), hyper eosinophilic syndrome was not seen in any of the patients (Table1).

Table1. Demographic data, clinical and allergic characteristics of eosinophilic esophagitis patients

Demographics	
6±3 (6-12)	**Age(year): mean(range)**
11 (36.7)	**Younger than 4 years, No.(%)**
23/7 (76.6)	**Sex: M/ F (%M)**
Atopic Diseases, NO.(%)	
8 (26.7)	**Asthma**
5 (16.7)	**Allergic Rhinitis**
3 (10)	**Eczema**
Serologic markers	
413.5±505.5 (high in 56.6%)	**Total IgE; mean (range)**
372.2±305.2 (high in 36.7%)	**Serum eosinophil count; mean(range)**
Symptoms, NO.(%)	
21 (70)	**Vomiting**
10 (33.3)	**Abdominal pain**
10 (33.3)	**Gaining weight failure**
5 (16.6)	**Heartburn**
3 (10)	**Cough**
3 (10)	**Fecal impaction**
2 (6.66)	**Constipation**
1 (3.3)	**Dysphagia**
2	**The mean duration of symptoms (year)**

The skin prick test findings showed that 28 patients (93%) tested positive to foods. Two patients were monosensetized to egg white, and one was monosensetized to milk. The rest were polysensetized to more than one food. The most common positive tests were reported for sesame (60%) and walnut(50%),followed subsequently by egg white, egg yolk, peanut, corn, soy, milk, wheat, shrimp, and cocoa; the less positive tests were for lamb, fish, and tomato(Table2). The results of the skin prick tests were not dependent on gender, level of IgE, and eosinophilia.

Results from the patch test showed that 17of 30 patients (56.6%) had positive test to foods. Three patients were monosensetized to peanut, walnut, and soya, and the rest were polysensetized. The most common positive test was for fish (27%), followed by egg yolk, peanut, walnut, cow's milk, egg white, soy, and wheat (Table2).

Based on allergy testing, elimination diets for selected foods were advised. Four of 30 patients did not obey the regimen due to non-compliance. Of 26 patients who met the elimination diet, 11(42%) achieved complete remission, 8 (30%) patients had partial remission, and 7(26%) did not respond. Sequential food rechallenge after achieving complete remission in 11 cases showed that the most common food allergy reactions were reported for milk (five cases), peanut (four cases), egg (three cases), and fish (two cases).

Table 2. Result of skin prick Test and skin patch test in eosinophilic esophagitis patients

Food Allergen	Skin prick test	Skin patch test
Sesame	18(60%)	-
Walnut	15(50%)	**5(16%)**
Egg white	13(43%)	**3(10%)**
Egg yolk	13(43%)	**6(20%)**
Peanut	12(40%)	**5(16%)**
Corn	11(36%)	-
Soy	11(36%)	**2(7%)**
Milk	10(32%)	**3(10%)**
Wheat	8(27%)	**1(3.3%)**
Shrimp	8(27%)	-
Cocoa	6(20%)	-
Tomato	6(20%)	-
Beef	5(10%)	-
fish	-	**8 (27%)**

DISCUSSION

EOE is a chronic inflammatory disease of the esophagus characterized by dense tissue eosinophilia. This disorder is identified by T-helper type 2 cell inflammation and cytokines, such asIL13, IL4, and IL5 in the gastrointestinal system.[11,12] The present study is consistent with a previously published article reporting higher rate of atopy and sensitization to foods.

Most studies show high level of total IgE in EoE patients. However, it does not seem that total IgEis specifically linked to EoE disease, and post-treatment level of total IgE has remained above normal for many years.[10,13,14,23]In the present study, the total IgE level was higher than normal level in 17(56.7%) cases. These findings are close to another study, which reported the prevalence of higher total IgE for about 70% of the patients: around 42.3% patients had very high level of total IgE.[5] Other presentations reported that 78% of the children with EoE had high levels of total IgE.[10,13,14]

In this study, the prevalence of eosinophilia was around 36.7% in EoE patients. This prevalence is most likely similar to other studies on EoE children. In another study on 18 patients with EoE, the prevalence of eosinophilia was 44.4%;[15] in other studies, the prevalence of peripheral eosinophilia was reported as 58 %.[16]

Associations of EoE with atopic disease were noted. In other studies, almost77–80% EoE patients had atopic bases; in some studies, EoE was related to atopic disease.[17,18] Possibly, having atopic disease with systemic sensitization is instrumental in pathogenesis of EoE, and exposure to allergens can lead to EoE.[12] In this study, asthma was seen in 8(26.7%) patients, and allergic rhinitis and eczema were seen in 5(16.7%) and 3(10%) patients respectively.

