М.Л. Теннакун, С.В.М.А. Самараккоди

ЭОЗИНОФИЛЬНЫЙ ЭЗОФАГИТ И РЕФЛЮКСНАЯ БОЛЕЗНЬ: ПАТОГЕНЕТИЧЕСКИЙ МЕХАНИЗМ И ПЕРЕКРЕСТ СИМПТОМОВ ПРИ ДИАГНОСТИКЕ

Научные руководители: канд. биол.. наук, доц. С.А. Жадан, ассист. К.С. Воробьева*

Кафедра патологической физиологии,
Кафедра патологической анатомии и судебной медицины
*с курсом повышения квалификации и переподготовки**
Белорусский государственный медицинский университет, г. Минск

M.L. Tennakoon, S.W.M.A. Samarakkody

EOSINOPHILIC ESOPHAGITIS AND REFLUX DISEASE: PATHOGENIC MECHANISM AND OVERLAPPING AT THE DIAGNOSES

Tutors: PhD in Biology, associate professor S.A. Zhadan, assistant K.S. Vorobyova*

Department of Pathological Physiology
Department of Pathological Anatomy and Forensic Medicine
*with a Course of Advanced Training and Re-training**
Belarusian State Medical University, Minsk

Резюме. Эозинофильный эзофагит (ЭоЭ) и ГЭРБ имеют схожие симптомы, но разную патофизиологию. В 63% преобладает ЭоЭ, в 27% – ГЭРБ, в 10% – смешанный фенотип. Хронический гастрит (40%) поддерживает воспаление.

Ключевые слова: эозинофильный эзофагит, ГЭРБ, патофизиология, перекрест симптомов, тип 2 воспаление.

Resume. Eosinophilic esophagitis (EoE) and GERD have similar symptoms but different pathophysiologies. EoE predominates in 63% of cases, GERD in 27%, and a mixed phenotype in 10%. Chronic gastritis (40%) promotes inflammation.

Keywords: eosinophilic esophagitis, GERD, pathophysiology, overlap of symptoms, type II inflammation

Relevance. Eosinophilic Esophagitis (EoE) is an increasing autoimmune/allergic disease of the esophagus. EoE and Gastroesophageal Reflux Disease (GERD) share many clinical features that may delay accurate diagnosis of EoE. The primary cause of GERD is due to lower esophageal sphincter (LES) dysfunction, which leads to acid injury of the esophageal epithelium. EoE occurs via a Type 2 inflammatory response and may lead to dysfunction of the epithelial barrier and motility (peristalsis) of the esophagus. Current studies demonstrate that convergence exists in the etiology of both diseases because GERD causes disruption of the epithelial barrier, allowing antigens access to the epithelium resulting in eosinophilic inflammation and that impaired motility noted in EoE may decrease clearance of acid from the esophagus, thus worsening GERD. It is, therefore, critical that providers understand the relationship between EoE and GERD to obtain accurate diagnoses and implement effective treatment plans. The increasing number of EoE in the last two decades, particularly in children, demonstrates the critical need for

better diagnostic algorithms that separate EoE from GERD, using clinical criteria in addition to histological criteria.

Aim: to evaluate the pathophysiology of eosinophilic esophagitis (EoE) and its link with gastroesophageal reflux disease (GERD) from a clinical standpoint based primarily on disease clinical associations, as well as system-based diagnostics (non-histologic criteria).

Objectives:

1. The study will assess how frequently pediatric patients have the predominant types of eosinophilic esophagitis (EoE) with or without GERD and indeterminate overlapping phenotypes.
2. The study will quantify the presence of other health conditions associated with eosinophilic esophagitis, such as chronic gastritis, atopy, duodenogastric reflux, cardia insufficiency, and ingestion of foreign bodies, in relation to their dominant phenotype.
3. To construct pathophysiological models to define the bilateral relationship between eosinophilic esophagitis and gastroesophageal reflux disease.
4. The study will evaluate the relationship between age and sex and disease phenotype.

Materials and methods. This study included 30 clinical cases of pediatric patients with Eosinophilic Esophagitis (EoE) seen at the Surgical Department No 3 of the Republican Scientific and Practical Center of Pediatric Surgery (Elective surgeries). The data collected from the clinical visit included demographic data (age ranging from 1 to 17 years, sex), presenting signs and symptoms (e.g., abdominal pain, heartburn, dysphagia and/or nausea/vomiting), and the presence of associated diseases (e.g., allergic rhinitis, asthma, atopic dermatitis, GERD [gastroesophageal reflux disease], chronic gastritis, duodenogastric reflux, hiatal hernia, foreign body ingestion). Each case of EoE was then classified using specific algorithms as EoE-predominant (allergic phenotype), GERD-predominant (mechanical reflux-eosinophilic) or an indeterminate classification that falls into the overlap of both. The diagnosis of EoE was based on the esophageal biopsy revealing greater than or equal to 15 eosinophils per high-power field (>15 eos/hpf) following an 8-week course of a proton pump inhibitor (PPI) in accordance with the current consensus guidelines for establishing a diagnosis for EoE. Clinical symptoms were then assessed using a validated clinical questionnaire, and associated conditions were determined by a review of the patient's medical record, endoscopy report(s), and available allergy test results.

