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Pediatric eosinophilic esophagitis: the Vanderbilt experience

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ABSTRACT

Background: Eosinophilic esophagitis (EoE) is a chronic allergic disease of the esophagus unresponsive to treatment with proton pump inhibitors. A combination of immediate, IgE-mediated and delayed, and non–IgE-mediated immune reactions to foods and aeroallergens is thought to contribute to disease pathogenesis. Optimal methods to assess for food allergen sensitization have been debated. Patients with EoE often have comorbid atopic diseases.

Objective: To characterize pediatric patients diagnosed with EoE at a single institution within the southeastern United States.

Methods: A retrospective study was conducted to evaluate 211 pediatric patients with EoE at Vanderbilt University Medical Center. Aeroallergen and food sensitization profiles obtained by skin prick testing (SPT), atopy patch testing (APT), and history of associated atopic diseases were analyzed.

Results: Older patients with EoE showed greater aeroallergen sensitization; the most common allergens were pollens and dust mite. Younger patients showed greater sensitization to foods by SPT and APT. The most common foods identified by SPT were peanut, egg, and soy. The most common foods identified by APT were potato, pork, and wheat. Comorbid atopic disease was common. Patients with atopic dermatitis did not show significantly greater sensitization to foods by SPT or APT compared with patients without atopic dermatitis.

Conclusion: In pediatric patients with EoE, sensitization to aeroallergens increases with age, whereas sensitization to foods decreases with age. Concomitant atopic disease is common. APT is useful to identify additional food allergens not detected by SPT. A history of atopic dermatitis does not appear to be associated with nonspecific positivity by SPT or APT.

Introduction

Eosinophilic esophagitis (EoE) is a chronic disease of the esophagus that is often confused with gastroesophageal reflux disease but is unresponsive to treatment with proton pump inhibitors (PPIs). According to the 2011 updated consensus recommendations, EoE is "characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation."[1,2] Diagnosis requires a minimum density of 15 eosinophils per 400× high-power field (HPF) in at least 1 biopsy specimen.[1] Endoscopic and histologic esophageal abnormalities have been associated with, but none are pathognomonic for, EoE.[1] Clinical presentation varies significantly with age; young children are more likely to present with nonspecific gastrointestinal complaints, such as feeding difficulties or vomiting, whereas specific symptoms of dysphagia and food impaction occur more commonly in adolescents and adults.[3,4] Previous studies have shown a white male predominance, although disease does occur in females and in all races.[2] Personal and family histories of atopic disorders are common.[1] Most studies have indicated increasing incidence and prevalence of EoE, which do not appear to be due entirely to increased disease recognition.

Although the exact pathogenic mechanisms are unknown, a combination of immediate, IgE-mediated and delayed, and non–IgE-mediated immune reactions to foods and aeroallergens is thought to contribute to disease pathogenesis.[5] Support for food as a definite

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trigger for EoE has been shown with improvement clinically and histologically in patients after elimination diets.[5–7] Optimal methods to assess for food allergen sensitization have been debated.[8–11] In a retrospective analysis of 941 pediatric patients with EoE, Spergel et al[6] found that the negative predictive value for the combination of skin prick testing (SPT) and atopy patch testing (APT) to identify causative foods averaged 92%, with the exception of milk at 44%. The positive predictive value was lower at 44%. Of those patients who followed a guided elimination diet based on results of combined testing plus the empiric elimination of milk, 77% had resolution of esophageal eosinophilia.[6] Use of APT in EoE has been criticized for its lack of standardization and difficulty in interpretation of results, particularly in patients with atopic dermatitis (AD), in whom irritant reactions are more common.[10]

Rates of aeroallergen sensitization have been reported to be as high as food sensitization rates in some patients[2] and seasonality to the diagnosis of EoE has been documented, supporting a role for aeroallergens in disease pathogenesis.[12–16] Retrospective studies have shown increased diagnosis in spring, summer, and autumn compared with winter months,[14–16] and correlations have been made between diagnosis and levels of pollen.[1,13] Geographic variation in disease frequency also has been reported, with the highest rates occurring in the cold and arid climate zones. It has been postulated that different geographic and climate patterns may aid in the identification of potential disease-triggering antigens.[17]

To the authors' knowledge, no published studies have analyzed the pediatric population with EoE from a single institution within the southeastern United States. This retrospective study aimed to characterize a group of pediatric patients evaluated for EoE at Vanderbilt University Medical Center (VUMC; Nashville, Tennessee) from January 1, 2009 through June 30, 2012. Information regarding demographic variables, presenting symptoms, personal and family histories of atopy, endoscopic and histologic findings, seasonality of diagnosis, and food and aeroallergen sensitization profiles was investigated. Potential differences between patients with and those without atopy were analyzed.

