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ORIGINAL PAPER

Clinico-pathological characteristics of children with eosinophilic esophagitis – single-centre experience

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ABSTRACT

Introduction: The aim of this study was to analyse the clinical picture of children with eosinophilic esophagitis (EoE).

Material and methods: The medical histories of 45 patients with EoE were retrospectively analysed. Analysis included demographic data, body weight, chronic diseases, family history, occurrence, and duration of symptoms, and endoscopic and histopathological findings.

Results: The study included 45 children, of whom 60% were boys and 40% girls. The mean age was 10 years (1–17 years). Twenty-eight (62.2%) children had at least one coexisting allergic disease. The co-occurrence of EoE and food allergy was significantly more common in younger children: the median age of patients with EoE and food allergy was 7 years, while the median age of those without food allergy was 12 years. The most common symptoms were eating or feeding difficulties (51.1%). Older children were more likely to have odynophagia, heartburn, dysphagia and abdominal pain. The mean age of children with vomiting was significantly lower than that in children without vomiting. The mean diagnostic delay was 16.3 months (1.4 years). Patients with regurgitation reported a significantly longer median duration of symptoms (21 months) than those without. A significantly shorter diagnostic delay was also noted among children with asthma. The most common type of endoscopic finding was linear oesophageal furrows. The numbers of eosinophils in oesophageal biopsies was in the range 15–100 in the high power field. A higher number of oesophageal eosinophils was noted in patients without chest pain.

Conclusions: The most common symptoms of EoE were difficulty with food intake, abdominal pain and food impaction. The clinical course varied in children according to age. Children with EoE and co-occurring asthma had a shorter diagnostic delay. The most common feature of EoE on endoscopy was linear oesophageal furrowing. The number of eosinophils in histopathology was not related to the endoscopic result.

KEY WORDS:

children, histopathology, symptoms, eosinophilic esophagitis.

INTRODUCTION

Studies indicate that the incidence of eosinophilic esophagitis (EoE) is increasing in both children and adults [1, 2]. Eosinophilic oesophageal a chronic inflammatory disease characterised by the presence of oesophageal symptoms and eosinophilic infiltrates in its mucosa. Although symptoms can occur at any age, adults and older children are more likely to report the typical oesophageal symptoms of EoE, i.e. dysphagia after solid food, a feeling of pressure and chest pain unrelated to swallowing, while infants and younger children tend to

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complain of extra-oesophageal symptoms, such as vomiting, abdominal pain, food refusal and stunted growth. Chronic symptoms negatively affect the quality of life of patients with EoE [3].

A diagnosis of EoE is based on histopathological examination of at least six biopsies taken at different heights of the oesophagus [1]. While the diagnostic cut-off for EoE is assumed to be a count of 15 eosinophils in the high- power field (HPF), other causes of peripheral or tissue eosinophilia must first be excluded before a diagnosis can be made [1]. The underlying chronic inflammatory process induces oesophageal wall fibrosis and oesophageal stricture formation [4]. Achieving histopathological remission, indicated by a decrease in eosinophil count below 15/HPF, does not always correlate with resolution of symptoms [5].

Eosinophilic esophagitis is known to be more common in patients with atopic diseases such as food allergy, allergic rhinitis, asthma and atopic dermatitis [6]. However, despite the large number of studies, the pathomechanism of the disease remains unclear and treatment still poses many problems for both physicians and patients. The course of the disease ranges from being almost asymptomatic and slowly progressive to severe; in the latter, oesophageal strictures develop that do not respond to pharmacological or dietary treatment, and surgical intervention is necessary [7]. To date, no relationship has been established between the clinical course of the disease and the severity of endoscopic lesions, medical history, or histopathological analysis of oesophageal biopsies.

