

Atopic Characteristics of Adult Patients With Eosinophilic Esophagitis

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Background & Aims: The association of sensitization to food allergens, atopic disorders, and eosinophilic esophagitis (EE) is well known in children, but not in adults. Our purpose was to identify the spectrum of specific allergic sensitivities to environmental and food allergens within a series of adult patients with EE. **Methods:** The case series consisted of 23 adult patients with biopsy-proven EE referred for allergy evaluation at an academic clinic. All patients had data that included serum measurement of specific immunoglobulin (Ig)E antibodies to common foods and spices. Patients diagnosed with allergic rhinitis had a relevant clinical history of respiratory allergy and evidence of specific IgE to environmental aeroallergens. **Results:** The series consisted of 16 men and 7 women with a median age of 34 years (range, 18–57 y). Eighteen of 23 had an atopic diathesis, allergic rhinitis being the most common. Seventeen of 21 patients were polysensitized to several different environmental allergens, and 19 of 23 (82%) had serum IgE specific for one or more food-associated allergens (median, 5 foods), with wheat, tomato, carrot, and onion identified most commonly. The preponderance of environmental and food allergy was similar across all age groups and did not favor younger adults. **Conclusions:** By using objective measures, our series confirms the high degree of atopy in adults with EE, similar to that seen in the pediatric population. These patients tend to be polysensitized to several environmental allergens, and the profiles of serum IgE specific for food allergens suggest that sensitization may partly be a response to inhaled allergens.

Eosinophilic esophagitis (EE), a condition that has been well described in children, is being increasingly diagnosed in adults.¹⁻⁵ The cardinal pathologic finding of the disease is eosinophilic infiltration of the superficial mucosa of the esophagus without inflammation in other parts of the gastrointestinal tract.⁶ In adults, this often results in symptoms that are poorly responsive to treatment for gastroesophageal reflux disease and include dysphagia, heartburn, chest pain, vomiting, or food impaction.⁵

Patients with EE often report either a personal or family history of atopic disorders, which include asthma, atopic dermatitis, or allergic rhinitis.⁵ Pediatric series have used objective measures to define the atopic characteristics of the study patients, such as serum immunoglobulin (Ig)E and allergen skin prick testing to both environmental and food allergens.⁷⁻⁹ Series examining EE in adults also have reported a strong association with atopic disease, although most of these findings are based on patient query and not by objective testing.¹⁻³ In a recent adult series, specific sensitivities to food allergens were assessed by radioallergosorbent tests, but the details of what

foods were tested or which were positive were not provided.⁴ In the present study, we describe the atopic characteristics and the spectrum of specific allergic sensitivities to environmental and food-associated allergens within a series of adult patients with EE.

Materials and Methods

Study Goal and Patient Selection

The goal of this study was to determine the demographics and allergic sensitivities of adult patients with confirmed EE referred by a gastroenterologist to the allergy clinical practice of the University of Pennsylvania. The diagnosis of EE was considered confirmed in each patient by the following criteria: (1) symptoms including epigastric or chest discomfort, dysphagia, or food impaction that were poorly responsive to pharmacologic acid suppression with at least 2 months of twice-daily proton pump inhibitors before esophageal biopsy; and (2) esophageal biopsy specimen containing intraepithelial eosinophils numbering 15 or more in 2 or more high-power fields (400× magnification) or 25 or more in any high-power field.¹ Allergy clinic charts of patients meeting these criteria were reviewed for atopic history (allergic rhinitis, asthma, atopic dermatitis), specific testing of environmental and food allergy, and laboratory results pertaining to the initial evaluation. Patients diagnosed with allergic rhinitis had a relevant clinical history of respiratory allergy and had evidence of specific IgE to environmental aeroallergens. Patients diagnosed with pollen-food syndrome (otherwise known as *oral allergy syndrome*) experienced symptoms of oropharyngeal pruritus with or without angioedema involving the lips, tongue, palate, or posterior oropharynx associated with the ingestion of uncooked fruits and vegetables. On review of laboratory data, in accordance with the widely accepted definition, peripheral blood eosinophilia was identified when there was an absolute eosinophil count greater than 600 cells/ μ L.¹⁰ Total serum IgE at a value greater than 180 kU/L was considered increased in accordance with the Hospital of the University of Pennsylvania clinical laboratory reference range. By using the commonly cited cut-off value,¹¹ specific IgE concentrations greater than 0.35 kU/L were considered positive. Patients lacking specific testing to food-associated allergens were excluded from the study. Together, this process yielded 23 study cases, and the protocol was approved by the Institutional Review Board of the University of Pennsylvania.

