Clinical presentation of eosinophilic esophagitis in the pediatric age

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Introduction and epidemiology

Eosinophilic esophagitis (EoE) is a chronic clinical-pathological disease characterized by symptoms of esophageal dysfunction, such as dysphagia and globus, in addition of an inflammatory infiltration with > 15 eosinophils per high-power field (eos/hpf), after having ruled out secondary causes of eosinophilia¹.

The incidence and prevalence of this disease varies significantly from country to country. In an epidemiological study including several countries, they found a pooled incidence of 3.7/100,000/year, and a pooled of 22.7/100,000, however, there was significant heterogeneity in the information. On the other hand, when evaluating the presence of EoE in endoscopies performed for any indication, the incidence was 2.4-6.6%².

In Mexico, there are few epidemiological studies about EoE. De la Cruz-Patiño et al.³ conducted a cross sectional study in adults with dyspeptic symptoms who underwent an esophagogastroduodenoscopy (EGD), finding an incidence of 1.75%. In another retrospective study, which included 4,700 endoscopies performed at referral center in Northeast Mexico, the EoE incidence was 0.76%⁴. However, they only performed biopsies in 47% of patients. Therefore, the real incidence may be

underestimated. Yu C. et al. studied the prevalence of EoE in Hispanic patients living in North America, finding a prevalence of 0.96% and 3.21% in El Paso, Tx, and Los Angeles, CA, respectively.

Interestingly enough, performing a specific genetic panel for EoE demonstrated that, at a genetic level, EoE prevalence is lower in Hispanic patients compared to Caucasians⁵. Brazil reported an EoE incidence in children similar to North America (5%), with a preference toward males of 2.5:1⁶.

In response to the lack of epidemiological knowledge of EoE in children, the Latin American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (LASPGHN) conducted a multicenter study including 36 centers in Latin America, reporting a prevalence of 3.69/1,000 visits to the outpatient clinic and 26/1,000 EGD⁷.

Undoubtedly, the chronicity and the associated costs with the management of this disease have caused an economic burden for patients and the healthcare system. Specifically in the United States, this cost has been estimated to be as high as 1.36 billion dollars a year⁸. EoE management is substantially more expensive compared to Crohn and celiac diseases, especially in the outpatient setting. Moreover, there is a greater cost associated in the management of children compared to adults with EoE⁹.

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Pathophysiology

EoE is a chronic inflammatory disease of Th2 lymphocyte predominance, characterized by an increase in the number of eosinophils in the esophageal mucosa. Multiple studies have proved the role of food as a cause of EoE in children and adults, after successful resolution of eosinophilic inflammation when elimination diet was instituted. This improvement reaches up to 90% with elemental diet^{10,11} and 72% with 6 food elimination diet (milk, eggs, wheat, soy, peanuts/tree nuts, and fish/shellfish)¹².

However, these interventions are not effective in all patients, which suggests other possible causes. Pollens have also been implicated in EoE pathogenesis, which could result from cross-reactivity with certain food allergens^{13,14}.

Multiple cytokines are elevated in the esophagus of patients with EoE, including Th2 cytokines (IL-4, IL-5, and IL-13), as well as TSLP (Thymic stromal lymphopoietin), IL-33 and other¹⁵. Understanding the role of these cytokines has implications in the treatment of this disease. IL-5 promotes eosinophilia in the esophageal mucosa, an effect that is evident with the significant histological improvement of patients treated with humanized monoclonal antibody anti-IL-5 compared to placebo. Nevertheless, these studies did not demonstrate improvement in clinical symptoms¹⁶. IL-13, produced by Th2 lymphocyte cells and activated eosinophils, plays a major role in disruption of the epithelial barrier integrity¹⁵. Additionally induces tissue remodeling by promoting collagen deposition and epithelial hyperplasia, which occurs independently to eosinophilia¹⁷. EoE treatment studies with anti-IL-13 showed improvement in esophageal eosinophilia and its symptoms¹⁸.

It is unclear if IgE plays a role in the pathogenesis of EoE. Patients with EoE commonly have elevated specific IgE and positive skin testing to allergens, however IgE production is not necessarily required to induce EoE as is demonstrated in animal models^{19,20}. Also, studies with anti-IgE have not been proved to reduce esophageal eosinophilia²¹.

Atopy in EoE

The association between EoE and atopic diseases (asthma, allergic rhinitis, atopic dermatitis, IgE-mediated food allergies, and pollen-food allergy syndrome) has been well established in different studies²²⁻²⁴, and has been suggested that EoE could be a late manifestation

Figure 1. Difference in the clinical presentation between children and adults with EoE. *Adapted from: Munoz-Mendoza et al.*³⁸

of the atopic march²⁵. Several studies demonstrate a high frequency of positive tests for food allergies in patients with EoE, in serum, and skin prick tests, especially at the pediatric age^{24,26-28}. Nevertheless, the usefulness of food tests to direct elimination diets in EoE remains controversial.

