CME

Early Life Exposures as Risk Factors for Pediatric Eosinophilic Esophagitis

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ABSTRACT

Objectives: Few etiologic studies of eosinophilic esophagitis (EoE) have been conducted. Early life exposures have been shown to predispose to other allergic disease, but their role has not been assessed in EoE. The present study sought to explore early life exposures as possible risk factors for developing EoE in the pediatric population.

Methods: This was a 2-phase case-control study conducted at the University of North Carolina. The first phase consisted of survey development for early life exposures via cognitive interview. In the second phase, a telephone-based questionnaire was administered to cases with EoE (n = 31) and 2 sets of controls, patients with gastroesophageal reflux disease, and siblings of nonsyndromic cleft lip/palate patients (n = 26 in each). Different controls were explored to identify controls reflective of the source population of the cases. Siblings of cleft lip/palate patients were identified as the more suitable control population. Odds ratios were calculated to evaluate the association between early life exposures and the development of pediatric EoE.

Results: Early life exposures were associated with increased odds of developing pediatric-onset EoE. Antibiotic use in infancy was associated with 6 times the odds of having EoE (95% confidence interval 1.7–20.8). Cesarean delivery, preterm birth, and formula-only or mixed (infant formula and breast milk) feeding also have trends toward increased odds for developing EoE.

Conclusions: A number of early life exposures may be associated with the development of EoE. These are potentially modifiable risk factors that if confirmed would have implications for improved understanding of EoE pathogenesis and disease prevention.

Key Words: antibiotics, cesarean delivery, eosinophilic esophagitis, infant feeding

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Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus characterized by dense eosinophilic infiltration of the esophageal mucosa (1). Among children, the clinical presentation of EoE may include symptoms of abdominal pain, heartburn, regurgitation, nausea, vomiting, dysphagia, feeding difficulties, and impaired growth (2–4). Only within the last 2 decades has EoE been recognized as a distinct disease (5). Since then, the incidence of EoE has increased steadily (6–9) and appears to be approaching the incidence of inflammatory bowel diseases (IBDs) such as Crohn disease and ulcerative colitis (10,11). At the University of North Carolina (UNC), where the present study was conducted, diagnosis of EoE has also increased markedly during the last decade (12).

To date, few studies have explored the etiologic factors associated with the development of EoE. Much of the literature suggests an association between EoE and food allergies, and the success of dietary elimination and elemental diets supports the role of an allergen-induced etiology of EoE in some patients (13,14). Several theories have been proposed to explain the increase in allergic responses that have led to the increased incidence of EoE, including changes in gut microbiota as a result of changes in diet; antibiotic exposure; increased cesarean deliveries; increased exposure to environmental allergens; changes in how food is grown, processed, and packaged; decreased prevalence of *Helicobacter pylori*; and reduced exposure to microbial disease (the hygiene hypothesis) in developed countries (15,16). Although there are few data to support these theories specifically in EoE, there has been a link between allergic disorders and gut microbiota alteration as a result of infant feeding practices and exposure to antibiotics in infancy, mode of delivery at birth, breast milk exposure (17,18), and cesarean delivery (19).

The overall aim of this study was to explore these potential early life exposures as risk factors for the development of EoE by conducting a case-control study. We hypothesized that early childhood exposures that may alter the development of the microbiota would predispose to development of EoE.

METHODS

We conducted a 2-phase case-control study at the UNC. Recognizing that there may be bias when control selection is not representative of the source population from which the cases arose, the first phase of the study consisted of survey development and assessment of feasibility of selection and recruitment of appropriate control groups. In the second phase, we evaluated the association between selected early life exposures and development of pediatric

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EoE. The study was approved by the UNC institutional review board.

Survey Development and Risk Factors of Interest

The survey instrument was developed and refined through an iterative process of cognitive interviews and survey revision. Cognitive interviews were conducted one-to-one for a period of approximately 2 hours per interview with biological mothers (n = 3) of children (younger than 18) recruited through the UNC Pediatric Gastroenterology Specialty Clinic; there were no restrictions on the reason the child was being seen in the clinic.

