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CARACTERIZAÇÃO ENDOSCÓPICA DE PACIENTES PEDIÁTRICOS DE ACORDO COM O NOVO SISTEMA DE GRADUAÇÃO E CLASSIFICAÇÃO ENDOSCÓPICA DA ESOFAGITE EOSINOFÍLICA

LUCIANE BORGES MARSON

MESTRADO

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito parcial para a obtenção do título de Mestre em Ciências da Saúde.

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Presidente da banca:

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RESUMO

Introdução: O EREFS foi utilizado para avaliação diagnóstica, predição da atividade e remissão da doença em pacientes adultos com EEo. No entanto, há alguns estudos em que a eficácia deste método endoscópica foi testada em crianças. **Objetivo:** Caracterizar os recursos do EREFS em uma população pediátrica submetida a endoscopia diagnóstica e avaliar o valor preditivo da sua pontuação para diagnóstico de EEo. **Métodos:** Coorte endoscópica prospectiva com pacientes pediátricos realizada em uma população brasileira, avaliando pacientes com queixa gastrointestinal sem diagnóstico definitivo. Os dados demográficos e clínicos foram avaliados. Após o procedimento endoscópico, o EREFS original foi marcado, sem conhecimento do diagnóstico final de EEo, DRGE ou Controle. **Resultados:** Foram incluídos 170 pacientes submetidos a endoscopias. As características inflamatórias foram mais freqüentemente encontradas do que as fibrostenoticas. O EREFS-T mostrou sensibilidade de 75%, especificidade de 85,7%, acurácia de 84,1% e área sob a curva foi de 0,80. As medianas de EREFS-T foram 2,5, 0,5 e 0,0 para EEo, DRGE e Controles, respectivamente. Houve diferença estatística significativa entre EEo EREFS-T x Controle EREFS-T ($p < 0,0001$) e EOE EREFS-T x DRGE EREFS-T ($p = 0,0375$). **Conclusão:** os dados sugerem que o EREFS-T é uma ferramenta de diagnóstico útil para EEo pediátrico com sensibilidade aceitável, boa especificidade e acurácia. As características inflamatórias são mais freqüentemente encontradas do que as características fibrostenóticas na avaliação do diagnóstico endoscópico de EEo pediátrico. Alguns recursos presentes no EREFS original provavelmente podem ser suprimidos para a análise pediátrica diagnóstica de EEo, como no EREFS modificado usado em adultos.

Palavras chave: Esofagite eosinofílica, EREFS, Doença do refluxo gastroesofágico, Pediatria.

ABSTRACT

Background: The EREFS has been used for diagnosis assessment and prediction of the activity and remission of the disease in EoE adult patients. However, there are a few studies in which the effectiveness of this endoscopic metric has been tested in children. **Aim:** To characterize the EREFS features in a pediatric population who underwent diagnostic endoscopy, and to assess the score utility for EoE diagnosis. **Methods**: Pediatric endoscopic prospective cohort conducted in a Brazilian population, evaluating patients with gastrointestinal complaints without definitive diagnosis. The demographic and clinical data were evaluated. After the endoscopic procedure the original EREFS was scored, unware of the final diagnosis of EoE, GERD or Control. **Results:** One hundred and seven patients undergoing endoscopies were included. The inflammatory features were more frequently scored than fibrostenotic. The T-EREFS showed the sensitivity of 75%, specificity of 85.7%, accuracy of 84.1%, and AUC was 0.80. The medians of T-EREFS were 2.5, 0.5, and 0.0 for EoE, GERD, and Controls, respectively. There was a significant statistic difference between EoE T-EREFS x Control T-EREFS ($p<0.0001$) and EoE T-EREFS x GERD T-EREFS ($p=0.0375$). **Conclusion:** The data suggest that T-EREFS is a useful diagnostic tool for pediatric EoE with acceptable sensitivity, good specificity, and accuracy. The inflammatory features are more frequently found than fibrostenotic features in the assessment of pediatric endoscopic EoE diagnosis. Some features present in the original EREFS may be likely suppressed for the diagnostic EoE pediatric analysis, as in the modified EREFS used in adults.

Key words: Eosinophilic esophagitis, EREFS, Gastroesophageal reflux disease, Pediatrics

LISTA DE ABREVIATURAS E SÍMBOLOS

EEo	esofagite eosinofílica
IBP	inibidor de bomba de prótons
DRGE	doença do refluxo gastroesofágico
EDA	endoscopia digestiva alta
EREFS	score de referência endoscópica
EREFS-T	score total de referência endoscópica
IR	índice de refluxo gastroesofágico

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1 INTRODUÇÃO

Esofagite eosinofílica é um enfermidade imunológica relacionada com atopia, com características genéticas ainda em estudo, mas de caráter crônico (DELLON, 2014; LIACOURAS et al., 2011; SLEIMAN; MARCH; HAKONARSON, 2015; SPERGEL, 2015). É uma doença que se apresenta com aumento de incidência em população adulta e pediátrica, e com necessidade de identificação e terapêutica precoces, devido a sua cronificação, com posterior remodelamento esofágico e disfunção esofágica (ATTWOOD; FURUTA, 2014; LUCENDO et al., 2017). Apesar de atingir população pediátrica e de adultos, a apresentação clínica e aspecto endoscópico são diferentes nas diversas faixas etárias. Isso se deve ao fato de ser uma doença inflamatória de caráter progressivo, evoluindo de uma fase inflamatória (geralmente presente na faixa etária pediátrica) para uma fase fibroestenótica com remodelamento esofágico (evidenciada na faixa etária adulta) (DELLON, 2014; SINGLA et al., 2015). Embora o diagnóstico e tratamento em fase inicial da doença no adulto possam evitar o remodelamento esofágico e a evolução para a estenose, que é relacionada com o tempo de doença (DELLON, 2014; SCHOEPFER et al., 2013; ACEVES et al., 2007), ainda não se pode afirmar que o mesmo acontecerá na população pediátrica. Portanto, justifica-se a necessidade de estudos abrangendo a população pediátrica e as características específicas da doença nesta faixa etária. Quando analisada a faixa etária adulta não se demonstra confiabilidade diagnóstica e de condução terapêutica por score clínico, sendo necessário scores endoscópico e histológico que possam detectar melhor a evolução da patologia (SAFRONEEVA et al., 2016).

