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Clinical features of eosinophilic oesophagitis in Polish paediatric patients: a single-centre retrospective study

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ABSTRACT

Introduction: To assess the clinical picture, risk factors and epidemiology of eosinophilic oesophagitis (EoE) in the Polish paediatric population.

Material and methods: A retrospective analysis of the medical data of patients hospitalised at the Department of Paediatric Gastroenterology and Hepatology of the First Independent Public Teaching Hospital in Zabrze during the years 2016–2023 was performed. The study included 40 children, aged 1–16 years, who met the criteria for EoE diagnosis, including 7 female and 33 male patients (17.5% vs. 82.5%, $p < 0.001$).

Results: The disease prevalence was significantly higher in the male patients and during puberty. As many as 67.5% of the children with EoE revealed other allergic diseases, most commonly bronchial asthma, while among the comorbidities of non-allergic origin gastroesophageal reflux had a significant prevalence rate (25%). The most commonly reported symptoms included abdominal pain and dysphagia with food sticking in the oesophagus (dysphagia). Half of the patients presented at least one symptom that could have suggested gastro-oesophageal reflux disease (GORD). The median time from symptom onset to diagnosis was 24 months. EoE was diagnosed earlier in patients with the dysphagia symptom. In children with regurgitation, the time from symptom onset to diagnosis was significantly longer. Over the last two years of observation, an increased incidence of EoE was reported compared to previous study periods.

Conclusions: The incidence rates of EoE have been increasing in recent years. In the study material, male patients and children in puberty were identified as a risk group for this condition. GORD was the most common non-allergic comorbidity of EoE, and half of the patients diagnosed with EoE presented symptoms indicative of GORD. At the same time, the occurrence of regurgitation was considered an independent factor delaying the diagnosis of EoE. Therefore, patients with symptoms of gastro-oesophageal reflux should be actively assessed for possible coexistence of EoE.

KEY WORDS:

children, gastroesophageal reflux disease, morbidity, symptoms, eosinophilic esophagitis.

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INTRODUCTION

Since it was first described by Landres *et al.* [1] in 1978, eosinophilic oesophagitis (EoE) has rapidly gained prominence in the clinical field. Numerous studies have documented the significantly rising incidence rates of EoE among paediatric patients in developed countries [2–5]. The prevalence rate among children was 5.1 per 100 000 individuals per year [6]. EoE manifests with upregulated eosinophil levels in the oesophagus – either equal to or exceeding 15 eosinophils per high-power field (eos/HPF) – and symptoms of oesophagus dysfunction [7]. Genetic and environmental factors can both contribute to EoE development [8], while their complex interactions disrupt the integrity of the epithelial barrier of the oesophagus, leading to abnormal exposure of the oesophageal lumen to allergens and other substances [9]. The affected barrier triggers localized release of signalling molecules – alarms – which promote differentiation of T helper 2 (Th2) effector cells and the recruitment of eosinophils [10]. The diagnosis of EoE requires a thorough medical history and an accurate assessment of symptoms, along with endoscopic observations and histological studies [7]. Due to the rather broad variety of symptoms and scarce information about its potential risk factors, the diagnosis of EoE is still likely to be delayed or incorrect, particularly in the first two decades. Prolonged diagnostic time periods worsen the prognosis in paediatric patients, being associated with subepithelial fibrosis and remodelling of the oesophageal epithelial barrier [11].

The aim of the reported study was to investigate and characterize the clinical features of patients with EoE, hospitalized at the Department of Paediatric Gastroenterology and Hepatology in Zabrze, Poland.