Methods

Study Design and Data Collection

A retrospective chart review was performed of all pediatric patients (0–20 years old) who were evaluated at the VUMC Pediatric Gastroenterology and/or Pediatric Allergy/Immunology Clinics for EoE from January 1, 2009 through June 30, 2012. Charts were identified through the electronic medical record database at VUMC using keywords *eosinophilic esophagitis*. Each chart was analyzed by a single physician to determine whether the patient met diagnostic criteria for EoE. Clinical data, including demographics (date of birth, race, sex), personal and family histories of atopic diseases (asthma, allergic rhinitis, AD, food allergy, EoE), presenting symptoms, date of diagnosis, gross endoscopic appearance of the esophagus, histologic features of esophageal biopsies, and results of allergy testing (SPT to aeroallergens and SPT and APT to foods), were collected and stored in a password-protected database. Data collection was approved by the VUMC institutional review board.

Diagnosis of EoE

The diagnosis of EoE was made in patients presenting with at least 1 of the following clinical symptoms of esophageal dysfunction: feeding difficulties, failure to thrive, weight loss, gastroesophageal reflux disease (including symptoms of heartburn, acid brash, and/or reflux), vomiting, abdominal pain, chest pain, dysphagia, or food impaction. Diagnosis was confirmed with esophagogastroduodenoscopy (EGD) by obtaining biopsy specimens from the esophagus, stomach, and duodenum. In some cases, biopsy findings were reported only for proximal or distal portions of the esophagus, not both. Biopsies were reviewed under a 400× HPF by a board-certified pathologist. Patients met criteria for diagnosis if they had at least 15 eosinophils per HPF (peak value) in the esophagus after treatment with a PPI. In some cases, patients were not initially on PPI therapy at the time of biopsy but were included in the analysis if they subsequently met the histologic criteria at a later date while on PPI therapy. Patients who had initial biopsies performed at outside institutions often had esophageal eosinophil counts reported in ranges (eg, >50/HPF), and those numbers were withheld from the analysis of median eosinophil counts in the proximal and distal esophagus.

Skin Prick Testing

Skin prick testing was performed for food and environmental allergens using commercial extracts (Greer Laboratories, Lenoir, North Carolina; Hollister-Stier, Spokane, Washington) applied to the skin using a puncture technique with QUINTEST and QUINTIP devices (Hollister-Stier). Positive histamine and negative saline controls were used. Reactions were recorded after 15 minutes by measuring the largest diameter of the wheal and flare in millimeters. Testing was considered positive if the wheal measured 3 mm larger than the negative control.

Skin prick testing for food allergens was performed using a standard panel, including peanut mix, fish mix, shellfish, egg, corn, cow's milk, soybean, wheat, almond, cashew, pecan, walnut, chicken, turkey, pork, beef, lamb, barley, oat, rice, rye, navy bean, string bean, carrot, pea, white potato, apple, peach, and mustard. Additional extracts were tested if there was clinical suspicion of a different offending food.

Skin prick testing for inhalant allergens was performed using a standard panel, including cat, dog, dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cockroach, and mold mix and regional mixes of grass pollen, weed pollen, and tree pollen.

Atopy Patch Testing

Atopy patch testing was performed by mixing 1 mL of sterile water with 1 teaspoon of dry powdered foods for egg, soy, wheat, rice, corn, oat, barley, potato (Barry Farm Foods, Wapakoneta, Ohio), and peanut (Byrd Mill, Ashland, Virginia). Dry powdered milk (Barry Farm Foods) was reconstituted using fresh milk instead of sterile water. Single-ingredient commercially prepared pureed baby foods were used to test beef, chicken, ham, turkey, peas, green beans, carrot, peach, and apple. Reconstituted dry foods and undiluted baby foods were loaded into 8-mm Finn chambers on Scanpore tape (Actavis AS, Norway/Norgesplaster) and taped in place on the patient's back. Reconstituted dehydrated cow's milk was loaded into a 12-mm Finn chamber and was similarly placed. Patches were removed at 48 hours and read at 72 hours after initial application, similar to methods described by Spergel et al.[9] Results were interpreted based on the classification proposed by Heine et al[18] in 2006.

Of note, patients were instructed to discontinue use of systemic steroids or other immunosuppressants 1 month before testing and topical immunosuppressants at the application site 1 week before testing. APT was not performed on foods for which the patient exhibited positive reactions to SPT.

Statistical Analysis

Descriptive statistics were calculated as the median with interquartile range for continuous variables. For categorical variables, frequencies and percentages were presented. Wilcoxon rank-sum test and Pearson χ^2 test were used to compare differences between patients with AD and those without and between those with a history of atopy and those without. All tests were 2-tailed, with a