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ORIGINAL ARTICLE

Clinical manifestations, treatment, and outcomes of children and adolescents with eosinophilic esophagitis☆

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KEYWORDS
Eosinophilic esophagitis;
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Abstract

Objective: This study aimed to describe the clinical, endoscopic, and histologic characteristics, as well as the response to conventional treatment of pediatric patients with the classical form of eosinophilic esophagitis (EoE).

Methods: Study of clinical, laboratory, endoscopic, and histologic data and response to conventional treatment of 43 previously followed pediatric patients with the classical form of EoE.

Results: A total of 43 patients diagnosed with EoE were included in the study, of which 37 were males (86%), with a mean age of 8.4 years. The most common symptoms were: nausea, vomiting, and abdominal pain (100%) in children younger than 7 years, and loss of appetite (60%), heartburn (52%), and food impaction (48%) in children older than 7 years and adolescents. Regarding the endoscopic findings, 12 (28%) patients had whitish plaques on the esophageal lining, 8 (18.5%) had longitudinal grooves, 2 (4.5%) had concentric rings, 3 (7%) had longitudinal grooves and whitish plaques, and the remaining 18 (42%) had esophageal mucosa with normal appearance. Despite the initial favorable response, 76.7% of patients required more than one course of corticosteroid therapy (systemic or aerosol) and diet (exclusion or elimination of food or elementary

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allergens). Persistence of eosinophil infiltration was found in some patients despite favorable clinical response.
Conclusions: The classic form of EoE typically shows different symptoms according age range. A significant number of patients required more than one treatment cycle to show clinical remission. Endoscopic and histologic improvement was observed; however, eosinophilic infiltration persisted in some patients.
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PALAVRAS-CHAVE
Esofagite eosinofílica;
Refluxo gastroesofágico

Manifestações clínicas, terapêutica e evolução de crianças e adolescentes com esofagite eosinofílica

Resumo
Objetivo: O objetivo deste estudo foi descrever as características clínicas, endoscópicas e histológicas, assim comoa resposta ao tratamento convencional de pacientes pediátricos com a forma clássica de esofagite eosinofílica (EEo).
Métodos: Levantamento de dados clínicos, laboratoriais, endoscópicos, histológicos e da resposta ao tratamento convencional de 43 pacientes pediátricos acompanhados previamente com a forma clássica de EEo.
Resultados: Foram incluídos 43 pacientes com diagnóstico de EEo, sendo 37 do sexo masculino (86%), com idade média de 8,4 anos. Os sintomas mais encontrados foram: náusea, vômito e dor abdominal (100%) em crianças menores de sete anos; e inapetência (60%), queimação retroesternal (52%) e impactação alimentar (48%) em crianças maiores de sete anos e adolescentes. Em relação aos achados endoscópicos, 12 (28%) pacientes apresentavam placas esbranquiçadas na mucosa do esôfago, oito (18,5%) sulcos longitudinais, dois (4,5%) anéis concêntricos, três (7%) sulcos longitudinais e placas esbranquiçadas, e os outros 18 (42%) apresentavam aparência normal da mucosa esofágica. Apesar da resposta favorável inicial, 76,7% dos pacientes necessitaram realizar mais de um ciclo terapêutico com corticoterapia (aerossol ou sistêmica) e dieta (de exclusão ou eliminação dos alérgenos alimentares ou elementares). Persistência do infiltrado eosinofílico foi encontrada em uma parcela dos pacientes, a despeito da resposta clínica favorável.
Conclusões: A forma clássica da EEo apresenta sintomas diferentes segundo a faixa etária. Parcela expressiva dos pacientes necessitou de mais de um ciclo terapêutico para apresentar remissão clínica. Observou-se melhora endoscópica e histológica; no entanto, a infiltração eosinofílica persistiu em parcela dos pacientes.
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Introduction

Eosinophilic esophagitis (EoE) was described in the late 1970s by Landers et al.,[1] and has been identified as a clinical pathological entity since 1993 by Attwood et al.[2] The Brazilian scientific literature in pediatrics is limited to two case series described by Cury et al.[3] and by Ferreira et al.[4]