Na tentativa de padronizar os achados endoscópicos e assim estabelecer sua gravidade e pregressão, foi criado o score de graduação endoscópica de EEo por Hirano *et al* (HIRANO et al., 2013) . Este score padroniza a descrição dos achados visuais durante o exame endoscópico. Sua utilização de forma sistemática em população adulta, pode ser utilizada para definição diagnóstica, indicação de perfil fenotípico da doença, além do uso em acompanhamento de remissão e resposta terapêutica (DELLON, 2012; KIA; HIRANO, 2016). No entanto, apesar de bem descrito na população adulta, sua utilização em população pediátrica é ainda restrita, pois possui apenas um estudo que utilizou um score modificado e objetivou apenas a descrição fenotípica da doença (SINGLA et al., 2015). Portanto, não há descrição diagnóstica em população pediátrica utilizando o score de graduação endoscópica de *Hirano et al* (HIRANO et al., 2013).

2 FUNDAMENTAÇÃO TEÓRICA

EEo é uma doença imunológica de característica inflamatória crônica, que apresenta infiltração do tecido esofágico por eosinófilos, mastócitos, basófilos e células T produtoras de citocinas Th2, gerando disfunção do órgão. Como fator desencadeante temos os alérgenos alimentares, e em menor proporção os aeroalérgenos (HILL; SPERGEL, 2016; SPERGEL, 2015; WECHSLER; BRYCE, 2014). EEo é uma doença crescente na população mundial, com emergência nas duas últimas décadas, sendo uma grande causa de morbidade gastrointestinal tanto na população adulta quanto população pediátrica (ATTWOOD; FURUTA, 2014).

Na população pediátrica a apresentação clínica é predominantemente com sintomas inespecíficos de intolerância alimentar, dor abdominal, náuseas, vômitos e presença de regurgitação. Já na população adulta está presente a disfagia com episódios de impactação alimentar. Esta característica inespecífica presente na população pediátrica dificulta a suspeição diagnóstica apenas por apresentação clínica (DELLON, 2012, 2014). Por este motivo foi criado um score de sintomas de EEo em pediatria (PESS v2.0), com o intuito de melhor avaliar os sintomas e correlacionar estes com resultados histológicos e marcadores biológicos (MARTIN et al., 2015).

O diagnóstico de EEo é clinico patológico, e inicialmente necessitava de: presença de disfunção esofágica, de 15 ou mais eosinófilos por campo de grande aumento em material histológico obtido em esôfago proximal e distal, associado a ausência de eosinófilos em amostras de outros locias do trato digestório somado a exclusão do diagnóstico de doença do refluxo gastroesofágico. Nesta definição, era necessário o uso de inibidor de bomba de prótons por 60 dias e uma nova contagem de eosinófilos em amostra histológica esofágica, definindo o diagnóstico apenas se esta segunda amostra também permanecesse alterada (DELLON, 2012). Esse conceito começou a ser modificado em 2011 no consenso de recomendação sobre EEo, quando surgiu a discussão sobre os pacientes que apresentam eosinófilos aumentados em numeração na primeira amostra esofágica, mas que respondem com diminuição do número de

eosinófilos para menor que 15 após o uso de IBP. Estes pacientes não eram considerados portadores de EEo, e foram denominados Eosinofilia esofágica respondedora a IBP (LIACOURAS et al., 2011). No entanto, diversas publicações posteriores identificaram semelhanças entre os pacientes com EEo e os pacientes com eosinofilia esofágica respondedora a IBP (ELURI; DELLON, 2015), considerando ser apenas espectros de uma mesma doença. Além disso, o diagnóstico de DRGE não excluiria o diagnóstico de EEo, pois poderia haver a coexistência das duas doenças (MOLINA-INFANTE; VAN, 2015). Diante dessas novas evidências, o diagnóstico de EEo foi definido como: paciente com sintomas de disfunção esofágica, associado a eosinofilia esofágica com número de eosinófilos maior ou igual a 15 por campo de grande aumento, sem que haja diagnóstico de outra patologia relacionada com eosinofilia esofágica (como doença de Chron, síndrome da hipereosinofilia, entre outras). Dentre os pacientes com EEo, definiu-se como um subgrupo o de EEo responsivo a IBP, são aqueles pacientes que após o diagnóstico inicial, receberam terapêutica de IBP por 60 dias e tiveram redução da eosinofilia esofágica inferior a 15 eosinófilos por campo de grande aumento (MOLINA-INFANTE et al., 2016, LUCENDO et al., 2017).

Atualmente o diagnóstico padrão ouro de EEo descrito necessita da presença de 15 eosinófilos por campo de grande aumento em biópsias esofágicas. No entanto há estudos em desenvolvimento de um novo sistema de score histológico para melhor avaliar as alterações histológicas, incluindo: densidade eosinofílica, hiperplasia da camada basal, abscessos eosinofílicos, camada superficial dos eosinófilos, dilatação do espaço intercelular, alteração da superfície epitelial, células epiteliais disceratóticas e fibrose da lâmina própria. Esse detalhamento e padronização na avaliação histológica busca um melhor conhecimento sobre a patologia e sua resposta às opções terapêuticas (COLLINS et al., 2016).

A EDA é necessária para a definição do diagnóstico da doença, pois possibilita a coleta de amostras histológicas esofágicas que define um dos critérios diagnósticos, além de ser utilizada para a monitorização da resposta a terapêutica. Apesar de serem identificados sinais endoscópicos presentes nos pacientes com EEo, estes sinais não são considerados no diagnóstico da

doença. Estudos descrevem que na população pediátrica em até 1/3 dos exames não há descrição destes sinais, sendo considerados exames endoscópicos normais (MUIR; MERVES; LIACOURAS, 2016).

Dellon et all 2012, realizaram revisão sistemática com meta-analise sobre a prevalência e a utilidade dos sinais endoscópicos no diagnóstico de EEo, como resultado encontraram que a heterogenicidade das populações estudas e a não padronização dos achados endoscópicos, não permitiram considerar os achados endoscópicos como adequados para o diagnóstico da doença, não sendo neste estudo indicando sua utilização para definição diagnóstica ou definição de coletar ou não biópsias esofágicas (DELLON, 2012; LUCENDO et al., 2017).