TABLE 1. Study group characteristics

Parameters	Children with EoE, *N* = 45 (100%)
Sex, *n* (%)	
Boys	27 (60)
Girls	18 (40)
Age (years)	
Min–max	1–17
Average	10
Median	10
Allergic diseases in family, *n* (%)	
Mother	7 (15.6)
Father	7 (15.6)
Siblings	6 (13.3)
Eosinophil count in peripheral blood 1×10^3/µl	
Min–max	0–1.64
Average	0.51
Body weight [kg]	
Min–max	8.1–92.6
Average	37.8
Median	36.3
Body weight, *n* (%)	
> 97	2 (4.4)
3–97	39 (86.7)
< 3c	4 (8.8)

EoE – eosinophilic esophagitis

MATERIAL AND METHODS

The study group consisted of 45 children with eosinophilic oesophagitis, aged between eight months and seventeen years. All were hospitalised at the Department of Paediatrics, Allergology and Gastroenterology at Dr Antoni Jurasz Memorial University Hospital No. 1 in Bydgoszcz between 2013–2022.

The medical histories of the patients were retrospectively analysed; all had previously been diagnosed with eosinophilic oesophagitis according to accepted guidelines [1]. Demographic data (age, sex), body weight, chronic diseases, family history and the occurrence and duration of symptoms were recorded. The analysis also included endoscopic and histopathological findings from the oesophageal sections taken during the first diagnostic gastroscopy: the number of eosinophils in the field of view and the presence of other additional characteristic lesions were noted.

Statistical analysis was performed using Statistica™ 13.3 software (TIBCO Software Inc., Palo Alto, CA, USA). The relationships between eos/HPF values, age, body weight and duration of symptoms were evaluated using the Mann-Whitney *U* test and Student's *t*-test for independent samples. The relationships between co-occurring qualitative characteristics were analysed using Fisher's exact two-sided test or the χ^2 test. In all cases, $\alpha = 0.05$ was assumed as the threshold for significance.

Approval for the study was obtained from the Bioethics Committee.

RESULTS

The study included 45 children, of whom 60.0% were boys ($n = 27$) and 40.0% girls ($n = 18$). Both the mean and median age were 10 years (1–17 years). The characteristics of the study group are shown in Table 1.

FAMILY INTERVIEW

No EoE was found among the parents or siblings of the studied children. Atopic diseases were reported in the parents of 13 children (28.8%), i.e. 6 mothers and 7 fathers, and in 6 siblings (13.3%).

CO-MORBIDITIES – ALLERGIC

Twenty-eight (62.2%) children were previously diagnosed with at least one coexisting allergic disease (Figure 1A).