Considering the recent and rapid evolution in the understanding of this condition, a group of researchers has updated the latest consensus on EoE,[5] characterizing it as an immunological esophageal disease with chronic evolution and frequent relapses, whose clinical manifestations are related to esophageal dysfunction and, histologically, to the presence of eosinophil accumulation in the esophageal mucosa more than 15 eosinophils per high-power field (HPF), in the absence of eosinophil infiltration in the gastric and duodenal mucosa. The symptoms and pathological findings should improve with medical treatment, which involves the exclusion of allergens (food or aeroallergens), use of topical corticosteroids, or both therapeutic measures. A subset of patients responsive to proton pump inhibitors (PPIs) has also been described, termed PPI responders, differentiating them from the group of patients with classic EoE, known as non-PPI-responders. All other recognized causes of EoE should be excluded, as there are no symptoms identified at physical examination, serum markers or pathognomonic endoscopic data of the disease.[5]

The aim of this retrospective study was to describe the clinical, endoscopic, and histological characteristics and response to conventional treatment of pediatric patients with the classical form of EoE.

Methods

This was a retrospective study using data collection in a series of cases addressing the clinical, laboratory, endoscopic, and histological data from the records of 43 patients treated in the period between February, 2004 and September, 2010 with a diagnosis of EoE in the Gastroenterology Outpatient Clinic of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP).

Inclusion criteria

All patients were referred to the specialized service with a history of previous upper endoscopy in their healthcare services of origin, with an initial diagnosis of reflux esophagitis resistant to treatment with PPI for at least three months.

All patients were symptomatic. After obtaining the clinical history, physical examination was performed and personal or family history of first-degree atopy was assessed; subsequently, patients underwent a new upper endoscopy. Two fragments of the esophagus were obtained (one proximal and one distal), as well as two fragments of the stomach and duodenum through upper endoscopy and biopsy forceps for histological evaluation. The number of eosinophils per high-magnification field (x400) was quantified in at least 10 fields; EoE was considered when ≥ 15 eosinophils/HPF[5] were found in the esophageal mucosa in at least 2 high-power fields and normal gastric and duodenal mucosa.

The presence of specific serum immunoglobulin E (IgE) was analyzed (ImmunoCAP®)[6] for the suspected food according to clinical history, to assist in the identification of food allergens involved in the EoE process, according to the standard method, considered positive when ≥ class II.

Exclusion criteria

All other known causes of EoE were excluded, such as gastroesophageal reflux disease (GERD), celiac disease, Crohn's disease, infection, hypereosinophilic syndrome, achalasia, drug hypersensitivity, vasculitis, pemphigus vegetans, connective tissue disease, and graft-*versus*-host disease.

As recommended in the consensus of 2007,[7] the possibility of GERD was ruled out by the lack of response to previous treatment with PPI.

The therapeutic modality adopted by the patients of the present study was in accordance with recent data from the literature on EoE.[5,7] PPI is not considered the primary treatment for EoE, but can be used as adjunctive therapy to relieve some of the symptoms. Systemic corticosteroid therapy was used for children younger than 2 years and topical therapy for the other patients. In the first case, prednisolone 1 mg/kg/day was used, divided in two daily doses for four weeks, with scheduled withdrawal up to the eighth week. In the second case, fluticasone propionate was used by oral route (children 2 to 4 years: 176 mcg daily; children 5 to 10 years: 444 mcg daily; adolescents > 11 years: 880 mcg daily). A suitable topical dose was administered in the form of an oral spray, divided in two doses per day. Patients were instructed not to use the spacer and that the content of the spray must be swallowed and not aspirated, and patients were not allowed to eat or drink for at least 30 minutes after medication. Treatment with fluticasone was carried out for three months.

Dietary therapy (removal of specific antigens or elementary diet) was patient-specific and considered as an effective part of the treatment, with adequate calories, vitamins, and micronutrients of the received diet at baseline and at follow-up.[7]

Patients were followed through regular visits to the outpatient clinic every two months, where parents and patients were asked about symptoms, treatment adherence, and side effects of drug therapy. The monitoring of upper endoscopy was recommended after 9 to 12 months of treatment initiation.

This study was approved by the Ethics Committee of the Department of Gastroenterology of HCFMUSP.

Results

Of the 43 patients, 37 were males (86%), and 41 were defined by their parents as white and two as black. Patient's age ranged from 1 month to 17 years, with a mean of 8.4 years. Approximately 44% of patients were identified by clinical history as having respiratory allergies, and 23% of first-degree relatives had respiratory, gastrointestinal, or skin atopy. The clinical manifestations of the 43 patients are shown in Table 1. Nausea, vomiting, and abdominal pain were more frequent in patients aged less than 7 years, while food aversion, food impaction, and heartburn were more prevalent in patients aged 7 to 17 years.

