A real-world characterization of a cohort with eosinophilic esophagitis: looking for severity biomarkers

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Abstract

Background: Eosinophilic esophagitis (EoE) is an immune-mediated chronic esophageal disease, with frequent association with atopy. A validated non/minimally invasive biomarker of disease severity has not been identified. **Objective:** We aimed to determine if sensitization to airborne and food allergens correlates with disease severity, and to evaluate the association between clinical and laboratory characteristics with the severity of EoE.

Methods: Retrospective study of EoE patients observed in a differentiated center, 2009-2021. The association between patients' diagnosis age, disease duration before diagnosis, sensitization to airborne/food allergens, serum total IgE and peripheral blood eosinophil values and severe clinical disease (presence of symptoms with a significant impact on quality of life and/or ≥ 1 hospital admission due to EoE complications, namely severe dysphagia, food impaction or esophageal perforation) and histological severe disease (≥55 eos/hpf and/or microabscesses in esophageal biopsies) was evaluated.

Results: 92 patients were observed, 83% male, 87% atopic. There was a mean delay in diagnosis of 4 years (range 0-31). 84% had aeroallergen sensitization and 71% food sensitization. Food impaction and dysphagia were the most frequent symptoms, and severe clinical disease was observed in 55%. Histologically, 37% had severity criteria. Patients with severe clinical disease had a significantly longer mean disease duration before diagnosis than patients without severe clinical disease (79 *vs.* 15 months; $p=0.021$). Patients who described food impaction were significantly older at time of diagnosis than those who have never had impaction (18 *vs.* 9 years; $p<0.001$).

There was no significant association ($p<0.05$) between sensitization, serum total IgE and peripheral blood eosinophil values and clinical or histological severity.

Conclusions: An older age at diagnosis and a longer disease duration before diagnosis appear to be useful for predicting EoE clinical severity. Despite having been demonstrated a high prevalence of allergic disease, the presence of sensitization to airborne and/or food allergens do not seem to be useful for predicting clinical or histological severity.

Keywords: atopy; eosinophilic esophagitis; food allergy; sensitization; severity biomarkers.

Impact Statement: Eosinophilic esophagitis has a male predominance and an early diagnosis is essential to avoid development and progression of disease. Despite the high prevalence of atopy and sensitization to airborne and food allergens, it does not appear to play a role as disease severity biomarker.

Introduction

Eosinophilic esophagitis (EoE), a complex and heterogeneous disease, first described in 1978, is a chronic immune-mediated inflammatory disorder characterized clinically by symptoms of esophageal dysfunction and histologically by an eosinophil-predominant inflammation of the esophagus (1, 2) response to inhalant and food allergens. It is more common in males, with a ratio of 3:1. Although 65% of cases occur during childhood, there is a second peak of incidence between 30 and 44 years of age (3, 4).

Briefly, it is known that the pathogenesis of EoE involves the interaction of genetic and environmental factors leading to impaired epithelial esophageal barrier function, allowing the interaction of environmental and food allergens with the antigen-presenting cells, leading to an inflammatory response mediated by Th2 interleukins (IL), IL-4, IL-5, and IL-13 secreted by Th2 cells, increasing eotaxin 3, recruiting and activating eosinophils, basophils, and mast cells, inducing chronic inflammation, tissue damage, fibrosis and dysmotility with smooth muscle cell constriction (1, 5).

EoE could be triggered by food, mainly milk, often associated with egg, wheat, and soy. It may be associated (15% of cases) with severe IgE-mediated reactions to some foods, mostly peanut, milk, and eggs. Atopic diseases are more prevalent in EoE than in the general population, manifested by asthma, allergic rhinitis, and atopic dermatitis. Besides, recent findings suggest that EoE is a late manifestation of the allergic march in some individuals and that sensitization to foods and/or aeroallergens early in life may predispose to EoE development. (6). Nevertheless, the allergic mechanisms remain poorly understood. EoE is associated with a high total Immunoglobulin E (IgE) level and with sensitization to food allergens (75%) and respiratory allergens (73%), but IgE-mediated mechanisms cannot account for all the changes observed and complex mechanisms involving the innate and adaptive immune system may be involved (5, 7).

The presenting symptoms vary with age: in adults the most common are dysphagia, gastroesophageal reflux disease symptoms, heartburn and food impaction, owing to the progressive evolution towards esophageal stenosis. In contrast, children present more commonly with vomiting, heartburn, regurgitation, emesis, and abdominal pain (5, 8). It is known that EoE may negatively affect the quality of life of patients and their families because of symptoms limiting normal feeding, with many patients reporting social and psychological implications of food-related illness (9, 10).

Recent consensus recommendations based on a systematic review of the literature and expert opinion led to the diagnostic criteria that EoE is a clinicopathological disease characterized by (a) esophageal symptoms including but not limited to dysphagia and food impaction in adults and feeding intolerance and gastroesophageal reflux disease (GERD) symptoms in children and (b) eosinophil predominant inflammation of ≥15 eosinophils per high power field (eos/hpf) in the esophageal tissue after exclusion of other disorders associated with similar clinical, histologic, or endoscopic features (11). Since eosinophilic infiltration of the esophagus may not be evenly distributed, at least six biopsies should be obtained from the proximal and distal esophagus to maximize the sensitivity (8).