Para melhor avaliar a presença destes sinais endoscópicos, foi desenvolvido um sistema de classificação e graduação dos achados endoscópicos em EEo, este sistema foi validado na população adulta. Tal sistema permitiu a uniformização das descrições endoscópicas, facilitando assim a comparação de achados entre populações (HIRANO et al., 2013).

EEo é uma doença de carater alérgico crônico, com deflagração de cascata inflamatória, com citocinas e recrutamento eosinofílico. Com o tempo de exposição a este ambiente inflamatório há uma evolução natural para a fibroestenose do tecido esofágico. Isto pode ser demonstrado fenotipicamente pela característica endoscópica inflamatória da população pediátrica com a doença, em contraposição ao fenótipo fibroestenótico presente na população adulta e na população pediátrica com longo tempo de exposição a doença sem tratamento (SINGLA et al., 2015). Essa hipótese é reforçada por estudo que descreveu que as estenoses associadas a sinais fibroestenóticos na EDA aparecem nos pacientes com maior tempo de diagnóstico e exposição a doença (SCHOEPFER et al., 2013). Isto demonstra a necessidade de diagnóstico em fase pediátrica, com curto período de exposição a inflamação crônica afim de se prevenir a progressão para remodelamento esofágico, que na fase adulta se mostra irreversível.

A progressão para o remodelamento esofágico causa prejuízo à qualidade de vida do paciente e traz risco de deficiências nutricionais por restrições alimentares. Sinais de remodelamento podem ser vistos por exame contrastado

com bário, ultrassonagrafia e manometria esofágica, além destes, temos evidentes sinais de remodelamento esofágico quando avaliada o aspecto fenotípico endoscópico do paciente utilizando o sistema EREFS (HIRANO; ACEVES, 2014). Além de definir o perfil fenotípico do paciente a EDA com o sistema EREFS também vem sendo utilizada na população adulta para acompanhamento terapêutico e definição de remissão de doença. Este remodelamento também pode ser analisado pelo diâmetro e distensibilidade esofágica, neste método, estudo recente comprovou que estes valores são alterados na população pediátrica portadora de EEo com sinais inflamatórios pelo sistema EREFS, e que nesta população a função esofágica pode estar alterada (MENARD-KATCHER et al., 2017).

Atualmente o manejo clínico de EEo, considerados tratamento de primeira linha, são o uso de corticosteróides tópicos, e a restrição alimentar, que está cada vez mais específica para cada paciente baseando-se em testes imunogênicos. Com o tratamento adequado tem se notado diminuição da atividade inflamatória da doença reduzindo processo de remodelamento esofágico e os sintomas (CONTRERAS; GUPTA, 2014; GONSALVES; KAGALWALLA, 2014; LIEBERMAN; CHEHADE, 2012; LUCENDO et al., 2017; SCHOEPFER; HIRANO; KATZKA, 2014).

3 OBJETIVO GERAL

Caracterizar os achados endoscópicos de acordo com score EREFS na população pediátrica, definindo assim a acurácia deste no diagnóstico de EEo nesta população.

4 ARTIGO CIENTÍFICO

TÍTULO: Is the Endoscopic Reference Score (EREFS) a good tool to improve the accuracy to predict the diagnosis of Pediatric Eosinophilic Esophagitis?

Title: Is the Endoscopic Reference Score (EREFS) a good tool to improve the accuracy to predict the diagnosis of Pediatric Eosinophilic Esophagitis?

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Structure summary

Background: The EREFS has been used for diagnosis assessment and prediction of the activity and remission of the disease in EoE adult patients. However, there are a few studies in which the effectiveness of this endoscopic metric has been tested in children.

Aim: To characterize the EREFS features in a pediatric population who underwent diagnostic endoscopy, and to assess the score utility for EoE diagnosis.

Methods: Pediatric endoscopic prospective cohort conducted in a Brazilian population, evaluating patients with gastrointestinal complaints without definitive diagnosis. The demographic and clinical data were evaluated. After the endoscopic procedure the original EREFS was scored, unware of the final diagnosis of EoE, GERD or Control.

Results: One hundred and seven patients undergoing endoscopies were included. The inflammatory features were more frequently scored than fibrostenotic. The T-EREFS showed the sensitivity of 75%, specificity of 85.7%, accuracy of 84.1%, and AUC was 0.80. The medians of T-EREFS were 2.5, 0.5, and 0.0 for EoE, GERD, and Controls, respectively. There was a significant statistic difference between EoE T-EREFS x Control T-EREFS ($p<0.0001$) and EoE T-EREFS x GERD T-EREFS ($p=0.0375$).

Conclusion: The data suggest that T-EREFS is a useful diagnostic tool for pediatric EoE with acceptable sensitivity, good specificity, and accuracy. The inflammatory features are more frequently found than fibrostenotic features in the assessment of pediatric endoscopic EoE diagnosis. Some features present in the original EREFS may be likely suppressed for the diagnostic EoE pediatric analysis, as in the modified EREFS used in adults.

Key words: Eosinophilic esophagitis, EREFS, Gastroesophageal reflux disease, Pediatrics

Introduction

Eosinophilic esophagitis is a chronic immunologic disease with determinant genetic mechanisms involved.(1, 2) It is the most frequent esophageal disease which shows quick increase in prevalence and incidence in both adult and pediatric populations.(3) The diagnostic criteria have suffered some changes since the first international consensus recommendation for diagnosis and treatment published ten years ago.(4) Nevertheless, the brand new guidelines and recommendations on EoE do not suggest the use of endoscopic findings as a diagnostic criterion of EoE, and do not propose some specific approach for pediatric diagnosis.(5)

EoE is defined clinically by symptoms of esophageal dysfunction, and histologically by the predominant eosinophilic inflammation in some esophageal tissue routine biopsies, extracted by upper gastrointestinal endoscopy.(5) Thus, the endoscopic procedure with biopsies is currently essential for EoE diagnosis. Endoscopic findings are not specific and include fixed or transient concentric rings, white exudates, linear furrows, edema with decrease of vascular markings, narrow caliber esophagus, strictures, and crepe paper appearance of esophageal mucosa. The absence of endoscopic features in patients with EoE is observed in 17% of the cases in retrospective studies, and 7% of the patients evaluated in prospective studies. The absence of specificity of EoE endoscopic features and symptoms, and its similarity to gastroesophageal reflux disease (GERD) manifestations are a diagnostic challenge,(6) especially in pediatric scenario.