The search results for specific serum IgE (ImmunoCAP®) are summarized in Table 2. Of the 43 patients studied, 18 (41.9%) had sensitization to more than one food protein or aeroallergens, 2 (4.6%) were sensitive to one studied protein, and the remaining 23 (53.5%) patients presented no sensitization.

Regarding the endoscopic findings of the 43 patients on admission, whitish plaques on the esophagus mucosa predominated in 12 (27.9%), longitudinal grooves in 8 (18.6%) patients, whereas in 18 (41.2%) the macroscopic esophageal aspect was normal. At the microscopy, the quantification of eosinophils/HPF varied from 15-100 eosinophils per HPF, with the highest concentration of eosinophils in the lesions characterized as whitish plaques, as shown in Table 3. It was also observed that the proportion of patients with the number of eosinophils between 15 and 30 per field in normal endoscopies (44.4%, 8/18) was higher than in those with endoscopic findings suggestive of EoE with higher eosinophil count (8.0%, 2/23, p = 0.009, Fisher's exact test).

The dietary and drug treatments were initially carried out for a period of three months. The dietary management was based on clinical history and the results of allergy tests, using the exclusion of identified allergen(s) in the clinical history and Rast ImmunoCAP®, or by eliminating the six major allergens (cow's milk, soy, egg, fish, peanuts, and wheat) in patients where it was not possible to identify them through the clinical history and/or food allergy test.

Table 1 Symptom distribution in 43 patients according to age range.

Clinical manifestation	Age range			p
	< 7 years n = 18	7-17 years n = 25	Total n = 43	
Nausea/vomiting	18 (100.0%)	5 (20.0%)	23 (53.5%)	0.000
Abdominal pain	18 (100.0%)	7 (28.0%)	25 (58.0%)	0.000[a]
Loss of appetite	10 (55.5%)	15 (60.0%)	25 (58.0%)	0.983[a]
Weight loss	1 (5.5%)	4 (16.0%)	5 (11.5%)	0.380[b]
Food aversion	0 (0%)	10 (40.0%)	10 (23.0%)	0.002[b]
Food impaction	0 (0%)	12 (48.0%)	12 (28.0%)	0.005[b]
Heartburn	0 (0%)	13 (52.0%)	13 (30.0%)	0.000[a]
Wheezing	7 (38.8%)	12 (48.0%)	19 (44.0%)	0.777[a,b]
Coughing	5 (27.7%)	6 (24.0%)	11 (25.5%)	1.000[b]

[a]Chi-squared test with Yates' correction.
[b]Fisher's exact test.

Table 2 Number of patients with eosinophilic esophagitis with positive IgE antibody (RAST) to aeroallergens and food allergens according to age range.

Specific IgE	Age range			p
	< 7 years n = 18	7-17 years n = 25	Total n = 43	
Cow's milk	8 (44.0%)	7 (28.0%)	15 (34.9%)	0.428[a,b]
Egg white	1 (5.5%)	2 (8.0%)	3 (7.0%)	1.000[b]
Fish	1 (5.5%)	1 (4.0%)	2 (4.5%)	1.000[b]
Peanuts	2 (11.0%)	1 (4.0%)	3 (7.0%)	0.562[b]
Soybean	2 (11.0%)	2 (8.0%)	4 (9.0%)	1.000[b]
Wheat	0 (0%)	0 (0%)	0 (0%)	Non-analyzable
House dust	4 (22.0%)	12 (48.0%)	16 (37%)	0.159[a]

[a]Chi-squared test with Yates' correction.
[b]Fisher's exact test.

Table 3 Association between endoscopic lesion severity and intensity of eosinophilic infiltrate in 43 patients with eosinophilic esophagitis.

	Eosinophil counts per high-power field			
	Total	15-30	31-50	> 50
Concentric rings	2	1	1	0
Longitudinal grooves	8	0	4	4
Whitish plaques	12	0	0	12
Longitudinal grooves + whitish plaques	3	1	2	0
Normal	18	8	8	2
Total	43	10	15	18

In four patients younger than 2 years, hypoallergenic formulas were used: protein hydrolyzate (2 cases) and amino acid formula (2 cases). In one child older than 2 years of age, a free amino acid formula was used, due to nutritional problems.

