

**Incidence of childhood eosinophilic esophagitis in central Brazil:
how many are we missing?**

Running title: Incidence of EoE in Brazil

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SUMMARY

Background: Few studies have assessed the incidence of eosinophilic esophagitis (EoE) in childhood. The study aim is to determine the incidence of EoE in pediatric patients submitted to upper gastrointestinal endoscopy (UGE), with analysis of epidemiological data regarding sex, age, symptomatology, the frequency of atopy and endoscopic and histological findings.

Methods: A retrospective, observational and analytical study performed with an evaluation of medical records of patients aged 0 to 14 years who underwent to upper gastrointestinal endoscopy in a tertiary hospital from January 2004 to January 2014.

Results: A total of 4071 upper digestive endoscopies were performed in 2651 patients. Esophageal eosinophilia was found on 405 biopsy reports, being 127 with 15 or more eosinophils per high-power field in 70 different patients. Sixty-three fulfilled diagnostic criteria for EoE, three for eosinophilic gastroenteritis and four were secondary to caustic ingestion. The mean annual incidence was 2.48/100,000 individuals/year and the cumulative incidence over ten years was 24.8/100,000. No statistical difference was found between PPI-responders and non-responders regarding age, gender, atopic diseases, symptoms and endoscopic findings.

Conclusion: The incidence of EoE found in the present study was similar to that described in the literature, however. These data may be underestimated due to the difficulties to access UGE. The increased knowledge around esophageal eosinophilic diseases on childhood requires associated improvement in the health systems infrastructure.

Key words: Eosinophilic Esophagitis; Proton Pump Inhibitor Responsive Esophageal Eosinophilia; Atopic Diseases; Childhood; Prevalence.

RESUMEN

Antecedentes: pocos estudios han evaluado la incidencia de esofagitis eosinofílica (EoE) en la infancia. El objetivo del estudio es determinar la incidencia de EoE en pacientes pediátricos sometidos a endoscopia gastrointestinal alta (UGE), mediante un análisis de datos clínico epidemiológicos incluyendo sexo, edad, sintomatología, frecuencia de atopia con relación a los hallazgos endoscópicos e histológicos.

Métodos: estudio retrospectivo, observacional y analítico cuya fuente de datos eran las historias clínicas de pacientes de 0 a 14 años a los que se había realizado una endoscopia digestiva alta en un hospital terciario, entre enero de 2004 y enero de 2014.

Resultados: Se realizaron un total de 4071 endoscopias digestivas altas en 2651 pacientes. Se encontró eosinofilia esofágica en 405 informes de biopsias, siendo 127 con 15 o más eosinófilos por campo de alta potencia, presentes en 70 pacientes diferentes. Sesenta y tres cumplieron los criterios de diagnóstico para la EoE, tres para la gastroenteritis eosinofílica y cuatro fueron tóxicas secundarias a ingestión cáustica. La incidencia media anual fue de 2,48 / 100.000 individuos / año y la incidencia acumulada durante diez años fue de 24.8 / 100.000. No se encontraron diferencias estadísticamente significativas entre los pacientes con respuesta a inhibidores de la bomba de protones (PPI) y los que no respondieron, con respecto a la edad, sexo, enfermedades atópicas, síntomas y hallazgos endoscópicos.

Conclusión: la incidencia de EoE encontrada en el presente estudio fue similar a la descrita en la literatura, sin embargo, estos datos pudieran ser subestimaciones debido a las dificultades para acceder a UGE. El aumento del conocimiento sobre las enfermedades eosinofílicas esofágicas en la infancia requiere una mejora asociada en la infraestructura de los sistemas sanitarios.

Palabras clave: Esofagitis Eosinofílica; Eosinofilia Esofágica Con Respuesta A Inhibidor De La Bomba De Protones; Enfermedades Atópicas; Infancia; Prevalencia.

Introduction

Eosinophilic esophagitis (EoE) is a chronic disease, immune/antigen-mediated, characterized clinically through signs of esophageal dysfunction and histologically by inflammatory infiltrate, predominantly eosinophilic [1,2]. Prior studies have identified an association between atopic diseases, such as food allergies, allergic rhinitis, atopic dermatitis and asthma, and EoE [3]. The clinical symptoms diverge with age; EoE should be considered in older children and adults who present with symptom of esophageal dysfunction and/or fibrosis such as dysphagia, odynophagia, or food impaction while in infants and younger children the symptoms often mimic those related with gastroesophageal reflux disease (GERD)[1]. The interacting relationship between GERD and EoE might be bidirectional, so, they are not mutually exclusive disorders and may coexist in a single patient, albeit not necessarily interacting [2].