Abbreviations used in this paper: CAP, ImmunoCAP allergen-specific IgE testing; EE, eosinophilic esophagitis; Ig, immunoglobulin; SPT, skin prick testing.

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Allergy Testing

Allergic sensitization to food-associated allergens was determined in vitro by the AB ImmunoCAP system (Pharmacia Diagnostics, Uppsala, Sweden) for measurement of specific IgE in peripheral blood (CAP test). All CAP tests were performed in Clinical Laboratory Improvement Act–certified commercial reference laboratories. At the initial visit, patients were given a list of 96 diverse foods and spices and were asked to indicate the following: (1) those that exacerbated symptoms of epigastric/chest discomfort or dysphagia, and (2) those that they ate at least twice weekly. Based on this questionnaire, CAP testing was ordered for all study patients. Environmental allergy evaluation was performed in 21 of 23 study cases by CAP tests. Patients with a relevant clinical history of respiratory allergy but negative results to CAP testing (3 patients) underwent skin prick testing (SPT) to environmental allergens to confirm absence of specific IgE with the more sensitive test. The panel of environmental allergens used in both CAP testing and SPT represented the predominate tree, grass, and weed pollens of the northeastern United States and common indoor allergens included dust mite allergen and pet dander (cat and dog). Atopy patch testing was not performed in this study.

Statistical Analysis

Statistical analysis was performed using the nonparametric 1-way analysis of variance (Kruskal–Wallis test) to test equality of population medians among groups (Figure 1). The Pearson product-moment correlation coefficient (r) was used to determine the tendency of 2 groups of variables to increase or decrease together, and a value greater than 0 was considered a positive correlation. All calculations were performed using GraphPad Prism software (GraphPad Software, San Diego, CA).

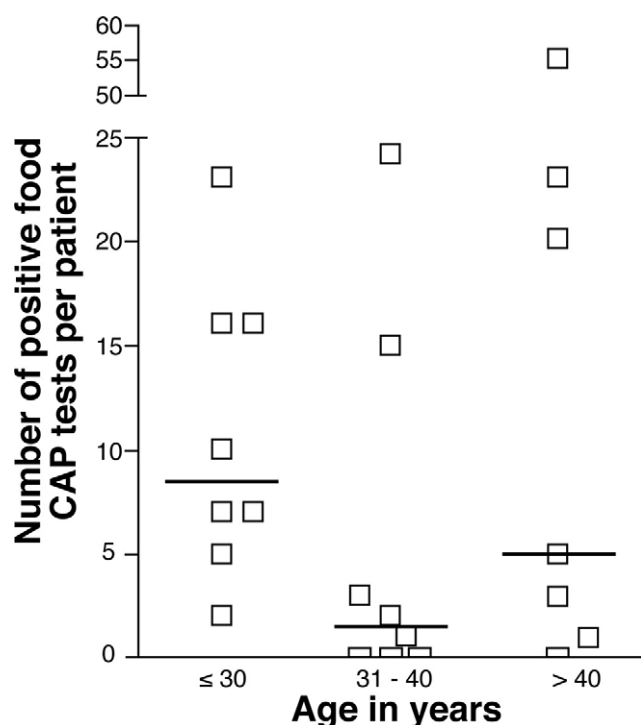


Figure 1. The numbers of food allergens to which patients were sensitized did not vary significantly by age grouping. Analysis by Kruskal–Wallis analysis of variance test. Horizontal bar, group median.

Table 1. Demographic Features and Atopic Characteristics

Mean age $\pm$ SD, y	35.2 $\pm$ 11
Median age, y	34
Age range, y	18–57
Sex: male/female	14/9
Atopy, no. of patients	
Asthma	6
Allergic rhinitis	18
Atopic dermatitis	1
Any atopic diathesis	18 (78%)
Specific IgE for food allergens, no. of patients	19 (83%)
Specific IgE for environmental allergens	18 of 21 (86%)
Birch pollen	17 of 21 (81%)
Timothy and ryegrass pollen	16 of 21 (76%)
Ragweed pollen	16 of 21 (76%)
Dust mite allergen	15 of 21 (71%)
Pet dander (cat and dog)	15 of 21 (71%)

NOTE. N = 23 unless otherwise specified.