The endoscopic EoE findings were recently standardized in the Endoscopic Reference Score (EREFS).(7) It provides grades of features severity, increasing the accuracy to predict the diagnosis, and measuring the response to therapeutic interventions. Another utility of this endoscopic metric tool is the identification of inflammatory or fibrostenotic EoE phenotypes, according to the set of observed findings.(8)

In the original study, Hirano et al.[7] have demonstrated that EREFS system has got a good inter-observer agreement among adult gastroenterologists. Another validated study in adult population, comparing expert with trainee endoscopists, has shown both inter-observer and intra-observer agreement from moderate to substantial levels. (9) Among the few studies using EREFS in a pediatric prospective cohort, EREFS has shown a clear trend to inflammatory disease rather than fibrostenotic disease in comparison with adults.(8, 10) However, there is no homogeneity in the methodologic use of EREFS system among the cited studies. Some of them have used the modified classification proposed by the original publication, summarizing the most significant signs for adult population (edema, fixed rings, exudate, furrows, and stenosis),(7) and others have done personal adaptions.

Thus, EREFS standardizes the description of the visual findings during the endoscopic procedure.(6) It can be used for diagnostic assessment and indication of the phenotypic profile, the activity or remission condition of the disease, prognostic prevision, and the therapeutic response. Although the EREFS has been well described for adults, it is still limited for pediatric population, because there are few validated studies. Therefore, there is no diagnostic description in an unselected pediatric population using the EREFS. The aim of this study is to characterize the EREFS features in a pediatric population who underwent diagnostic endoscopy, and to assess the EREFS utility for EoE diagnosis.

Methods

Study design and Population

The patients were prospectively recruited in a pediatric endoscopic cohort from January 2015 to August 2016, at Clinical Hospital of Federal University of Uberlândia, Minas Gerais, Brazil. A survey was applied to parents to investigate the eligibility of the patient, and to collect demographic data at the waiting room of the endoscopy unit. All the patients who were taking PPI, antihistamine medications, and steroids (topical or systemic) within the last 4 weeks prior to the endoscopy were not enrolled. The eligible patients were followed up in an outpatient clinic after the endoscopic procedure for the diagnostic investigation. The exclusion criteria included a prior or new diagnosis of some eosinophilic gastrointestinal disorder (eosinophilic gastroenteritis/colitis, celiac disease, inflammatory bowel disease, or Barrett's esophagus, Connective disease, or hypereosinophilic syndrome) and the impossibility to complete the diagnostic investigation process. The Ethics Committee of Universidade Federal de Uberlândia had given the approval under the number CAAE 36787714.0.0000.5152, and written informed consent was provided from parents of all children. Teenagers older than 12 years of age signed a statement of assent.

Diagnostic definitions

The diagnoses of EoE and GERD were done based on current clinical diagnostic guidelines.(1, 11) [1] EoE patients were defined as having the presence of any symptom related to esophageal dysfunction with at least one esophageal biopsy with 15 or more eosinophils per high-power field [eos/hpf], and their outcome did not reveal any evidence of esophageal infection or other eosinophilic disorder. The number of eosinophils on the stomach and duodenum mucosa was normal. [2] GERD patients (infants and children under the age of 8) showed the presence of some symptoms related to reflux disease, associated to erosion esophagitis or, in its absence, abnormal esophageal pH monitoring study (reflux index - RI ≥ 7%). For older children and adolescents the same criteria were used adding heartburn improvement upon PPI therapy, if it was indicated. [3] Controls

patients consisted of those whose esophageal epithelium was unremarkable, without esophageal eosinophilia. Their outcome did not reveal eosinophilic disorders or GERD.

Endoscopy procedure, histological biopsies and EREFS analysis

All esophagogastro-duodenoscopies were performed with general anesthesia, using a pediatric gastrpscope for children under 10 kg and standard adult gastroscope for the others.(12) The evaluations were done by two pediatric endoscopists, who fulfilled the Endoscopy Reference Score (EREFS) based on the esophageal features, which could be observed at the moment of the procedure. The reference for both endoscopists was the original slides from the published classification (7). The EREFS score consisted of classification of the severity of some signs – fixed esophageal rings (trachealization) (0–3), exudates (0–2), furrows (0–2), edema (0–2), and the presence of others – strictures (0–1), transient esophageal rings (felinization) (0-1), narrow caliber esophagus (0–1), and crepe paper esophagus (0–1). The total range score could be from 0 to 13 points.(7) The inflammation score was calculated by the sum of exudates, furrows, transient esophageal rings, and edema, ranging from 0 to 7 points. The fibrostenotic score was the sum of fixed rings and any type of strictures features (strictures, narrow caliber, and crepe paper esophagus), ranging from 0 to 6. The EREFS features were analyzed considering the inflammatory, fibrostenotic, and total scores, according to the endoscopic findings.

Three samples were collected from each of these four places – distal and mid-proximal esophageal tissue, stomach, and duodenum. All samples were analyzed by a senior pathologist and an hpf area (40 objective; 400 total magnification) of 0.225 mm^2 was used for analyses.

Statistical Analysis

Comparative statistical analyzes were performed using non-parametric Kruskal-Wallis tests followed by Student-Newman-Keuls post-test and Binomial Proportions Test for Independent Data. The baseline characteristics of the study population are described by means of percentages, median, interquartile range (IQR) and body mass index (BMI) Z-score. The control and case groups (EoE and GERD) were described by means: minimum value, first quartile, median, third quartile and maximum value besides interquartile range (IQR), amplitude and n-sample. Predictive epidemiological parameters of diagnostic efficiency were calculated by measuring sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive value, and accuracy. The cutoff point was also estimated. All statistical analyses were performed using PASW Statistics 17 and BioEstat 5.3 software. The *significance level was considered* to be less than 0.05

Results

Demographic characteristics and diagnostic classification

A hundred and ten patients from age 0 to 17 with general complaints were enrolled and submitted to endoscopy and biopsies over the study period. Among them, three patients were excluded because they did not complete the diagnostic investigation process. The final cohort included 107 pediatric patients who received the diagnosis of EoE, GERD or Controls after completing the diagnostic investigation. The baseline characteristics of the study population with demographic and clinical features, according to the final diagnosis, are summarized in Table 1.