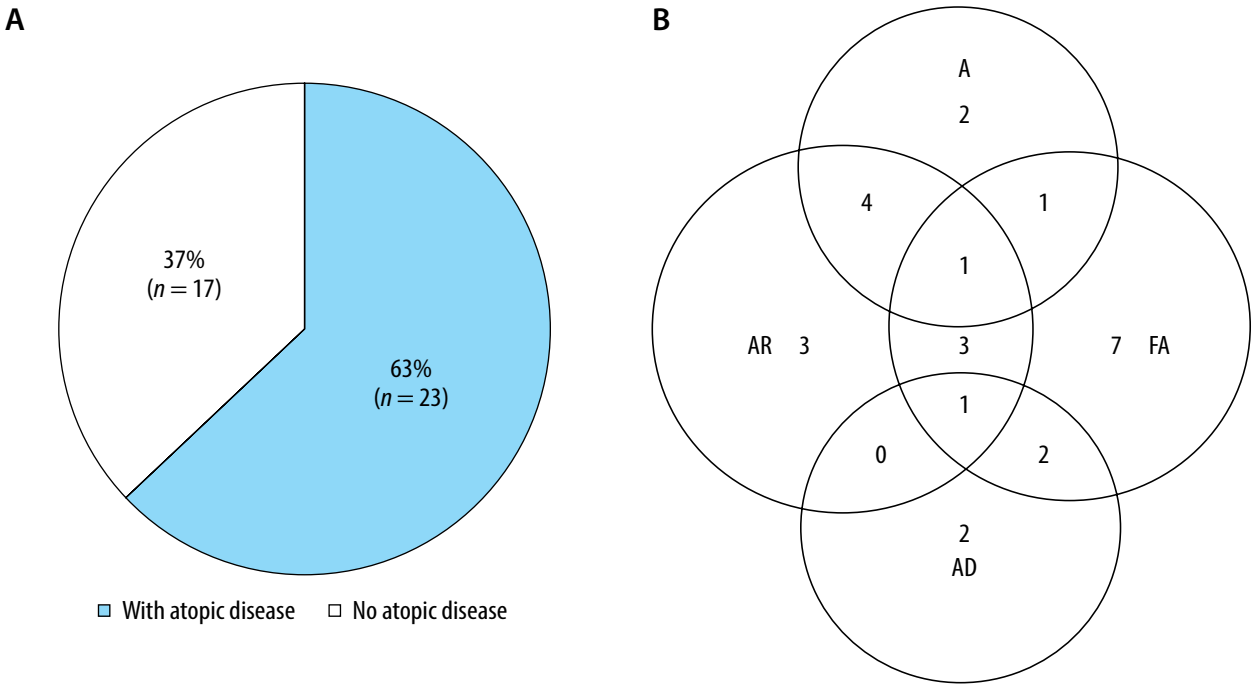

FIGURE 1. A) Atopic diseases in children with eosinophilic esophagitis (EoE). **B**) Number of patients with atopic diseases among children with EoE
A – asthma, AD – atopic dermatitis, AR – allergic rhinitis, EoE – eosinophilic esophagitis, FA – food allergy

Among these, the most common were food allergies, affecting 16 (35%) children, and the rarest was atopic dermatitis, reported by seven (15.6%) children. Allergic rhinitis was present in 13 (28.9%) and asthma in 10 (22.2%) children with EoE. In general, allergic diseases were individually present in 14 (31%) children, while two were found to be present in seven children (15.5%) and at least three were noted in two children (4.5%) (Figure 1B).

The co-occurrence of eosinophilic oesophagitis and food allergy was significantly more common in younger children: the median age of patients with EoE and food allergy was seven years, while the median age of those with EoE but without food allergy was 12 years ($p = 0.011$).

COMORBIDITIES – OTHER

In addition a number of other co-morbidities were found in children with EoE. These included hiatal hernia (in two patients) and hearing loss (in three patients), as well as various gastrointestinal diseases, such as short bowel syndrome, irritable bowel syndrome, functional stool constipation, gastritis and duodenitis, as well as duodenal ulceration in individual patients. Some patients had previously been treated for oesophageal atresia, oesophageal polyp and other non-gastrointestinal conditions.

SYMPTOMS

The most common symptoms observed in the studied children were eating or feeding difficulties ($n = 23$; 51.1%), abdominal pain ($n = 22$; 48.9%), food impaction ($n = 19$; 42.2%), dysphagia ($n = 17$; 37.8%), regurgitation ($n = 12$; 26.7%), vomiting ($n = 11$; 24.4%), heartburn ($n = 9$; 20.0%), chest pain ($n = 8$; 17.8%), odynophagia ($n = 6$; 13.3%), halitosis ($n = 5$; 11.1%), weight deficiency or weight loss ($n = 5$; 11.1%) (Figure 2).