Results

The demographic features and atopic characteristics of the study cohort are summarized in Table 1. The median age of the EE patients was 34 years, with ages ranging from 18 to 57 years. The male-to-female ratio was 1.6:1, with women distributed equally throughout the age range (Table 2). All 23 patients were receiving treatment for EE with topical corticosteroid delivered by swallowing the spray of a metered-dose inhaler. Eighteen of the 23 patients had an atopic diathesis, which was defined as physician-diagnosed atopic dermatitis, asthma exacerbated by allergen exposure, and/or allergic rhinitis. Allergic rhinitis was the most common clinical manifestation, and all 6 patients with asthma also had allergic rhinitis.

Of the 21 patients who underwent specific testing for environmental sensitivities, 18 were positive and 17 showed polysensitization because tests were positive to environmental allergens in at least 3 distinct categories (Table 2). In addition, 17 of 18 patients with environmental sensitization showed specific sensitivity to allergen associated with Birch tree pollen, and 11 of 18 described symptoms consistent with the pollen-food syndrome when eating uncooked fruits and vegetables. Furthermore, at least 1 positive test for food-specific IgE was present in 19 of 23 patients, with the median number of positive tests for food-specific IgE being 5 (mean, 10.3 ± 12.8 ; range, 0–55). Dividing the study cohort into 3 groups according to patient age (≤ 30 y, 31–40 y, and > 40 y), the median number of food-associated allergens patients were sensitized to within each sample did not vary significantly by age grouping ($P = .1758$) (Figure 1).

Total serum IgE was increased in 6 of the 13 patients in whom it was measured, and in 2 of the patients (Table 2, patients 19 and 21), IgE was increased markedly. Patient 21 had atopic dermatitis, which is associated with increased total IgE, but no associated cause was identified on review of patient 19. For the 13 patients that had total serum IgE measured, analysis suggested a modest positive correlation of total serum IgE with the number of positive tests for food-specific IgE ($r = 0.58$), and this relationship persisted, although was diminished, when data from patients 19 and 21 were excluded ($r = 0.37$). However, this observation is limited because the majority of patients that did not have data on total serum IgE, and thus were excluded from

Table 2. Allergic Profile of Adult Patients With EE

Patient ID	Age, y	Sex	Environmental sensitization	No. eosinophils per microliter of blood	No. positive CAP tests	Serum IgE, kU/L
1	18	Male	tr	435	7	528
2	18	Female	tr, gr, rw, m, d	N/A	16	200
3	21	Male	tr, gr, rw, m, d	284	10	224
4	25	Female	tr, gr, rw, m, d	545	2	N/A
5	27	Male	None ^a	N/A	5	N/A
6	27	Male	tr, gr, rw, m, d	348	7	N/A
7	27	Male	tr, gr, rw	107	23	576
8	30	Female	tr, gr, rw, m, d	496	16	161
9	31	Male	tr, gr, rw, m, d	N/A	15	N/A
10	31	Male	None ^a	N/A	0	N/A
11	33	Male	gr, rw, m, d	55	0	N/A
12	34	Female	tr, gr, rw, m, d	323	3	88
13	35	Male	tr, gr, m	248	1	N/A
14	36	Male	tr, gr, rw, m, d	247	24	137
15	37	Male	tr, gr, rw, m, d	N/A	0	N/A
16	38	Male	tr, gr, rw, d	312	2	N/A
17	42	Female	N/A	140	5	62
18	42	Female	None ^a	N/A	0	92
19	48	Male	tr, rw, m, d	840	23	4034
20	49	Male	tr, gr, rw, m, d	324	20	166
21	50	Male	tr, gr, rw, m, d	186	55	2409
22	54	Male	N/A	278	1	N/A
23	57	Female	tr, gr, rw, m, d	149	3	91

CAP test, in vitro specific-IgE by ImmunoCAP; d, danders; gr, grass pollen; m, mite allergen; N/A, not available; rw, ragweed pollen; tr, tree pollen.

^aConfirmed by CAP followed by skin prick testing to environmental allergens.

the analysis, had relatively fewer positive tests for food-specific IgE ($P = .02$). There was no association between total serum IgE or the number of positive tests for food-specific IgE with the density of eosinophils per high-power field on the most recent esophageal biopsy. Furthermore, the counts of peripheral blood eosinophils were within the expected range in 16 of the 17 patients in whom it was measured, with 1 patient having only a mild increase (Table 2, patient 19, 840/ μ L).