Guidelines for the treatment of EoE were recently revised by the American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (JTF) (12). Swallowed topical corticosteroids are a popular primary therapy for EoE and were the only therapy in the AGA-JTF guideline to receive a strong recommendation based on moderate-quality evidence. Although response to PPIs is lower than reported with most corticosteroid studies, their safety and ease of administration can make them a good first-line treatment option in some patients (12).

Diet therapy is also a first-line option recommended for treatment of EoE in the AGA-JTF guidelines, although considered a conditional recommendation, due to low-quality evidence. Currently available strategies include elemental diets and empirical or target elimination diets. There may be challenges with long-term adherence to dietary elimination and a major limitation to the use these diets in treatment of EoE is the need for repeated endoscopic biopsy assessment during the food reintroduction process (12, 13).

There are some patients who may respond to treatment with endoscopic dilation, which will reduce the risk of future food impaction, but there is no associated benefit in terms of improving histological eosinophilia (10). Whenever possible, treatment should be oriented by a multidisciplinary team, consisting of a gastroenterologist, immunoallergologist and nutritionist for assessment of diet feasibility and nutritional follow-up (12, 13).

Presently, histological examination of esophageal mucosal biopsies is required to establish the diagnosis, assess response to therapy, document disease remission, and evaluate symptom recurrence. The necessity for numerous endoscopies to monitoring the disease and the lack of validated non-invasive invasive biomarkers or tools are the main reasons for the significant burden on patients and on the healthcare system. There is an urgent need for non-invasive or minimally invasive biomarkers. Although, in recent years, several efforts have been tried to identify potential biomarkers for diagnosing, monitoring and predicting severity, and some promising candidates have been described in literature, it continues to be elusive (14).

The aim of this study, that included patients with EoE followed in a Immunoallergology department of a tertiary Portuguese hospital along 12 years, was to evaluate potential clinical and laboratory biomarkers that could correlate with clinical and histological disease severity and be obtained in a minimally invasive manner, namely patients' diagnosis age, disease duration before diagnosis, presence of sensitization to airborne and food allergens, serum total IgE and peripheral blood eosinophil values, , which could contribute to precision medicine in predicting disease severity.

Materials and methods

Study design and population

A real-world, single-center, retrospective, cross-sectional, study was conducted in our Immunoallergology department in Lisbon, Portugal. We performed an analysis of database of all patients diagnosed with EoE, followed in our department, from 2009 to July 2021. The association

between patients' diagnosis age, disease duration before diagnosis, sensitization profile, serum total IgE and peripheral blood eosinophil values and severe clinical disease and severe histological disease were evaluated (the criteria used to define the clinical and histological severity of EoE are defined in sections "Clinical Analysis" and "Laboratory and Endoscopic Analysis", respectively).

The population was characterized according to demographic data, personal history of atopy, defined as personal tendency to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins, according to the World Allergy Organization (15), symptoms associated with the diagnosis of EoE, aeroallergens sensitization and food sensitization by skin prick test (SPT), food atopy patch tests (APT) and specific IgE, according to SPT.

SPT were performed for common aeroallergens with commercial extracts (Bial-Aristegui®, Bilbao, Spain), namely house dust and storage mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Euroglyphus maynei*, *Lepidoglyphus destructor*, *Blomia tropicalis*, *Glycyphagus domesticus*, *Acarus siro*, *Tyrophagus putrescentiae*), dog and cat's fur, *Alternaria alternata*, *Aspergillus fumigatus*, mixtures of grasses, *Phleum pratense*, *platanus*, *Olea europaea*, *Parietaria judaica*, *Artemisia vulgaris* and *Plantago lanceolata*. Patients underwent SPT to selected foods according to clinical history suggestive of IgE-mediated food allergy, in addition to a standard panel of milk and proteins (alfa-lactoalbumin, beta-lactoglobulin, casein), soy, egg (yolk, white, ovalbumin, ovomucoid), meats (beef, chicken, turkey, pork and rabbit), fish (bream, hake, besugo, sea bass, sardine, horse mackerel, cod, tuna, salmon), seafood (shrimp), cereals (rice, wheat, barley, corn, rye, and oat), fresh fruits (apple, pear, and peach), tree nuts (walnut, hazelnut, cashew, almond, chestnut, pistachio, pinion) and peanut. The SPT were performed by an appropriately trained experienced professional. The positive control was performed using histamine dihydrochloride 10 mg/ml and the negative control was performed using isotonic saline solution. The SPT result was read after 15 minutes by measuring the wheals (mm) using a graduated ruler. Papules with an average diameter measuring 3 mm larger than the negative control was considered positive (16).