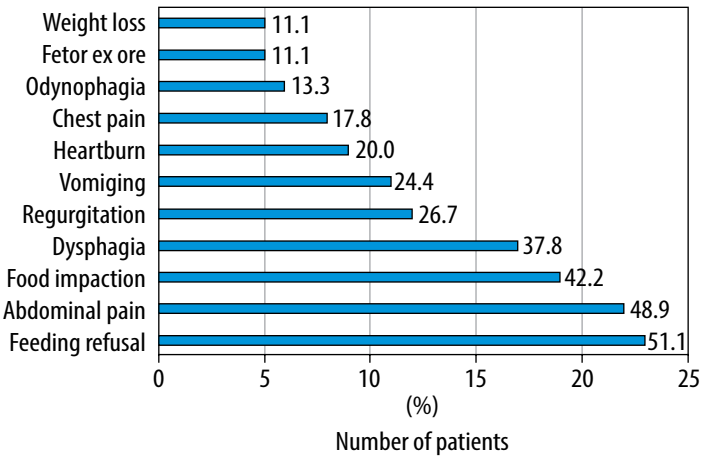

FIGURE 2. Symptoms in patients with eosinophilic esophagitis

TABLE 2. Average age of a child presenting specific symptom (from the youngest to the oldest)

Symptoms	Age of symptom occurence (years)	
	Average	Median
Vomiting	6.55	7
Underweight/weight loss	7.40	8
Feeding refusal	9.07	7.5
Fetor ex ore	9.40	8
Regurgitation	9.46	9
Food impaction	9.58	8
Nausea	11.44	11.5
Chest pain	11.75	10.5
Dysphagia	11.76	12
Abdominal pain	11.78	12
Heartburn	12.38	12.5
Odynophagia	13.60	15

SYMPTOMS AND AGE

The mean ages of children presenting with underweight or stunted growth were 6.5 and 7.4 years, respectively. Older children were more likely to have odynophagia (mean age 13.6 years), heartburn (mean age 12.4 years), dysphagia and abdominal pain (mean age 11.8 years) (Table 2).

The mean age of children with EoE manifested by vomiting was significantly lower than that of children without EoE ($p = 0.006$) (Figure 3A). Also, the children with EoE and abdominal pain were significantly older (mean age = 11.6 years) than those without abdominal pain (mean age = 8.5 years) ($p = 0.036$) (Figure 3B).

DIAGNOSTIC DELAY

The mean duration of symptoms from onset to diagnosis was 16.3 months (1.4 years). Patients with regurgitation were reported to have a significantly longer median duration (21 months) than those who did not (6 months) ($p = 0.038$) (Figure 4A). A significantly shorter diagnostic delay was also noted among children with asthma: the median time to diagnosis was 2.5 months in patients with asthma compared to 12 months in those without ($p = 0.015$) (Figure 4B).

No other statistically significant associations were identified between diagnostic delay and clinical data.

GASTROSCOPY RESULTS

Forty-three (95.6%) children presented macroscopic lesions on endoscopic examination. The most common type consisted of linear oesophageal furrows ($n = 30$; 66.7%). Other common abnormalities included whitish exudates ($n = 18$; 40.0%), mucosal pallor ($n = 15$; 33.3%), mucosal rings ($n = 6$; 13.3%), ulcerations ($n = 6$; 13.3%) and oesophageal strictures ($n = 5$; 11.1%). Two patients (4.4%) had no macroscopic lesions.

Interestingly, the median delay before the diagnosis of EoE differed with regard to the oesophageal mucosal pallor visible on gastroscopy: children with a mucosal pallor were characterised by significantly longer diagnostic delay (Me = 24 months) than those without (Me = 5 months) ($p = 0.013$). Additionally, none of the patients with mucosal pallor ($n = 15$) were diagnosed with asthma ($p = 0.0185$, φ coefficient = –0.377 – weak correlation according to Fisher's exact two-sided test).