Results and their discussion. The sex of patients with EoE also conformed to previously reported sex differences associated with type 2 inflammation in that 70% of study patients were male and 30% were female. The average age at diagnosis for the patients in this study was 12.1 and 53% of them were adolescents aged 13-17 years. This high prevalence of adolescents with EoE suggests that these patients have experienced cumulative antigen exposure over time and have progressive dysfunction of their epithelium barrier. Chronic gastritis was recorded as the most frequently associated diagnosis (40% of patients); the next most frequently associated diagnosis was GERD (37%); followed by duodenogastric reflux (30% of patients); allergy/atopy (27%); abnormality of the cardia (20%); and foreign body ingestion (10%). Most studied patients had more EoE symptoms than GERD symptoms (63%); 27% of patients had more GERD

symptoms; and 10% had indeterminate symptoms. Indeterminate patients reported heartburn and/or reflux symptoms but did not have associated allergy symptoms.

The distribution of clinical phenotypes showing that majority of patients exhibited an EoE- predominant pattern (63%), while GERD-predominant (27%) and indeterminate overlap (10%) phenotypes were less frequent (Fig. 1).

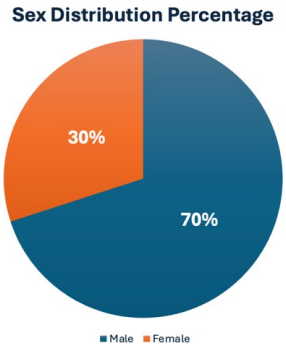

Fig. 1 – Distribution of clinical phenotypes

Most of the patients in this group are male; a finding which has also been shown by research studies that show men (2-3X more than females) are more likely to be diagnosed with EoE. Therefore, the gender difference suggests hormonal influences may play a role in type II immune response and in particular sex hormones may affect the development of eosinophils through their effect on eosinophil's ability to activate and survive. More research needs to be performed to determine the reasons for the above findings at a molecular level. The fact that there were more patients (53%) in the 13–17-year age range would lend support to the theory that EoE is a progressive disease that develops because of cumulative exposure to antigens and progressive reduction in the integrity of the epithelial barrier. There were very few (13%) EoE patients in the 1–6-year age group indicating that the incidence of the disease is likely lower in that age group and/or their symptoms are not usually associated with EoE but rather are attributed to other conditions such as feeding difficulties and/or reflux.

Three models explain how GERD and EoE are related. The first suggests that acid reflux is the cause of GERD, which causes damage to the barrier and allows allergens to penetrate, creating a reaction in type 2 immune cells. The second explains that the main cause of EoE is type 2 cytokines impairing the movement of food through the esophagus, making it less likely to clear acid quickly and possibly leading to GERD. The third model describes a bidirectional relationship whereby both GERD and EoE influence each other, causing worsening symptoms of both diseases. The high prevalence of chronic gastritis in patients with these diseases suggests that inflammation at the proximal stomach may play a role in creating both defective barriers and dysmotility in these individuals. Ingestion of a foreign object may also act as a mechanical trigger for the infiltration of eosinophils in individuals who are at risk for EoE, and those who present with dysphagia from an impacted foreign object have eosinophilic inflammation; therefore, the presence of an impacted food bolus could be the first clinical sign of pre-existing EoE.

On the Fig. 2 (a) age distribution of patients with a higher prevalence in adolescents (13-17 years: 53%) compared to younger children (1-12 years: 47%) is shown. On the Fig. 2 (b) the frequency of associated conditions observed in the study population is

demonstrated. Chronic gastritis (40%) & GERD (37%) were the most common comorbidities, followed by duodenogastric reflux (30%) and allergic/ atopic diseases (27%).

