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EOSINOPHILIC ESOPHAGITIS: A LITERATURE REVIEW

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a recently recognized clinical entity that is currently defined as a chronic pathology of the esophagus, of immunoallergic etiology, characterized by an inflammatory process of the esophageal wall, with symptoms related to esophageal dysfunction and histological findings of inflammation with a predominance of eosinophils (NELSON, 2018).

According to Harrison (2020), EoE is a cause detected with increasing frequency in children and adults around the world. Current prevalence estimates in the United States calculate 4 to 6/10,000 cases, with a predominance of white men aged 30 to 40 years. This increasing prevalence of EoE is attributable to a combination of increases in incidence and recognition of this problem.

EoE is a chronic, immunologically mediated disease of the esophagus, characterized clinically by manifestations of esophageal dysfunction and histologically by predominantly eosinophilic inflammation. Infants and younger children may experience feeding difficulties, vomiting and reflux symptoms, while older children, adolescents and adults also experience dysphagia and the sensation that food is obstructing the esophagus (food impaction).

The diagnosis is clinicopathological. Patients must have clinical presentations, associated with upper digestive endoscopy (EDA) with biopsies that reveal an eosinophilic infiltrate in the esophagus greater than or equal to 15 eosinophils per high-power field and no increase in eosinophils in other segments of the digestive tract.

Whereas many patients with EoE have other atopic diseases and associated food allergies. This fact can make it difficult to differentiate from gastroesophageal reflux disease (GERD). Therefore, further investigation and review of literature on the topic is considered pertinent.

DEFINITION

According to Nelson (2018), EoE is a chronic disorder of the esophagus characterized by infiltration of the esophageal epithelium by eosinophils, normally at a density exceeding 15 per high-definition field and can be characterized by presenting symptoms similar to those of GERD.

EoE is likely caused by an aberrant antigenic or immunological response to foods and aerolergens that trigger chronic inflammation in the esophageal mucosa (CECIL, 2018).

It is important to highlight that EoE is classically defined as an exclusively esophageal disease, and the finding of eosinophils in large quantities in other sites of the gastrointestinal tract leads us to other diseases. By this definition, it is clear that it is not just an eosinophilic infiltrate in the esophagus, as increased epithelial infiltration of the esophagus by eosinophils can be present in several diseases.

Therefore, this increase requires interpretation in the clinical context in which it was obtained, and alone does not define EoE. (VEIGA, 2017).

It is a common disease in children and adolescents, but adults are also affected. Patients often have a personal and family history of other allergic disorders. Genetic predisposition is suggested by the finding of abnormal genetic profiles in almost 50% of children with this disorder.

ETIOLOGY AND EPIDEMIOLOGY

EoE is a disease that has a worldwide distribution with a prevalence that is not yet known, but it appears to be increasingly increasing. When it was first described, it was thought that GERD was the basis of EoE, but studies carried out over the last few years have refuted this hypothesis.

There is a strong association between EoE and other pathologies with an atopic

background, namely asthma, rhinitis and atopic eczema. It is estimated that 28-86% of adults and 42-93% of children with EoE have at least one other allergic disease (VEIGA, 2017).

It is more common in males, but can affect patients of all ages and genders. A genetic component is suggested, as EoE is much more common in Caucasians and there are many familial cases. However, despite the reported existence of these cases, the exact locus that determines genetic susceptibility is unknown.

Data show a higher prevalence in adults than in children (34.4 cases for every 100,000 inhabitants per year, 42.2 in adults and 34.4 in children). Individuals in all age groups can present with EoE, with this being more common in adults between the third and fourth decades of life and, in children, between five and ten years of age.

It is also noted that there is a delay in diagnosis of 4.5 years in adults and 2.3 years in children, from the moment the first symptoms begin. (BRAZILIAN SOCIETY OF PEDIATRIA, 2018).

There has been an increase in the incidence and prevalence of this disease, but it is not known for sure whether this reflects a real increase in the number of cases, or simply the fact that there is greater awareness regarding this entity.

There are other hypotheses that may justify this increase, such as reduced exposure to environmental antigens in developed countries, the eradication of Helicobacter pylori (an inverse relationship has been demonstrated between the presence of H. pylori and eosinophilic infiltration), the use of antibiotics in the first years of life and the association between EoE, connective tissue diseases and other autoimmune diseases (CANARIAS, 2018).

PATHOPHYSIOLOGY

As mentioned above, the etiology of the immune response in EoE is not yet completely understood. It is known that the main immunological mechanism involved is mediated by T helper 2 (Th2) cells. External factors stimulate Th2 cells to produce interleukins (IL) such as IL-4, IL-5 and IL-13, with the contribution of a pathway mediated by type E immunoglobulin (IgE) and other mediators such as eotaxin- 3.

Eotaxin-3 turns out to be the molecule most related to EoE and studies have shown its relationship with the concentration of eosinophils found in esophageal biopsies. They contribute to the recruitment, maturation and activation of effector cells such as eosinophils and mast cells.

