

# Eosinophilic Esophagitis: Demographic, Clinical, Endoscopic, Histologic, and Atopic Characteristics of Children and Teenagers in a Region in Central Spain

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## ■ Abstract

*Background and objective:* Eosinophilic esophagitis (EoE) is an increasingly prevalent chronic inflammatory disease of the esophagus with an immunologic etiology. Few studies have been published on EoE in children and adolescents. The objective of this study was to analyze the demographic, clinical, serologic, endoscopic-histologic, and atopic characteristics of pediatric patients with EoE and to identify atopic and digestive comorbidities.

*Methods:* We conducted a prospective observational study in children and adolescents (<16 years) assessed in a specialized multidisciplinary EoE unit in a tertiary referral hospital in a central region of Spain between 2011 and 2015.

*Results:* Thirty-five patients were included in the study. Twenty-eight (80%) were male. The mean age was 9.6 years, 83% were atopic, and 28% reported a family history of atopy. The most common symptom was dysphagia (51%). Eosinophilia was detected in the blood of 60% of patients. Eosinophil cationic protein and total IgE were elevated in 88% and 77% of patients, respectively. The most frequent endoscopic finding was linear grooves (57%). Skin tests with aeroallergens were positive in 82% of patients (pollen 62% and food 60%). The main atopic comorbidities were asthma (48%) and rhinoconjunctivitis (37%). Digestive diseases were more often associated with gastritis and *Helicobacter pylori* infection (17%).

*Conclusions:* Our results are similar to those previously reported. EoE is more common in boys and in individuals with a history of atopy and sensitization to airborne allergens and food. These results support the consideration of EoE as an atopic disease and underline the important role of allergists in early diagnosis and treatment.

**Key words:** Children. Teenagers. Eosinophilic esophagitis. Atopic comorbidities. Digestive comorbidities. Allergens. Esophagoscopy.

## ■ Resumen

*Introducción y objetivos:* La esofagitis eosinofílica (EoE) es una enfermedad inflamatoria crónica, emergente del esófago, con etiología inmunoalérgica. Hasta ahora, pocos estudios sobre esta enfermedad en niños y adolescentes han sido publicados. El objetivo de este estudio era estudiar las características epidemiológicas, clínicas, serológicas y endoscópico-histológicas de estos pacientes y las comorbilidades alérgicas y digestivas.

*Metodología:* Es un estudio observacional descriptivo en niños y adolescentes (<16 años), estudiados en una unidad multidisciplinar en un hospital de tercer nivel en una región del centro de España.

*Resultados:* Se incluyeron en el estudio 35 pacientes. 28 eran hombres (80%). La edad media era 9,6 años, el 83% eran atópicos y tenían antecedentes familiares de atopia el 28%. El síntoma más común fue la disfagia (51%). Se detectó eosinofilia en sangre en el 60% de los pacientes. La proteína catiónica del eosinófilo y la Ig E total estaban elevadas en el 88% y 77% de los pacientes, respectivamente. El hallazgo endoscópico más frecuente fueron los surcos lineales (57%). Los tests cutáneos fueron positivos en el 82% de los pacientes (polen 62%, alimentos 60%). Las comorbilidades atópicas fueron, asma (48%) y rinoconjuntivitis (37%). Las enfermedades digestivas más asociadas fueron gastritis e infección por *Helicobacter pylori* (17%).

*Conclusiones:* Nuestros resultados son similares a los publicados previamente. La EoE es mas frecuente en niños, con historia de atopia, sensibilizados a aeroalérgenos o alimentos. Estos resultados apoyan que la EoE pueda considerarse una enfermedad atópica y el importante papel del alergólogo en el diagnóstico y tratamiento precoz de esta enfermedad.

*Palabras clave:* Niños. Adolescentes. Esofagitis eosinofílica. Comorbilidades atópicas. Comorbilidades digestivas. Alérgenos. Esofagoscopia.

