

Original article

Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis

Background: Eosinophilic esophagitis (EE) is an emerging condition where patients commonly present with symptoms of gastroesophageal reflux disease and fail to respond adequately to anti-reflux therapy. Food allergy is currently recognized as the main immunological cause of EE; recent evidence suggests an etiological role for inhalant allergens. The presence of EE appears to be associated with other atopic illnesses.

Objectives: To report the sensitization profile of both food and inhalant allergens in our EE patient cohort in relation to age, and to profile the prevalence of other allergic conditions in patients with EE.

Method: The study prospectively analyzed allergen sensitization profiles using skin prick tests to common food allergens and inhalant allergens in 45 children with EE. Patch testing to common food allergens was performed on 33 patients in the same cohort. Comorbidity of atopic eczema, asthma, allergic rhinitis and anaphylaxis were obtained from patient history.

Results: Younger patients with EE showed more IgE and patch sensitization to foods while older patients showed greater IgE sensitization to inhalant allergens. The prevalence of atopic eczema, allergic rhinitis and asthma was significantly increased in our EE cohort compared with the general Australian population. A total of 24% of our cohort of patients with EE had a history of anaphylaxis.

Conclusion: In children with EE, the sensitization to inhalant allergens increases with age, particularly after 4 years. Also, specific enquiry about severe food reactions in patients presenting with EE is strongly recommended as it appears this patient group has a high incidence of anaphylaxis

**K. K. N. Sugnanam¹, J. T. Collins¹,
P. K. Smith², F. Connor³, P. Lewindon³,
G. Cleghorn³, G. Withers⁴**

¹Medical School, Griffith University, Southport, Australia; ²Medical School, Bond University, Robina, Australia; ³Medical School, University of Queensland, Herston, Australia; ⁴Gastroenterology Department, Royal Children's Hospital, Herston, Australia

Key words: aeroallergens; anaphylaxis; eosinophilic esophagitis; food allergens.

Pete K Smith
Bond University
Medical School
Robina
Queensland 4229
Australia

Accepted for publication 7 May 2007

Eosinophilic esophagitis (EE) is an emerging condition which has come to the forefront of gastroenterology and allergy over the past several years. Eosinophilic esophagitis is a disorder in which the esophagus is chronically inflamed with infiltration of eosinophils into the esophageal wall. It often presents with symptoms similar to gastroesophageal reflux disease, but does not respond as reliably to anti-reflux medication (1). Patients may present as children or adults (1). The most common presenting symptoms in pediatric patients with EE are feeding disorders, vomiting, abdominal pain, dysphagia, and food impaction (2), while adult patients are more likely to present with dysphagia with food impaction and heartburn (3).

At this stage, the etiology of EE is not entirely understood. Early evidence implicating food allergy was provided by Kelly et al. (4) who showed improvement in symptoms and mucosal biopsies in infants with EE fed an elemental, amino acid based diet. Food allergens have been identified as playing an important role as pathogenic factors in children (1). Food allergy does not completely

explain the development of EE. In murine models, Mishra et al. (5) induced eosinophilia in the esophagus via intranasal exposure of *Aspergillus* aeroallergen. More recently evidence of aeroallergens causing EE in humans was provided by Fogg et al. (6) who reported a patient with seasonal exacerbation in EE (symptoms and mucosal histology) which was related to seasonal pollen levels.

In adults, dietary modification does not appear to be as effective as a treatment strategy; a recent study by Simon et al. (7) showed that a 6-week allergen specific elimination diet was not helpful in improving symptoms in adult EE patients. Further, the development of allergic airway disease that precedes the development of EE has been described in an adult population, suggesting that the initial allergen sensitization might take place in the airways (8) in this group.

The first objective of the present study was to report the sensitization profile of both food and inhalant allergens in our EE patient cohort compared with age. We hypothesized that with increasing patient age, the degree of sensitization to food allergens will decrease and

sensitization to inhalant allergens will *increase*. We propose that this shift from food allergens to inhalant allergen sensitivity – the atopic march (9) has implications for allergen testing, avoidance and therapeutic strategies for EE patients.

Studies have shown that in pediatric populations with EE more than 80% of individuals will have other allergic disorders (1, 10). Similarly, Simon et al. (8) demonstrated that 68% of adults with EE in their study had a history of pre-existing atopic diseases, such as allergic rhinitis, bronchial asthma and atopic dermatitis. Thus, EE appears to be associated with concomitant atopic diseases in both adult and pediatric populations. As such the second objective of this study was to compare the prevalence of asthma, atopic eczema, allergic rhinitis, and anaphylaxis in our patient cohort with EE with their prevalence in the Australian population.