Of the 43 cases studied, 41 received topical glucocorticoids, and only two patients received oral corticosteroids, due to the young age. All 43 patients received acid suppression with PPIs as adjuvant treatment.

33 (76.7%) of 43 patients received at least two courses of treatment, because when diet and medication were discontinued, the symptoms returned within four to eight weeks; however, after the second course of treatment, all patients were asymptomatic.

Of the 43 patients, 28 agreed to undergo a control endoscopy. Table 4 shows that the six patients who had a normal endoscopy at baseline remained with a normal endoscopy, while of the 22 who initially had endoscopic

Table 4 Evolution analysis of endoscopic findings in 28 patients with eosinophilic esophagitis who underwent control evaluation nine to 12 months after treatment initiation.

After treatment	Before treatment					
	Concentric rings	Longitudinal grooves	Whitish plaques	Longitudinal grooves + whitish plaques	Normal	Total
Concentric rings	2					2
Longitudinal grooves		6				6
Whitish plaques			5			5
Longitudinal grooves + whitish plaques				1		1
Normal		2	5	1	6	14
Total	2	8	10	2	6	28

abnormalities, eight had normal esophageal mucosa in the second endoscopy (McNemar's test, p = 0.013). Regarding eosinophil count, initially all patients had increased eosinophil count (10 patients with 15 to 30 eosinophils; 10 with 31-50 eosinophils; and 8 with eosinophil count > 50). All had fewer than 15 eosinophils in the second biopsy after treatment.

Discussion

The Brazilian scientific literature on EoE in the pediatric population is limited to two case series described by Cury et al.[3] and by Ferreira et al.,[4] highlighting symptom refractoriness to standard treatment of GERD in both articles. Another report[8] emphasized EoE as differential diagnosis of achalasia. In the present study, the clinical and endoscopic manifestations and response to therapy of 43 patients treated in the period between February 2004 and September 2010 and whose final diagnosis was the classic form of EoE are described. The subgroup of patients with EoE responsive to PPIs, in relation to symptoms and histopathological findings were not included, as all patients were combined before the inclusion of this subgroup in the updated EoE criteria.[5]

Additionally, the updated consensus included a small number of patients with fewer than 15 eosinophils/HPF, who are treated with PPIs, provided they show other signs of eosinophilic inflammation, including eosinophilic microabscesses, accumulation of eosinophils in the superficial layer of the esophageal mucosa, or extracellular eosinophilic granules. The reasons pointed out by researchers were the possibility of inadequate biopsies, sample errors, and coping with chronic disease or partial response to treatment. The present study did not evaluate these histological findings, considering only the infiltration of at least 15 eosinophils/HPF.[5]

The mean age of the patients at diagnosis was 8.4 years (1 month to 17 years); patients were predominantly males (86%), and the majority were white. Although it appears to be an absolute majority, racial classification by skin color is controversial, especially in Brazil, where miscegenation is high. The mean age of disease prevalence was similar to that in the literature.[9] There is also agreement in the literature on male predominance.[10-15]

It is interesting to stress that this disease has been described in all continents, except for Africa, probably due to the absence of the gene(s) responsible for the disease or absence of environmental factors.[16]

Another aspect to highlight is that these patients were treated during a six-year period, and most patients were referred from the Pediatric Gastroenterology outpatient clinic of the Complexo Hospitalar do Mandaqui, corresponding to the frequency of 7 patients/year; however, there are no data on the total of patients presenting with suspected GERD/year and responders to PPIs during this period, among which the subset of EoE responders to PPIs, who did not participate in this study, was found.

Some authors have called attention to the increasing prevalence of EoE in children and adolescents.[11,12,17]

When comparing the prevalence of symptoms in the present study with those of other authors, an agreement in the variability in clinical presentation according to age was observed; most symptoms of nausea, vomiting, and abdominal pain were observed in children younger than 7 years, while heartburn, food aversion, and food impaction were mostly observed in children older than 7 years and adolescents.[7,9,10,13,14]

Regarding the presence of atopy, respiratory symptoms were observed, such as recurrent wheezing (44%) and cough (25.5%), which reinforced the suspicion of EoE; these findings are similar to those found by other authors.[12,14]

Endoscopic findings suggestive of EoE at the diagnosis were observed in 58% of case, and apparently normal esophageal mucosa were found in 42% of cases. Other studies showed endoscopic alterations suggestive of EoE in greater proportions, around 73% of cases.[7,10,14] Although none of these endoscopic findings is pathognomonic of EoE, finding at least one of them is strongly suggestive of the disease. It is noteworthy that some of the present patients had an initial diagnosis of monilial esophagitis, due to the endoscopic finding of whitish plaques on the esophageal mucosa.

