

The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis

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Background: Eosinophilic esophagitis is a disease entity in which patients have (1) elevated eosinophils on esophageal biopsy and (2) symptoms of gastroesophageal reflux. The symptoms do not improve on aggressive acid blockade but do improve on elimination diet or corticosteroid treatment, which tentatively links food allergies to this disorder.

Objective: The purpose of this study was to identify potential food antigens in eosinophilic esophagitis.

Methods: Patients with eosinophilic esophagitis were identified by biopsy. Potential food antigens were identified prospectively by skin prick testing and patch testing, which were performed through use of standard methods. Atopic tendencies, demographics, and potential food allergies were identified. Repeat esophageal biopsies were reviewed when possible.

Results: A total of 26 patients (22 male, 4 female) with a biopsied-confirmed diagnosis of eosinophilic esophagitis underwent both skin prick testing and patch testing to identify potential causative foods. Milk and egg were the most common positive foods with skin prick testing. Wheat was the most common positive food with patch testing. The patients were advised to avoid positive foods as identified by skin prick testing and patch testing. In all, 18 patients had resolution of their symptoms, 6 patients had partial improvement, and 2 were lost to follow-up. Overall, after intervention, esophageal eosinophil counts improved from 55.8 to 8.4 eosinophils per high-power field. The foods most commonly identified by patients as causing symptoms were milk and egg.

Conclusion: The combination of skin prick testing and patch testing can identify potential causative foods that might contribute to the pathogenesis of eosinophilic esophagitis. (*J Allergy Clin Immunol* 2002;109:363-8.)

Key words: Food allergy, eosinophilic esophagitis, skin prick testing, patch testing

Eosinophilic gastroenteritis has been found in all age groups with a predominance in young to mid adulthood.¹ Eosinophilic gastroenteritis presents with a variety of symptoms, including abdominal pain, diarrhea, melena,

Abbreviations used

EE: Eosinophilic esophagitis
GERD: Gastroesophageal reflux disease
HPF: High-power field

and weight loss. Eosinophilic esophagitis (EE) is a subset of eosinophilic gastroenteritis.² Patients with EE present with symptoms similar to those of gastroesophageal reflux disease (GERD) but are unresponsive to antireflux medication and have normal or mildly positive pH probe study results. These patients can present as children or adults. The most common symptoms are vomiting and abdominal pain,³ but other common symptoms include anemia (occult blood loss), weight loss,⁴ achalasia,⁵ dysphagia, and failure to thrive.

The link between food allergies and EE has been suggested in case reports in which patients' GERD symptoms improved when they avoided particular foods.⁶⁻⁹

Recently, 4 case series have examined EE in children. Kelly et al¹⁰ examined 75 children with classic symptoms of gastroesophageal reflux whose symptoms did not improve on standard treatment. Of these 75 patients, 23 had elevated eosinophils on biopsy without symptoms of other diseases, thus meeting the criteria of EE; another 12 patients were treated with an elimination diet of Neocate or oral corticosteroids with improvement of their symptoms and biopsies. Foods were identified in open food challenges at home; symptoms were caused by milk in 7 patients, soy in 4 patients, wheat in 2 patients, peanut in 2 patients, and egg in 1 patient.

Results of studies by Liacouras et al¹¹ and Walsh et al¹² indicated that allergies might play a role in EE. The investigators identified populations meeting the criteria for EE (elevated eosinophils in the esophagus, normal pH probe results, and poor response to standard GERD therapy). Patients in a study at The Children's Hospital of Philadelphia¹¹ had elevated serum IgE, and 81% of them had histories of allergy. In 8 of 10 patients in a study at The Children's Hospital of Boston,¹² allergen skin test results were abnormal.