Methods

Patient representation

Forty-five consecutive patients who were referred to the senior author, a pediatric allergist (PS), and diagnosed to have EE by endoscopy and esophageal biopsy were studied. The diagnostic criteria used were the histopathological presence of ≥ 15 epithelial eosinophils in ≥ 2 high power fields (HPF) or ≥ 25 epithelial eosinophils in any HPF. Ages ranged from 3 months to 16 years (median 5.3 years). At the time of the study, patients lived in various locations in eastern Australia, ranging from metropolitan areas, regional areas and remote rural areas and are representative of the Australian population.

Patch testing

Patch testing was completed on 33 patients out of the cohort of 45. Patch testing was performed following protocols established by Niggeman et al. (11) using cow's milk, hen's egg, soy, wheat, and corn. The foods being tested were placed into 12 mm aluminium cups (Finn Chambers on Scanpor, Epitest, Finland) and adhered to patient's backs. The efficacy of patch testing in determining late-phase allergic reactions has been established elsewhere (11) and studies have confirmed its efficacy in identifying potential food allergens in EE (1). Patch cups were removed at 48 h and the results were read at 72 h. Reactions were rated either as 0 for no reaction, 1 for erythema and/or < 4 mm papules, 2 for moderate erythema/induration and/or 4–7 mm papules and 3 for marked erythema with induration and/or > 7 mm papules.

Skin prick testing

Skin prick testing was performed on all 45 patients. Skin prick testing was carried out for both food allergens and inhalant allergens using standard extracts (Hollister-Stier, Spokane, WA USA). Skin prick testing for food allergens was performed using extracts of cow's milk, hen's egg, soy, wheat, peanut, cashew, fish, and corn, as these have been shown to be among the most common food allergens causing hypersensitivity in Australian children (12). Skin prick testing for inhalant allergic disease was based on common inhalant allergens in the area for atopic dermatitis. Extracts of house dust mite, cat, dog, feather, cockroach, grass

mix, tree mix, and the mould *Alternaria* were used. Positive histamine and negative diluent controls were used. Reactions were recorded as the diameter of the wheal size (in mm) at 15 min.

Comorbidities

Each of the comorbid conditions (atopic eczema, allergic rhinitis, asthma, and anaphylaxis) was physician diagnosed for each patient. Anaphylaxis was defined as per the 2005 JACI published classification (13).

Data analysis

The total wheal diameter was determined for each patient by summing the reaction size for each of the eight food allergens and for each of the eight aeroallergens tested on every patient. A total wheal diameter for food allergens and a total wheal diameter for aeroallergens for each patient in the study were derived.

The total severity was determined for patch testing by summing the severity of patch test results (0, 1, 2, or 3) for each of the food allergens. Thus, a total patch severity between 0 and 15 was determined for each patient who was patch tested.

A linear regression was performed on this data using SPSS v12.0.1. The dependent variables were total food allergen skin prick test (SPT) wheal size (mm), total inhalant allergen SPT wheal size (mm) and total patch severity (range 0–15), and, the independent variable was patient age at testing (in months).

The prevalence of the comorbidities was determined as a proportion of positive diagnoses for each condition (atopic eczema, allergic rhinitis, asthma, and anaphylaxis). These comorbidities were compared with national prevalence figures for allergic rhinitis and asthma (14), atopic eczema (15), and anaphylaxis (16).

Results

Skin prick and patch testing

The graphical representation of the data is shown (Fig. 1) with an overlaid linear trend line. First, there is a *positive* relationship between age and degree of inhalant allergen reactivity as determined by skin prick testing; 25.6% of the variation in inhalant allergen reactivity is accounted for by age alone, ($P = 0.001$). Secondly, there is a *negative* relationship between age and food allergen reactivity as determined by skin prick testing; 6.2% of the variation in IgE-mediated food allergen reactivity is accounted for by age alone, ($P = 0.046$). Similarly, there is a *negative* relationship between age and food allergen reactivity as determined by patch testing; 13.7% of the variation in non-IgE-mediated food allergen reactivity is accounted for by age alone ($P = 0.005$). The trend lines for food and inhalant allergen SPT wheal diameter intersect at a patient age of approximately 50 months (4.2 years).