The goal of this phase of the project was to develop questions that would specifically elicit reliable and accurate information about the early childhood exposures of interest. In particular, questions were drafted about the following exposures: infant feeding (breast milk or formula, age of introduction of infant formula and solid foods, special dietary requirements): the presence of preterm birth: mode of delivery (vaginal vs cesarean): birth weight: antibiotic exposure for mother before or during delivery: antibiotic exposure to mother while breast-feeding: antibiotic exposure during the child's first year of life: and child or family history of allergic disorders. The final survey instrument was designed to be administered by study personnel via telephone and consisted of 69 primarily closed-response questions.

Case and Control Group Definitions

Cases of EoE were identified from the UNC EoE Clinicopathologic Database, a resource with confirmed EoE cases that has been previously described (12,20,21). For study inclusion, cases had to meet the following criteria: confirmed diagnosis of EoE (as per published consensus diagnostic guidelines (1,22): $\geq$15 eosinophils per high-power field on esophageal biopsy, clinical symptoms of esophageal dysfunction, and use of a proton-pump inhibitor trial to exclude other competing conditions such as gastroesophageal reflux disease [GERD] and proton-pump inhibitor–responsive esophageal eosinophilia), diagnosis of EoE between 2004 and 2010, present age 1 to 17 years, child residing with biological mother.

As noted above, because bias can be introduced into case-control studies if control selection is not representative of the source population from which cases arose, a priori we decided to evaluate 3 possible control groups, neighborhood controls identified through cases, children without EoE who had an upper endoscopy at UNC between 2004 and 2010 and were diagnosed as having GERD, and siblings of patients seen for nonsyndromic cleft lip/palate and/or congenital nevi at the UNC Pediatric Plastic Surgery Specialty clinic. The first group was chosen to provide a nonhospital, community-based control group. The second was chosen as a group that would reflect the source population from which cases arose and because GERD controls have been frequently used in studies of EoE. The third control was chosen to select subjects from a similar catchment area to the source population referred to a specialty clinic at UNC, but without introducing the potential for shared etiologic factors in using a control population with symptoms of, and seeking evaluation for, a related disease process. Case-control–designed studies can produce biased estimates when the distribution of exposure(s) of interest among controls is not representative of the distribution of exposure(s) in the source population from which cases arose (23). As such, a priori we hypothesized that controls selected from the Pediatric Plastic Surgery Specialty Clinic would provide the best opportunity for minimizing selection bias.

To select neighborhood controls, we sent letters and e-mails to mothers of cases with EoE who had participated in the study with a solicitation to provide contact information of a friend or neighbor with a child who could serve as a control. The controls with GERD were identified from patients who underwent upper endoscopy between 2004 and 2010 at UNC. GERD was defined clinically as troublesome symptoms of gastroesophageal reflux (including heartburn, regurgitation, vomiting) and with no other potential causes identified upon upper endoscopy or biopsy (24). The control group of siblings of patients seen in the Pediatric Plastic Surgery Clinic was identified via a roster of clinic visits from 2004 through 2010.

All of the patients serving as controls had to be between the ages of 1 and 17 years and had to reside with their biological mother. All telephone surveys were administered to the biological mother of the patient identified as a case or control, and all of the data were collected from the mother. Cases and controls were recruited initially by letter, and then a minimum of 3 additional contact attempts by telephone were made.

Statistical Analysis

Recruitment rates were calculated for each of the 3 control groups. To assess the generalizability of the control groups to the population of North Carolina, we compared selected statewide demographic and birth-related statistics to the survey results. We analyzed the survey data to assess distribution of exposure measures across cases and controls. We calculated the odds ratio (OR) for EoE for the primary exposures of interest (25), specifically infant feeding practices, use of antibiotics, mode of delivery, and exposure to maternal smoking. We used exact methods for generating confidence intervals (CIs) in instances in which expected cell counts were too sparse (n < 5) for asymptotic CIs (26). Given the small sample size of this pilot study, we did not perform multivariate analysis to adjust for potential confounders or hypothesis testing on multiple bivariate comparisons.

RESULTS

Case and Control Recruitment

A total of 70 pediatric cases with EoE were identified, of whom 44% (n = 31) were successfully contacted and agreed to participate. Eighteen were unable to be contacted because of incorrect contact information in the patient's electronic medical record, and 27% (n = 19) were unresponsive to the letter and telephone contacts. Two cases were ineligible for participation based on study criteria. None of the cases refused participation.