Orenstein et al¹³ tried to more definitively link food allergies to EE. They studied 30 patients with EE retrospectively on the basis of the diagnosis of elevated eosinophils (>5 cells per high-power field [HPF]) in biopsy specimens. This population had a strong atopic background; 62% of the patients had histories of allergy. Food allergy testing was done in 28 children by percutaneous

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skin testing and/or in vitro testing; 12 children were negative by either method, and there was a significant discordance between the 2 methods with positive reactions. Of the 16 patients with positive test results, 15 were tried on an elimination diet. Three patients were not compliant, but 12 patients had symptomatic improvement and 1 had a poor response. However, the exact foods to which patients were positive and that were eliminated are not discussed in the report.¹³ The study confirmed that food allergies could play a significant role in EE for a subset of the patients with EE.

In our study, we examined 26 patients with EE confirmed on esophagogastroduodenoscopy and biopsy. We describe our experience with food identification by either skin prick testing or patch testing and subsequent improvement in symptoms and biopsies.

METHODS

Diagnosis of EE

The diagnosis of EE was made in each of 26 patients (4 girls, 22 boys) who had at least 1 of 4 symptoms—vomiting, regurgitation, abdominal pain, and dysphagia—despite at least a 3-month therapeutic trial of proton pump inhibitors. To make the diagnosis, all patients underwent esophagogastroduodenoscopy, which included biopsies of the esophagus, stomach, and duodenum. At least 3 individual biopsy specimens were obtained from the esophagus. Two biopsies were taken in the distal esophagus (3–5 cm above the lower esophageal sphincter) and 1 biopsy was taken from the mid esophagus (10–12 cm above the lower esophageal sphincter). The biopsy specimens were evaluated under a 40× high-powered microscopic field. EE was presumed if an isolated esophageal eosinophilia was identified and >20 eosinophils were present in the most densely involved 40× HPF.

Patients had no eosinophils in the stomach or duodenum biopsy specimens and predominantly eosinophils in the distal esophagus. In addition, a repeat endoscopy was performed after 1 month of dietary change either with total food elimination (Neocate 1+, SHS North America, Gaithersburg, Md) or elimination of specific foods or with corticosteroids (methylprednisolone 1.5 mg/kg/day to a maximum of 90 mg). EE was diagnosed if the esophageal eosinophilia resolved. A board-certified pathologist reviewed all biopsy specimens.

Study design and dietary challenges

After the diagnosis of EE was made, a careful dietary history was obtained so that foods for skin and patch testing could be selected. Patch testing and skin prick testing were then performed. Patients were instructed to avoid all positive foods for a minimum of 6 weeks. Seven patients were placed on elemental diets of Neocate 1+ because multiple positive foods had been identified on testing. New foods were introduced at home every 5 to 7 days, and positive foods identified last on skin prick and patch testing were reintroduced last into the diet. Other atopic disorders were treated at the time of diagnosis and treated simultaneously with the start of the elimination diet. Families were contacted by telephone or in outpatient clinics and current dietary histories were reviewed. Biopsy results after food avoidance were reviewed if available.

Control patients were 5 adults (aged 25 to 40 years) and 3 children (aged 3 to 7 years) who had no history of gastrointestinal disorders or food allergy. The protocol was approved by the Institutional Review Board of The Children's Hospital of Philadelphia.

Skin prick tests

Skin prick testing with commercial extracts (Greer Laboratories, Inc, Lenoir, NC) was performed on the forearm with a bifurcated

needle (Allergy Labs of Ohio, Inc, Columbus, Ohio); in each instance, we pricked through a drop of the extract, which was then absorbed. Positive histamine and negative diluent controls were used. Reactions were recorded on the basis of the largest diameter (in millimeters) of the wheal and flare at 15 minutes. A wheal of 3 mm greater than the negative control was considered positive.

Patch tests

On the test day, 2 g of dry food (soy infant formula and skim milk powder; dried egg white; wheat, oats, barley, rye, and rice flour; corn meal; dehydrated potatoes) was mixed with 2 mL isotonic saline solution. The mixtures were placed in aluminum cups (Finn Chambers on Scanpore, Allerderm Laboratories, Inc, Petaluma, Calif) and adhered to the patient's back according to methods previously described.^{14–18} Commercially prepared, single-ingredient baby food fruits, vegetables, and meats were placed in the Finn Chambers undiluted. The patch was removed at 48 hours, and the results were read at 72 hours. Reactions were classified as follows: +, erythema and slight infiltration; ++, erythema and papules; +++, erythema and vesicles.