In 2011, the expert panel recommended for EoE diagnosis the existence of 15 or more eosinophils per high power field (hpf) in one or more fields of biopsy specimens (minimal of 4 specimens) while the patient is on adequate dosage of proton pump inhibitor (PPI), exclusively in the esophagus, as well as the exclusion of other diseases associated with esophageal eosinophilia [1]. Cumulative evidences since then have clearly demonstrated that PPI-REE and EoE are completely overlapping diseases in term of symptoms, endoscopic and histologic findings, molecular signature and gene signature and patients achieving clinical and histological remission on PPI therapy are part of the EoE continuum, rather than a separate entity [2]. Other endoscopic findings such as thickening and opacity of the mucosa, esophageal rings and white exudates are common in EoE, although an endoscopically normal esophagus cannot exclude the disease [1,2,4,5]. On histology, esophageal tissue of patients with EoE is characterized by esophageal barrier alterations such as basal layer cell hyperplasia, papillary elongation, dilation of the intercellular space, presence of microabscesses and eosinophil infiltrates [1,2,5]. Untreated EoE can result in significant impairment in quality of life and once diagnosed, the control of esophageal inflammation, through topical corticosteroid therapy and/or allergen identification and avoidance should be initiated in order to relieve symptoms and prevent food impaction due esophageal stricture formation [2].

Limited studies with different designs, including prospective and retrospective registries of cases, series of endoscopies and population-base studies, have shown that incidence and prevalence of EoE have increased [6]. One important aspect related to the

prevalence of EoE is the access to digestive endoscopies, which can lead to a variability in the prevalence purely through the difficulty or not of accessing procedures, and thus it is underestimated, since the diagnosis depends on histological confirmation [7]. The incidence and/or prevalence of eosinophilic esophageal diseases are not known in Brazil; previously published studies were focus on isolated or a series of cases [8,9]. The knowledge of diseases prevalence is extremely important to understand their impact on the population and also is an essential tool for the dimensioning of the infrastructure necessary for control and control of the same.

We perform a retrospective cohort study aimed to determine the annual incidence of EoE in pediatric patients and the cumulative incidence over a ten-year period, through demographic and clinical data analysis, endoscopic reports and biopsy results from patients.

Materials and Methods

The unit of gastrointestinal endoscopy at the Clinical Hospital of Universidade Federal de Uberlandia (HC-UFU) is the only provider of upper gastrointestinal endoscopy (UGE) for pediatric population from 30 cities that make up our reference macro-region, with a total of 253,706 children at range 0-14-year-old age, with a relative stable individuals number over a decade, according to the IBGE/census, a Brazilian agency in charge to provide populational data [10]. This estimation for regional population was used for the prevalence calculation.

We extracted data from the hospital electronic records of 4071 performed UGE in children in our hospital between January 2004 and January 2014, to generate a retrospective cohort. Direct patient identifiers were removed to create a dataset with limited identifiers (eg, date of birth, date of UGE performance, diagnoses, UGE code, etc.). According to hospital electronic records, these 4071 endoscopies were performed on 2651 different patients. After the analysis of the biopsies, all patient medical records that presented ≥ 15 eos/hpf were analyzed and data related to clinical features and UGE findings were added to the previous patient's datasheet. The diagnosis of EoE, PPI-REE and other eosinophilic diseases were reviewed according the guidelines [1,2,4]. The research study was approved by the ethics committee of Universidade Federal de Uberlandia.

A Student's t-test was used for the analysis of continuous variables and Fisher's exact test for the categorical variables. The level of significance used was $p < 0.05$ with two tails using the program GraphPad Prism 5.0 (La Jolla, CA).