Several studies have confirmed the association of food allergy as a trigger of EoE. The first study describing the potential causation of EoE by dietary allergens was reported by Kelly et al. in1995. In this study, 10 children with EoE responded to aminoacid based formula and were observed to then have a significant decreased count of intraepithelial eosinophil.[9]Many additional studies have supported these findings.[19]Kagalwalla et al. showed that22 of 25 (88%) children with EoE treated with elemental diet and 26 of 35 (74%) treated with elimination of cow's milk, soy, wheat, egg, and sea foods achieved significant improvement of esophageal inflammation (≤10 eosinophils/high-power field).[20] In a more recent

study, histologic remission was found in 10 of 12 (83%) children with a mean age of 4.6±6.0 years treated with an exclusive elemental formula.[21]

In one study, a total of 26 patients (22 males, 4 females) with eosinophilic esophagitis underwent both skin prick testing and patch testing. Milk and egg were the most common positive foods with skin prick testing. Wheat was the most common positive food with patch testing. The patients were advised to avoid these positive foods. Overall, 18 patients witnessed resolution of their symptoms and six patients had partial improvement: after intervention, esophageal eosinophil counts improved from 55.8 to 8.4 eosinophils per high-power field.[10]In one study on94 children, the combination of patch, skin, and RAST testing could accurately predict causative food antigens in 70% patients.[13]

About 93% EoE patients evaluated in this study had positive skin prick tests. In another study in which these tests were carried out on EoE children, 73% participants tested positive after prick test: the sample size was approximately close to the current study. Most positive tests were reported regarding sesame, walnut, and egg white. In the study above, most positive skin prick tests were for milk, egg, and peanut respectively.[17] Milk had the seventh rank and peanut the fourth as positive in skin prick tests.[17,22] Differences between the prevalence of the so-called positive tests in Iran and other countries are obvious, which is due to differences in food allergen sensitizations in different communities. These findings are different from other studies, which reported sensitization to milk, egg, and wheat as common food allergens.

These findings demonstrate that 56.6% of EoE patients tested positive upon patch test: this is less than similar studies, where this figure was about80%.[20] Positive patch tests were highest for fish and egg yolk respectively. In another study, highest positive tests were for wheat, corn, and beef. Wheat had the least prevalent positive test.[17]These differences could be because of different eating cultures in different countries as various patch tests were used in these studies for different populations.

The main treatment of EoE is dietary modification or pharmacologic treatment. The most common drugs to treat EoE are swallowed steroids. Although the response is excellent, dietary approach is preferable because of the side effects of topical and systemic corticosteroids and relapse of symptoms after discontinuation. There are different dietary treatments for EoE patients, such as amino acid based elemental diet, six-food elimination diet, and allergy testing guided-dietary restriction. Despite reports on remission following different EoE elimination diets, in daily practice a strict diet is difficult to apply and may have a major impact on the quality of life of pediatric patients and their families. Therefore, empirical or allergy test-directed approaches are more accepted than elemental diet because of better compliance, fewer removal of foods, less food reintroduction, and fewer endoscopies.[23] The use of combined allergy tests to evaluate the immediate and delayed allergic sensitivity to foods allows a select elimination diet with less impact on the daily and social life of these patients.

Recent meta-analysis of all published retrospective and prospective studies revealed that the overall effectiveness of all available dietary treatments with regard to inducing histologic remission in EoE was 66.3% (95% confidence interval 56.9-75.0): there were no significant differences in response between pediatric and adult patients.[24]In this survey, about 72% of the patients who underwent elimination diet and obeyed the regimen responded to the treatment (42% complete and 30% partial remission). The most common food allergy reactions detected in our patients were milk, peanut, egg, and fish.

This study supports previous studies in which allergic sensitization based on allergic testing does not necessarily prove food allergy. Therefore, elimination diet and consequently reintroduction of single foods areneeded.[25]In this study, endoscopy was not repeated after remission because of low compliance of the patients.

Most of the patients were male, which is similar to other studies.[26]In another study, the prevalence of EoE was more in males than females. Clinical characteristics were evaluated in EoE patients in another study: the prevalence in males was57.1%.Yetanother study found that in 30 adult patients with EoE, about 73.3%, were male.[27,28] There are studies that reviewed EoE patients and reported that typically most of them were male.[29]

Evaluating symptoms in our patients showed that vomiting (70%) is the most prevalent symptom in EoE patients. In other studies on EoE patients, the most prevalent symptom was dysphagia with prevalence of 60% and more than 90 %.[28-30] Similar to the present study, in a study on35 EoE children younger than10

years, the most prevalent symptoms were vomiting (71.4%) and abdominal pain (51.4%).[27]Possibly, differences in the prevalence of symptoms associated with EoE are affected by patients' nutritional habits or medication history.

This study was undertaken to evaluate demographic factors including age, gender, chief complaint, total IgE level, and the results of food allergic tests in Isfahan because detecting food allergens is necessary in every community to prescribe the best treatment. This is the first such study conducted in Iran. The limitation of this study is its small sample size. All patients were selected from one pediatric hospital in a specific city; further studies with larger sample sizes from different cities are recommended for better and more reliable findings. Another limitation was that the study lacked skin prick test and patch test for majority of allergens. Also, it did not evaluate the eliminating effect of environmental allergens-such as aeroallergens—which are important in the pathogenesis of EoE.

Our series confirms the high degree of atopy in Iranian children with EoE. These patients seem to be polysensitized to several food allergens. Food allergic tests may be useful in detecting relevant food sensitivities and in making a more select approach to food avoidance possible. Because of different eating cultures in different countries, considering special foods in selecting allergens for allergic tests is necessary. Pursuing such studies in larger groups in different cities of Iran is suggested.

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