## Introduction

Eosinophilic esophagitis (EoE) has been defined as a chronic immune/antigen-mediated esophageal inflammatory disease characterized clinically by esophageal dysfunction and histologically by eosinophil-predominant inflammation [1]. Its prevalence varies from 0.89 cases per 10 000 inhabitants in Western Australia to 4 cases per 10 000 infants in Ohio, United States. In Europe, an annual incidence of 0.16 cases per 10 000 population has been reported in southern Denmark [2]. According to recent reports, the incidence and prevalence of EoE has increased notably throughout the world [3].

Studies conducted in children suggest that the symptoms of EoE are triggered by food allergens in many cases [1]. A recent report described the development of EoE in 3 adults after exposure to aeroallergens [4]. Whether this also occurs in pediatric patients remains to be demonstrated, although seasonal exacerbation of the disease has been reported in children [5].

The lack of an early diagnosis and treatment during childhood or adolescence may result in sequelae or complications, even in proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) [6].

Because of its similarities to other allergic diseases, EoE has been considered to be an allergic condition, or more specifically, a form of food allergy because patients tend to have food sensitization and experience an improvement in symptoms and inflammation after the elimination of certain foods [7]. The optimal means of identifying causative foods remains unclear. A food is considered to cause EoE if its elimination from the patient's diet leads to resolution of esophageal eosinophilia and its reintroduction leads to recurrence of EoE [8].

The objectives of this study were to describe the demographic, clinical, endoscopic, histologic, and atopic characteristic of pediatric patients with EoE in the city and province of Ciudad Real in central Spain; evaluate relevant laboratory parameters such as total IgE, serum eosinophil cationic protein (ECP), and peripheral blood eosinophil count; calculate the frequency of allergic sensitization to foods and aeroallergens; determine the prevalence of EoE in patients with a history of oral immunotherapy with foods (milk and egg); and identify atopic and digestive comorbidities.

## Methods

### *Patient Selection and Eligibility*

This was a prospective observational study including children and teenagers (<16 years of age) consecutively

assessed in a specialized multidisciplinary EoE unit in a tertiary referral university hospital in Ciudad Real. The unit is composed of the following services: pediatric gastroenterology (children aged 0-13 years), adult gastroenterology (teenagers aged 13-16 years), and allergology (children and teenagers aged 0-16 years). Patients diagnosed with EoE from January 2011 to December 2015 by any of the 3 services were included.

The diagnostic criteria for EoE included: *a*) upper gastrointestinal symptoms (nausea and vomiting, abdominal and chest pain, lump in throat or chest, deglutition disorder, halitosis) dehydration, chronic cough, and symptoms of esophageal dysfunction (dysphagia, choking, etc.); *b*) infiltration of esophageal epithelium by  $\geq 15$  eosinophilic leukocytes (eos) per high power field (HPF) at 400x light microscopy; and *c*) exclusion by clinical history of drug intake, parasites, caustics, hematological neoplasms, or other illnesses that could give rise to EoE. Biopsies were taken from the upper and lower thirds of the esophagus, with a minimum of 5 specimens taken from each location. The specimens were routinely processed for histopathologic analysis. All endoscopic exams were carried out by an endoscopist trained in EoE.

The inclusion criteria for the study were a definitive diagnosis of EoE and written informed consent from the children's parents or legal representatives. In the patients diagnosed in 2011 (n=6), gastroesophageal reflux disease was ruled out by prescribing treatment with omeprazole (1mg/kg/d for 2 months) prior to the endoscopy. In the remaining patients (n=34), omeprazole was prescribed only after the first endoscopy, and the dose was doubled to rule out PPI-REE [1].

The study was approved by the hospital's ethics and clinical research committee and conducted in accordance with the principles of the World Medical Association and the Declaration of Helsinki.

### *Demographic Assessment*

The following data were recorded for each patient: age, sex, family and personal history of atopy, exacerbation of symptoms of EoE in the pollen season, and place of residence (rural or urban).