EREFS findings

The EREFS features found in this cohort are showed in Figure 1, except for feline esophagus which is a dynamic finding. The frequency of all findings was higher in EoE than GERD or Controls patients (Table 2). Feline esophagus and edema (Grade 1) are not significantly higher in EoE than in Controls. Between EoE and GERD patients, fibrostenotic features, edema (Grade 1), and exudate (Grade 1) could not differentiate the groups either. The signs of inflammatory score were present in 13 (81.2%) patients of the EoE group, and each feature could be found in a frequency of 50% or higher (exudate 50.0%, furrows 56.2%, edema 81.2%, and felinization 6.2%). In this cohort the signs of fibrostenotic score were infrequent in all groups. In EoE patients, they were fixed rings (12.5%) and strictures (6.3%) only.

The description of total EREFS, inflammatory EREFS, and fibrostenotic EREFS

The frequencies of each feature according to inflammatory or fibrostenotic profile are demonstrated in Table 2. The descriptive analysis of these scores, as well as the total EREFS according to the groups is shown in Table 3. With this analysis, it can be observed that 75% of the EEo group presents I-EREFS and T-EREFS greater than 2 points. This occurs in less than 50% of the GERD group, and less than 10% in the Control group. None of the analyzed groups there was more than 1 point in F-EREFS. The comparison of medians between EoE and Control groups showed a statistically significant difference in all EREFS types. However, in the analysis of EoE and GERD, there was statistical difference only in the I-EREFS and T-EREFS (Table 4).

Accuracy of EREFS to predict the EoE diagnosis

The predictive values from all EREFS features, I-EREFS, F-EREFS, and T-EREFS, considering 16 EoE patients as positive cases and 91 Controls/GERD patients as negative cases were analyzed (Table 5). The I-EREFS and the F-EREFS generally have

more specificity than sensitivity, except for the feature edema in I-EREFS. Although the fibrostenotic scores (F-EREFS, fixed rings, and strictures) showed accuracy >80%, sensitivity and specificity were unbalance, with very low specificity. Edema at cutoff point 1 was the only inflammatory feature which showed balanced sensitivity and specificity with accuracy near 70%. Nevertheless, T-EREFS at cutoff point 2 seems to be the best diagnostic test for predict EoE diagnosis with an acceptable sensitivity, good specificity and accuracy >80%. The Receiver-Operating Characteristic curve was built for T-EREFS at cutoff point 2, and the area under the curve (AUC) was 0.80 (Figure 2).

Discussion

This is the first epidemiological prospective study using EREFS for EoE diagnostic investigation in an unselected pediatric population. The characteristics of EoE symptoms and endoscopic features, similar to GERD manifestations request special approach in the diagnostic process. This process requires an endoscopy procedure with biopsies, carefully indicated by the presence of the symptoms. There is a spectrum of non-specific clinical manifestations in pediatric EoE, that usually vary with age. The infants and younger children have symptoms such as nausea, vomiting, abdominal pain, failure to thrive, and difficulty in introducing solid foods, or food aversion. Older children and adolescents may report more specific symptoms such as solid food dysphagia, food impaction, and non-swallowing associated with chest pain in similarity to adult manifestation.(13) Our cohort did not demonstrate in the baseline characteristics any special clinical condition that allows the prediction of EoE among GERD or other diagnoses. Only the male gender seems to be more frequent in EoE in comparison with analyzed groups (Table 1). In pediatrics, EoE affects mainly school-aged patients, with a peak incidence around 10 years of age, and with a greater predominance in males.(14)

Due to the presence of non-specific clinical data, the EREFS could be considered as a useful metric tool which proposes to increase the diagnostic accuracy of the disease before the histological analysis, as additional biomarkers of EoE. (15) The first meta-analysis including EoE patients and non-EoE controls demonstrated modest sensitivity and predictive values for endoscopic features to predict esophageal inflammation, and the prevalence of endoscopic features was very heterogeneous.(16) However, in our study, we can observe that the presence of endoscopic findings from EREFS was frequent in EoE patients (>81%). This may occur by the fact that this study has prospective design, using the EREFS metric immediately after the procedure without any information about the patient diagnosis, only their symptoms.

Endoscopic features of children and adults with EoE usually show different presentation. Children typically present inflammatory features, and fibrostenotic features are more commonly seen in adolescents and adults. (8, 16) The analysis of phenotype EoE in inflammatory or fibrostenotic profile was based on a publication, which carried out a multicenter prospective cohort with 25% of pediatric population.(8) The physiopathology mechanism has not been totally known, but maybe it depends on the patients' age and the untreated time of the disease.(10) The fibrostenotic features are thought to be the result of esophageal remodeling by fibrotic repair in an evolution of eosinophilic inflammation. However, this natural evolution of the inflammatory disease to fibrostenotic condition has not been proved yet. (17) The risk for a fibrostenotic phenotype seems to be twice as much for every 10-year increase in age.(18) A recent published pediatric cohort has demonstrated that there is some relationship between the period of esophagus exposure to a chronic inflammation, and signs of decreased esophageal distensibility, as the result of esophageal remodeling.(10) We found plenty of inflammatory endoscopic profiles, unlike the fibrostenotic profiles. This result seems to be in agreement with the epidemiological data from this study, which detected EoE

diagnosis in children with school-age presenting nonspecific symptoms, as abdominal pain, vomiting, regurgitation, and nausea.