Results

The algorithm flowchart representation of our study cohort is shown in the Figure 1. 4071 UGE were performed in 2651 different patients in the period; from these 4071 UGE, only 2158 (53%) accomplished esophageal biopsies, and esophageal eosinophilia was reported on 405 of these anatomopathological analysis, being 127 with more than 15 eos/hpf. The medical files analyses from these 127 reports were accomplished in 70 different patients, representing 2.64% of 2651 patients who underwent UGE (Figure 1). Among this group, the diagnosis criteria for EoE were found in 63 (2.38%) and 3 (0.11%) for eosinophilic gastroenteritis. Other four (0.15%) patients among this group of 70 patients presented more than 15 eosinophils/hpf in the UGE after caustic ingestion; two improved the esophageal eosinophilia after treatment with PPI and other two patients did not performed a subsequent UGE. Other intriguing data found among with EoE was the existence of nine patients with cerebral palsy.

The statistics was calculated considering the total children aged from 0 to 14-year-old living in the macro-region reference for our hospital, estimated in a total number of 253,706, as referenced previously. The mean incidence of EoE was 2.48 cases per 100,00 individuals/year and the annual data is demonstrated in the Table 1. The 10 years cumulative incidence of confirmed EoE was found to be 24.8 children per group of 100,000 over the 10 years. In our cohort, 11 out 63(17.46%) patients were found to have histologic response to PPIs while 31(49.21%) were considered as PPI non-responders. Other 21(33,33%) did not complete the follow up UGE and we are not able to classified as a PPI responder or not.

The comparison between the groups of confirmed PPI responders and non-responders did not show significant differences regarding gender, age, the presence of atopic diseases or symptomatology, as shown in Table 2. Although there are no statistical differences, only the non-responder group presented cases of food impaction. The complaint of vomiting was greater than that of dysphagia in the PPI non-responder group and the opposite was seen in the PPI responders group (Table 2).

Although endoscopic alterations were more frequent in the PPI non-responder group, where 28 cases were registered (90.3%), there were no significant differences

shown in relation to the PPI-responder group (Table 3). The same occurs when we compared the number of eosinophils among the groups, which is also demonstrated in Table 1.

Eosinophilic gastroenteritis was diagnosed in only three patients, all male and with a history of food allergies in two (66.6%), and the findings were no different to those from the other groups (data not shown).

Discussion

The present study was the first designed to determine the incidence and cumulative incidence of pediatric EoE in our country and also, in Latin America countries. A systematic review and meta-analysis was performed recently to estimate incidence and prevalence rates of EoE. After analysis of 1334 references, only 13 population-based studies from North America, Europe and Australia were included showing a high heterogeneity in the results [6]. The reported annual incidence ranged from 0.28 [11] to 19.6[12] per 100,000 inhabitants/year and an overall incidence rate estimate of 3.7 per 100,000 inhabitants/year considering the studies were pooled [6]. The results also showed a slightly higher incidence in adults (7/100,000 persons/year) than in children (5.1/100,000) [6].

Considering the pediatric population, only six studies were selected by the meta-analysis and one previous cited after meticulous evaluation, being 5 from USA and one from Denmark [6, 13-18] and the annual incidence in children ranged from 0.7 [13] to 16.8 [14] per 100,000 individuals/year, both conducted in the USA. Although the mean annual incidence of EoE found in our study (2.48/100,000 individuals/year) is lesser than observed in the final results of the recent meta-analysis (5.1/100,000), the value is in the range of the participants studies and is pretty similar to the annual incidence found in a large nationwide database study (2.9) [18]. The lower incidence before 2007 also was seen in a previous systematic review and is related to the absence of a systematic guidelines to perform the correct EoE diagnosis [6].

Other study from the Middle East had focus on the EoE frequency in those submitted to an upper endoscopy, as an example, one study performed in a pediatric population who underwent UGE in the Saudi Arabia had found an EoE frequency of 0.85% after the evaluation of 2,127 endoscopies [19]. In our study, 31 of the 2651

patients who underwent UGE had confirmed EoE, reaching a slight superior frequency (1.17%).

The clinical and endoscopic characteristics of EoE in PPI-responder and non-responders are quite similar in our study as described previously [20-24]. This reinforces the recent EoE consensus that considered the EoE and PPI-REE as a different spectrum of the same disease that should be recognized as EoE [2,23-27]. A previously published study evaluated children with esophageal eosinophilia with the aim of identifying response predicting factors for PPI; however, no factor was observed. In a univariate analysis patients with abnormal pH and an eosinophil count of between 15 and 20 eos/hpf seemed to respond better to PPI [26].