The food APT were performed using the following standard fresh foods: cow's milk, egg white (raw and cooked), egg yolk (raw and cooked), wheat flour, cornflour, walnut, hazelnut, cashew, almond, pistachio, pinion, beef, pork, chicken, turkey, shrimp (raw and cooked), hake, codfish and soy. Foods were mixed with isotonic saline and placed in aluminum cups (8-mm Finn Chambers® in scanpor tape, Smartpractice Europe GmBH, Germany) and adhered to the patient's back. The patches were removed at 48 hours and results were read at 72 hours. Reactions considered positive were classified as + for erythema and scattered papules, ++ for erythema and papules, and +++ for erythema and vesicles as per standard patch testing protocols (17).

A written informed consent was obtained from all patients or from the parents or legal guardians of those under 18 years old signed by all patients to use their clinical data in an anonymous form. Patients were treated according to ethical standards established in the Declaration of Helsinki.

Clinical Analysis

Severe clinical disease was defined based on our clinical practice as presence of symptoms with a significant impact on quality of life and/or ≥ 1 visit to the Emergency Department and/or hospitalization due to EoE complications, namely severe dysphagia, food impaction and/or esophageal perforation due to the progression of esophageal stricture. In the present study, the burden of disease on quality of life was subjectively assessed as reported by the patient and/or families in 3 domains, including emotional distress, limited normal feeding and restricted social activities, as the scores currently available for this assessment are not validated for Portuguese (9, 10). The criteria for defining EoE complications were adapted from Furuta GT et al (18) and Gomez Torrijos E et al. (19).

Laboratory and Endoscopic Analysis

Laboratory parameters (serum total IgE, peripheral blood eosinophil count) and findings in upper digestive endoscopy and the respective esophageal biopsies were also analyzed.

The diagnosis of EoE was performed using the established consensual clinical and histological criteria, which consider the presence of ≥ 15 eos/hpf in biopsy samples.

In this study, histological severe disease was defined by ≥ 55 eos/hpf and/or presence of microabscesses in esophageal biopsies. These criteria were adapted from van Rhijn BD et al., who divided patients in a group with high peak eosinophil count, characterized by 55–120 eos/hpf and a group with low peak eosinophil count characterized by 4–50 eos/hpf. This study showed that higher fibrotic and inflammatory signs scores in endoscopy, presence of esophageal stricture and eosinophilic microabscesses are associated with higher peak eosinophil counts (20).

Statistical Analysis

Statistical analysis was performed using Excel (Microsoft Office 2021) and IBM SPSS Software, Version 25.0 (IBM Corp.). Continuous variables were presented as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions, and categorical variables as frequencies and percentages. Normal distribution was confirmed using Shapiro-Wilk test or skewness and kurtosis. For bivariate analysis, t-independent test or Mann Whitney test were used to compare parametric and non-parametric variables, respectively. Categorical variables were compared using Fisher's exact test or Pearson's chi-square (χ^2) test, as appropriate. P-values lower than 0.05 were considered statistically significant.

Results

Clinical characteristics

A total of 92 patients with eosinophilic esophagitis were included, of whom 76 were male (83%). Currently, twenty patients (22%) were <18 years. Mean age at the onset of symptoms was 17 years (standard deviation (SD) 14, range 1-63) and at diagnosis 21 years (SD 15, range 1-67). It was observed

a mean time gap between onset of symptoms and diagnosis of 4 years (range 0-31). In 47 (51%) patients' diagnosis was established at adult age and in 45 (49%) patients at pediatric age (< 18 years).

Most patients (n=80, 87%) had a history of allergic disease: 83% (n=76) allergic rhinoconjunctivitis, 36% (n=33) food allergy, 28% (n=26) asthma and 13% (n=12) atopic dermatitis **(Table I)**.

A seasonal spring exacerbation was considered when patients reported symptomatic esophageal complaints of EoE over this interval of time, translating flares of disease activity. Specifically, 6 (7%) patients allergic to tree and grass pollen reported clinical exacerbation in the spring months.

Patients with severe clinical disease had a significantly longer mean disease duration before diagnosis than patients without severe clinical disease (79 versus 15 months, respectively; p=0.021). It was not demonstrated an association between disease duration before diagnosis and severe histological disease (p=0.858).

Sensitization patterns

The skin prick tests with airborne allergens demonstrated a positive result in 77 (84%) patients. Among the patients with aeroallergens sensitization, house dust mites (n=66, 86%) and pollens (n=53, 69%) were the most common sensitivities observed. (**Figure 1**).

Sixty-five patients (71%) had food sensitization, demonstrated by skin prick tests in 45 patients (69%) and by food atopy patch tests in 34 (52%). All patients with food sensitization demonstrated by skin prick tests had also positive specific IgE. The foods with the highest frequency of sensitivity were seafood (n=24, 37%), cow's milk (n=19, 29%), nuts (n=18, 27%) and cereals (n=14, 21%). The complete distribution of food sensitization pattern of the studied population is represented in **Figure 2**.

Symptoms

The symptoms most frequently reported by patients and which led to the suspicion of the diagnosis of EoE were food impaction (n=63, 68%), dysphagia (n=56, 61%), gastroesophageal reflux (n=40, 43%) and vomiting (n=23, 25%), followed by chest pain (n=19, 21%), abdominal pain/bloating (n=17, 18%) and, at least, poor weight progression (n=2, 2%). Both patients with impairment weight development were pediatric.