Regarding the histological aspects, at least two fragments were obtained from the esophageal mucosa for the quantification of eosinophils/HPF. The literature recommends obtaining at least one fragment in each esophageal segment (proximal-medium and distal) as esophageal inflammation may be focal and involve apparently healthy areas.[5,7] This procedure increases the diagnostic sensitivity to 97% of cases.[18]

Eosinophilic infiltration of 15-30 per HPF was found in 89% of apparently normal mucosa, probably because the eosinophilic inflammatory infiltrate had not yet reached the mucosa and thus had not manifested any lesions suggestive of the disease.

The determination of specific IgE only assists in identifying IgE-mediated food allergy of type I or immediate type.[6] The detection of specific IgE has been considered indicative of sensitization to food, confirmed only after its exclusion, with improvement of all symptoms and return of symptoms after oral provocation test.[19] Regarding the research of aeroallergens through tests involving specific IgE, there have been only case reports in adults showing its probable role in the triggering of EoE.[20] Among the patients evaluated in this study, the presence of sensitization by cow's milk protein was found in 15 (34.9%) patients, and by aeroallergens in 16 (37.0%) patients identified through ImmunoCAP. The frequency of sensitization (positive ImmunoCAP) to inhalants and foods in this group of patients was 46.5%, which should be compared with previously published Brazilian data in normal and atopic children of 25.8% and 79%, respectively.[21]

The treatment of these patients involved dietary therapy, with the exclusion of the main allergenic foods (cow's milk, soy milk, eggs, fish, peanuts, and wheat) when allergens were not identified through clinical history or ImmunoCAP performed as indicated in literature.[5,7,22]

The use of the elemental formula diet removes all potential food allergens, and is especially indicated for infants, whose oral intake tolerance is increased.[23]

After histological confirmation of EoE, in addition to dietary therapy, patients received topical steroids with spray inhalers (41/43) or by oral route for children younger than 2 years (2/43). Studies have shown that the use of systemic or topical corticosteroids has been effective in resolving the clinical and pathological manifestations of EoE, but its systemic use must be reserved for severe cases.[14,24,25]

The use of topical corticosteroids for the maintenance treatment of EoE in adults and children has not been established, as well as dose, frequency, and mode of administration, as these formulations were not designed for use in the esophagus.[5,7,24] The doses suggested by the current literature vary from 440 to 880 mcg/day for children and 880-1760 mcg/day for adolescents and adults, continuously for six to eight weeks.

28 of 43 patients underwent control endoscopy; clinical, endoscopic, and histological improvement was observed between six and nine months after treatment, with a decrease in the number of eosinophils/HPF to approximately 0-12 eosinophils/HPF.

It is noteworthy the fact that 75% of patients remained temporarily asymptomatic after finishing the first treatment cycle and withdrawing medication; however, after exposure to food allergens, they started to present the same symptoms again, requiring a second treatment cycle. The clinical outcome of the present patients with EoE, although chronic, was satisfactory. There was no loss of patients during outpatient follow-up; however, parents or guardians of the patients did not always accept the performance of a third upper endoscopic assessment.

Treatment duration has not been established, nor has the importance of treating asymptomatic patients who remain with histological signs of EoE after initial treatment and the frequency of endoscopic controls during follow-up.[5]

Patients gained quality of life, reflected by changes in feeding behavior reported by the parents, demonstrating improved mood and better social behavior, and began to have meals with their families once again. The families felt gratified and many felt embarrassed of having wrongly classified their children as being too selective and as having a social disorder.

In patients with the classic form of EoE, symptoms vary according to age, with nausea, vomiting, and abdominal pain most often found in young children, and lack of appetite, heartburn, and food impaction in older children and adolescents. Patients with suspected EoE should undergo biopsies in the proximal and distal locations of the esophagus, stomach, and duodenum, in order to attain a complete diagnosis. A favorable response to treatment from the clinical and histological standpoint was achieved by all patients, requiring at least two treatment cycles in 76.7% of 43 patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

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