The frequency of positive CAP tests for individual food or spice allergens identified in at least 2 patients is shown in Table 3. Greater than one third of the patients in the series had serum IgE specific for wheat grain, carrot, onion, or tomato allergens. Wheat and carrot were the most common because 9 of 23 patients showed specific IgE to each of these foods. In addition, a variety of other commonly eaten plant- and animal-derived protein sensitivities were shown (Table 3).

Discussion

In this case series we describe allergic sensitivities of adult patients with EE as assessed by measurement of specific IgE to environmental and food allergens. Other case series have examined EE in adults, and, similar to ours, have reported a strong association with atopic disease.¹⁻⁴ Nonetheless, in 3 of these studies, atopy was established by patient query and not by objective testing.¹⁻³ In another recent series, specific sensitivities to food allergens were assessed by radioallergosorbent tests, but the details of what foods were tested or which were positive were not provided.⁴ In this series, 19 of 23 adult patients with EE had detectable serum IgE specific for 1 or more food-associated allergens, and 17 of 21 patients were polysensitized to several different environmental allergens.

Of the variety of foods identified in our study (Table 3), the most common were associated with plant-related allergens, such as carrot, wheat, onion, and tomato. In addition, foods identified on skin-prick testing in children with EE, such as milk, egg, soy, wheat, beef, peanut, chicken, corn, and potato, also were represented disproportionately in our series.^{7,8} To establish that a particular food is the cause of EE, its elimination in the diet should result in biopsy normalization and reintroduction of the suspect food should result in a return of esophageal eosinophils.⁷ We acknowledge that in our study the relevance of CAP testing to multiple food-associated allergens was difficult to determine because (1) there was no control population who underwent CAP testing to a similar extent, and (2) we provided no data on dietary intervention. In addition, the small sample size and the incomplete data set as a result of the retrospective nature of the study were further limiting. Nevertheless, it is interesting that several of the patients in this series showed specific IgE to what could be considered class 2 food allergens. These generally are plant-derived proteins that are heat-labile, highly homologous among some plant families, and often are cross-reactive with pollen-associated allergens, especially birch tree and ragweed pollen.¹² Thus, sensitization to class 2 food allergens is thought to occur via the respiratory tract in response to aeroallergen rather than in the gastrointestinal tract in response to food protein as in traditional or class 1 food allergies.

Evidence that aeroallergen sensitization is associated with EE was provided initially by Mishra et al.¹³ These investigators found that repeated intranasal exposure of mice with *Aspergillus fumigatus* or dust mite allergen resulted in a localized eosinophilia in the esophagus whereas oral or intragastric exposure

Table 3. Roster of Positive CAP Tests to Food Allergens

Hops	2 (9%)
Pistachio	2 (9%)
Strawberry	2 (9%)
Lemon	2 (9%)
Broccoli	2 (9%)
Pecan	2 (9%)
Walnut	2 (9%)
Tuna	2 (9%)
Cocoa	3 (13%)
Hazelnut	3 (13%)
Beef	3 (13%)
Almond	4 (17%)
Black pepper	4 (17%)
Orange	5 (22%)
Honeydew	5 (22%)
Lettuce	5 (22%)
Celery	6 (26%)
Garlic	6 (26%)
Apple	7 (30%)
Banana	7 (30%)
Sesame seed	7 (30%)
Onion	8 (35%)
Carrot	9 (39%)
Grains	
Gluten	2 (9%)
Oats	3 (13%)
Rye	3 (13%)
Barley	4 (17%)
Rice	4 (17%)
Malt	5 (22%)
Corn	6 (26%)
Wheat	9 (39%)
Legume	
Green bean	4 (17%)
Navy bean	4 (17%)
Soy bean	5 (22%)
Peanut	6 (26%)
Potato family	
Chili pepper	2 (9%)
Potato	6 (26%)
Tomato	8 (35%)
Bird	
Turkey	2 (9%)
Chicken	4 (17%)
Egg yolk	4 (17%)
Egg white	7 (30%)
Dairy	
α -lactalbumin	2 (9%)
Cheddar	3 (13%)
Casein	3 (13%)
Whey	3 (13%)
β -lactoglobulin	3 (13%)
Cheese mold	6 (29%)
Cow milk	7 (30%)

NOTE. Number of patients with a positive CAP result to a particular food allergen that was found in at least 2 patients are shown.

did not.¹³ Evidence that this mouse model may be relevant to EE disease in human beings comes from a case report by Fogg et al¹⁴ that described a patient with aeroallergen sensitivity and allergic rhinitis but no clinical food allergy. This patient developed symptomatic EE during the relevant pollen season with remission when out of the pollen season, suggesting a role for

aeroallergen in exacerbating EE. Given these findings, our goal was to survey allergic sensitization in adult EE patients, not to use CAP tests as a means to guide dietary restriction.