IL-5 is the most specific cytokine for eosinophils, contributing to their growth, differentiation, activation, survival and maturation. IL-13, a less specific interleukin, is associated with atopy at the systemic level - local and systemic eosinophilia, overproduction of mucus, increased reactivity of the upper airways - leading to asthma, allergies. The development of conditions such as rhinitis and eczema, for example, atopy. Mast cells and eosinophils release mediators that induce smooth muscle contraction and increase vascular permeability, while releasing leukotrienes and TGF-β, leading to the recruitment of inflammatory cells and subsequent tissue fibrosis (CANARIAS, 2018; VEIGA, 2017).

It is important to emphasize that although several immunological markers have been identified and studied, there are still no less invasive tests than endoscopy with biopsies for the diagnosis and monitoring of EoE. The pathogenesis of EoE is incomplete, but involves an interaction between genetic, environmental and host immune system factors (BRAZILIAN SOCIETY OF PEDIATRICS, 2018).

CLINICAL MANIFESTATIONS

Symptoms are diverse, vary with age and can be very similar to GERD. In children under 2 years of age and children of preschool age, they predominantly present food refusal or intolerance and poor weight status progression. In school-aged children, the most prevalent symptoms are vomiting, epigastric pain, heartburn and regurgitation.

According to Nelson (2018), adolescents and adults generally report dysphagia with solid foods with occasional food impactions or strictures and may complain of chest or epigastric pain. As previously mentioned, the majority of patients are male, the average age at diagnosis is 7 years (range: 1-17 years) and the duration of symptoms is 3 years.

In adolescents and adults, food impaction is common and esophageal dysmotility may also occur, suggesting involvement of the muscular layer of the esophageal wall. Particularly, in this age group, an episode of severe food impaction, which requires endoscopic intervention to extract the food, is a frequent presentation that must raise suspicion of EoE (VEIGA, 2017).

DIAGNOSIS

Upper digestive endoscopy is an essential complementary exam. In addition to its diagnostic role, when combined with biopsies, it allows checking the therapeutic response and confirming disease remission, documenting and dilating strictures and evaluating the recurrence of symptoms.

There are no pathognomonic findings of EoE on endoscopy and many of the changes frequently found are also present in GERD. Additionally, up to 30% of children and 7% of adults will have unchanged esophageal mucosa, which makes it essential to perform biopsies even in areas with apparently normal mucosa, for histological confirmation (BRAZILIAN SOCIETY OF PEDIATRICS, 2018).

The diagnosis of EoE is clinicopathological: there must be clinical manifestations of esophageal dysfunction combined with mucosal changes, eosinophilic infiltrate and inflammation, on endoscopy and esophageal biopsies.

Several sets of criteria have been proposed for the diagnosis of EoE. As an example, the criteria of the First International Gastrointestinal Eosinophil Research Symposium (FIGERS) are presented, which consist of four conditions that must be present for the diagnosis of EoE: presence of a clinical picture suggestive of EoE, exclusion of GERD, eosinophilia in the esophageal epithelium and absence of eosinophilia in other segments of the digestive tract. (BRAZILIAN SOCIETY OF PEDIATRIA, 2018).

EoE is confirmed through EDA with 4 to 6 biopsies of the 3 esophageal thirds, namely the upper, middle and lower thirds, generally performing 2 biopsies for each region, even without any type of visual change. The amount is indicated due to the irregular form of infiltration of the disease in the affected organ. It is also recommended to perform joint biopsies of the stomach and duodenum to confirm eosinophils present only in the esophagus, as there are no eosinophils present in the healthy mucosa (CANARIAS, 2018).

During the EDA exam, we can find changes such as narrowing of the esophageal caliber; strictures; edema and consequent erasure of the vascular network; vertical grooves or striations; lacerations, nodules, white plaques/ whitish punctate exudates; transitional or fixed concentric Schatski rings, providing trachealization; Granular exudate and mucosal fragility may present nonspecific changes, such as edema, erythema and friability, as well as changes more suggestive of EoE, such as "crepe paper" mucosa (NELSON, 2018).

TREATMENT

The treatment of EoE is based on mitigating esophageal inflammation, in order to alleviate symptoms, avoid possible complications, such as esophageal tissue leading to remodeling and fibrosis, and, consequently, provide a better quality of life for the patient. This therapy can be mediated by drugs, that is, by Proton Pump Inhibitors (PPIs) and corticosteroids, by diet, by mechanical dilation and by biological medications (BRAZILIAN SOCIETY OF PEDIATRICS, 2018).

Despite today being the first line of therapy in the treatment of EoE, the response to PPIs was considered, in the guidelines published in 2007, a factor of diagnostic exclusion. This is because the improvement in the clinical picture due to the therapeutic administration of these medications was considered suggestive of gastroesophageal reflux disease. However, studies indicate that most patients with EoE are responsive to treatment with this class of drugs, with no clinical, endoscopic and histological distinctions between responsive and non-responsive patients (CANARIAS AG, 2018).