MATERIAL AND METHODS

This retrospective analysis involved 40 paediatric patients, 7 girls and 33 boys (17.5% and 82.5%, respectively $p < 0.001$), aged from 1 to 16 years (median age: 11 ± 4.5), all of them having been referred to the Paediatric Gastroenterology and Hepatology Tertiary Care Centre in Zabrze, Poland during the years 2014–2023. Patients with gastrointestinal symptoms were included in the analysis,

all of them with ≥ 15 eos/HPF in biopsy specimens, obtained from the oesophageal squamous epithelium during oesophagogastroduodenoscopy (OGD), and a final EoE diagnosis fulfilling the required criteria [7].

Based on the medical history records, the patient group was streamlined by age, age at diagnosis, sex, anthropometric data, the presence and character of symptoms, family history, and past medical history. Patients with a positive allergic history were defined as those with symptoms, documented positive IgE results for inhaled or food allergens, or positive skin prick test (SPT) results, documented anaphylactic reactions, or a diagnosis of allergic disease obtained by an allergist.

See Table 1 for characteristic features the study group.

A statistical analysis of the data was performed, using the R language in the RStudio environment and Excel Microsoft Office (Microsoft Corp., Redmond, WA, USA) worksheets. Normally distributed quantitative variables were presented as means with standard deviations, while quantitative variables with a distribution significantly deviating from normal were presented as medians with interquartile ranges. The Shapiro-Wilk test and ggqqplot graphs were used to assess normality of distribution, while the χ^2 test (Pearson's χ^2) was used to compare qualitative variables between the groups. A comparative analysis of the quantitative variables with distributions significantly deviating from normal was performed using the Wilcoxon test, with p -values less than 0.05 being considered significant.

RESULTS

EoE was significantly more often diagnosed in the male patients (7 vs. 33; $p < 0.001$). The prevalence rates were higher among adolescents (14 vs. 26; $p < 0.001$). The median age at diagnosis was 11 years.

Food and/or respiratory allergies coexisted in 67.5% of the children diagnosed with EoE. The concomitant allergic diseases in the study group included bronchial asthma ($n = 17$, 42.5%), atopic dermatitis ($n = 8$, 20%) and atopic rhinitis ($n = 5$, 12.5%).

Non-allergy concomitant diseases were identified in 17 patients (42.5%). The highest prevalence rate was demonstrated by gastro-oesophageal reflux disease (GORD) ($n = 10$; 25%), followed by autism spectrum dis-

TABLE 1. Characteristic features (age and anthropometric parameters) of the study group

Parameter	Study group ($n=40$), median $\pm$ IQR	Minimum value	Maximum value
Age [years]	11 ± 4.5	0	16
Weight [kg]	36.45 ± 28.95	9.1	102.8
Weight [percentile]	51.79 ± 72.95	1.91	99.9
Height [cm]	145 ± 31.38	78	184
Height [percentile]	59.61 ± 43.58	3.84	100
BMI [kg/m^2]	17.3 ± 6.39	12.2	35.2
BMI [percentile]	43.82 ± 68	0	99.6

order ($n = 5$; 12.5%). See Figure 1 for the reported non-allergy concomitant diseases.

All the patients reported a variety of symptoms, with abdominal pain being the most frequent one, reported by 18 out of 40 patients (45.0%). The next most frequent symptoms, equal in their prevalence rates, were dysphagia and food impaction, both being reported by 13 out of 40 patients (32.5%). Vomiting was the third most common symptom, present in 10 out of 40 patients (25.0%). The majority of the patients demonstrated at least 2 of the above-mentioned symptoms (34 vs. 6; $p < 0.001$).

Interestingly, as many as half of our patients presented at least one symptom that may have suggested either typical or atypical GORD, such as vomiting ($n = 10$), heartburn ($n = 3$), regurgitation ($n = 6$), chest pain ($n = 4$) and/or cough ($n = 3$).

All the reported symptoms and their prevalence rates in the study group are presented in Figure 2.

All the patients underwent OGD, which revealed at least one macroscopic change in 35 out of 40 children (87.50%). No statistically significant correlations were found among sex, age of onset, presence of concomitant diseases, clinical symptoms or endoscopic findings.