The distribution of the inflammatory features showed a significant predominance of these signs in EoE children in comparison with both GERD and Control patients (Table 2). The prevalence of these findings were considerable and the power of the test was acceptable to reduce the type II error (β) and consequently the risk of false negative, which is an important condition of a diagnostic test. The analyses of predictive values have suggested good accuracy for EoE diagnosis only for the feature edema and T-EREFS. This favorable capacity from edema to distingue the EoE patient may occurred because in this study the analyses were conducted by pediatrics endoscopists. This is a subtle endoscopic sign usually evaluated in pediatric GERD, in initial levels of esophagitis without erosion, as described by Hetzel & Dent Classification.(19) The T-EREFS showed the best accuracy (>80%) for the EoE diagnoses with acceptable sensitivity and good specificity, and AUC>0.7 (Table5 and Figure 2). Although, the original EREFS publication suggest the suppression of some analyzed features which despite of the good specificity showed low prevalence and a small role in the accuracy of the score.(6, 7) Our data have not demonstrated some EREFS features, as crepe paper esophagus and narrow caliber of esophagus; and very low prevalence of feline esophagus. Maybe, these features would be also suppressed for the diagnostic EoE pediatric analysis, as in the modified EREFS classification used in adults.

Two strengths of this study were the validation of EREFS in an unselected pediatric Brazilian population, and the suggestion of EREFS is capable to differentiate EoE from GERD (Table 3). The major of EoE studies are concentrated in north hemispheric, and in Caucasian population. This is one of the few Brazilian studies in pediatric EoE, and the first prospective endoscopic cohort analyzing the EREFS characteristics at the moment of the diagnoses. A new publication raises the need to promote a better understanding about the demographic influence in EoE behavior, because some

underdiagnosed population may present the disease with atypical characteristics, such as African Americans.(20) The second point is the significant difference between T-EREFS and I-EREFS medians from EoE x GERD. This result has demonstrated that they are actually different diseases, despite of the similarity and the possibility of concomitant presentation.(21)

The major limitation of this study is low prevalence of EoE patients, and the possibility of a low variance of the data. Other drawback of the manuscript is the absence of inter-observer analysis which may compromise the reliability of the assigned scores and the reproduction of the results. Therefore, we suggest a validated multicenter prospective study using the original EREFS in pediatric population with inter-observer analysis to better validate the use of this endoscopic metric tool for diagnostic purpose.

In conclusion, this study suggests that total EREFS is a useful diagnostic tool for pediatric EoE with acceptable sensitivity, good specificity, and accuracy. The inflammatory features are more frequently found than fibrostenotic features in the assessment of pediatric endoscopic EoE diagnosis, which is in agreement with the clinical presentation of the disease in the pediatric age group. Some features present in the original EREFS (transient rings – felinization and “crepe paper” esophagus) may be likely suppressed for the diagnostic EoE pediatric analysis, as in the modified EREFS classification used in adults.

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Table 1 - Baseline characteristics of the study population

Demographics/Clinical Features	Controls	EoE	GERD	p-value		
Diagnostic	77(71.3%)	16 (14.8%)	14(13.0%)			
Median age [P25-P75] (range)	9 [7-12] (0-16)	8.5 [4-10.75] (1-17)	10 [8.75-11] (5-12)		0.5120[a]	
Male n(%)	36 (46.8)	12 (75)	7 (50)	0.4203[b]	0.0047[b]*	1.000[b]
Median BMI Z score (P25,P75)	0.03 (-0.32,1.14)	0.51 (-0.77,0.51)	0.09 (-1.06,1.47)		0.9350[a]	
		Symptom n(%)		**Controls x EoE[b]**	**Controls x GERD[b]**	**EoE x GERD[b]**
Abdominal pain	39 (50.6)	6 (37.5)	3 (21.4)	0.1691	0.0218*	0.169
Vomiting, regurgitation, nausea	24 (31.2)	8 (50.0)	8 (57.1)	0.0745	0.0306*	0.3478
Heartburn	3 (3.9)	1 (6.3)	2 (14.3)	0.3364	0.2928	0.2321
Disphagia	3 (3.9)	1 (6.3)	0 (0.0)	0.3364	0.6129	0.5484
Food impactation	2 (2.6)	0 (0.0)	0 (0.0)	0.69	0.7202	1

[a] Kruskal Wallis Test, [b] binomial test proportions

*considered statistically significant at a level < 0.05;

EoE = Eosinophilic oesophagitis GERD= Gastroesophageal reflux disease EREFS = Endoscopy Reference Score

Table 2 - Comparison between EREFS findings from the Eosinophilic Esophagitis, Gastroesophageal Reflux Disease and Control groups by binomial test for two independent proportions

		Control		EoE		GERD		Control x EoE		Control x GERD		EoE x GERD	
		n_i	%	n_i	%	n_i	%	p-value	power	p-value	power	p-value	power
Inflammatory EREFST	Furrows (Grade 0)	76	98.7 %	7	43.8 %	13	92.9 %	<0.0001*	99.7 %	0.085**	29.5 %	0.0022*	93.2 %
	Furrows (Grade 1)	0	0.0%	4	25.0 %	0	0.0%						
	Furrows (Grade 2)	1	1.3%	5	31.3 %	1	7.1%	<0.0001*	87.2 %	0.085**	29.5 %	0.0498*	51.2 %
	Exsudates (Grade 0)	74	96.1 %	8	50.0 %	12	85.7 %	<0.0001*	98.0 %	0.0583**	36.4 %	0.0192*	68.7 %
	Exsudates (Grade 1)	3	3.9%	4	25.0 %	2	14.3 %	0.0018*	68.2 %	0.0583**	36.4 %	0.2321	17.7 %
	Exsudates (Grade 2)	0	0.0%	4	25.0 %	0	0.0%						
	Edema (Grade 0)	54	70.1 %	3	18.8 %	7	50.0 %	<0.0001*	99.6 %	0.0703**	41.0 %	0.035*	56.4 %
	Edema (Grade 1)	19	24.7 %	3	18.8 %	4	28.6 %	0.3059	12.0 %	0.3788	8.9%	0.2629	15.4 %
	Edema (Grade 2)	4	5.2%	10	62.5 %	3	21.4 %	<0.0001*	99.8 %	0.018*	50.0 %	0.0118*	75.7 %
	Feline esophagus (Grade 0)	75	97.4 %	15	93.8 %	12	85.7 %	0.2259	18.5 %	0.0249*	43.3 %	0.2321	17.8 %
	Feline esophagus (Grade 1)	2	2.6%	1	6.3%	2	14.3 %	0.2259	18.5 %	0.0249*	43.3 %	0.2321	17.8 %
	Inflammatory score (score 0)	52	67.5 %	3	18.8 %	7	50.0 %	0.0002*	99.1 %	0.1032	33.9 %	0.035*	56.4 %
	Inflammatory score (score 1)	19	24.7 %	1	6.3%	1	7.1%	0.0513**	60.5 %	0.0725**	50.2 %	0.4610	5.3%
	Inflammatory score (score 2)	4	5.2%	3	18.8 %	5	35.7 %	0.0307*	45.6 %	0.0002*	80.5 %	0.1473	27.1 %
	Inflammatory score (score 3)	1	1.3%	2	12.5 %	0	0.0%	0.0105*	48.8 %				
	Inflammatory score (score 4)	1	1.3%	1	6.3%	0	0.0%	0.1071	27.7 %				
	Inflammatory score (score 5)	0	0.0%	3	18.8 %	1	7.1%					0.1754	23.5 %
	Inflammatory score (score 6)	0	0.0%	3	18.8 %	0	0.0%						