A total of 63 potential controls with GERD were identified and 41% (n = 26) were recruited and surveyed. Nearly 40% (n = 25) were unable to be contacted because of incorrect contact information. Eleven possible controls with GERD were unresponsive to the letter and telephone contacts, and 1 refused participation.

Among controls identified through the Pediatric Plastic Surgery Specialty Clinic (n = 126; hereafter referred to as Plastics), 21% (n = 26) were successfully recruited and surveyed. An additional 33% (n = 42) were unable to be contacted because of incorrect contact information and 25% (n = 32) did not respond to contact attempts. Ten percent (n = 13) refused participation and an additional 10% were found to be ineligible as a result of the patient not having a sibling within the study age parameters. Attempts to identify neighborhood-based controls were largely unsuccessful. Only 5 of the study cases provided contact information for recruitment of neighborhood controls. As such, this recruitment approach proved to be unfeasible and was not pursued further, and only the

controls with GERD and the Plastics controls were further analyzed for the study.

Patient Characteristics and Early Childhood Exposures

Patients with EoE were of similar age to the GERD and Plastics controls (mean ages 11, 12, and 8 years, respectively) and also had a similar racial distribution (73%, 85%, and 77% white, respectively; Table 1). As expected, the frequency of food allergies, environmental allergies, and asthma was higher for cases than controls, particularly for the Plastics controls. A comparison of the clinical, endoscopic, and histological features of cases with EoE and controls with GERD indicated some shared clinical features between the groups. The 2 groups were distinct in endoscopic and histological presentation (Table 1).

There were also differences in the frequency of certain early life exposures between the case and control groups (Table 2). For example, preterm delivery and cesarean section were more common in the EoE group (26% and 58%) compared with the GERD group (20% and 31%) and the Plastics group (8% and 38%). Although breast-feeding initiation rates were moderate to high in all groups, exclusive breast-feeding was lowest in the EoE group (6%) compared with both GERD and Plastics controls (23% and 19%, respectively). Antibiotic use during the first year of life was higher in the EoE and GERD groups (81% and 73%, respectively) than in the Plastics group (42%).

Further analysis of this pilot data comparing cases with EoE with controls recruited through the Pediatric Plastic Surgery Clinic suggests that there may be an association between early life exposures and development of EoE (Fig. 1). Antibiotic use in infancy was associated with 6 times the odds of having EoE (95% CI 1.7–20.8), and cesarean delivery, preterm birth, mixed (infant formula and breast milk) or formula-only feeding, and infants of mothers identified to be group B *Streptococcus* positive trended toward increased odds for developing EoE.

Comparison of the cases with EoE with controls with GERD yielded some similar patterns of association, with increased odds of EoE for cesarean delivery (OR 3.1; 95% CI 1.0–9.3) and a trend toward increased odds for EoE for mixed or formula feeding (OR 4.4; 95% CI 0.8–23.8); however, the strength of the association with both antibiotic use and preterm birth was attenuated (OR 1.6; 95% CI 0.4–6.0 and OR 1.4; 95% CI 0.4–4.9, respectively).

TABLE 1. Clinical, endoscopic, and histological features of patients with EoE and GERD

	EoE cases (n = 31) n (%) or mean ± SD	GERD controls (n = 26) n (%) or mean ± SD
Clinical features		
Dysphagia	10 (32)	2 (8)
Food impaction	3 (10)	2 (8)
Heartburn	13 (42)	14 (54)
Chest pain	4 (13)	4 (15)
Abdominal pain	7 (23)	21 (81)
Nausea	6 (19)	14 (54)
Vomiting	12 (39)	15 (58)
Failure to thrive	11 (36)	11 (42)
Endoscopic features		
Rings	4 (13)	0 (0)
Stricture	2 (7)	0 (0)
Narrowing	2 (7)	0 (0)
Furrows	9 (30)	1 (4)
Crepe paper	4 (13)	0 (0)
White plaques	6 (20)	2 (8)
Decreased vascularity	7 (23)	1 (4)
Histological features		
Maximum eosinophils/hpf	93.5 ± 62.5	1.8 ± 2.5

EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease; hpf = high-power field; SD = standard deviation.

