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Role of Acid and Nonacid Reflux in Children With Eosinophilic Esophagitis Compared With Patients With Gastroesophageal Reflux and Control Patients

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Abstract

Objectives—Because of the relationship between food and eosinophilic diseases, we hypothesize that patients with eosinophilic esophagitis (EE) may be repeatedly exposed to nonacid ingested foodstuffs compared with patients without EE. Because inflammation is found throughout the esophagus in patients with EE, we further hypothesize that there would be more full-column reflux in EE patients compared with patients with gastroesophageal reflux disease (GERD) and control patients.

Materials and Methods—We retrospectively reviewed pH-multichannel intraluminal impedance tracings of EE patients who were age-matched with control and GERD patients and compared the reflux profiles among the 3 groups.

Results—There were no significant differences between the mean numbers of nonacid reflux events in EE patients (4.7 ± 3.3) compared with GERD (7.5 ± 5.3) or control patients (6.8 ± 4.6) (P = 0.36). There were significantly more acid reflux events in patients with GERD (47.4 ± 17.1) compared with patients with EE (24.9 ± 20.0) and control patients (28.4 ± 16.5) (P = 0.02). Patients with EE did not have a higher percentage of full-column reflux (31.9 ± 20.9) compared with control patients (24.4 ± 19.8) or patients with GERD (30.5 ± 14.9) (P = 0.64).

Conclusions—Neither full-column reflux nor nonacid reflux is a significant contributor to the pathogenesis of EE.

Keywords

Eosinophilic esophagitis; Nonacid reflux; Gastroesophageal reflux; Impedance

Eosinophilic esophagitis (EE) is an idiopathic clinicopathological disease characterized by dysphagia, food impaction, and feeding difficulties that occur in association with dense esophageal eosinophilia. Typically, symptoms and histopathology are unresponsive to proton pump inhibitor treatment. They are responsive to anti-allergic treatments including dietary restriction and corticosteroids, and laboratory studies demonstrate that ubiquitous

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aeroallergens or Th2 cytokine interleukin-13 can induce esophageal eosinophilia (1–6). Because of the relationship between food and eosinophilic diseases, we hypothesized that the esophageal mucosa of patients with EE may be repeatedly exposed to ingested foodstuffs compared with patients without EE. Because most reflux occurs in the postprandial period when stomach contents are typically neutralized, we investigated whether EE patients had longer duration or more proximal reflux of nonacid contents than patients with gastroesophageal reflux disease (GERD) or control patients.

MATERIALS AND METHODS

We retrospectively reviewed all pH-multichannel intraluminal impedance (MII) tracings performed between January 2002 and May 2005. All patients with a diagnosis of eosinophilic esophagitis were identified, defined as those with esophageal eosinophilia (>20 eosinophils per high-power field) that did not respond to 8 weeks of proton pump inhibitor therapy. These patients were age matched as closely as possible with patients with GERD and control patients who underwent pH-MII testing. Patients with GERD were defined as patients with reflux symptoms and abnormal pH recordings. Control patients included those without gastrointestinal symptoms (ie, patients with respiratory disease) who had normal esophageal biopsies and normal pH recordings off all reflux medications. Each study was performed using either the Sleuth ambulatory pH-MII system or the stationary pH-MII system (Sandhill Scientific, Denver, CO). All of the patients were admitted to Children's Hospital Boston during the pH-MII recording and measurements were performed for a minimum of 20 hours. None of the patients received sedation before catheter placement and all of the patients were taken off acid suppression medications a minimum of 48 hours before pH-MII testing. Three different, age-appropriate impedance catheters were used: infant (ages 0–2 years), pediatric (2–10 years), and adult (>10 years old). Each catheter had 7 impedance sensors and 1 distal pH sensor. Catheter location was confirmed by chest radiograph. The catheters were adjusted following the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition guidelines so that the pH sensor was at the third vertebral body above the diaphragmatic angle (7).

All of the patients ate their regular diet with a minimum of 3 hours between each meal and could not drink apple juice or soda during the study. Patients and parents recorded meal and symptom times on a log. All of the information from the logs was manually entered into the pH-MII tracing. Data collected during meals were excluded from the analysis.

Analysis of pH monitoring was completed using GERD analysis software (Sandhill Scientific, Denver, CO). An acid reflux episode was defined as a drop in pH to <4 for ≥5 secconds. Acid clearance time was calculated as the time from a drop in pH to <4 to the time of its recovery to pH >4. A pH probe was considered abnormal if the pH was <4 for >6% of the time for children >1 year old and for >12% of the time for children <1 year old (8).