Patients with EoE also have higher rates of positive tests to aeroallergens compared to the general population, being 44-46% through serum specific IgE testing and 71-93% through skin tests²⁹.

Clinical presentation

Risk factors

EoE is a complex, multifactorial disease, where genetic factors, history of atopic diseases, early exposure to antibiotics, use of proton-pump inhibitors (PPI), and passive smoking are some of the risk factors associated with EoE³⁰⁻³².

Clinical presentation

The clinical presentation depends on the patient's age (Fig. 1) and his/her ability to communicate obstructive and irritative esophageal symptoms³³. Adolescents behave more like the adult population, where dysphagia and globus are the predominant symptoms. Infants and preschoolers may present most commonly with reflux symptoms, vomiting, choking, and feeding dysfunction (FD) (Table 1) and should alert the clinician about possible dysphagia in this age group³⁴⁻³⁸.

In a retrospective study in patients with eosinophilic gastrointestinal disorders (EGIDs), Mukkada et al. found 17% of patients had FD, 93% had learned maladaptive feeding behaviors, followed by vomiting, nausea, and choking in 85%³⁹. A similar study proved that FD, in addition to occurring at an earlier age (< 7 years of age), tends to be more severe and linked with greater stress in parents⁴⁰.

Mehta et al. studied prospectively the characteristics of FD in children under 7 years of age with gastroesophageal reflux diseases and EoE. An abnormal feeding behavior characterized by requiring over 20 min to finish their meals, preferring liquids rather than solid foods, and “negotiating” the type of foods they preferred to eat was found in both pathologies⁴¹. Interestingly, EoE treatment with elimination diets improved FD in patients with EoE.

Other symptoms commonly reported are abdominal pain, retrosternal pain, early satiety, loss of appetite, regurgitation, and dyspepsia. Patients with EoE presenting with abdominal pain as a cardinal symptom seem to have a different clinical behavior from those with dysphagia, as a study by Gunasekaran et al. suggests⁴². This study showed that the classic endoscopic changes are more frequent in patients with dysphagia and have a better response to treatment than those with abdominal pain. However, symptoms can also be underestimated due to its chronicity and the adaptation behavior developed by patients with dysphagia^{33,43}. (Table 2).

The dissociation between symptoms and disease activity has been described. Pentiuk et al.⁴⁴ created a clinical instrument to evaluate symptoms in children with EoE, the Pediatric Eosinophilic Esophagitis Symptom Score, (PEESS). They did not find a correlation between symptoms and esophageal eosinophilia. Additionally, 88% of patients in remission reported persistent abdominal pain.

In 2011, Francois et al.⁴⁵ developed and validated the new version of PEESS (PEESS v2.0) which was written in order for patients or parents to answer the questionnaire. It also incorporates descriptive questions to better assess dysphagia in children.

Martin et al.⁴⁶ used the PEESS v2.0 to evaluate the different symptoms with histological and genetic findings in pediatric patients with EoE. Despite having a small sample, exclusively Caucasian males, there are several significant findings worth highlighting. The first one is that the PEESS v 2.0 has an intrinsic validity. Secondly, there was a positive correlation between dysphagia and the eosinophil derived

Table 1. Clinical presentation of feeding dysfunction in children

Dysphagia or discomfort in the esophageal phase of swallowing
Food refusal or oral aversion
Decrease in quantity and variety of foods accepted
Coughing during swallowing, vomiting, or a choking sensation
Delay in the acquisition of mature eating patterns
Delay in acquiring skills to eat independently
Chronic pain or discomfort associated with food or mealtime
Learned behavioral or eating problems
Compromised nutritional status

Table 2. Adaptive behavior in patients with dysphagia

Prolonged time to eat, eats more slowly than the rest of the family
Retention of food in the mouth
Prolonged chewing
Drink water after each bite to dilute the bolus
Cut the food into smaller pieces
Lubricate food with sauces or dressings
Avoid foods with a hard or dry consistency. Avoid pill/tablet medications

peroxidase, and proximal esophageal eosinophilia. Third, there was a significant difference between patients with active and inactive disease at the genetic level.

In general, we conceptualize the behavior of this disease as an inflammatory or fibro-stenotic process. But far from being a dichotomic reality, it is more a progression or a spectrum of severity. A retrospective study conducted in the Netherlands that included children and adults found that the risk of presenting esophageal stenosis or food bolus impaction was 9% for every year that the patient remains without a diagnosis⁴⁷.

