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Jacobs Journal of Allergy and Immunology

Investigative Study

Extra-Esophageal Symptoms in Pediatric Eosinophilic Esophagitis: A Case Control Study

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Received: 06-03-2016

Accepted: 07-25-2016

Published: 07-29-2016

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Abstract

Background: The presence of extra-esophageal gastrointestinal symptomatology in children with eosinophilic esophagitis (EoE) has not been prospectively evaluated.

Objective: We sought to determine if children with EoE have significant accessory gastrointestinal symptoms.

Methods: Twenty-five newly diagnosed children with EoE were age and gender matched with children with allergic diseases, but not an EoE diagnosis. An esophageal and extra-esophageal gastrointestinal questionnaire was used to compare the two groups.

Results: Neither constipation nor diarrhea alone was significantly different between the groups. Combining the presence of constipation and/or diarrhea was significantly present in EoE children compared to their allergic controls. Any abdominal pain was significantly more common in EoE children as compared to allergic controls. Conclusions: Extra-esophageal symptoms may accompany the patient with eosinophilic esophagitis

Keywords: Eosinophilic Esophagitis; Pediatric; Constipation; Diarrhea

Introduction

Now recognized as an important disease, eosinophilic esophagitis (EoE) has a pattern of recognizable esophageal-based gastrointestinal features [1]. Most EoE symptoms focus at the esophagus itself, abdominal pain being the main exception [1]. The presence of exaggerated esophageal eosinophilia after a sufficient course of therapy with a proton-pump inhibitor serves as the predominate proof of the diagnosis of EoE [1].

To investigate the prevalence of extra-esophageal presentations in EoE, we prospectively enrolled newly recognized EoE patients with an age and gender-controlled group of allergic children without EoE symptoms, and compared extra-esophageal gastro-intestinal symptoms between the two groups.

Methods and Materials

Twenty-five new pediatric EoE subjects, ages 1-17 years, were enrolled consecutively from patients seen at two institutions. All EoE subjects were on a Proton pump inhibitor (PPI), 1-2 mg/kilogram, at the time of the definitive diagnostic endoscopic evaluation with biopsies, to ensure proper pharmacological support for the EoE diagnosis [1]. Greater or equal to 15 eosinophils/HPF was histological criteria. Not all EoE children had a colonoscopy at either the first or 2nd (confirmatory on a PPI) endoscopy, but all the EoE children had at least one gastric and proximal small bowel endoscopy with biopsies. Children were

excluded from the enrolled cohort if either the first or conformational endoscopy reveals any extra-esophageal abnormal eosinophilia. Pathological services were provided at two institutions with extensive experience in gastrointestinal pathology, but no blinded 2nd cross-reading of subjects was obtained. EOE children may have had other allergic diseases, but were not necessarily a patient in the author's clinic (RH) prior to the EOE diagnosis. In large part they were sent by a gastroenterologist after the diagnosis of EOE. Being atopic was not a criteria for being enrolled in this protocol for the EOE subjects.

After the completion of the EoE cohort enrollment, an age and gender and ethnicity (except one) match was obtained from the clinical allergy clinics of an author (R.H.). A mixture of asthma, allergic rhinitis, and atopic dermatitis disease(s) (or multiple diagnoses) was represented in the allergic control group (asthma = 18, allergic rhinitis = 11, atopic dermatitis = 15). Allergic controls were managed by the author (RH), and were all atopic. There was wide allergen sensitization background, depending on age and disease. Food allergic children only were not enrolled to allow for a comparison of more systemically based allergic diseases, not treated with a food avoidance only approach.

Parents of children in both groups completed an ISAAC-derived questionnaire of allergic disease questions (Table 1) [2].

1. Has your child ever had asthma? ___Yes ___No
2. Has your child ever had wheezing or whistling in the chest? ___Yes ___No
3. Has your child had wheezing or whistling in the chest in the last 12 months? ___Yes ___No
4. In the last 12 months, has your child's chest sounded wheezy during or after exercise? ___Yes ___No
5. In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection? ___Yes ___No
6. Has your child ever had a problem with sneezing, a runny or blocked nose when he/she DID NOT have a cold or the flu? ___Yes ___No
7. In the past 12 months, did your child have a problem with sneezing, a runny or blocked nose when he/she DID NOT have a cold or the flu? ___Yes ___No
8. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes? ___Yes ___No
9. Has your child ever had hay fever? ___Yes ___No
10. Has your child ever had an itchy rash which was coming and going for at least six months? ___Yes ___No
11. Has this itchy rash, at any time, affected any of the following places?
    - The fold of the elbows ____
    - Behind the knees ____
    - In the front of the ankles _____
    - Under the buttocks _____
    - Or around the neck, ears or eyes _____

Table 1. Allergic disease questionnaire.

The presence of esophageal and extra-esophageal gastrointestinal symptoms was obtained from both groups (Tables 2 and 3). Included were both esophageal and abdominal based symptoms along with stool patterns, but from a non-standardized questionnaire.The demographics and presence of extra-esophageal gastrointestinal symptoms between the two groups was compared using Fischer t-test and chi-square analysis. A p-value < 0.05 was considered significant.