### *Clinical Assessment and Comorbidities (Allergic and Digestive Disorders)*

Symptoms of esophageal dysfunction [9] and other common digestive symptoms in children with EoE were recorded (Table 1) together with clinical symptoms related to the ingestion of the most frequent foods involved in EoE.

Information on allergies (rhinoconjunctivitis, asthma, atopic dermatitis, anaphylaxis, food allergy, aeroallergen

allergy) and digestive diseases (gastroesophageal reflux disease, stomach inflammation, *Helicobacter pylori*, celiac disease, Crohn disease) was also obtained from the patients' medical records.

### Serologic Markers

Peripheral blood eosinophil count, ECP levels, and IgE levels were determined [10] together with specific IgE to a series of foods (cereals, legumes, milk, egg, fish, crustaceans, and nuts) and aeroallergens (mites, pollens, epithelia, and fungi) by ImmunoCAP (Phadia). Concentrations of over 0.35 kU/L for specific IgE and over 15 µg/mL for serum ECP were considered to be positive.

### Endoscopic and Histological Assessment

All endoscopic procedures were performed under conscious sedation with propofol supervised by an anesthetist. The explorations were performed with a flexible HD gastroscope with an outer diameter of 9 mm and a working channel of 2.8 mm (GIF-H180, Olympus Medical Systems) and an Exera II image processor (Olympus Medical Systems). Biopsy specimens were taken with a conventional needle clamp (Radial Jaw 4, Boston Scientific) from the proximal and distal third of the esophagus; at least 5 samples were taken from each section. Samples were fixed with 4% formaldehyde and sent for histologic analysis. Endoscopic signs suggestive of esophageal dysfunction, such as longitudinal grooves, pseudo rings, and microabscess in the mucosa, were recorded.

The biopsy specimens were sent to the pathology laboratory, where they were embedded in paraffin; serial sections of 3 to 5 µm were subsequently prepared and stained with hematoxylin and eosin. The samples were examined under a Nikon Eclipse 80i optical microscope with an HPF (x400) of 0.24 mm<sup>2</sup>. Samples were also stained with periodic acid-Schiff to exclude the presence of fungi. A sample was diagnosed as histologically compatible with EoE when 15 eos/HPF or more were detected, with or without microabscesses. The presence of hyperplasia of the basal layer and the number of eos/HPF sections in the upper, middle, and lower sections were also analyzed.

### Allergy Workup

The allergy study consisted of a standard series of tests [11] to ensure homogeneity and avoid bias. Skin prick tests (SPTs) were performed with a commercial series of aeroallergens (*Dactylis glomerata*, *Lolium perenne*, *Olea europaea*, *Cupressus arizonica*, *Platanus acerifolia*, *Artemisia vulgaris*, *Chenopodium alba*, *Plantago lanceolata*, *Salsola kali*, *Cladosporium*, *Alternaria*, *Aspergillus*, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Lepidoglyphus destructor*, and cat and dog dander); food (peanut, corn, wheat, soy, egg white, cod, tuna, prawns, cow's milk, lentils) [11]; and panallergens (lipid transfer protein, profilins, and tropomyosin). These tests were carried out following the recommendations of the European Academy of Allergy and Clinical Immunology. The allergens were supplied by ALK-Abelló Laboratories (Madrid, Spain). Histamine (10 mg/mL) and normal saline were used as positive and negative controls. A wheal with an

Table 1. Demographic, Serologic, Clinical, and Endoscopic Characteristics of 35 Children and Adolescents with EoE