Children with EoE often have unspecified symptoms, in contrast to adults where there are reports of dysphagia and impaction, thereby contributing to the delay in reaching a diagnosis in this age range [2,4,5]. Complaints such as difficulties when eating, vomiting episodes and abdominal pain are the most frequent, with these symptoms affecting more than half of all patients. The frequency of the symptoms found in this study is similar to data from the North American studies [15].

Although a normal UGE examination does not exclude the disease, macroscopic alterations during the endoscopy procedure are frequently observed, such as white plaques, mucosal edema, longitudinal furrows and esophageal rings as seen in the present study [1,2,4,5]. Again, no statistical difference was found between PPI-responder and non-responder group.

Emphasis on the high prevalence of EoE that was found in patients with cerebral palsy should be noted. It is known that gastrointestinal diseases are common in children with psychomotor impairment, although reflux disease is more common, we should suspect EoE in those patients without response on conventional GERD treatment [28].

The limitations of the present study include the retrospective assessment of clinical records, the lack of a structured study protocol used when patients were assessed and the reduced accuracy of the data derived from the retrospective assessment, especially the esophageal features of EoE observed in the UGE. The number of patients with EoE may not have been satisfactory, albeit we enrolled all patients with esophageal eosinophilia treated at our institution over 10 years. There may have been some underestimation regard to the enrollment since the biopsy reports were obtained from 53% of UGE procedures. Other important point to remember is the difficult to perform the UGE in our region, especially in children, resulting in a long

waiting leading patients to quit the medical investigation and consequently, the EoE diagnosis.

In conclusion, the incidence of EoE in the present study was similar to that described in the literature. These data may be underestimated due the difficulties to access UGE and the number of UGE without biopsies. Larger multicenter prospective studies will be necessary to obtain more accurate results. Finally, the increase knowledge around esophageal eosinophilic diseases on childhood requires associated improvement in the healthy system infrastructure to provide adequate diagnosis, treatment and follow-up of patients.

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Table 1. Incidence of EoE per year and the cumulative incidence in 10 years of Eosinophilic Esophagitis in 0-14 year old children in the reference macro-region served by Universidade Federal de Uberlândia, Brazil

Year	EoE (number of cases)	Incidence (per 100,000 inhabitants)
2004	2	0.78
2005	3	1.19
2006	5	1.96
2007	9	3.54
2008	6	2.36
2009	9	3.54
2010	7	2.76
2011	8	3.15
2012	7	2.76
2013	7	2.76
Mean (10 years)	6.3	2.48
Total (10 years)	63	24,80

Table 2. Demographic and clinical characteristics of patients in PPI-responder and non-responder groups of EoE

	NR group n = 31, (%)	R group n = 11, (%)	P value
Age (months)	87.10 ± 8.95	106.3 ± 12.68	0.2395 ^{&}
Gender			
Masculine	17 (54.83)	7 (63.63)	0.7306*
Feminine	14 (45.16)	4 (36.37)	
Atopy			
Asthma	9 (29.03)	2 (18.18)	0.6959*
Rhinitis	16 (51.61)	6 (54.54)	1.0000*
Food allergy	19 (61.29)	4 (36.37)	0.1719*
Atopic dermatitis	4 (12.90)	1 (9.09)	1.0000*
Symptoms			
Abdominal pain	18 (58.06)	5 (45.45)	0.5038*
Vomit episodes	10 (32.25)	4 (36.37)	1.0000*
Dysphagia	8 (25.80)	5 (45.45)	0.2700*
Impaction	6 (19.35)	0 (0.00)	0.1724*

NR: PPI-non responder eosinophilic esophagitis; **R:** PPI-responder eosinophilic esophagitis

* Fisher's exact test

[&] Student's t-test

Table 3. Endoscopic and histological characteristics of PPI responders and non-responder groups of EoE