Please consider these possible problems in your child in the past six months

1. Does your child complain regularly of abdominal pain? ___Yes ___No
2. Does your child vomit more than once a month? ___Yes ___No
3. Does your child complain of frequent chest pain? ___Yes ___No
4. Does your child complain of a sour taste in their mouth or throat? ___Yes ___No
5. Does your child ever get food stuck in their throat after swallowing? ___Yes ___No
6. Does your child refuse to eat some foods? ___Yes ___No
7. Is your child small and a very picky eater? ___Yes ___No
8. Has a doctor said your child has (had) reflux for spitting up? ___Yes ___No
9. Did your doctor put your child on reflux medication? ___Yes ___No
10. Does your child have constipation? ___Yes ___No

Table 2. Gastrointestinal symptoms questionnaire.

1. In the past 3 months has your child had frequent episodes of diarrhea? ___Yes ___ No
2. If yes, does your child have the diarrhea problem on most days? ___Yes ___No
3. If Yes to Question 2, Answer the questions below: (If No, skip to Question 5)

Number of stools each day
- (a) 1-3
- (b) 4 or more

Consistency
- (c) Watery stool
- (d) Stool is the thickness of pancake batter

Blood
- (e) Very bloody stool
- (f) Only sporadic blood present
- (g) Blood not present in stool
- (h) Bright red blood present
- (i) Dark, tarry blood present

Degree/Frequency
- (j) Entire stool is soft or watery
- (k) Only portions of the stool are soft or watery
- (l) Diarrhea with each bowel movement
- (m) Diarrhea is sporadic (some bowel movements are normal)
- (n) Only 1 or 2 bowel movements per day
- (o) More than 4 bowel movements per day

Amount
- (p) Increased, large amount of stool
- (q) Decreased or normal, small amounts of stool

5. In the past 3 months has your child been constipated? ___Yes ___ No
6. If No, this completes the questionnaire
7. If yes, is your child constipated on most days? ___Yes ___ No
8. If yes, how many days between stools does your child have?
   - (a) 1-2 days
   - (b) 2- 5 days

Table 3. Gastrointestinal symptoms questionnaire.

The protocol was approved by the institutional review board at Creighton University

Results

Twenty-five EoE subjects, and 25 age, gender and ethnicity matched allergic controls were evaluated. The male/female ratio in the EoE subject was 18 males/7 females. The ethnic background for the EoE subjects was 22 Caucasian, 1 Hispanic, 1 Asian, and one mixed. The allergic control children were gender and age matched (with-in year). The allergic child

match for the Asian and mixed race children were Caucasian. There was no significant difference for age, weight and height between the two groups (Table 4).

Demographics	EoE N = 25	Allergic N = 25
Age	8.2 +/- 4.4	8.1 +/- 4.6
Gender	18 M and 7 F	18 M and 7 F
White/Other	23/2	24/1
Height	127 +/- 27 cm	128 +/- 28 cm
Weight	36.6 +/- 30.9 kg	33.5 +/- 16.7

Table 4. Demographics of subjects.

We examined the presence of any esophageal symptom in the allergic control children. Fifteen of the allergic children had at least one esophageal symptom, and twelve had two or more. An association between asthma, allergic rhinitis or atopic dermatitis was not found to influence the esophageal symptoms. None of the allergic children had required an esophageal endoscopy.

There was no significant increase in constipation in the allergic children with esophageal symptoms (3 of 15 children) as compared to allergic children without esophageal symptoms (2 of 10). Additionally, 1 of 15 allergic children with esophageal symptoms had diarrhea and 1of 10 allergic children without esophageal symptoms had diarrhea. As the difference in constipation or diarrhea in allergic group was not significantly different in the face of esophageal symptoms, the entire group of 25 allergic children were compared to the EoE children for the incidence of constipation and diarrhea. The specific questions on the gastrointestinal questionnaire concerning diarrhea and constipation were compared between the two groups. An affirmative answer for the question: "In the past 6 months has your child been constipated?" was compared between the two groups. Secondly, an affirmative answer to the question "in the past 3 months has your child had frequent episodes of diarrhea?" was also compared. Lastly, an affirmative answer to either question was compared between groups. One child in each the EoE and atopic group answered affirmative for both questions, and each were included in both gastrointestinal symptoms for the analysis. Removing them from the analysis did not change the significance. Forty percent of the EoE children had constipation, and 24% had diarrhea; however, these specific individual extra-esophageal symptoms were not statistically different from allergic controls. The Results are presented in Table 5.

An affirmative answer to either question about diarrhea or constipation was combined. The summated presence of either constipation or diarrhea (n= 16) was significantly different than either combined compliant in atopic children (n=7). The Results are presented in Table 5.

Results	EoE N = 25	Allergic N = 25	p value
Constipation Yes	10	5	.30
Diarrhea Yes	6	2	.12
Either Diarrhea or Constipation Yes	16	7	.011

Table 5. Comparison of gastrointestinal symptoms in EoE and allergic controls.