Demographics	
Sex M/F (% M)	28/7 (80)
Age, mean (range), y	9.6 (4-16)
Rural (vs urban) residence	10 (28.5)
Personal history of atopy, No. (%)	9 (26)
Family history of atopy, No. (%)	10 (28.5)
Atopy, No. (%)	29 ( 83)
Milk oral immunotherapy, No.	3 (8.5)
Egg oral immunotherapy, No.	3 (8.5)
Serologic markers	
Serum eosinophil count, mean (range) cells/cm <sup>3</sup>	519 (100-1700) (high in 60%)
ECP, mean (range), mcg/L	36 (8-171) (high in 88%)
Total IgE, mean (range), kU/L	508 (11-10 550) (high in 77%)
Positive genetic test for celiac disease, No. (%)	1 (3)
Seasonal reactivation of EoE, No. (%)	0 (0)
Clinical findings, No. (%)	
Dysphagia	18 (51)
Food impaction	7 (20)
Choking	2 (6)
Regurgitation	3 (8.5)
Heartburn	2 (6)
Abdominal pain	11 (31)
Chest pain	3 (8.5)
Lump in the throat	2 (6)
Nausea and vomiting	7 (20)
Lump in the chest	1 (3)
Halitosis	2 (6)
Deglutition disorder	5 (14)
Dehydration	1 (3)
Stunted growth	2 (6)
Chronic cough	2 (6)
Endoscopic and histologic findings	
Normal macroscopic endoscopy, No. (%)	8 (23)
Phenotypes (inflammatory/fibrosis), No.	27/0
Edema, No. (%)	9 (26)
Acanthosis, No. (%)	3 (8.5)
Furrows, No. (%)	20 (57)
Rings, No. (%)	2 (6)
Exudates, No. (%)	10 (28.5)
Alterations in the mucus, No. (%)	5 (14)
Intestinal villous atrophy, No. (%)	3 (8.5)
Eos/hpf upper tract, mean (range), No.	37 (0-100)
Eos/hpf medium tract, mean (range), No.	16 (0-70)
Eos/hpf lower tract, mean (range), No.	47 (0-100)
Basal hyperplasia, No. (%)	12 (35)
Degranulation of eosinophils, No. (%)	3 (8.5)

Abbreviations: ECP, eosinophilic cationic protein; EoE, eosinophilic esophagitis; Eos/hpf, eosinophils per high-power field.

area 7 mm<sup>2</sup> larger than or a diameter 3 mm longer than the negative control (saline solution) was considered positive.

We also measured serum total IgE and specific IgE (kU/L) to foods that have been linked to EoE in our setting (milk, egg, wheat, lentils, peanuts, shrimp, and hake).

### Statistical Analysis

Absolute frequencies were calculated for qualitative variables and means, SD, 95% confidence intervals, and ranges were calculated for quantitative variables.

## Results

Thirty-five patients (28 males and 7 females; mean age, 9 years and 6 months; range, 4-16 years) were diagnosed with EoE between 2011 and 2015 at the multidisciplinary EoE unit at our hospital. The demographic, clinical, laboratory, histologic/endoscopic characteristics are summarized in Table 1 together with details of atopic and digestive comorbidities.

It is important to note that although 83% of the patients were atopic, no seasonal variations in EoE symptoms were observed; dysphagia was present in more than half of the patients and abdominal pain in nearly one-third. The most common endoscopic finding was linear grooves, followed by exudates. The macroscopic appearance of the endoscopy was normal in 20% of patients. Eosinophils were more abundant in the distal portion of the esophagus (Table 1). Over 80% of patients were sensitized to airborne allergens (SPT) and 60% were sensitized to food. The atopic comorbidities present in more than half of the patients were bronchial asthma, food allergies, and rhinoconjunctivitis. Digestive comorbidities were less prevalent (<12% of patients had *Helicobacter pylori* infection and stomach inflammation (Table 2).