DISCUSSION

During the last decade, EoE has become a major source of upper gastrointestinal symptoms in both children and adults (27). The reasons for the increasing incidence and prevalence of this disease are not presently known, but have been presumed to be linked to the overall increase in atopic diseases (15). Although much progress has been made toward understanding the immune-mediated pathogenesis of EoE (28,29), to our knowledge, no epidemiologic studies have explored possible etiologic factors associated with development of pediatric EoE. The overall purpose of this study was to conduct a pilot study of the association between early life exposures and EoE. Given the opportunities for introduction of bias in inappropriate selection of controls from a hospital-based setting, we also explored the suitability of different control groups.

For the control groups, we found that it was not feasible to recruit neighborhood controls with the methodology that we performed, but that both GERD controls and Plastics controls were willing to participate; however, after examining the characteristics of the control groups, we believed that siblings of patients treated in the Pediatric Plastic Surgery Clinic were the most suitable control population for studying the association between early life exposures and pediatric EoE. First, a number of their characteristics closely matched those of the general population in North Carolina. Second, the Plastics controls reflected the source population of cases with EoE that are seen at UNC, a tertiary care referral center with a large catchment area. Third, we believed that the controls with GERD not only had the potential for misclassification but also because they had another chronic gastrointestinal illness, which resulted in medical treatments and doctor visits, they were less well-suited to compare with cases with EoE in terms of early life exposures. Controls with GERD experienced a higher proportion of otitis media and respiratory illness in infancy and a higher occurrence of antibiotic use than Plastics controls, highlighting a significant limitation in using patients with GERD for controls. Other limitations of the GERD control group include the potential for altered infant feeding practices as a result of having GERD, and the fact that this group did not represent the source population of the cases with EoE as well as the Plastics controls. For these reasons, it is likely that using patients with GERD as controls in etiologic studies of EoE may introduce selection bias, whereby the exposure distribution among controls is not reflective of the exposure distribution in the source population or population from which the cases with EoE arose. This finding does not preclude the possibility of GERD controls in other studies of EoE. For example, it may be reasonable to select controls with GERD for studies that are designed to elucidate the diagnostic features of EoE.

The data suggest that the pathogenesis of EoE may be rooted, at least in part, in factors encountered early in life. In particular, we saw significantly elevated odds of EoE with antibiotic administration during the first year of life, and a trend toward increased odds for several other early life events including cesarean delivery, preterm birth, and not having exclusive breast-feeding. Because of the small sample size and pilot nature of this study, additional

TABLE 2. Distribution of study covariates among cases and controls

	EoE cases, (n = 31) n (%) or mean ± SD	GERD controls (n = 26) n (%) or mean ± SD	Plastics controls (n = 26) n (%) or mean ± SD	North Carolina*, %
Age, y	11 ± 4	12 ± 4	8 ± 4	—
Race				
White	22 (73)	22 (85)	20 (77)	73
Black	4 (13)	2 (8)	1 (4)	23
Other	4 (13)	2 (8)	5 (19)	4
Missing	1 (3)	0 (0)	0 (0)	—
Ethnicity				
Hispanic	1 (3)	1 (4)	4 (15)	16
Non-Hispanic	29 (97)	25 (96)	22 (85)	84
Missing	1 (3)	0 (0)	0 (0)	—
Preterm delivery	8 (26)	5 (20)	2 (8)	12
Low birth weight	5 (16)	6 (23)	2 (8)	9
Birth weight, g	3213 ± 714	2970 ± 799	3235 ± 652	—
Maternal smoking	4 (13)	5 (19)	6 (23)	18
Cesarean delivery	18 (58)	8 (31)	10 (38)	31
Breast-feeding initiation	26 (84)	17 (65)	19 (73)	69†
Exclusive breast-feeding	2 (6)	6 (23)	5 (19)	—
Family history of EoE	3 (9)	3 (9)	0 (0)	—
Group B *Streptococcus* + during pregnancy	5 (17)	3 (13)	2 (8)	—
Antibiotic use in infancy	22(81)	19 (73)	11 (42)	—
History of food allergies	20 (65)	8 (31)	1 (4)	—
History of environmental allergies	23 (74)	14 (54)	9 (35)	—
History of asthma	18 (58)	10 (38)	6 (23)	—

EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease; SD = standard deviation.
* 2006–2010 North Carolina State Center for Health Statistics. 2012 county level health data book. *http://www.schs.state.nc.us/schs/data/databook*.
† 2008 North Carolina Child Health Assessment and Monitoring Program (CHAMP). 2008 North Carolina statewide CHAMP survey results. *http://www.schs.state.nc.us/schs/champ/2008/k04q01.html*.

data need to be collected on a larger scale to confirm these findings. More important, a larger study is needed to provide the sample size necessary to adjust for possible confounders in the associations observed.