Comorbidities

The prevalence of atopic eczema, allergic rhinitis, asthma and anaphylaxis in our EE patient cohort is shown in Table 1. In our EE cohort, the prevalence of atopic eczema, allergic rhinitis and asthma significantly

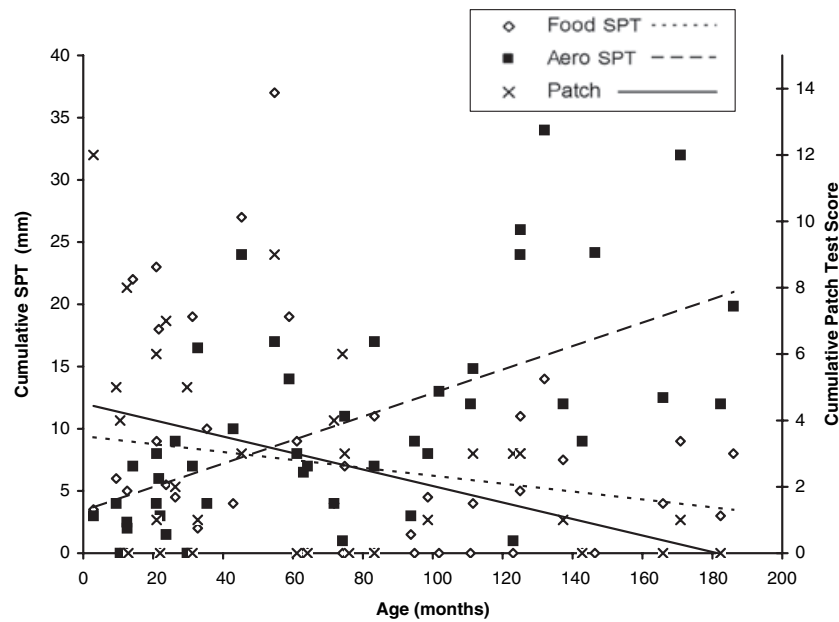


Figure 1. Association between patient age (in months) and food allergen skin prick test (SPT) wheal size ($P = 0.046$), age and aeroallergen SPT wheal size ($P = 0.001$), and age and patch test severity ($P = 0.005$).

increased compared with the Australian population. Of particular interest was that the prevalence of anaphylaxis in our cohort was 100 times that recognized in the Australian population.

Discussion

Currently, there are a number of therapies in use for the treatment of EE. These include dietary modification (food elimination and elemental diets), medical therapies (systemic or topical corticosteroids, leukotriene receptor agonists and cromolyn sodium) and esophageal dilatation (17). The efficacy of food-elimination and elemental diets in improving clinical symptoms in children and adolescents was shown in a number of previous studies (4, 18, 19).

Our results suggest that as age increases in children and adolescents with EE, inhalant allergen sensitization increases. We report a decrease in food allergen sensitization and age. This inverse relationship appears to involve both IgE and non-IgE-mediated reactions as indicated by the decrease in both SPT sensitivity and patch test sensitivity with age. These findings indicate an age specific sensitization profile transition from food allergen sensitivity to inhalant allergen sensitivity as age

increases in EE (the authors, of course, recognize that sensitization does not necessarily always equal allergy). This trend in atopic progression was previously established (9, 20) but has not yet been specifically described in EE. We believe our cohort, though small, can be applied to other EE populations.

As mentioned previously, other studies are now indicating a possible role for inhalant allergen sensitization in the development of EE, especially in adult populations (5–8). In light of this emerging evidence, the results of our study add weight to the idea that treatment of inhalant allergen allergy may play a role in the treatment of EE. Such treatments could include allergen-specific immunotherapy, inhaled corticosteroids and exposure minimization. The treatment of inhalant allergen allergic disease would most likely be appropriate in older patient groups, but also may be appropriate in younger patients refractory to dietary modification, or could even prove to be effective when combined with dietary modification. Of course, further investigation is required in this area to determine the efficacy of treating inhalant allergen allergy.