The inaugural symptom most reported was food impaction (n=38, 41%), followed by dysphagia (n=28, 30%), and vomiting (n=13, 14%) (**Figure 3**).

In adult patients the most common presenting symptoms were food impaction (n=28, 60%) and dysphagia (n=15, 32%), whereas children presented predominantly with dysphagia (n=13, 29%) and vomiting (n=10, 22%).

Of the total of 51 patients with severe clinical disease (35 adults and 16 children), 88% (n=45) reported a significant impact of the disease on quality of life, with emotional disturbance being the most affected domain, and 49% (n=25) had clinical complications requiring urgent medical care and/or hospitalizations.

Patients who described food impaction (with or without the need for medical care) were significantly older at time of diagnosis than those who have never had impaction (median 18 years older versus 9 years older, respectively) ($p<0.001$).

Laboratory parameters

The mean value of total IgE of the population was 525 IU/mL. When comparing the means of total IgE in the group of patients with food sensitization (629 IU/mL) and without food sensitization (188 IU/mL), there was a statistically significant difference ($p=0.03$). Nevertheless, there was no statistically significant difference in the means of total IgE when comparing the groups with and without aeroallergen sensitization ($p=0.194$).

The mean value of peripheral blood eosinophils was 489/μL. There was no statistically significant difference in peripheral blood eosinophils mean values of patients with food sensitization and without food sensitization (537/μL versus 502/μL, respectively; $p=0.29$). Similarly, there were also no statistically significant differences in the mean peripheral blood eosinophil values between the groups with and without aeroallergen sensitization ($p=0.408$).

No statistically significant difference was demonstrated between mean total IgE and mean eosinophil values and severe clinical or histological disease or presence of clinical complications ($p >0.05$) (**Table II**).

Endoscopic and histological findings

In upper digestive endoscopy, linear furrows (n=47, 51%) and white plaques (n=39, 42%) were the most common detected findings. Esophageal stenosis was detected in 20 (22%) patients, and absence of alterations in 2 (2%) (**Figure 4**).

When analyzing endoscopic findings by age, the most common were linear furrows (n=25, 53%) and mucosal rings (n=24, 51%) in adults and linear furrows (n=22, 49%) and white plaques (n=21, 47%) in pediatric age.

In the histological evaluation of biopsy samples, all patients had ≥15 eos/hpf, of whom 27 (29%) had ≥ 55 eos/hpf. Severe histological disease was identified in 34 (37%) patients, namely 21 (62%) children and 13 (38%) adults: ≥ 55 eos/hpf and/or presence of microabscesses. All histological features are represented in **table III**.

No association was found between ≥ 55 eos/hpf and/or presence of microabscesses on histology (severe histological disease) and clinical severe disease ($p=0.572$).

Treatment and complications

In most patients (n= 68, 74%), combined treatment with swallowed fluticasone and high-dose proton pump inhibitor (PPI) was initiated. Twelve (13%) patients were medicated with isolated PPI and 11 (12%) with isolated swallowed fluticasone. Simultaneously, in 58 (63%) an elimination diet guided by positive food skin tests was instituted, and 2 (2%) patients were on an empiric elimination diet. One of

the patients (1%) was not complying with any pharmacological treatment due to his own refusal, remaining asymptomatic on an elimination diet based on allergy skin tests but with no histological response (**Table IV**).

Pre-diagnostic (n=25, 27%) and post-diagnostic (n=19, 21%) complications with urgent hospital admission were observed, in the latter mainly due to pharmacological treatment interruption (n=14, 74%) (**Table V**).

Sensitization patterns and severity of disease

There was no significant association ($p > 0.05$) between aeroallergen or food sensitization and severe clinical disease, presence of complications alone and severe histological disease. It was also not demonstrated an association between environmental aeroallergen (mite and pollens) and respective seasonal exacerbations.

Discussion

This study included 92 patients diagnosed with EoE, both children and adults, of whom 83% were male (n=76), which is in line with recent literature. Male predominance may be explained by a genetically male predisposition to develop this disease. There is a strong genetic component involved in the pathogenesis of EoE and a high concordance reported for EoE among family members. The pioneer study that described the genetic basis for EoE was a study of genome-wide microarray expression profile analysis, which reported that the gene responsible for EoE was TSLP (thymic stromal lymphopoietin) which is located in the 5q22 region of male X chromosome (21). EoE is generally diagnosed at least three years after the start of symptoms (22), consistent with our results. However, we have also noticed that some cases of EoE had a late diagnosis, remaining under-diagnosed for several years. This might explain the development of complications, such as food impactions, that represented the main symptom of the studied patients (n=38, 41%), predominantly in adults (n=32, 51%). Also, in our population it was demonstrated that patients with severe clinical disease had a significantly longer disease duration before diagnosis than patients without severe clinical disease and that patients who described food impaction (with or without the need for observation in Emergency Department and/or hospitalization) were significantly older at time of diagnosis than those who have never had impaction. This delay in diagnosis emphasizes the importance of actively searching for patients with compatible symptoms, as an early diagnosis is crucial to avoid the development and progression of disease. Noteworthy, according to literature, the pathogenic process that leads to esophageal remodeling, may goes on to develop clinically relevant long and short segment narrowing, with progression of disease, as in our patients, but some other times may lead to direct mucosal healing without sequelae. In favour of this, CAPN14 has been implicated in eliciting and repairing the epithelial damage associated with

EoE, suggesting that remodeling could involve a genetically controlled balance between these two processes (21).