Each of the pH-MII tracings was analyzed manually by 1 investigator who was blinded to the clinical history of the patient (RR). A reflux episode detected by impedance was defined as a retrograde drop in impedance to >50% of baseline in the distal 2 channels. Bolus clearance time was defined as the time from a drop in impedance to >50% of its baseline value to its recovery to >50% of its baseline value in the most distal impedance channel. Acid reflux episodes are those episodes detected by both pH and impedance sensors. Nonacid episodes are those episodes detected by impedance sensors only, and pH-only episodes are those episodes detected by the pH sensor only and a minimum of 5 seconds long. Full-column reflux was defined as an episode that reached the highest pair of impedance sensors. The percentage of time that reflux is in the esophagus (exposure time), as detected by impedance, was calculated by dividing the sum of the bolus clearance times

for reflux events by the total study duration and multiplying by 100. The acid exposure time does not include the sum of acid clearance times (the duration of time that the pH is <4).

Tracings of patients with a confirmed diagnosis of EE were compared with tracings of patients with GERD and control patients. Statistical analysis was performed using SPSS version 11.5 (SPSS, Chicago, IL). Baseline characteristics were compared using Student *t* test or χ^2 analysis. Analysis of variance was performed to compare each of the 3 groups. Kruskal-Wallis testing was used to compare medians. The institutional review board at Children's Hospital Boston approved this study.

RESULTS

During the course of this review, 10 patients in each of the 3 groups (EE, GERD, and controls) were identified. All of the patients in the EE and GERD groups were older than 1 year of age. Eight of the control patients were older than 1 year of age. The presenting complaints in control patients were chronic cough (3), abdominal pain not responsive to acid suppression (4), wheezing (1), chronic lung disease (1), and subglottic stenosis due to prolonged intubation at birth (1).

Patient characteristics including pH monitoring results are shown in Table 1. The acid reflux index was significantly higher in patients with GERD compared with EE and control patients (P <0.0001).

The total time that reflux, as detected by impedance, was present in the esophagus is shown in Table 2. Patients with EE had significantly shorter durations of esophageal acid, nonacid, and total reflux than patients with GERD. In addition, no significant differences in reflux exposure were measured between patients with EE and control patients (P >0.05). There was, as expected, a greater percentage and number of acid reflux events in patients with GERD compared with patients with EE and control patients (Table 3).

Finally, median numbers of reflux events in each of the 3 groups is shown in Table 4. There were significant differences in the median values of total, acid, and pH-only reflux events between patients with GERD and either patients with EE or control patients.

Because patients with EE have panesophageal inflammation extending along the length of the esophagus and appear to be more prone to proximal esophageal strictures, we assessed whether patients with EE had more full-column reflux episodes than patients with GERD. Over the duration of these studies, there was no significant difference in the number of full-column reflux events between patients with EE and patients with GERD as shown in Table 3.

DISCUSSION

Eosinophilic esophagitis, defined as eosinophilic infiltration of the esophagus in the face of normal pH monitoring of the distal esophagus or a lack of histological response to proton pump inhibitors, responds both clinically and histologically to a hypoallergenic diet (5,6,9). Because food antigens are likely contributors to the pathogenesis of this disease in many patients, we hypothesized that patients with EE could have more refluxate of food particles than control patients or patients with acid reflux. Because most reflux occurs in the postprandial period when the refluxate is typically nonacid, we hypothesized that patients with EE would have more nonacid reflux than control patients or patients with GERD (10). The results of our study do not support this hypothesis; patients with EE had similar amounts of nonacid reflux compared with control patients. Consistent with previous studies, children with EE do not have increased acid reflux index compared with children with

GERD or normal controls (9,11). In addition, our data show that nonacid reflux is not increased in children with EE compared with normal controls.

Because neither acid nor nonacid reflux is increased in patients in EE, we next determined whether impaired esophageal clearance of refluxate could play a role in its pathogenesis. The results of this study show that the mean esophageal exposure time in children with EE was no different from normal controls, and thus the results again do not support a role for refluxate in the pathogenesis of EE.

Finally, because EE typically involves multiple levels of the esophagus (12,13), we postulated that refluxate would reach the proximal esophagus with more frequency than in patients with GERD or control patients. However, our study suggests that this is not the case, because full-column reflux is no more common in patients with EE than in controls or patients with GERD.

In addition to the data provided focusing on EE, limited control data for pH-MII monitoring in children older than infants is presented for the first time in this study. The only pH-MII values available in asymptomatic patients are from a study of 21 preterm infants with feeding tubes; in this preterm infant study, the median number of reflux events was 72, 25.4% of which were acid and 72.9% nonacid (14). Although the numbers in our study are small, we describe pH-MII values in children >1 year of age with normal esophageal biopsies, normal pH probe data, and symptoms not responsive to acid suppression. Our median reflux numbers in control patients are nearly identical to adult normal data (15,16), but the number of reflux events in this study is fewer than the number in normal preterm infants (14); we found a median of 31 reflux episodes per 24 hours of study, of which the majority were acidic. We hypothesize that our results differ from those of Lopez-Alonso et al (14), who found higher numbers of all reflux events and a greater proportion of nonacid events, because we did not have a catheter stenting open the lower esophageal sphincter for the purposes of feeding, which has been shown to increase the number of reflux events (17); our patients were older and were fed less frequently than preterm infants, so there may be less postprandial gastric neutralization in our patients compared with preterm infants; and very young infants have more reflux than older infants and children >1 year of age (18). We recognize that these control patients included in our study are not truly “healthy controls” because they have some atypical symptoms necessitating referral for impedance. However, given their negative gastrointestinal evaluation, including pH studies, and that the impedance results are consistent with adult normal values and are not significantly different from the EE population who traditionally do not have pathological reflux (15,16), we feel that they serve as a good control population.