The median symptom duration prior to diagnosis was 24 months. EoE was diagnosed significantly faster in the patients with food impaction (10 ± 21 vs. 24 ± 33 months; $p = 0.026$), while those complaining of regurgitation were diagnosed later (48 ± 18 vs. 24 ± 18 months; $p = 0.011$).

There was a significant increase in the incidence rates of EoE in the last two of the evaluated calendar years (see Figure 3).

DISCUSSION

The incidence rate of EoE was constant during the early years of the observed period, followed, however, by its significant increase in the last two years, corresponding to the rapid rise in the global EoE prevalence and incidence rates [12–14]. It was likely due to the much higher awareness of the condition, together with the increasingly common diagnostic endoscopy with paediatric biopsy of material for histopathological studies [12]. The identification of the proton pump inhibitor-sensitive EoE also contributed to improved detection and, consequently, to higher epidemiological indicators of the disease. At the same time, the impact of environmental factors should also be taken into account. Gómez *et al.* [15] examined the incidence and prevalence rates of EoE versus the annual counts of aeroallergens, detecting a positive correlation between the incidence of EoE and the intensity of *Platanaceae* pollen. Also, Moawad *et al.* [16] found a significant association between the number of EoE cases, diagnosed seasonally, and the mean grass pollen counts recorded. However, a meta-analysis failed

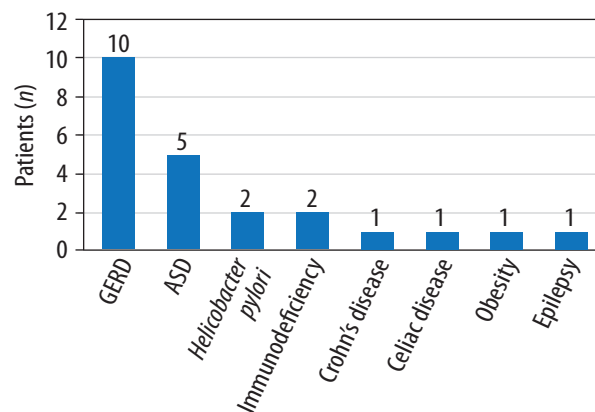


FIGURE 1. Non-allergy diseases concomitant to eosinophilic oesophagitis

GORD – gastro-oesophageal reflux disease, ASD – autism spectrum disorder

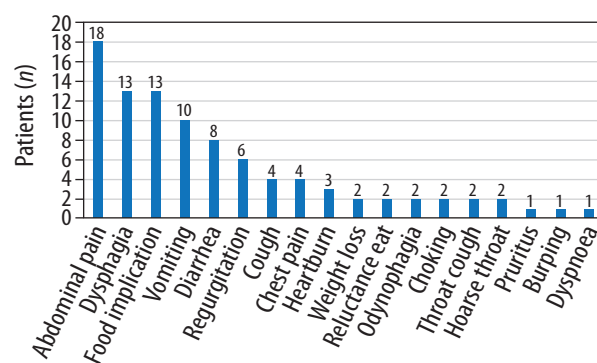


FIGURE 2. Prevalence of reported symptoms in all the patients diagnosed

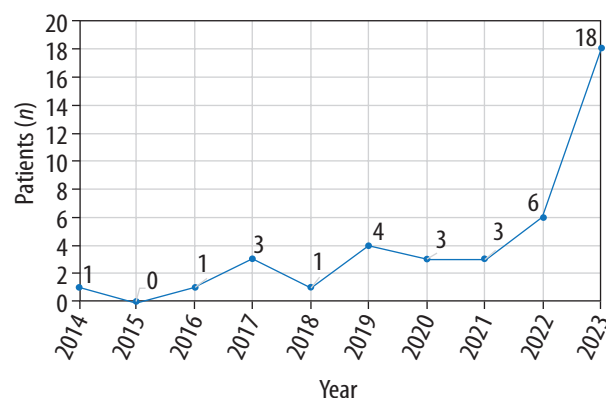


FIGURE 3. The number of newly diagnosed eosinophilic oesophagitis cases in the evaluated calendar years

to confirm any stronger causal evidence for aero-allergens and EoE [17]. In our study, we did not find any seasonal patterns for either the newly diagnosed EoE cases or specific symptoms.