In view of the demonstrated ability of aeroallergens to trigger and/or exacerbate EoE and strong association of EoE with atopy it is recommended assessment of sensitization profile in all patients (5). There is recent evidence that suggests that EoE may be an element of the allergic march that classically begins with atopic dermatitis and progresses to IgE-mediated food allergy, asthma, and allergic rhinitis (6). Most patients have a history of atopy, having been observed a high prevalence in the studied population (n=80, 87%). Allergic respiratory disease (allergic rhinoconjunctivitis and asthma) affected 83% (n=76) and 28% (n=26) of our patients, respectively. The values described in the literature are similar to those presented (3).

Seventy-seven (84%) patients in this population presented aeroallergen sensitization, more frequent to house dust mites (n=66, 86%) and pollens (n=53, 69%).

When analyzing data on food sensitization, it is known that IgE-based testing does not reflect the triggering mechanism in patients with EoE and atopy patch testing, although reflecting the delayed-type hypersensitivity mechanism of EoE, is not standardized, or validated. Despite there was considerable heterogeneity between studies, attributable to varying methods of allergy testing, a meta-analysis that combined the results of all studies using allergy-based testing to identify food triggers in patients with EoE provided a summary estimate for effectiveness in achieving histological remission of 32.2% in adults and 47.9% in children (23, 24). Also, according to a systematic review of 16 studies published between 2002 and 2020, the positive predictive value (PPV) of the SPT+APT combination was 67.1%, with 65–88.3% of patients presenting symptom improvement after following a SPT+APT-based elimination diet (25). The combination of SPT+APT+sIgE was studied only by Dalby et al. (26) stating symptoms' improvement in 67% of patients. It can be presumed that the detection of both humoral and cellular sensitization to food allergens and the food elimination of all allergens with positive results from any of the allergy methods offers an increased PPV. Considering these results and once difficulties in patients' compliance with empirical avoidance diets are real and frequently observed in our clinical practice, we think that allergy tests, SPT and APT, may continue to be considered, especially in children, as a complement to first-line pharmacological therapy (swallowed corticosteroids and/or PPI) and not as a replacement for it (10, 24). Additionally, SPT are particularly important to confirm or exclude the suspected diagnosis of concomitant IgE-mediated food allergy (25).

Sixty-five (71%) patients presented food sensitization, and we observed being the most prevalent sensitization to seafood (n=24, 37%), cow's milk (n=19, 29%), nuts (n=18, 27%) and cereals (n=14, 21%). These are atypical sensitizations, as we would expect the most prevalent sensitizations to be to milk, egg, wheat, soy, and peanuts, which according to European EoE patients' series are the most frequently reported as food allergies. (5, 8).

As widely described, presenting symptoms vary according to age, as previously mentioned. In younger children, nonspecific symptoms, including eating refusal, nausea and vomiting are more frequent,

whereas in older children, teenagers and adults, the predominant symptoms are mechanical complaints, such as dysphagia and food impaction (27). We have observed in pediatric age a predominance of dysphagia (n=13, 29%) and vomiting (n=10, 22%), and in adults food impact (n=32, 51%) and dysphagia (n=19, 30%). As paediatric age includes both younger children and teenagers, these findings are in conformity with the published data. Reported symptoms also included non-specific suggestive complaints of gastroesophageal reflux (n=40, 43%) and episodes of chest pain (n=19, 21%).

Most EoE patients have elevated serum total IgE levels (for a reference value < 100 KUA/L) and about 50% have peripheral eosinophilia (for a reference value < 300/μL) (1, 3, 21). The mean value of total IgE of the population was 525 IU/mL, having been evidenced a statistically significant higher value (p=0.03) in the group of patients with food sensitization (629 IU/mL), when compared to without food sensitization (188 IU/mL). As well as the mean total IgE value, the mean value of eosinophils was also elevated (489/μL). No difference was demonstrated between these values and disease severity (p > 0.05). The physical examination of patients with EoE is often completely normal, so the diagnosis of EoE is dependent not only on the clinical manifestations and high degree of suspicion, but also on the endoscopic findings and histological examination of esophageal mucosal biopsies (27). Endoscopic features can be subtle and missed on endoscopy, and therefore multiple esophageal biopsies, are required in all patients suspected of having EoE, irrespective of endoscopic appearance, with recommendations ranging between four and six, in which six biopsies correspond to a 97%–100% chance of making a positive diagnosis. Therefore, latest guidelines recommend that six biopsies should be taken from at least two different sites in the esophagus and that these six biopsies should include a combination of targeted biopsies from visible areas of mucosal surface abnormality, whenever they are apparent, and non-targeted biopsies (24, 28, 29). The most common endoscopic features in adults with EoE include linear furrows and mucosal rings. Children often present with similar endoscopic features, but the findings may be more subtle. In a large clinical series of 381 children, the most common endoscopic features were normal appearance (32%), linear furrows (41%), esophageal rings (12%), and white plaques (15%) (30). When evaluating this population endoscopic findings by age, the most common were linear furrows (n=25, 53%) and mucosal rings (n=24, 51%) in adults, which is in accordance with the data in literature. In pediatric age linear furrows (n=22, 49%) and white plaques (n=21, 47%) were the most frequent. Only 2% (n=2) had a normal result in endoscopic examination, a lower percentage than the described, which might indicate a delay in referral and diagnosis of these children.