Abdominal pain is a frequent compliant in children with EoE. In our study 12 of 25 children answered affirmative to that question, as compared to 2 of 25 atopic controls. This was significantly different (p = .0002)

Discussion

Our pre-study clinical hypothesis was children with EoE have an increased incidence of constipation. Our current prospective study did not verify this clinical impression, and, in addition, diarrhea alone was not more significant between the EoE children and allergic controls. Based on the questionnaire combining affirmative answers for diarrhea or constipation proved to be a significant co-morbidity in EoE as compared to allergic controls.

The allergic disease questions were directly taken from The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [2]. Children in the EoE and allergic match group answered the same allergic disease questions. The allergic subjects were gender and age matched controls for the EoE subjects, and were patients of a single investigator (R.H.) prior to their inclusion in this protocol.

There are several limitations. The questionnaire used to determine the presence or absence of esophageal symptoms in both groups was not standardized, but at the time of the development of the protocol there was no standardized EoE questionnaire. A recent manuscript details a standardized questionnaire (PESSS v 2.0) for both EoE symptoms, and although not as detailed our non-standardized questionnaire has overlapping questions [3]. The EoE questionnaire, as used by Martin et al, does not have questions on diarrhea or constipation [3]. Of the 46 pediatric subjects in the report of Martin et al with EoE, 37% percent had diarrhea and 17% had constipation [3]. Combining their results with our report, both studies demonstrate a high rate of extra-esophageal gastrointestinal symp-

toms in pediatric subjects with EoE. The summation of these two studies, ours with the direct intent to assess and diarrhea and constipation, and one showing the frequent presence of these symptoms in pediatric EoE, strongly points to an actual presence of extra-esophageal gastrointestinal symptomology in EoE. Larger controlled studies would have little to contribute to the observation of this clinical phenomenon, and in fact there are no large placebo-controlled studies of medication in pediatric EoE, in which a broad based collection of information about pediatric EoE could be gleaned.

As mentioned, the questions on stool status including constipation or diarrhea were non-standardized. In support of the findings, both the EoE group and allergic group answered the same questions, thus allowing for comparison of the answers. Not all children with EoE had colonoscopies, thus reducing the information that exaggerated colonic eosinophilia might be an explanation of extra-esophageal lower gastrointestinal symptomatology in the EoE group. The EoE children who had colonoscopies had no evidence of exaggerated colonic eosinophilia. It is exceeding uncommon to have both EoE and eosinophilic enteritis and/or eosinophilic colitis.

There was no endoscopy in the allergic children to prove non-existence of EoE. However, all the atopic children were patients of a single investigator (RJH), and none of the atopic children with or without esophageal symptoms have required an endoscope, or had advancement of esophageal complaints, at the time of submission of this manuscript. The author (RJH) uses no 1st generation antihistamines in his practice, and no information is available suggesting intranasal steroids or leukotriene receptor antagonists cause constipation or diarrhea.

It is possible that the proton pump inhibitor used to separate EoE histology from other eosinophilic esophageal histology (gastroesophageal reflux or PPI-REE) could result in either diarrhea or constipation. Omeprazole, the most commonly used pediatric PPI, lists both constipation and diarrhea as side effects. The package insert for omeprazole and lansoprazole show a 1.0 and 1.9 % incidence of constipation and a 1.6 and 3,8% incidence of diarrhea, respectively. As it's required by standard of care to utilize a PPI at the time of an endoscopy the side effects of diarrhea and constipation caused by the PPI seems an unlikely explanation, or an avenue for explaining our results.

The presence of enhanced lower gastrointestinal symptoms in EoE has no clear explanation. The presence of constipation is common in children. Constipation in children tends to equal sex distribution and is common in all pediatric age groups [4]. EoE is generally considered a male dominated disease [1]. The explanation for potential enhanced lower intestinal symptomatology in EoE is not well understood. It's possible that the eosinophils in the esophagus release eosinophilic granular proteins that have a deleterious effect, either thru interference of gastric-colic reflex, or by direct action on colonic neurons. Neither theory has direct evidence, however. There is however, mouse model support for eosinophilic granular proteins in asthma pathophysiology [5]. Similarly, eosinophilic granular proteins play a role in gastrointestinal pathology and neuronal injury in eosinophilic mediated gastrointestinal disease, as demonstrated in a mouse model [6].

Finally, abdominal pain is a frequent symptom of EoE patients [1]. In our study 48% of EoE subjects as compared to 8% of allergic subjects had affirmative answers to the question of regular abdominal pain. The etiology of abdominal pain in EoE is not well understood, and also supports the concept of a spectrum of extra-esophageal symptomology in EoE.

Conclusion

The presence of extra-esophageal gastrointestinal symptoms in a child also presenting with major concerns for potential esophageal disease should enhance the clinical suspicion for eosinophilic esophagitis, and accelerate the decision to start proton pump inhibitors prior to scheduling an endoscopy, and lessen the concern for a more pervasive gastrointestinal disease.

Acknowledgement

The authors acknowledge the participation of and Nancy Wise, Joel Van DeGraff M.D., Jordan Fritch, and Ted Grask, and to Drs. Sharad Kunnath, Jonathan Spergel, Jeffrey Stokes for valuable comments.

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