HISTOPATHOLOGICAL FINDINGS

The peak numbers of eosinophils in oesophageal biopsy specimens of all patients were in the range 15–100/HPF. The mean value of peak numbers of eosinophils was 39/HPF. In addition, the microscope examination identified basal zone hyperplasia ($n = 11$; 24.4%) and fibrosis of the lamina propria ($n = 3$; 6.7%). No eosinophilic microabscesses were found in any biopsy. A higher number

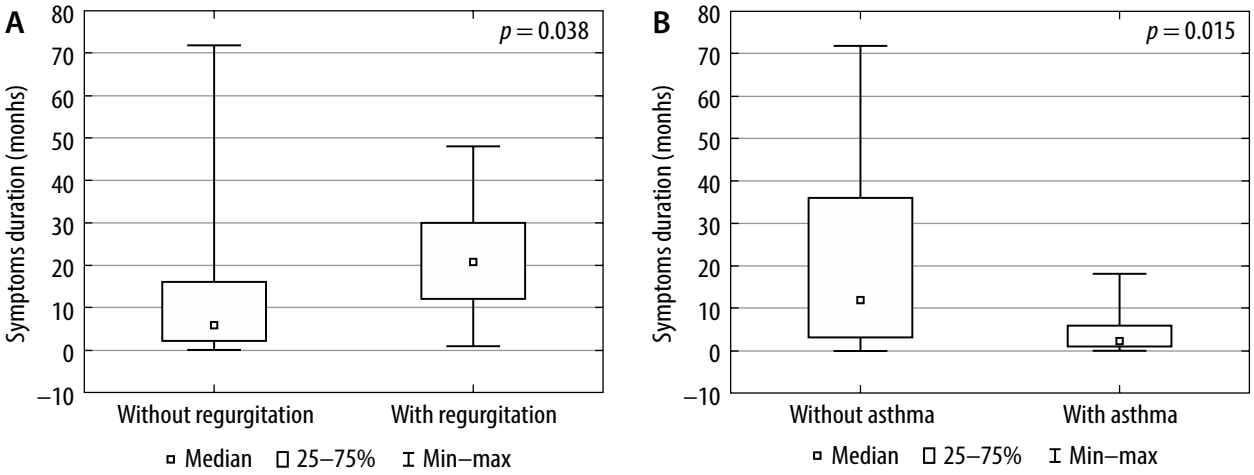

FIGURE 3. A, B) Average age of children in relation to vomiting and abdominal pain

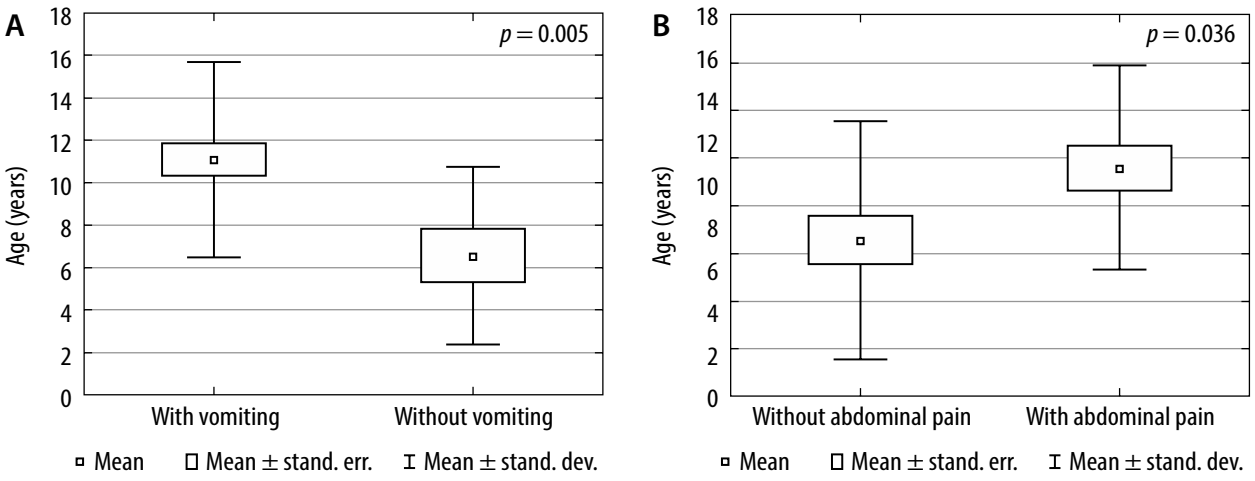

FIGURE 4. A, B) Diagnostic delay in relation to symptoms and co-occurring diseases

of oesophageal eosinophils was noted in patients without chest pain (Me = 40; 15–100/HPF) than in patients with pain (Me = 29; 15 –45/HPF) ($p = 0.038$).