Histology is similar between children and adults, although collagen deposits increase with the patient's age. Biopsies are currently mandatory to evaluate eosinophil infiltrates and optional additional histological markers such as eosinophils microabscesses or basal zone hyperplasia. In addition, biopsies from the duodenum and stomach should be collected to rule out eosinophilic gastroenteritis (29). It must be highlighted that severe histological disease was identified in 34 (37%) patients, defined by ≥55

eos/hpf (n=27, 29%) and/or presence of microabscesses (n=28, 30%). The presence of ≥55 eos/hpf on histology was not associated with a more severe clinical disease.

The practical goals of treatment of EoE are to prevent complications, stabilize the disease, and reverse fibrosis. Whether this last goal is achievable by current treatment is unclear (9).

Pharmacologic therapy consists of either PPIs and/or topical steroids. High doses of PPIs given twice daily for 8 weeks are 40% to 60% effective for achieving histologic remission. The mechanism of PPI efficacy seems to be at least partly independent of acid suppression and perhaps due to anti-inflammatory effects and restoration of esophageal barrier function. Topical steroids have efficacy of 60% to 95% (30, 31). Dupilumab is the only medical therapy to date that has been approved by the U.S. Food and Drug Administration to treat eosinophilic esophagitis. It has recently been approved in patients 12 years of age and older weighing at least 40 kilograms (32, 33).

In agreement with published recommendations, the majority of patients (n= 68, 74%) were medicated with a combined treatment with swallowed fluticasone and proton pump inhibitor (PPI), 12 (13%) with isolated PPI and 11 (12%) with isolated swallowed fluticasone.

Regarding efficacy of food elimination diets (FED), another available therapeutic option, results in literature are heterogeneous according to different studies, even referring to the same diet.

A meta-analysis by Arias et al., reports that the effectiveness of an amino-acid-based elemental diet is approximately 90% in both children and adults, and the 6-FED show effectiveness for 72.1% of cases, while the allergy-test-directed elimination has shown efficacy in only 45.5% of the cases. However, in a recently published systematic review by Dalby et al., formerly stated, allergy-test-driven elimination diets are effective in 66–88.3% of the cases, similarly to empirical diets (25, 34).

As efficacy of allergy-test-driven elimination diets do not seem to be superior to empiric FED based on most involved foods or food groups (e.g., two-, four-, and six-food diets), we assume that the decision any of these options, or alternatively a 4- or 2-FED (corresponding respectively to 54%-64% and 43% response rates), are valid and should be individualized and selected according to patient's diet adherence and lifestyle (24, 25).

Elemental diets produce histologic remission in most patients. However, practical limitations limit their use (e.g. cost, palatability, gastrostomy tube placement, quality of life). From our experience, allergy test-directed diets have a significantly higher rate of adherence in clinical practice. It should be noted that a higher percentage of our patients were on allergy test-directed diets (n=58, 63%) compared to empiric elimination diets (n=2, 2%). This low number reflects the challenges in long-term adherence to 6-food elimination diet (34, 35). Both patients started this diet as indicated by Gastroenterology. One of them was referred to Immunoalergology for study due to lack of clinical improvement and histological remission despite treatment with swallowed corticosteroids and PPI, admitting not being able to carry out the suggested dietary restrictions. The patient had a history suggestive of cow's milk IgE-mediated allergy and SPT were positive to cow's milk, egg, fish and shellfish, and negative for wheat, soy, tree nuts and peanut. The patch tests were positive for shrimp. He started an avoidance diet

based on these results, which he managed to comply, and the intake of wheat, soy, nuts and peanuts was liberalized. A symptom resolution has been reported, and a histological remission was observed. The other patient presented histological remission under therapy with swallowed corticosteroids, PPI and 6-FED but, due to the difficulty of maintaining adherence to the established diet, with a significant negative impact on quality of life, he was referred to Immunoallergology to consider less restrictive diet based on allergy skin tests. There was no history of IgE-mediated food allergy and allergy tests were negative to the standard panel of food allergens tested, namely, milk and proteins (alfa-lactoalbumin, beta-lactoglobulin, casein), soy, egg (yolk, white, ovalbumin, ovomucoid), meats (beef, chicken, turkey, pork and rabbit), fish (bream, hake, besugo, sea bass, sardine, horse mackerel, cod, tuna, salmon), seafood (shrimp), cereals (rice, wheat, barley, corn, rye, and oat), fresh fruits (apple, pear, and peach), tree nuts (walnut, hazelnut, cashew, almond, chestnut, pistachio, pinion) and peanut. It was decided to start a 4-food empiric elimination diet, allowing the intake of fish, shellfish, nuts and peanuts, which proved to be effective in recent studies, providing 54–64% of effectiveness in terms of inducing clinical and histological remission of EoE (23). This patient reported quality of life improvement, managed to maintain the diet and maintained remission of the disease.