Of the 18 patients with EoE and food allergy, 6 had been treated with oral immunotherapy. Milk was confirmed as the causative agent in the 3 patients treated with oral immunotherapy for cow's milk allergy. The other 3 patients had undergone oral immunotherapy for egg allergy, but a causal link was not established with egg as 2 of the patients did not respond to an egg-free diet and the third refused to continue the study

## Discussion

The demographic characteristics of the series of children and adolescents with EoE described in this study match those reported by other authors [9,12]. EoE is more common in white males and in our series it was much more common in those who lived in an urban rather than a rural area. We did not find information on this sociodemographic variable in relation to EoE in the literature, but EoE has been reported to be more prevalent in developed countries [13]. Both the mean age at diagnosis (9.6 years) in our area (central Spain) and the proportion of atopic children and adolescents are similar to those reported by researchers in Texas, United States. A family history of atopy, however, was more uncommon in our series. The authors of the Texan study suggested that early

Table 2. Allergy Study and Comorbidities<sup>a</sup>

Positive SPT to aeroallergens 28/35 (82%)	Positive sIgE to aeroallergens
Mites	3 (8.5)
Pollens	4 (11.5)
Fungi	3 (8.5)
Epithelia	4 (11.5)
Positive SPT to foods	Positive sIgE to foods
Milk	15 (43)
Egg	11 (31.5)
Wheat	9 (26)
Lentils	14(40)
Prawn	4(11.5)
Hake	5(14)
Peanut	13 (37)
Positive SPT to panallergens	
Lipid transfer protein	5 (14)
Profilin	4 (11.5)
Tropomyosin	2 (6)
Atopic comorbidities	Digestive comorbidities
Asthma	Gastritis 4 (11.5)
Rhinoconjunctivitis	<i>Helicobacter pylori</i> 4 (11.5)
Atopic dermatitis	Celiac disease 1 (3)
Urticaria/angioedema	GERD 1 (3)
Anaphylaxis	Crohn disease 0 (0)
Food Allergy	
Aeroallergen allergy	

Abbreviations: GERD: gastroesophageal reflux disease; sIgE, specific IgE; SPT, skin prick test.

<sup>a</sup>Data expressed as number (%) of patients.

onset of allergy in parents may be a predisposing factor for EoE in offspring.

Clinical manifestations of EoE vary with age. Infants and young children typically have nonspecific symptoms, such as vomiting, unexplained feeding difficulties [14,15], abdominal pain, and swallowing disorders [16]. In adolescents, dysphagia and food impaction are predominant [12,13]. In exceptional cases, chronic and recurrent cough can be a symptom of EoE in children [17]. EoE should be ruled out in children with stunted growth [18]. The most common symptom in our series was dysphagia, probably because the mean age at diagnosis of EoE was between 9 and 10 years. As in other studies, our patients did not manifest symptoms elicited by the foods most frequently involved in EoE.

As in adults, analytical parameters such as peripheral blood eosinophilia and elevated total IgE indicate the presence of atopy in children. ECP is a marker of eosinophilic inflammation, which can be located in any of the organs (esophagus, bronchi, etc). None of the above parameters are useful, however, for the diagnosis of EoE [1,10]. Endoscopy with esophageal biopsies is necessary to confirm EoE in children, adolescents, and adults [1].

The macroscopic appearance of the esophageal mucosa may be normal in one-third of patients [19], making it mandatory to take esophageal biopsies by sections. In our series, the endoscopic findings were normal in 23% of patients. The combination of endoscopy and biopsy findings helped to define the 2 phenotypes of EoE (inflammatory and fibrostenotic) [20]. Stenosis was rare in our series, probably because of the young age of our patients, as stenosis becomes more common as the disease develops [12].

Elimination diets are considered the first-line therapy for EoE in children [21], although they appear to be less effective in adult patients [22,23]. That said, in recent years, EoE remission rates of over 70% have been reported for adults treated with an empiric 6-food elimination diet [24] and diets based on allergy tests [25]. The allergic mechanism of EoE involves both IgE and non-IgE processes [26], possibly explaining why treatment with diets based on immediate hypersensitivity test results fails in approximately 30% of cases.

A higher prevalence of sensitization to food extracts has been detected by ImmunoCAP than by skin prick testing in both adults and children [9,27]. A similar situation was observed in our series (Table 1).