RESULTS

Demographics

A total of 26 patients with confirmed EE were referred by the Gastrointestinal and Nutrition Department of The Children's Hospital of Philadelphia. The mean age was 6.93 ± 3.48 years (range, 2.38 to 14.3 years; Table I). Of the 16 patients who underwent skin prick testing for environmental allergies, 14 were positive, dust mite and animal dander being the most commonly responsible allergens. Twenty-one of 26 patients had an atopic background, which was defined as physician-diagnosed atopic dermatitis, allergic rhinitis, or asthma. Asthma and allergic rhinitis were the most common diagnosis, and 11 patients had more than one atopic diathesis.

Skin prick testing and patch testing

Careful history-taking with regard to tentative causative foods was done, and all 26 patients underwent skin prick testing and patch testing. Nineteen patients had positive skin prick test results and 7 patients had negative skin prick test results. The foods most commonly identified were milk, egg, peanut, shellfish, peas, beef, fish, rye, tomato, and wheat (Table II). Patients were positive to an average of 2.7 ± 3.3 foods (range, 0–13 foods). Twenty-one patients had positive patch test results; 5 patients had negative patch test results, including 1 patient who was also negative on skin prick testing. The foods most commonly identified on patch testing were wheat, corn, beef, milk, soy, rye, egg, chicken, oats, and potato. Patients were positive to an average of 2.7 ± 1.8 foods (range, 0–7 foods).

A total of 68 foods were identified by skin prick testing in 19 patients, and a total of 67 foods were identified by patch testing in 21 patients. In all, 338 foods were tested by skin prick testing and 299 foods by patch testing, the per-patient average being 13 foods in skin prick testing and 11.5 foods in patch testing. Fourteen patients were positive in both patch testing and skin prick testing (egg, 4 patients; milk and corn, 3 patients each; wheat, 2 patients; beef and oats, 1 patient each).

All 8 control patients were negative on patch testing. Interestingly, 7 patients with food protein–induced enterocolitis had patch and prick testing done; in all 7 of these patients, skin prick test results were negative (similar to previous published reports¹⁹), and in 5 of them, patch test results were negative.

Clinical follow-up

Patients were instructed to eliminate positive foods and have routine follow-up with a gastroenterologist to review their reflux symptoms. In addition, patients' asthma, allergic rhinitis, and atopic dermatitis were treated. Patients were contacted by telephone or in routine clinic appointments 4 to 12 months after evaluation by skin prick testing and patch testing. Two patients were lost to follow-up. Six patients reported partial improvements of their symptoms, but 5 of these patients were not avoiding the foods identified by testing. Eighteen patients reported that they were asymptomatic. Biopsies were done in 24 patients; biopsy findings were normal in 13 patients, and 11 patients had significant improvement, the mean overall improvement being 55.8 ± 24.6 eosinophils/HPF to 8.4 ± 8.4 eosinophils/HPF (Table III).

Causative foods

Interviews by telephone or at clinical appointments with families 4 to 12 months after food testing also identified potential causative foods. Causative foods were assumed to be positive if avoidance led to resolution of the symptoms and/or reintroduction led to reemergence of the symptoms. Foods were introduced (1 food every 5 to 7 days) after symptoms resolved with either a complete elimination diet of Neocate1+ or elimination of all positive foods. Milk, egg, wheat, rye, and beef were the causative foods most commonly noted by the families (Table II). An average of 3.61 ± 2.06 causative foods were identified in each patient (range, 1-8 foods).

DISCUSSION

In this study, we have described for the first time the use of skin prick testing and patch testing to determine potential food antigens as the cause of EE. We studied 26 patients with EE in whom the diagnosis had been confirmed on biopsy and there was a lack of clinical response to aggressive acid suppressive therapy. We found that the elimination of positive foods identified by both skin prick testing and patch testing led to complete resolution of the clinical symptoms in 18 of 24 patients. In addition, there was a concurrent improvement in esophageal biopsy specimens that matched the clinical improvement in these patients. Reintroduction of the foods caused a re-emergence of symptoms in select cases.