We also report novel pediatric data regarding the duration of time that the esophageal mucosa is exposed to acid and nonacid luminal contents, also referred to as the esophageal exposure time. Previous studies in children focused only on the number of reflux events occurring during a 24-hour period. However, these descriptions do not take into account the length of reflux episode; the importance of this measurement relates to the fact that children with poor esophageal clearance may have a small number of total reflux episodes but a prolonged esophageal exposure time. One striking aspect of the esophageal exposure time detected by pH-MII is that it is <50% of the exposure time as recorded by pH probe. Both adult and pediatric studies have reported that the bolus clearance time as measured by impedance is significantly less using pH-MII than with pH probe alone (15,19). Based on fluoroscopic studies in adults, the presence of fluid in the esophagus is accurately detected by pH-MII, suggesting that exposure time as measured by pH-MII may be a more accurate representation of esophageal contents than the reflux index (the percentage of time that the pH is <4 in the esophagus) (20). The pH sensor may be surrounded by an acidic

microenvironment, requiring multiple swallows to effectively clear the single sensor. Another explanation for the discrepancy between bolus presence by impedance and bolus presence by pH sensors is that the accepted standard definition of reflux as detected by impedance is too stringent—a drop and subsequent return to 50% of the impedance baseline may be too great—and that small volume reflux may be occurring with drops in baseline impedance to only 20% or 30% of baseline values. Additional studies are warranted to determine the cause of this discrepancy.

In conclusion, patients with EE do not have more nonacid or full column reflux than control patients, suggesting that reflux does not play a role in the pathogenesis of this disease. In addition, our data are novel regarding pH-MII values for control patients and may provide valuable information for studies of other esophageal diseases.

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TABLE 1

Demographic and pH characteristics in patients with eosinophilic esophagitis (EE), gastroesophageal reflux disease (GERD), and controls

	EE	GERD	Control
Sex, M:F	8:2	2:8	3:7
Mean age, y (SD)	10.5 ± 6.8	6.2 ± 3.8	7.8 ± 6.8
Time pH <4, % (SD)	2.8 ± 1.9	11.3 ± 4.3	2.6 ± 1.9

SD = standard deviation.

TABLE 2

Percentage of time (as a proportion of total study duration) that total reflux, acid reflux, and nonacid reflux is present in the esophagus as determined by pH-multichannel intraluminal impedance

	EE	GERD	Controls	*P*
Total reflux, % (SD)	0.99 ± 1.28	1.83 ± 0.77	0.89 ± 0.70	0.07
Acid reflux, % (SD)	0.80 ± 0.92	1.63 ± 0.62	0.70 ± 0.56	0.01
Nonacid reflux, % (SD)	0.19 ± 0.38	0.20 ± 0.37	0.14 ± 0.11	0.85

EE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease; SD = standard deviation.

TABLE 3

Mean number of reflux events per study in each of the eosinophilic esophagitis (EE), gastroesophageal reflux disease (GERD), and control groups

	EE	GERD	Controls	*P*
Acid reflux (SD)	24.9 ± 20.0	47.4 ± 17.1	28.4 ± 16.5	0.02
Nonacid reflux (SD)	4.7 ± 3.3	7.5 ± 5.3	6.8 ± 4.6	0.36
pH-only reflux (SD)	7.7 ± 5.9	22.1 ± 14.1	13.6 ± 11.2	0.02
Total reflux that is full column, % (SD)	31.9 ± 20.9	30.5 ± 14.9	24.4 ± 19.8	0.64

SD = standard deviation.

TABLE 4

Median number of reflux events in the eosinophilic esophagitis (EE), gastroesophageal reflux disease (GERD), and control groups (5%, 95%)

	EE	GERD	Controls	*P*
Acid reflux	19 (9, 74)	47 (14, 83)	24.5 (8, 58)	<0.0001
Nonacid reflux	4.5 (0, 11)	7 (0, 15)	8.5 (1, 13)	0.4
pH-only reflux	5.5 (0, 16)	19 (7, 56)	8 (0, 35)	0.008
Total	24 (11, 80)	51 (23, 98)	31 (10,69)	0.01