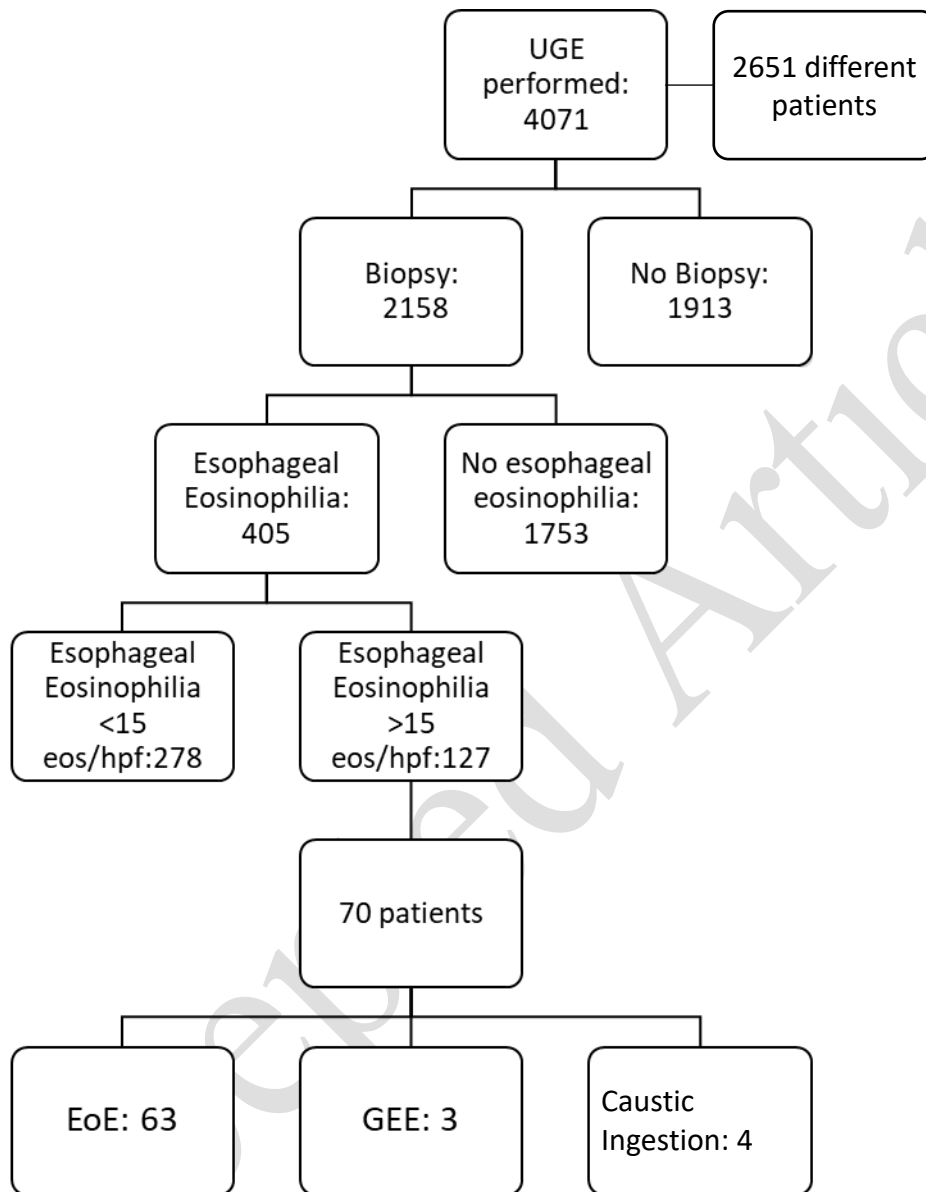
	NR n = 31	R n = 11	P value
Endoscopic alterations			
Thickening, n(%)	10 (32.25)	3 (23.07)	0.7223*
Opacity, n(%)	15 (48.38)	5 (38.46)	0.7416*
Longitudinal furrows, n(%)	11 (35.48)	2 (15.38)	0.2825*
White exudates, n(%)	10 (32.25)	1 (7.69)	0.1321*
Rings, n(%)	10 (32.25)	3 (23.07)	1.0000*
Hyperemia, n(%)	2 (32.25)	3 (23.07)	0.1441*
Average for eos/hpf, average \pm SD	41.45 \pm 5.853	28.85 \pm 6.496	0.2143 ^{&}

* Fisher's exact test

[&] Student's t-test

NR: PPI-non responder eosinophilic esophagitis; **R:** PPI-responder eosinophilic esophagitis

Figure 1. Study flowchart.



UGE: upper gastrointestinal endoscopy; EoE: eosinophilic esophagitis; GEE: eosinophilic gastroenteritis.