In order to tailor an individual and specific treatment, we assumed it would be important to know whether sensitization to airborne or food allergens is relevant for causing and/or eliciting a more severe disease. According to the latest adult and paediatric guidelines of the British Society of Gastroenterology and British Society of Paediatric Gastroenterology, Hepatology and Nutrition there are links to EoE exacerbations during pollen season, associated with higher pollen exposure (low grade evidence). However, definite conclusions on the causal association of seasonality and aeroallergen exposure remain to be established (24).

In our study, there was no demonstrated association between airborne sensitization patterns and clinical and histological severity, nor between food sensitization patterns and disease severity, which has also been published in the scarce available literature (36, 37).

Conclusions

In our population of patients with EoE, like others, it was observed a predominance of male patients, and a high prevalence of atopy, with a high sensitization to environmental aeroallergens and food allergens. Severe situations of food impaction were more frequent as a presenting symptom in adults, presumably because of esophageal remodeling that occurs with the progressive evolution of the disease, which may develop clinically relevant long and short segment narrowing. Children presented predominantly with dysphagia.

At the time of diagnosis, approximately half of the patients presented severe clinical disease (55%), of which 88% reported a significant disease burden on quality of life, and one third severe histological disease (37%). According to our results, an older age at diagnosis and a longer disease duration before diagnosis appear to be useful for predicting EoE clinical severity, whereas specific sensitization

patterns, serum total IgE and peripheral blood eosinophil values do not. No association was found between histological and clinical severe disease. Our study draws attention to the need for education/training on EoE, to optimize early diagnosis and treatment, reduce associated real comorbidities and/or complications, and increase patient's quality of life.

More studies with large numbers of patients are needed to better understand this disease and its mechanisms.

Conflict of interests

The authors declare that they have no conflict of interests.

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Previous Presentation

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Table I. Demographic and clinical characterization of patients with eosinophilic esophagitis

Characteristics	EoE patients (n=92)
Gender, n (%)	
- Male	76 (83%)
- Female	16 (17%)
Mean age, years [range]	
- At the onset of symptoms	17 (SD 14) [1-63]
- At diagnosis	21 (SD 15) [1-67]
- Mean time gap between onset of symptoms and diagnosis	4 [0-3]
EoE diagnosis, n (%)	
- < 18 years	45 (49%)
- ≥ 18 years	47 (51%)
Atopic comorbidities, n (%)	**80 (87%)**
- Allergic rhinoconjunctivitis	76 (83%)
- Food allergy	33 (36%)
- Asthma	26 (28%)
- Atopic dermatitis	12 (13%)

EoE: eosinophilic esophagitis; SD: standard deviation.

Table II. Mean total IgE and mean eosinophil values according with severity

	Severe Clinic	**No severe clinic**	**P value**	**Clinical complications**	**No clinical complications**	**P value**	**Severe histology**	**No severe histology**	**P value**
Mean value of total IgE (IU/mL)	398 (SD 123)	445 (SD 110)	.653	415 (SD 120)	459 (SD 91)	.771	334 (SD 85)	520 (SD 101)	.07
Mean number of eosinophils (/µL)	457 (SD 73)	512 (SD 101)	.349	431 (SD 51)	546 (SD 58)	.182	436 (SD 39)	526 (SD 64)	.718

SD: Standard deviation.

Table III. Characterization of histological evaluation of biopsy samples

Histological evaluation	**n (%)**
15-54 eosinophils/ hpf	65 (71%)
Basal zone hiperplasia	36 (39%)
Presence of microabscesses	28 (30%)
≥55 eosinophils/ hpf	27 (29%)
Degranulation	21 (23%)

hpf: per high power field

Table IV. Characterization of performed treatment

Pharmacological treatment	**n (%)**	**Elimination diet**	**n (%)**
Swallowed fluticasone + PPI	68 (74%)	Allergy testing-based* - Swallowed fluticasone + PPI - Swallowed fluticasone - PPI - No pharmacological therapy	58 (63%) 51 4 2 1
Isolated PPI	12 (13%)		
Isolated swallowed fluticasone	11 (12%)		
None	1 (1%)		
		Empirical* - Swallowed fluticasone + PPI - PPI	2 (2%) 1 1

*In association with pharmacological treatment; PPI: proton pump inhibitor

Table V. Mentioned complications related to the disease

Disease complications	**n (%)**
Pre-diagnostic complications	25 (27%)
Post-diagnostic complications	19 (21%)
Identified triggering factor	15 (79%)
▪ pharmacological treatment interruption	14 (74%)
▪ non-adherence to the elimination diet	2 (11%)