Fibrotic EREFS	Fixed rings (Grade 0)	76	98.7%	14	87.5%	14	100%	0.0105*	48.8%	0.3340	0.0%	0.0855**	40.1%
	Fixed rings (Grade 1)	1	1.3%	2	12.5%	0	0.0%	0.0105*	48.8%				
	Stricture (Grade 0)	77	100%	15	93.8%	13	92.9%	0.0137*	39.5%	0.0092*	40.1%	0.4610	5.3%
	Stricture (Grade 1)	0	0.0%	1	6.3%	1	7.1%					0.4610	5.3%
	Fibrotic score (score 0)	76	98.7%	13	81.3%	13	92.9%	0.0009*	65.3%	0.085**	29.5%	0.1754	23.5%
	Fibrotic score (score 1)	1	1.3%	3	18.8%	1	7.1%	0.0009*	65.3%	0.085**	29.5%	0.1754	23.5%
Total EREFS	Total score (score 0)	52	67.5%	3	18.8%	7	50.0%	0.0002*	99.1%	0.1032	33.9%	0.035*	56.4%
	Total score (score 1)	18	23.4%	1	6.3%	1	7.1%	0.061**	55.5%	0.0846**	45.5%	0.4610	5.3%
	Total score (score 2)	5	6.5%	4	25.0%	4	28.6%	0.0114*	57.3%	0.0055*	62.4%	0.4127	7.2%
	Total score (score 3)	1	1.3%	1	6.3%	1	7.1%	0.1071	27.7%	0.085**	29.5%	0.4610	5.3%
	Total score (score 4)	1	1.3%	0	0.0%	0	0.0%						
	Total score (score 5)	0	0.0%	3	18.8%	1	7.1%					0.1754	23.5%
	Total score (score 6)	0	0.0%	3	18.8%	0	0.0%						
	Total score (score 7)	0	0.0%	1	6.3%	0	0.0%						

*considered statistically significant at a level < 0.05; ** significant at a level of 0.05 <α <0.10

EoE = Eosinophilic oesophagitis GERD= Gastroesophageal reflux disease EREFS = Endoscopy Reference Score

Table 3 - Descriptive analysis of the Fibrostenotic, Inflammatory and Total EREFS

	Control			EoE			GERD		
	F-EREFS	I-EREFS	T-EREFS	F-EREFS	I-EREFS	T-EREFS	F-EREFS	I-EREFS	T-EREFS
n sample	77	77	77	16	16	16	14	14	14
Minimum	0	0	0	0	0	0	0	0	0
Maximum	1	4	4	1	6	7	1	5	5
Total Amplitude	1	4	4	1	6	7	1	5	5
Median	0	0	0	0	3	2.5	0	0.5	0.5
First Quartile (25%)	0	0	0	0	1.75	1.75	0	0	0
Third Quartile (75%)	0	1	1	0	5	5.25	0	2	2
Interquartile range (IQR)	0	1	1	0	3.25	3.5	0	2	2

EoE = Eosinophilic oesophagitis, GERD= Gastroesophageal reflux disease, F-EREFS = Fibrostenotic Endoscopy Reference Score, I-EREFS = Inflammatory Endoscopy Reference Score, T-EREFS = Total Endoscopy Reference Score

Table 4 - Comparison between the EREFS of the Eosinophilic Esophagitis (EoE), Gastroesophageal Reflux Disease (GERD) and Control by Kruskal-Wallis and Student-Newman-Keuls post hoc test

Teste de Kruskal-Wallis

	H	gl	p-value
F-EREFS	1.2285	2	0.5411
I-EREFS	20.9167	2	<0.0001**
T-EREFS	20.3443	2	<0.0001**

Student-Newman-Keuls

Inflammatory EREFS

	R (middle post)	Control x EoE		Control x GERD		EoE x GERD	
Control	46.487	Post dif.	p-value	Post dif.	p-value	Post dif.	p-value
EoE	84.6875	38.2005	< 0.0001*	13.763	0.1269	24.4375	0.0314*
GERD	60.25						

Student-Newman-Keuls

Total EREFS

	R (middle post)	Control x EoE		Control x GERD		EoE x GERD	
Control	46.5455	Post dif.	p-value	Post dif.	p-value	Post dif.	p-value
EoE	84.1563	37.6108	< 0.0001*	13.9903	0.1207	23.6205	0.0375*
GERD	60.5357						

* significant at a level $\alpha < 0.05$; ** significant at a level $\alpha < 0.0001$

EoE = Eosinophilic oesophagitis, GERD= Gastroesophageal reflux disease, F-EREFS = Fibrostenotic Endoscopy Reference Score, I-EREFS = Inflammatory Endoscopy Reference Score, T-EREFS = Total Endoscopy Reference Score

Table 5 – Description of predictive values from EREFS features considering 16 EoE patients as positive cases and 91 controls + GERD as negative cases