Of the remaining 6 patients, all noted improvement but not complete resolution of their symptoms. Five of these 6 patients were not following the recommended dietary advice.

We recognize that definitive evidence that a food is causing EE depends on biopsy normalization with an elimination diet and return of esophageal eosinophils on

TABLE I. Demographic data (N = 26)

Age (y): mean (range)	6.93 $\pm$ 3.48 (2.38-14.357)
Sex: male/female	22/4
Atopy (no. of patients)	
Asthma	16
Allergic rhinitis	13
Atopic dermatitis	6
Any atopic diathesis	21
Environmental allergies (no. of patients)	14 of 16

TABLE II. Skin prick and patch testing

Food	No. of patients*		
	Skin prick tests	Patch tests	Implicated food†
Milk	9 (36%)	6 (24%)	13
Egg	9 (36%)	6 (24%)	12
Soy	2 (8%)	6 (24%)	5
Wheat	3 (12%)	9 (36%)	5
Beef	3 (12%)	6 (24%)	5
Rye	3 (12%)	7 (28%)	5
Peanut	4 (16%)	0 (0%)	3
Chicken	2 (8%)	5 (21%)	3
Corn	2 (8%)	6 (24%)	3
Peas	4 (16%)	2 (8%)	2
Potato	3 (12%)	4 (16%)	2
Rice	2 (8%)	2 (8%)	2

*Numbers of patients found to have positive skin prick test and patch test results to specific foods.

†Foods implicated on dietary challenges.

reintroduction of foods. In 1 patient who reintroduced foods, the esophageal biopsy finding reverted from normal to moderate esophageal eosinophilia, indicating the definitive role of foods in this case. Additional evidence is not available, inasmuch as multiple repeat biopsies in pediatric patients are not feasible. We therefore used challenge information to identify foods. Double-blinded, placebo-controlled food challenges would not be useful in this population, because symptoms can occur up to 5 days after reintroduction of a food. Therefore, our patients were instructed to add 1 new food every 5 to 7 days to identify causative foods. We found this method very helpful in identifying potential causative foods in these patients. However, if a patient does not respond to the elimination diet with normalization of symptoms and biopsy findings, an alternative diagnosis should be considered.

The foods most commonly identified in our study were milk and egg (Table III). The roster of foods that were found to be causative was similar to the roster of foods most commonly responsible for atopic dermatitis and other IgE-mediated food allergies in children (milk, egg, soy, peanut, wheat).²⁰ This suggests that either some inherent property of these foods causes them to be more allergenic or the foods are more staple in the diet than other foods.

Previous studies have established the link between EE and atopy over the last 8 years. It was these initial associations that suggested that food allergies might play a role in the pathogenesis of the disease.^{8,10,11,13} The role of food sensitivity was confirmed as patients improved