The other assumed reasons for the rising EoE morbidity observed include climate change, air pollutants and early-life exposures to many substances, such as acid suppressants, antibiotics, folic acid supplements or the type and timing of labour [18].

The observed dominant prevalence of male patients (82.5%) among the studied groups of EoE-diagnosed

patients seems likely to be consistent with several other studies and meta-analyses [19]. What is more, the mean age at disease onset (10.55 ± 3.90) is similar to the age reported in other studies [20].

An analysis of the symptoms observed indicates that most of our patients complained of abdominal pain as the initial symptom. However, it is difficult to verify whether it was due to or concomitant with EoE. Dysphagia, which could have been attributable to oesophageal dysfunction in the reported study, was found in 32.5% of our cohort, which was lower than the prevalence reported in other studies and thus may have stemmed from the differences in the number, age and sex of the patients in our project [20]. Although food impaction is reported as one of the main clinical manifestations of EoE, the percentage of patients with this symptom in our analysis was 32.5%, which was in contrast to the outcomes of previous studies from Poland, New Zealand and Brazil, in which no children were reported with bolus impaction problems [20–23]. On the other hand, the same percentages of the patients complaining of dysphagia and food impaction, observed in our study, may have resulted from subjective feelings and a poor understanding of these two manifestations. Moreover, those children may have avoided certain foods or textures, may have taken smaller bites, chewed foods more thoroughly, or added lubricants to facilitate food bolus transits as a compensatory mechanism, all of which may have impaired the evaluation of the food bolus impaction symptoms in our paediatric patients [22, 23]. Other reasons for these differences may include the rather small cohort with a low number of infants and young children diagnosed with EoE.

Regurgitation, identified in 15% of the patients in our analysis, was another symptom that was analysed more closely.

The patients who suffered from regurgitation were diagnosed with EoE much later than those with food bolus impaction, which may have been due to the fact that regurgitation is a major symptom of GORD and, as such, is more likely to indicate GORD rather than EoE. For example, researchers from Brazil reported delayed EoE identification mainly due to earlier misdiagnosis, caused by an impaired distinction between GORD and EoE due to the fairly similar symptoms and possible presence of eosinophils in both conditions. This resulted in inappropriate treatment and the persistence of symptoms, worsening the patients' well-being and their quality of life [23, 24]. For these reasons, symptoms should carefully be analysed, especially when they persist despite the treatment applied. Apart from GORD, EoE should be differentiated from other gastrointestinal conditions such as achalasia, due to their similar symptoms, including difficulty swallowing, regurgitation and vomiting. Celiac disease, inflammatory bowel disease and connective tissue disorders, such as systemic sclerosis, can also affect the oesophagus and cause symptoms similar to those exerted

by EoE. Fungal and viral infections, caused, for example, by the herpes simplex virus or cytomegalovirus, may bring about eosinophilic inflammation in the oesophagus and should be differentiated from EoE.