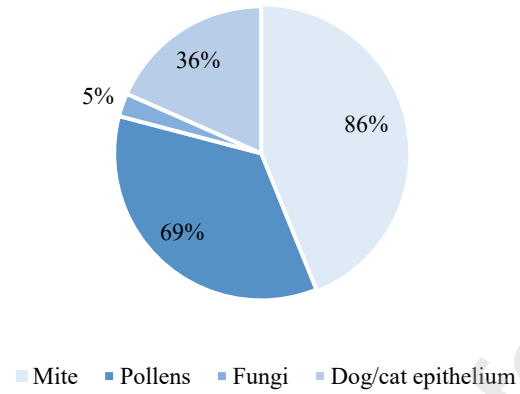

Figure 1. Aeroallergen sensitization pattern of studied population

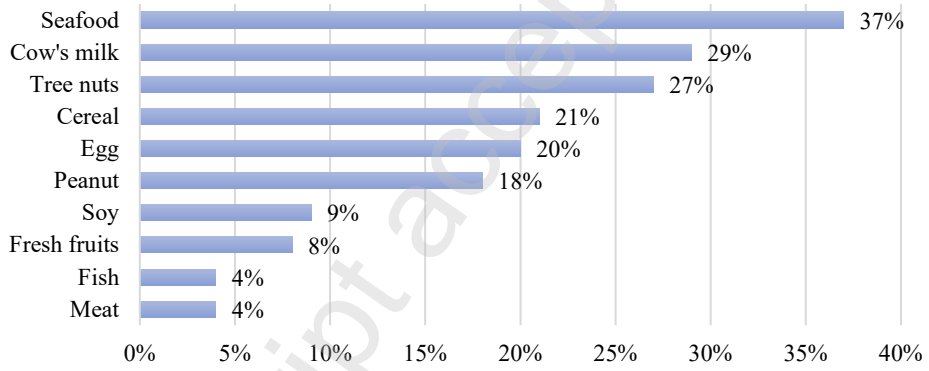

Figure 2. Food sensitization pattern of studied population

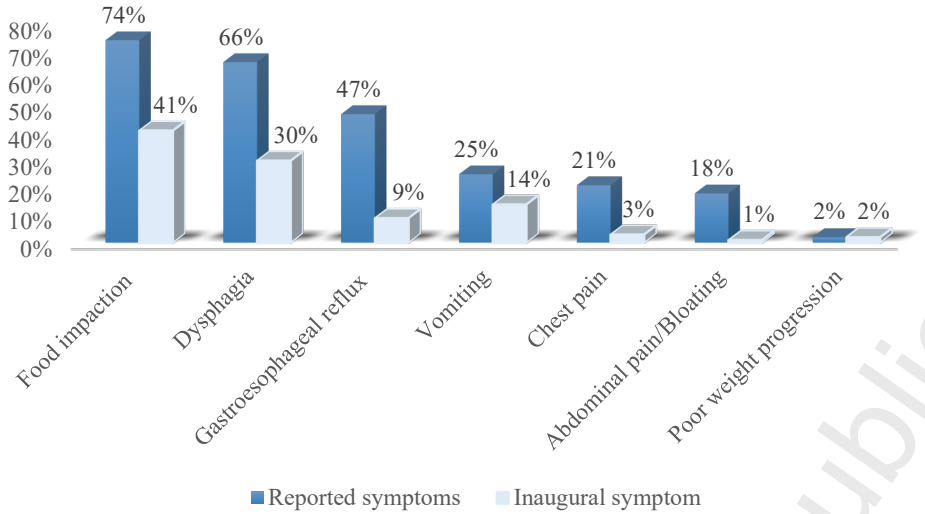

Figure 3. Description of symptoms reported by patients

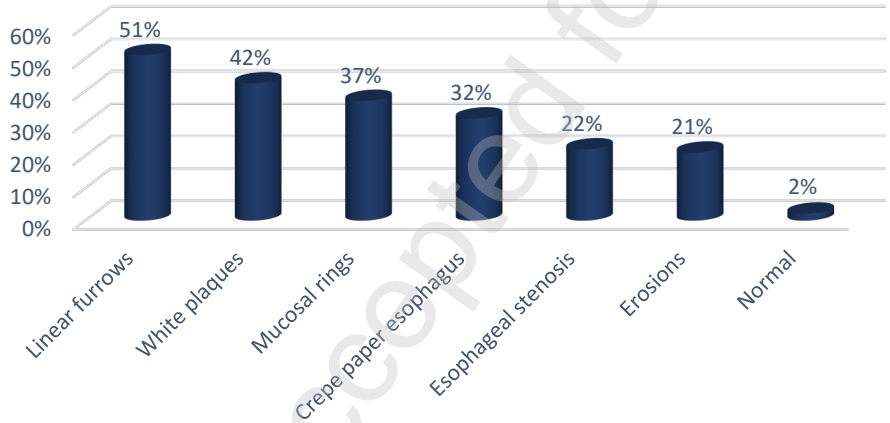

Figure 4. Endoscopic findings in upper gastrointestinal endoscopy