From the description of cases responsive to PPI treatment, a new diagnostic class was created: PPI-responsive Eosinophilic Esophagitis (PPI-R EoE). However, due to the inability to distinguish patients with EoE and PPI-R EoE, new studies and scientific consensus suggest that the name "PPI-R EoE" is inappropriate, as it is based only on the response to treatment with a drug, without considering, therefore, responsiveness to PPI as a diagnostic exclusion criterion for EoE (CANARIAS, 2018; BRAZILIAN SOCIETY OF PEDIATRICS).

Proton pump inhibitors (PPIs) are currently considered the first therapeutic option for these patients. They must be used in doses of 1 to 2 mg/kg/dose every 12 hours. In general, 1 mg/kg/dose every 12 hours is used for 8 to 12 weeks, when the endoscopy will be repeated. If biopsies from this endoscopy show a decrease in eosinophils below 15 eos/CGA, the patient can be maintained on PPI alone and an attempt will be made to reduce the dose to once a day. On the other hand, if the patient does not respond to PPIs, with persistence of eosinophilia, dietary treatment or corticosteroids can be chosen (CANARIAS, 2018).

If the patient remains clinically well, endoscopy must be repeated one year later. Current therapeutic options include the use of elimination or restriction diets, empirical or based on the identification of allergens through allergy tests, and the use of ingested topical or, occasionally, systemic corticosteroids. The use of leukotriene receptor antagonist (montelukast) was used in small series of patients, however these findings have not been consistently confirmed.

Neutralization of interleukin (IL)-5 using the anti-IL-5 monoclonal antibody (mepolizumab), which blocks this inflammatory mediator synthesized by eosinophils, has been evaluated in the treatment of EoE. The results of these studies demonstrate benefits such as a decrease in peripheral and esophageal eosinophilia, suggesting that mepolizumab may be a promising therapy in the intervention of patients with EoE, but the clinical significance of these observations has not yet been fully established (CANARIAS, 2018; BRAZILIAN SOCIETY OF PEDIATRICS 2018; VEIGA, 2017).

Systemic corticosteroids are effective in the treatment of EoE and are capable of inducing clinical and histological improvement. However, they must be considered in situations of greater severity of symptoms, for a short period of time, as relapse after discontinuation makes it necessary to repeat their use with a greater chance of developing side effects.

The use of swallowed topical corticosteroids (fluticasone and budesonide) has demonstrated good results and advantages in terms of safety and efficacy when compared to systemic corticosteroids. The presentation is the same as that used in the treatment of asthma, being administered so that the patient swallows the medication. Preparations that adapt the medication to the swallowed viscous form (budesonide mixed with sucralose) seem to be more effective than the aerosol form, as they allow for a longer time of contact of the substance with the esophageal mucosa. The patient is advised not to take food or liquids orally for 30-60 minutes after administering the medication to encourage this contact (BRAZILIAN SOCIETY OF PEDIATRICS, 2018).

Dietary treatment appears to be quite effective in patients with EoE, especially in children, and is based on the cause of the pathology: the immune-mediated inflammatory response, with three options in this treatment modality: the elementary diet, elimination diets and diets of restriction. The elementary diet proved to be effective in most patients, culminating in symptomatological remission and histological improvement, but the cost, palatability and symptomatic recurrence after the reintroduction of some dietary proteins are potential obstacles to adopting this therapeutic option.

In elimination diets, it is chosen to eliminate from meals foods linked to allergic responses, such as milk, eggs, fish, shellfish, nuts, peanuts, soy and wheat. Another option in this regard is food restriction based on an allergy assessment, which is carried out through hypersensitivity tests (CANARIAS AG, 2018; BRAZILIAN SOCIETY OF PEDIATRICS, 2018).

The endoscopic procedure with dilation is indicated for patients who have not responded to pharmacological or dietary therapy and who present intense symptoms, with esophageal narrowing and stenosis that cause food impaction, with temporary symptomatic improvement as it does not alleviate esophageal inflammation, with reintervention being inevitable (CANARIAS, 2018; BRAZILIAN SOCIETY OF PEDIATRICS, 2018).

Assessment of response to treatment and prognosis Interruption of exposure to allergens in specific foods, with or without anti-inflammatory therapy or PPI, clinical symptoms, changes in esophageal gene expression and the anatomopathological changes of EoE is generally reversible. However, long-term treatment is necessary to prevent recurrence. Therefore, patients must be monitored and if there is a recurrence of symptoms or esophageal eosinophilia, treatment is restarted or continued for a longer period. To assess response to treatment, consider clinical symptoms and findings, endoscopic/histological tests, along with esophageal eosinophil counts, after 8 to 12 weeks of treatment. Monitoring these patients often becomes difficult as EDA with biopsies is recommended each time patients present new symptoms (BRAZILIAN SOCIETY OF PEDIATRICS, 2018).

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