Diagnosis

Endoscopy

The endoscopy plays a major role in the diagnosis and follow-up of this disease. The description of endoscopic findings has been standardized using a

validated instrument [EoE Endoscopic Reference Score (EREFS)]. It evaluates the presence and severity of different inflammatory (furrows, exudates, and edema) and fibro-stenotic (stenosis, rings/ridges, and crêpe-paper mucosa) findings of EoE⁴⁸. The presence of more than one finding in the EREFS during a diagnostic endoscopy has a sensitivity of 90% and a specificity of 88% for identifying patients with EoE⁴⁹.

Without a doubt, patients with EoE will require a greater number of endoscopies throughout their lives, exposing them to more anesthetics, school/work absenteeism, and an economic burden for patients/families. Trans-nasal esophagoscopies without sedation have emerged as a response to this concern. This modality of endoscopy has been linked to greater satisfaction in patients and their parents, have been able to obtaining similar biopsies to those obtained during a EGD and is associated with 62% reduction of costs^{50,51}.

EoE diagnosis is based on clinical presentation in combination with the histological changes, which are characteristic of this disease (> 15 eos/hpf). In 2018, new guidelines were published for the diagnosis of EoE. It has simplified the approach of patients under suspicion of EoE, since the esophageal eosinophilia responsive to PPI is considered part of the EoE spectrum rather than being a factor which discriminates between reflux and EoE¹. The list of differential diagnoses to consider is described in Table 3.

Image studies

A barium esophagogram, despite having a low diagnostic sensitivity in children⁵², can provide complementary information to the endoscopy, particularly to evaluate fibro-stenotic complications (i.e., rings, stenosis, and small caliber esophagus)⁵³. It can be a useful study, especially in those patients with a normal endoscopy and persistent dysphagia. Diniz et al.⁵⁴ found that despite half of the esophagograms performed in patients with EoE being normal, 25% of these had fibro-stenotic complications. On the other hand, endoscopy alone can overlook half of the esophageal stenosis in children⁵⁵. Similarly, in adults, it was proved that the sensitivity of detecting esophageal stenosis < 13 mm through endoscopy is 26%⁵⁶.

Cytosponge®

The Cytosponge® is a 3 cm spherical polyurethane sponge wrapped with a gel capsule, wich has a string.

Table 3. Differential diagnosis of eosinophilic esophagitis

Gastroesophageal reflux disease
Infectious esophagitis
Fungal esophagitis (<i>Candida albicans</i>)
Viral esophagitis (herpes or cytomegalovirus)
Connective tissue diseases
Ehlers–Danlos syndrome
Marfan syndrome
Hypermobility syndrome
Crohn's disease
Hypereosinophilic syndrome
Vasculitis
Hypersensitivity to medications
Graft versus host disease

After swallowing the capsule, it will dissolve inside the stomach, releasing the sponge. With gentle traction of the string, the sponge is retrieved until it comes out through the mouth. During its path through the esophagus, the sponge obtains a sample of the esophageal epithelium for cytological analysis, focus on the detection of esophageal cancer or Barrett's esophagus.

In a viability study, Katzka et al. compared the sample obtained by the Cytosponge versus other biopsies obtained during an EGD. The sensitivity was 85%, and specificity was 56% to detect > 15 eosinophils per high-power field⁵⁷. A subsequent study proved that eosinophils obtained with the Cytosponge are strongly correlated with those obtained through an endoscopic biopsy. Moreover, it is a minimally invasive, safe, and well-tolerated procedure⁵⁸. There have not been any similar studies conducted in patients under 18 years of age for the time being.

String test

The string test, or Entero-test, is a device consisting of a capsule that releases a string in the duodenum to identify pathogens. In 2013, Furuta et al.⁵⁹ utilized this device to measure products derived from the eosinophils as a minimally invasive method to evaluate EoE activity. Pediatric patients were included in this study. Findings showed that the string test was able to differentiate between patients with active/inactive EoE gastroesophageal reflux, and a normal esophagus. Recently, a multi-center, prospective study assessed the use of the string test in children and adults with EoE, but with a period of string retention of 1

hour instead of the 16 hours of the original study. The hour-long string test was capable of distinguishing between active and EoE in remission in children and adults⁶⁰.

Conclusion

EoE is a chronic inflammatory disease of the esophagus, with the potential of progressing to a fibrostenotic phenotype. The It's etiology is multifactorial, yet with a clear atopic footprint. Its clinical presentation varies with age and is characterized by esophageal dysfunction symptoms. To reach a diagnosis, clinical suspicion together with characteristic histological and endoscopic findings are required.

Conflicts of interest

The authors have no conflicts of interest to declare.

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