TABLE III. Prebiopsy, postbiopsy, and challenge data

Patient no.	Pre-Tx Bx*	Initial Sx	Food	Skin test†	Patch test†	Post-Tx Bx*	Sx on challenge
IgE-mediated							
1	80	Regurgitation	Milk (w8), egg (w4)	2 pos; 10 neg	0 pos; 14 neg	7	Resolution; foods not reintroduced
2	20	Dysphagia	Milk (w7), egg (w7), soy (w5), peas (w5), kidney bean (w5), almond (w5), brazil nut (w4), crab (w4)	8 pos; 20 neg	0 pos; 6 neg	1	Resolution; foods not reintroduced
3	45	Vomiting	Soy (w3), peanut (w3), rye (w3)	3 pos; 10 neg	0 pos; 15 neg	0	neg Sx with 2 foods (soy, peanut); pos Sx with 1 food (milk)
4	100	Dysphagia GERD	Milk (w7), egg (w9), soy (w5), peanut (w4), corn (w4), potato (w5), beef (w7), pork (w8), string bean (w3), cucumber (w3), grape (w4), broccoli (w4), garlic (w3)	13 pos, 26 neg	0 pos; 6 neg	1	Diarrhea with 7 foods (milk, eggs, string beans, pork, beef, broccoli, garlic); neg Sx with 6 foods (soy, peanut, cucumber, grape, corn, potato)
Non-IgE-mediated							
5	40	Vomiting	Barley (p3), wheat (p3), rye (p2)	0 pos; 16 neg	3 pos; 9 neg	0	Vomiting with pos foods
6	25	Regurgitation	Soy (p3), wheat (p3), rye (p1)	0 pos; 10 neg	3 pos; 7 neg	7	Resolution; foods not reintroduced
7	75	Vomiting	Rye (p3), corn (p3)	0 pos; 20 neg	2 pos; 12 neg	30‡	Vomiting with pos foods
8	75	GERD	Pork (p2), lamb (p1), potato (p1)	0 pos; 26 neg	3 pos; 18 neg	15	neg Sx with all foods
9	50	Vomiting	Wheat (p1), oats (p1), turkey (p1), beef (p2)	0 pos; 12 neg	4 pos; 5 neg	10	neg Sx with 4 foods (wheat, oats, turkey, beef); pos Sx with 1 food (milk)
10	50	Vomiting	Oat (p3), chicken (p2), beef (p2)	0 pos; 24 neg	3 pos; 18 neg	10	Resolution; foods not reintroduced
Mixed reaction							
11	50	Regurgitation	Peanut (w3), rye (p3)	1 pos; 11 neg	1 pos; 19 neg	25	Lost to follow-up
12	100	GERD	Apple (w3), peas (w6), peanut (w7), rye (p1), oats (p1), corn (p1), turkey (p2)	3 pos; 10 neg	4 pos; 5 neg	20§	Resolution; foods not reintroduced
13	45	Dysphagia	Milk (w4, p1), egg (w3, p1), corn (p3), wheat (p2)	2 pos, 10 neg	4 pos, 8 neg	0	Resolution; foods not reintroduced
14	100	GERD	Rice (w3), barley (p1), beef (p1), peas (p2)	1 pos; 25 neg	3 pos; 16 neg	15	neg Sx with 2 foods (barley, rice); pos Sx with 2 foods (beef, peas)
15	75	GERD	Milk (w5), egg (w10, p3), beef (w3), soy (p1), wheat (p2)	3 pos; 16 neg	3 pos; 10 neg	15	Patient not avoiding all foods
16	25	Vomiting	Potato (w3), milk (p2), rice (p2), soy (p1), wheat (p2), beef (p1), lamb (p1), pork (p3)	1 pos; 23 neg	7 pos; 16 neg	10	Vomiting with pos foods
17	45	Regurgitation	Crab (w7), lobster (w4), clam (w4), oregano (w3), mustard (w3), shrimp (w9), oats (p2), chicken (p2)	7 pos; 11 neg	2 pos; 11 neg	1	Resolution; foods not reintroduced
18	50	GERD	Milk (w4), egg (w5, p3), chicken (w6), peas (w5), peanut (w6), beef (p1), wheat (w3 p1)	6 pos; 5 neg	3 pos; 9 neg	10	neg Sx with 5 foods (milk, peas, peanut, beef, wheat); pos Sx with 2 foods (egg, chicken)

(continued)