Our results indicate that the prevalence of asthma, atopic eczema and allergic rhinitis are significantly higher in our EE cohort than the general population in Australia. Of particular note is the striking prevalence of anaphylaxis in our cohort. This was a surprising finding

Table 1. Prevalence of atopic eczema, allergic rhinitis, asthma, and anaphylaxis in eosinophilic esophagitis (EE) cohort and Australian prevalence figures (14–16)

	Atopic eczema	Allergic rhinitis	Asthma	Anaphylaxis
EE population ($n = 45$)	55.56%	93.33%	66.67%	24.44%
Australian population	32.3% ⁽¹⁵⁾	10.65% ⁽¹⁴⁾	11.3% ⁽¹⁴⁾	0.22% ⁽¹⁶⁾
	($n = 2968$)	($n = 25\ 906$)	($n = 25\ 906$)	($n = 142$)

and indicates a significantly increased risk of anaphylaxis in EE patients. This figure may represent referral bias with only more severe patients being referred to a pediatric allergist and could be compounded with a type II error because of a moderately sized cohort. However, other larger centers are finding similar results; personal communications with Jonathan Spergel (Philadelphia, PA, USA) indicate that the prevalence of anaphylaxis is significantly increased (10%) in EE populations; he had estimated the prevalence to be up to 10% in his patients (patient series of over 400). This represents a high prevalence of anaphylaxis. It is therefore, vital that children presenting with EE are asked specifically about severe food reactions, particularly by the gastroenterologist who may not routinely address this aspect.

Conclusion

We report a *positive* relationship between increasing patient age and degree of aeroallergen sensitization, while

there is a *negative* relationship between increasing patient age and degree of food allergen sensitization. The therapeutic implication is that the treatment of inhalant allergic disease should be considered more as patient age increases and in those who are refractory to dietary modification.

Asthma, atopic eczema, allergic rhinitis, and anaphylaxis show increased prevalence in this EE population. Anaphylaxis rates are particularly pertinent, as there is a high prevalence compared with the general Australian population, therefore specific enquiry and comprehensive allergy evaluation of severe food reactions in patients presenting with EE is important.

Acknowledgments

The authors thank Prof. Rod McClure (Professor of Community Care and Epidemiology, Griffith University School of Medicine) for his assistance with the data analysis.

References

1. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002;**109**:363–368.
2. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;**351**:940–941.
3. Straumann A, Spichtin H, Grize L, Bucher K, Beglinger C, Simon H. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003;**125**:1660–1669.
4. Kelly KJ, Lazenby AJ, Rowe PC. Eosinophilic esophagitis attributed to gastroesophageal reflux; improvement with an amino acid-based formula. *Gastroenterology* 1995;**109**:1503–1512.
5. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;**107**:83–90.
6. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol* 2003;**112**:796–797.
7. Simon D, Straumann A, Wenk A, Spichtin H, Simon H-U, Braathen LR. Eosinophilic esophagitis in adults – no clinical relevance of wheat and rye sensitizations. *Allergy* 2006;**61**:1480–1483.
8. Simon D, Marti H, Heer P, Simon H-U, Braathen LR, Straumann A. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol* 2005;**115**:1090–1092.
9. Bergmann RL, Wahn U, Bergmann KE. The allergy march: from food to pollen. *Environ Toxicol and Pharmacol* 1997;**4**:79–83.
10. Orenstein SR, Shalaby TM, Di Lorenzo C, Putnam PE, Sigurdsson L, Mousa H et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol* 2000;**95**:1422–1430.
11. Niggeman B, Reibel S, Wahn U. The atopy patch test (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy* 2000;**55**:281–285.
12. Hill DJ, Hoskin C, Zhie CY, Leung R, Baratwidjaja K, Iikura Y et al. The frequency of food allergy in Australia and Asia. *Environ Toxicol Pharmacol* 1997;**4**:101–110.
13. Sampson HA, Munoz-Furlong A, Bock SA, Schmitt C, Bass R, Chowdhury BA et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005;**115**:584–591.
14. Australian Bureau of Statistics. National health survey: summary of results. Canberra: ABS, 2006. ABS publication 4364.0; 16.
15. Robertson CF, Roberts MF, Kappers JH. Asthma prevalence in Melbourne school children: have we reached the peak? *Med J Aust* 2004;**180**:273–276.
16. Brown A, Mckinnon D, Chu K. Emergency department anaphylaxis: a review of 142 patients in a single year. *J Allergy Clin Immunol* 2001;**108**:861–866.
17. Liacouras CA. Eosinophilic esophagitis: treatment in 2005. *Curr Opin Gastroenterol* 2006;**22**:147–152.
18. Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastro Hep* 2005;**3**:1198–1206.
19. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol* 2003;**98**:777–782.
20. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999;**103**:1173–1179.