Studies of EoE epidemiology and pathophysiology support the link between EoE and allergy in general, while studies of food allergy testing and elimination diets support a link between EoE and food allergy. Although food elimination diets can resolve symptoms in children with EoE, the results of allergy tests and elimination diet studies are not as clear in adults. In addition, aeroallergen sensitizations may play a larger pathophysiological role in adult EoE. Although the consideration of EoE as a form of food allergy is supported by several studies in children and adults, the usefulness of SPT and atopy patch testing for food allergies is still uncertain, and an optimal elimination diet for disease management has yet to be found [28].

The higher prevalence of EoE in patients with atopic diseases suggests a common background with allergy, but neither its etiology nor pathophysiology is clearly understood [21].

EoE shares features with other atopic diseases in terms of pathogenesis, genetics, epidemiology, and treatment options. EoE patients have a higher rate of atopic disease (asthma, allergic rhinitis, atopic dermatitis and food allergy) than the general population [15,29]. The patients in our series had a higher proportion of asthma than in other series of EoE patients and the general population. Elevated serum IgE levels have also been associated with a greater risk of bronchial hyperreactivity in individuals with EoE [30]. In our series, bronchial asthma was the most common comorbid allergic disease, coinciding with results from an Asian study [31].

Coexistence of EoE should be suspected in all children who undergo upper gastrointestinal endoscopy for suspected celiac

disease, as higher rates of EoE have been reported in children with celiac disease than in the general population (prevalence of 10.7% in a recent cohort) [32]. Other authors are of the opinion that patients with celiac disease are no more likely to have EoE than patients in whom endoscopy was performed for other reasons [33]. None of the patients in our series had Crohn disease.

EoE reactivations have been reported in the pollen season [5]. In our study we asked about worsening of gastrointestinal symptoms in the pollen season. There was, however, just 1 case of histologically confirmed EoE symptoms in spring and the patient did not experience remission at the end of the season.

Around 2.7% of children treated with oral immunotherapy with food subsequently develop EoE [34,35]. Our results show a higher rate, as 3 of the 62 patients treated with oral immunotherapy for milk allergy (4.8%) developed EoE. The patients had complained of dysphagia and a diagnosis of EoE was confirmed after endoscopy with esophageal biopsies; the condition resolved in 3 patients on removing milk from their diet [36]. Three patients on oral immunotherapy with egg also began with dysphagia, but another patient who had discontinued oral immunotherapy with egg 2 years earlier also developed EoE. Therefore, milk may be considered the cause of EoE in the patients who underwent oral immunotherapy for milk allergy. However, the food to which a patient is desensitized may not always be responsible for the EoE, as was the case with egg in our series. In these cases, EoE may be a comorbidity.

Cough was the predominant symptom in 2 children in our series, highlighting the importance of remembering that young children may exhibit a range of symptoms other than the typical gastrointestinal symptoms associated with EoE [37].

Effective treatment of EoE requires a multidisciplinary approach involving gastroenterologists, pediatricians, pathologists, allergists, and sometimes nutritionists and otorhinolaryngologists [16,38]. This multidisciplinary approach is important to prevent both short- and long-term complications of this chronic disease and treatment-related adverse effects [39].

Recent studies support the role of the allergist in the management of EoE, especially for food allergen testing and interpretation and the management of food allergies and concurrent atopic diatheses. In addition, allergists have made significant research contributions to our understanding of EoE [40].

EoE is currently considered to be a chronic health condition whose increasing prevalence is placing a significant burden on the health care system [41].

In conclusion, it is important to rule out EoE both in children with characteristic gastrointestinal symptoms of this disease and in children with atypical manifestations such as chronic cough, stunted growth, or swallowing difficulties. This is particularly important in the case of atopic boys. An upper gastrointestinal endoscopy with biopsies should be performed to ensure an early diagnosis and prevent complications. Allergists play a critical role as they are experts in the treatment of atopic diseases, including avoidance strategies that can improve the quality of life of pediatric patients and their families.

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### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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