The histopathological findings did not correlate with age, family history, allergic comorbidities, duration of symptoms, endoscopic findings or peripheral eosinophilia. However, a weak correlation was found between sex and basal zone hyperplasia: this feature was ten times more common in boys ($n = 1$) than in girls ($n = 10$) on histopathological examination ($\varphi = -0.36$, $p = 0.031$).

LABORATORY TESTS

The mean number of eosinophils in the peripheral blood was $0.51 \times 10^3/\mu l$ ($0–1.64 \times 10^3/\mu l$); 19 (42.2%) patients demonstrated values higher than normal ($0.5 \times 10^3/\mu l$). No association was found between peripheral eosinophilia and any symptoms or gastroscopic or histopathological findings. Peripheral blood counts also revealed no statistically significant differences in the red blood cell system or platelet count, or in white blood cells other than eosinophils.

No other significant correlations were noted between individual symptoms and the following characteristics: symptom duration, family history of allergic diseases, age, sex, body weight macroscopic changes of the oesophagus on gastroscopic examination, histopathological features, tissue eosinophilia in the oesophagus or peripheral eosinophilia.

DISCUSSION

Although EoE is a relatively rare condition, its prevalence continues to grow [7–11]. Unfortunately, its pathogenesis, symptoms and optimal treatment continue to challenge both the scientific community and medical practitioners.

The disease affects both children and adults [7, 8], and although it can manifest as early as infancy, the mean age of patients with EoE in the paediatric population has been found to be 10 years [12]; this age is in line with our present findings. Previous studies also indicate a predominance among male children with EoE in all study populations [13–18]; indeed, a meta-analysis by Arias *et al.* found EoE to be twice as common in boys as in girls [8]. This again is confirmed in our present study, where the condition was predominant among male patients.

One risk factor for the development of EoE is the presence of allergic diseases in the patient or in the family [6, 19]. Indeed, approximately 28.8% of children with EoE reported a family history of atopy in our present study, and 62% of children in a similar-sized group of patients in a previous retrospective study [20]; these differences may be attributed to the fact that the studies were conducted on different populations. Although EoE is not an inherited disease, some genes are known to predispose to its development, and a higher prevalence has bee reported among parents of EoE patients compared to the general population [21, 22]. A study of a large group by Chehade *et al.* found EoE to be present in 3% of parents and 4.5% of siblings of children with EoE [14]. None of the parents or siblings of the children in the present study had EoE.

Allergic diseases are more common in patients with EoE than among those without [6, 15, 23]. In our study, 62.2% of patients reported a previous diagnosis of an allergic disease. A previous study by Redd *et al.* identified a single comorbid allergic disease in 21% of studied EoE patients, and two or more allergic diseases in 35% [23]. This is similar to our present findings, where one allergic disease was present in 31% of patients, and two or more co-occurred in 27%. A meta-analysis by González-Cervera *et al.* found the most common allergic diseases in EoE patients to be asthma and allergic rhinitis [6], while the most common in the present study were food allergy (33% of all children) and allergic rhinitis (27%).

Among the symptoms of EoE, vomiting, lack of weight gain and refusal to take food have been found to be more common in younger children [24–27]. Similar results were obtained in our present study, with the younger children tending to present these symptoms.

The most common symptoms in older children have been found to include dysphagia, heartburn and food impaction, which are associated with oesophageal changes and remodelling and better symptom reporting by older children [24–26, 28]. In our study, odynophagia and heartburn were reported most frequently by older children.