In this and other studies, it is interesting that most EE patients have evidence of specific IgE to food allergens, although immediate hypersensitivity reactions to foods, such as cutaneous or systemic anaphylaxis, are not a common feature of this disorder. Recent literature has proposed that T-cell-mediated delayed hypersensitivity reactions to food allergens are responsible for disease in some EE patients.^{7,8} In these studies, this hypothesis was supported by the use of atopy patch tests, which unlike SPT and CAP are not yet standardized for widespread clinical use. Furthermore, the specificity of atopy patch tests and their use in the evaluation of EE remains an issue of considerable contention.^{15,16} Considering the indurations that may occur on the skin of EE patients with positive atopy patch tests, we are unaware of published data that characterize the cellular infiltrate of these lesions (Jonathan M. Spergel, personal communication). Because eosinophilic inflammation is the cardinal feature of this disorder, one could only assume that the indurations would contain a preponderance of eosinophils. In accordance with the data from the mouse model of EE,^{13,17–20} it is likely that antigen-specific helper T cells that produce type 2 cytokines (interleukin-4, interleukin-5, interleukin-13) and eotaxin are responsible for orchestrating eosinophilic inflammation. Given this effector cytokine profile, it also is likely that responder T cells enhance the antigen-specific production of IgE, but why pathology localizes to the esophagus and immediate hypersensitivity reactions to food allergens are uncommon needs further study.

When used in conjunction with clinical history, measurement of specific IgE in sera by the ImmunoCAP system provides an objective, accurate, and quantitative method of determining allergic sensitization to specific allergens.²¹ Testing by this method is available commercially in certified laboratories and is considered the reference standard for serum measurement of specific IgE. The sensitivity and specificity of the Pharmacia CAP system (Pharmacia Diagnostics) derived from 5170 comparisons with the clinical diagnosis of respiratory allergy has been shown to be 89% and 91%, respectively.²² With respect to food allergy evaluation, CAP tests have been used to predict the likelihood of pediatric patients having an immediate hypersensitivity reaction on challenge with suspect foods, and these tests are gaining increasing acceptance for this purpose.^{23–25} In general, when comparing CAP tests with SPT, studies show SPT to be more sensitive and of better negative predictive value, whereas the quantification of specific IgE antibodies in the serum affords greater specificity.^{26–29} Because adult patients have more variety in their diet than children, we chose CAP testing as a more practical means to survey sensitization to several food antigens with minimal patient discomfort. Given that these patients did not have a clinical history of immediate hypersensitivity to foods (low pretest probability), we consider CAP testing appropriate for these purposes. It must be noted, however, that the results of this testing may not accurately predict either the clinical or histologic response in the esophagus to withdrawal of identified dietary allergens as shown in prior studies.^{30,31} This is reflected in a recent EE consensus statement suggesting the use of skin testing over radioallergosorbent test.³²

Our series provide evidence that the majority of adult patients with EE are polysensitized to environmental allergens

and suffer from atopic illness. The high degree of atopy in this series is consistent with other studies.^{1-3,8,9} Furthermore, these patients show IgE in their sera specific for multiple food allergens with profiles that suggest sensitization was in part a response to inhaled aeroallergens. This held true across all age groups and did not just favor younger adults, although these findings may be limited by the small sample size of this study. It is unknown if food-specific IgE in these patients provides a nonspecific sign of severe atopy or plays a role in EE by perpetuating organ-specific allergic inflammation on ingestion of cross-reactive food proteins. Because allergy is considered a systemic immune disorder, we recommend optimal treatment of all atopic disease in patients diagnosed with EE. Nonetheless, it remains unclear how aggressive management of environmental allergies will affect the course of EE in adults, and what the overall clinical significance of these findings will be in management of EE, providing important questions in need of further study.

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