	Cutoff point	Sensitivity	Specificity	Likelihood Positive Ratio	Positive predictive value	Likelihood negative ratio	Negative predictive value	Accuracy
Fixed rings	1.0000	12.50%	98.90%	11.36	66.73%	0.88	86.50%	85.94%
Stricture	1.0000	6.30%	98.90%	5.73	50.27%	0.95	85.68%	85.01%
Narrow calibre	insufficient data							
Crepe paper oesophagus	insufficient data							
F-EREFS	1.0000	18.80%	97.98%	8.55	60.13%	0.83	87.22%	85.95%
Exudates	insufficient data							
Furrows	insufficient data							
Edema	1.0000	81.30%	67.00%	2.46	30.30%	0.28	95.31%	69.15%
Feline esophagus	1.0000	4.40%	93.80%	0.71	80.09%	1.02	14.76%	17.81%
I-EREFS	insufficient data							
T-EREFS	2.0000	75.00%	85.70%	5.24	48.07%	0.29	95.10%	84.10%

F-EREFS = Fibrostenotic Endoscopy Reference Score, I-EREFS = Inflammatory Endoscopy Reference Score, T-EREFS = Total Endoscopy Reference Score

Figure 1: EREFS endoscopic features found in the study population. (a) edema - loss vascular markings; (b) fixed rings - trachealization; (c) furrows - vertical lines ;(d) exudate - white plaques; (e) strictures.

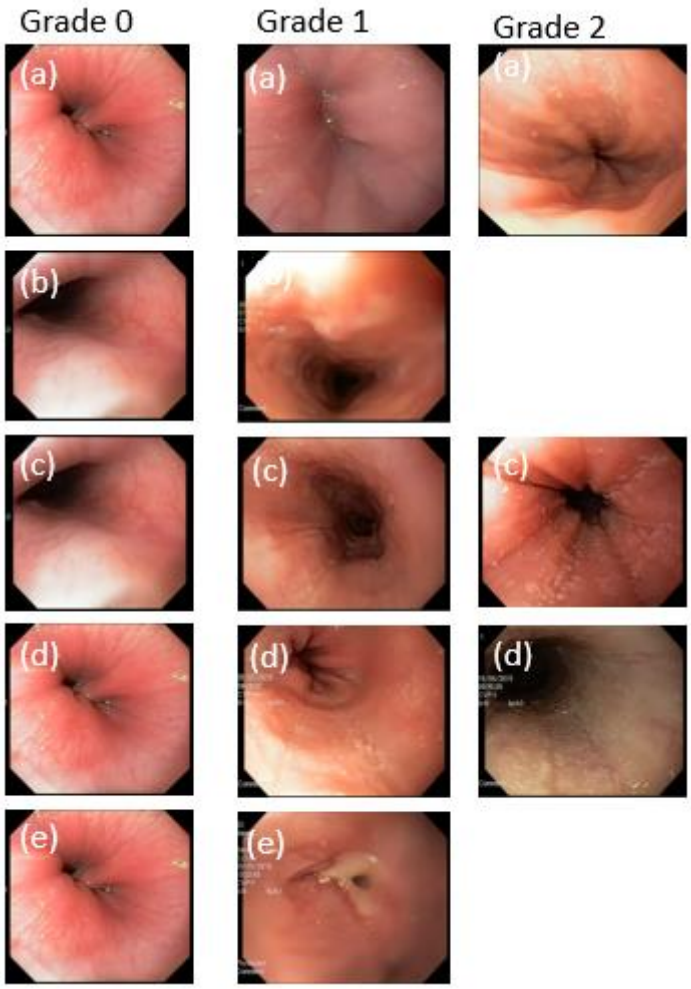
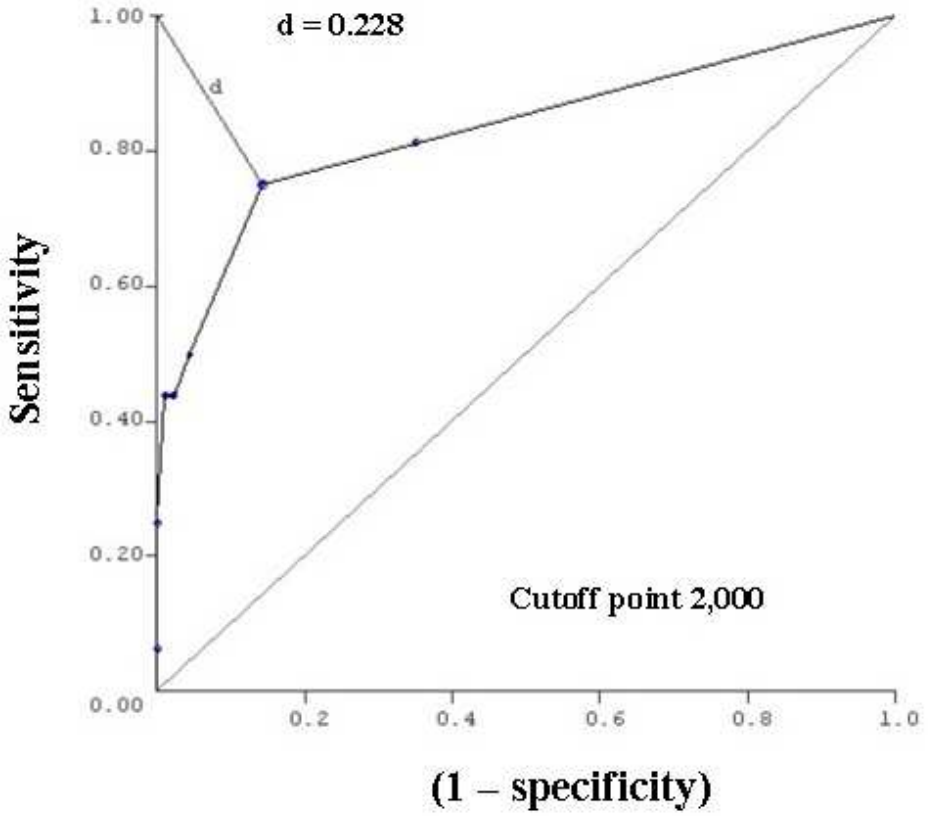


Figure 2: The Receiver-Operating Characteristic curve for T-EREFS at cutoff point 2.



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