A longer diagnostic delay, and thus a longer time to treatment, results in complications related to the development of oesophageal strictures, which can require surgical intervention, and impaired growth and puberty [4, 29]. In a meta-analysis of 47 studies by Shaheen *et al.* on the epidemiology and course of EoE the mean time from symptom onset to diagnosis was found to be in the range 1.2–3.5 years in children [30]. In the present study, this time was 1.4 years. The shorter duration may suggest a high level of vigilance and awareness of this disease among practitioners in our region, as well as good local accessibility to diagnosis in specialist centres.

The symptoms of EoE are varied and often similar to those of other gastrointestinal diseases. It generally took a longer time to establish a diagnosis of EoE in patients reporting regurgitation; this extra duration may have been related to a delay in diagnosis caused by a suspicion of oesophageal reflux disease, with the attempted empirical treatment resulting in partial resolution of symptoms. The significantly shorter diagnostic delay demonstrated by patients with concomitant asthma compared to those without (2.5 vs. 12 months) can be explained by the high vigilance of allergologists dealing with asthmatic patients.

Although a diagnosis of EoE is based on histopathological findings, most patients present typical features which can be identified by gastroscopic examination. These include mucosal rings, white exudates, linear furrows, oedema or pallor of the mucosa, strictures and mucosal fragility [31, 32]. A meta-analysis by Kim *et al.* found the most common endoscopic changes identified in children with EoE to be oesophageal mucosal pallor (58%), linear furrowing (46%) and white mucosal exudates (36%), with 21% having no oesophageal macroscopic changes [33]. Our present findings are slightly different, with the most common being linear oesophageal furrowing (66.7%), followed by whitish mucosal exudates (40.0%) and mucosal pallor (33.3%); only 4% of children with EoE demonstrated no oesophageal changes. These differences may be influenced by the small size of the study group and the population type.

The typical EoE lesions identified by histopathology include eosinophilic infiltration in the mucosal layer, dilation of intercellular spaces (spongiosis), basal zone hyperplasia, lamina propria fibrosis and eosinophilic abscesses [34, 35]. Collins *et al.* reported that the most common lesions were dilation of intercellular spaces (100%), basal zone hyperplasia (88%) and lamina propria fibrosis (85%). In our study group, the most common finding was basal zone hyperplasia (24.4%) with lamina propria fibrosis being observed less frequently (6.7%). Interestingly, our present findings indicate a lower incidence of additional histopathology features associated with EoE, such as basal zone hyperplasia, lamina propria fibrosis or eosinophilic micro-abscesses, compared to other studies [35]. These discrepancies may be influenced by the method of biopsy collection (depth), the experience of the pathomorphologist and the level of detail in the description of histopathological findings [36].

While peripheral blood eosinophilia count is not a measure of disease activity, it is often elevated in patients with EoE [37, 38]. Choudhury *et al.* and Marlais *et al.* reported that 48–78% of patients demonstrated an elevated eosinophil count, with a mean count of 0.58 and $0.86 \times 10^3/\mu l$, respectively [37, 38]. In comparison, in our study, 42.2% of children exhibited an above-normal eosinophilia count, with a mean value of $0.51 \times 10^3/\mu l$.

CONCLUSIONS

The most common symptoms observed in the children with EoE in the present study were difficulty with food intake, abdominal pain and food impaction. The clinical course of EoE varies in children according to age. Children with EoE often have co-occurring allergic diseases, and children with EoE and co-occurring asthma typically demonstrate a shorter diagnostic delay. The most common feature of EoE on endoscopic examination was the presence of linear oesophageal furrowing. The number of eosinophils in histopathology samples varies between patients and is not related to the endoscopic result.

DISCLOSURES

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2. We thank the National Research Centre (in-house office for research projects) for the research grants supporting this work. This study was part of a project No. 10010324. granted by the National Research Centre Egypt.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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