On the other hand, GORD was also the most frequent concomitant disease among our patients with the diagnosis of EoE, with the prevalence rate of 25%, which was similar to the corresponding figures in other reports [21, 25]. EoE and GORD may coexist in the same patient; thus those patients already diagnosed with GORD should also be assessed for EoE, mainly due to the frequent diagnostic delays regarding EoE in these patients. However, it is not yet entirely clear whether GORD should be approached as merely a condition concomitant to EoE, despite the interactions between these two conditions observed, identified and confirmed over the two recent decades [26]. Eosinophils, lining the oesophagus, both in EoE and GORD, disrupt the smooth muscle functions through the agents they secrete. The agents are then responsible for the reduced lower oesophageal sphincter tension, which, in turn, contributes to reflux and regurgitation [27, 28]. Furthermore, the presence of eosinophils may trigger immune responses to food allergens. Contacts with food allergens may lead to allergic reactions with production of IgE antibodies specific to particular allergens. Consequently, the T regulatory and T helper type 2 cells, while being activated through re-exposure, secrete cytokines, leading to eosinophilic inflammation [29]. Eosinophils and other cells in the inflammatory microenvironment of the oesophagus affect the integrity of the mucosal barrier and epithelium, making it more vulnerable to damage from refluxed gastric contents, exposing other epithelial cells and nerves to harmful acidic effects. In contrast, the patients with GORD are more prone to exposure to food allergens, demonstrating oesophageal mucosal barrier disorders, increased mucosal permeability and dilatation of inter-cellular spaces in the oesophageal epithelium as the recognized features of this disease [24]. This confirms the necessity of diagnostics for EoE in patients with GORD, as the confirmed diagnosis of GORD does not at all exclude the presence of EoE.

The mechanisms of correlation of allergies with EoE are still unclear. Following the reports from numerous studies, the atopic diseases most commonly mentioned as typical for EoE include rhinitis, dermatitis, asthma and conjunctivitis [30]. Comparing the results of the present study with the incidence rates of allergic diseases, recorded in patients with EoE during studies performed in the years 2015–2019, the patients in the present study less frequently complained of comorbid rhinitis, while other allergic diseases seemed to match a similar incidence range [31]. Coexistence of food allergy (67.5%) and respiratory allergy (62.5%) was identified in our patients, which is a significantly higher value both compared to a study from Ecuador with allergic diseases in 47.1% of the children examined and a North-Eastern

Poland study with the allergic diseases present in 34.19% of the patients enrolled [21, 32]. Interestingly, hypersensitivity reactions to food allergies have been confirmed by numerous researchers as leading to EoE development, while the epithelium, damaged through eosinophilic inflammation, is also more sensitive to aeroallergens [33]. For example, since the 1990s, many patients treated with an elemental diet, or allergy testing-directed food elimination diets, have presented with EoE resolution [34]. The beneficial effect of allergen avoidance in EoE is similar to that in other allergic disorders, especially if we draw attention to EoE pathophysiology. In addition, the effective EoE therapies with topical steroids indicate some immunopathological associations between EoE and other allergic manifestations [32]. Taking into account the allergic nature of EoE, the type 2 inflammatory response in EoE and the coexistence of the disease with other allergic conditions, such as atopic dermatitis, food allergies, asthma, and allergic rhinitis, EoE may really be considered as a part of the allergic march [35]. The classification of EoE among other disorders in the allergic march could pave the way for active diagnostic screening for EoE in children with already diagnosed allergic diseases, resulting in faster diagnosis, better overall management and future prognosis.

Our results emerged from a group of paediatric patients with EoE, the general incidence of which has been growing significantly in recent years. We acknowledge the limitations of the study, especially the sample size. With the data available, we were not able to evaluate endoscopic features by the EoE Endoscopic Reference Score (EREFS).

CONCLUSIONS

In the light of our results, male sex and adolescence are independent risk factors for EoE, while no significant correlations were found between EoE and sex, age of onset, presence of concomitant diseases, clinical symptoms or endoscopic findings. Interestingly, GORD was the most frequent concomitant disease in our cohort, and GORD-like symptoms were observed in half of the study group. Taking into account the frequently delayed EoE diagnoses in children with regurgitations, careful differential diagnostics seem to be crucial in this patient group.

DISCLOSURES

1. Institutional review board statement: The study was approved by the Bioethics Committee of the Medical University of Silesia in Katowice under approval number: BWN/NWN/0052/KB/221/24.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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