Although the observation about the potential role of early life exposures has not been reported previously for EoE, it has been noted for some other atopic diseases (30,31) and also for IBD, particularly Crohn disease. For example, in a recent nested case-control study, antibiotic use in the first year of life was found to be associated with a 3-fold increase in the odds of having pediatric Crohn disease (32). Similarly, in a population-based, prospective study of antibiotic use and development of pediatric-onset IBD, the rate ratio for all IBDs was increased nearly 2-fold for antibiotic users compared with nonusers (33), and in a registry-based case-to-control–matched design study, the odds of Crohn disease was nearly 3-fold the odds of no disease for children who were prescribed ≥3 cephalosporins (34). The mechanism for an association is not well understood, but animal model data suggest that gut colonization of commensal microbes in early life has a role in developing tolerance to environmental exposures encountered later in life (35).

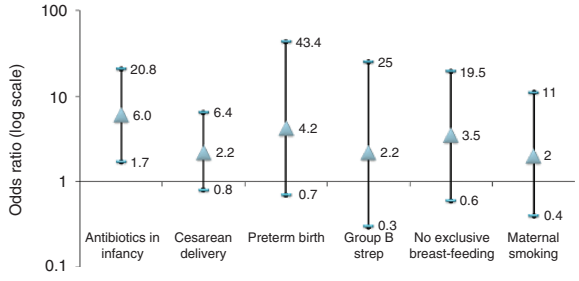

FIGURE 1. Association between early life factors and development of eosinophilic esophagitis.

Are there possible explanations for how these early life exposures may cause EoE or other atopic disorders? The early life factors explored in this study are potentially associated with altered gut microbiota, including antibiotic use, preterm delivery, cesarean delivery, and early introduction of infant formula. These factors may also serve as proxy measures for other unknown factors not collected in the present analysis. For example, preterm birth may arise through a precipitating factor in utero that is also associated with EoE; however, more detailed information on pregnancy complications, cesarean delivery, and antibiotic use is needed to explore these hypotheses and differentiate between mediating versus etiologic factors for EoE. As more genetic studies of EoE are conducted, epidemiologic studies of early life exposures may help inform studies of gene–environment interactions in developing EoE.

This study has some potential limitations. In addition to the relatively small sample size, this study has the potential for recall bias because the survey focused on factors experienced by either the mother or her child during pregnancy and early life. Although many factors such as birth weight, preterm birth status, and mode of delivery are not likely to be difficult to recall, perinatal use of medications, group B *Streptococcus* status, and initiation of the use of antibiotics in infancy may be difficult to recall for some patients. Although we attempted to minimize the effect of recall bias during

our survey development phase with cognitive interviews, in the future, medical record abstraction may be needed to supplement data collected through surveys. This study also has the potential for confounding bias through indication. Children who receive antibiotics in infancy may be exhibiting early manifestations of EoE or there may be atopic-associated comorbidities with EoE such as otitis media, bronchitis, asthma, and sinusitis that are associated with antibiotic use; however, the mean age at diagnosis for EoE was 6.6 years, with a mean duration of symptoms of 2.4 years, suggesting that these exposures likely preceded disease development. This study is strengthened by the use of patients with EoE whose case status had been previously validated, the exploration of the optimal control group to minimize bias owing to case-control design, and the excellent response rates among subjects whom we were able to contact. Because we could not locate a proportion of potential subjects, there is the possibility of selection bias if there was a systematic difference between the groups for those patients we successfully and unsuccessfully contacted.

In conclusion, this study suggests that patients with GERD undergoing endoscopy at a hospital-based clinic are not an optimal control group for etiologic studies of EoE; however, siblings of patients seen in a plastic surgery clinic for nonsyndromic cleft lip/palate and/or congenital nevi may serve as relatively unbiased controls. In addition, a number of early life exposures, most prominently antibiotic use during infancy, may predispose to EoE. This intriguing finding paves the way for larger studies to confirm this finding and to explore the mechanisms of early life exposures in the pathogenesis of EoE.

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