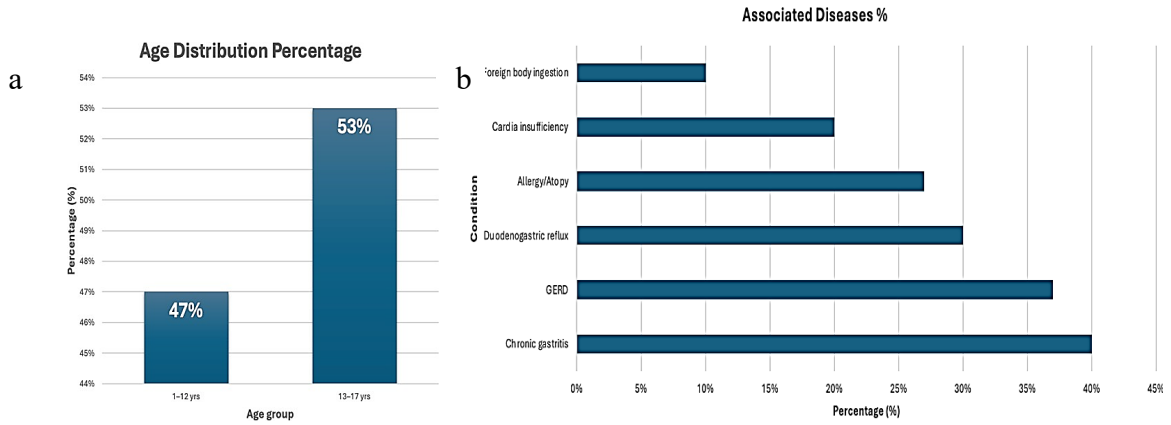

Fig. 2 – **a.** Age distribution of patients and frequency of associated conditions observed in the study population

Duodenogastric reflux (30 percent of cases) and cardiac insufficiency (20 percent) also indicate the mechanical aspect of the overlap, and thus contributes to the overall hypothesis that mechanical factors also contribute to symptom severity and disease progression in eosinophilic esophagitis (EoE) predominates, as well; that is, the presence of mechanical factors (reflux) may also affect symptom severity in GERD predominates (27 percent) even if the patient does not have any systemic atopy. For the indeterminate group (10 percent), the typical reflux symptoms will not be enough to identify an allergy, yet many patients in this group do not respond adequately to PPI therapy alone. This suggests that patients in this subgroup may need to try empiric dietary restrictions or topical corticosteroids to see whether they develop any eosinophilic inflammation, even if they do not present with any apparent history of systemic atopy.

The results of our study can be compared to the literature. For example, Dellon et al. in a large US cohort documented a similar 71% male predominance, however; our data shows 40% of patients with chronic gastritis, while the range for Western populations has historically been 25-30%. This discrepancy may be due to geography. Other factors, such as H. pylori rates, dietary habits, or genetic predisposition can play roles in these differences. Furthermore, 10% of patients ingested foreign bodies which coincides with recent literature identifying food impaction to be a frequent first. Please note this Anomaly serves its purpose for both allergic mechanical treatment by requiring an individualized plan of care.

Conclusions:

1. Several common pathological mechanisms are involved in the development of GER or EoE. There appeared to be a consistent relationship between barrier dysfunction, dysmotility, and type-2 immune response, which affected three-fourths of patients. Most of these patients (63%) had an EoE-predominant phenotype, while only 27% had a GERD-predominant phenotype.

2. EoE is classified as an atopic condition, and GERD is classified as a mechanical or non-atopic reflux condition occurring in 10% of mixed phenotypes. Exposure to a foreign body can also trigger EoE.

3. The prevalence of men with EoE is 70%, which may suggest that female hormones are involved in modulating EoE. Chronic gastritis is present in 40% of individuals with EoE. Therefore, in all children suspected of having eosinophilic esophagitis, an endoscopic examination should be performed.

4. There are three models of the pathogenesis that are etiologic explanations for the clinical overlap between EoE and GERD: the GERD-first model, the EoE-first model, and the bidirectional model. Each patient requires identification of the predominant pathophysiology to provide a focused therapy. The indeterminate phenotype (10% of patients) needs further studies for optimal diagnostic and treatment strategies.

Literature

1. Loi, R., Ceulemans, M., Wauters, L., & Vanuytsel, T. (2024). An update on Eosinophilic Esophagitis. Acta Gastro Enterologica Belgica, 86(4), 533 542. https://doi.org/10.51821/86.4.12001

2. Masterson, J. C., Biette, K. A., Hammer, J. A., Nguyen, N., Capocelli, K. E., Saeedi, B. J., Harris, R. F., Fernando, S. D., Hosford, L. B., Kelly, C. J., Campbell, E. L., Ehrentraut, S. F., Ahmed, F. N., Nakagawa, H., Lee, J. J., McNamee, E. N., Glover, L. E., Colgan, S. P., & Furuta, G. T. (2019). Epithelial HIF-1α/claudin-1 axis regulates barrier dysfunction in eosinophilic esophagitis. Journal of Clinical Investigation, 129(8), 3224–3235. https://doi.org/10.1172/jci126744

3. Helin, N. (2021). Outcomes of early childhood non-specific gastrointestinal symptoms: from diagnosis to long-term follow-up. Työväentutkimus Vuosikirja. http://hdl.handle.net/10138/328533