TABLE III. continued

Patient no.	Pre-Tx Bx*	Initial Sx	Food	Skin test†	Patch test‡	Post-Tx Bx*	Sx on challenge
19	70	GERD	Milk (w4, p2), egg (w5), peanut (w3), tomato (w5), barley (w3), chicken (p3), potato (p2)	5 pos; 23 neg	3 pos; 10 neg	0	neg Sx with 3 foods (tomato, barley, potato); pos Sx with 4 foods (peanut, milk, egg, chicken)
20	25	GERD	Milk (w4), egg (p1), wheat (p2), carrots (p2), bananas (p1), peas (p2)	1 pos; 19 neg	5 pos; 15 neg	0	pos Sx and increased no. of eosinophils/ HPF on reintroduc- tion
21	45	GERD	wheat (w3, p1), beef (w6, p2), egg (w5), chicken (w4), peas (w4), string bean (w4), cabbage (w3), tomato (w4)	8 pos; 8 neg	2 pos; 16 neg	5	pos Sx with pos foods
22	40	GERD	Egg (w10, p3), chicken (p2), milk (p1), soy (p2), wheat (p1)	1 pos; 16 neg	6 pos; 14 neg	0	pos Sx with pos foods
23	75	GERD	Milk (w3, p1), egg (w3, p1), wheat (p2), corn (p3)	2 pos; 9 neg	4 pos; 12 neg	ND	Resolution; foods not reintroduced
24	80	Vomiting	Soy (w5), rye (p3), corn (p2), turkey (p1)	1 pos; 14 neg	3 pos; 10 neg	ND	Lost to follow-up
25	30	Vomiting	Egg (p1, w6), corn (p2), rye (p3)	1 pos; 7 neg	3 pos; 7 neg	10	Resolution; foods not reintroduced
Mechanism-unknown 26	50	GERD	None	0 pos; 11 neg	0 pos; 15 neg	0	Resolution; milk not reintroduced

Tx, Treatment; Bx, biopsy; Sx, symptom; pos, positive; neg, negative; w, size of positive wheal; GERD, gastroesophageal reflux disease symptoms of abdominal pain and regurgitation; p, patch test score (1 to 3); ND, not done.

*Number of eosinophils per HPF.

†Number of foods positive on testing; number of foods negative on testing.

‡Not completely avoiding positive foods.

§Biopsy done before complete elimination of foods.

on elemental diets. However, individual causative foods and immunologic mechanisms have not been described by other authors, the exception being Kelly et al, who noted that milk allergy and soy allergy were common.

Because 7 of our 26 patients were shown to be negative on skin prick testing or in vitro IgE testing, we decided to further examine food sensitivity in this population by patch testing to detect non-IgE-mediated reactions. The decision to use patch testing was based on positive results for patch testing in patients with atopic dermatitis in previous investigations.¹⁴⁻¹⁸ In those studies, patients with atopic dermatitis and negative skin prick test results were patch-tested to milk and to wheat and other grains. Positive patch tests results correlated with food sensitivity, and this was confirmed on oral challenges. In addition, Isolauri and Turjanmaa¹⁶ found that more than 80% of patients with delayed reactions of vomiting and diarrhea after a food challenge had positive patch test results to a food antigen, whereas 25% had positive percutaneous tests, suggesting that patch testing might detect gastrointestinal food allergies. We were able to detect non-IgE-positive foods by patch testing in 23 of 26 patients, confirming a possible role for a non-IgE mechanism in this disorder.

Previous studies have shown that biopsy specimens of positive patch test sites in patients with atopic dermatitis show CD4⁺ T cell infiltration and express a predomi-

nance of T_H1 cytokines and eosinophils.^{21,22} The finding that patients with EE have both positive patch test results and positive skin prick test results indicates that both IgE-mediated and T_H1-mediated reactions might be involved, as is the case in patients with atopic dermatitis. Additional evidence for the duality of the pathogenesis in EE is the time course of symptoms. In accord with previous findings, we determined that elimination of the food did not lead to resolution of the symptoms within 1 day¹⁰; symptoms took approximately 2 weeks to 1 month to resolve after removal of the causative antigen. Moreover, symptoms did not occur immediately after reintroduction of the foods. The time frame varied from minutes to days, indicating both the role of IgE and a delayed mechanism in the pathogenesis of the disease. This time course is also consistent with a finding of positive results in both IgE-mediated testing (skin prick testing) and T cell-mediated testing (patch testing; Table III). Interestingly, 80% of the foods used in the study were positive on either patch testing or skin prick testing; only 14 of 139 positive foods were positive on both. If the pathogenesis of EE involves IgE and/or a T cell-mediated mechanism, the observed poor correlation with skin prick test results and symptoms would be expected.

One difficulty in this study is the lack of standardization in patch testing as opposed to skin prick testing.

Nevertheless, we were able to get consistent results with the food concentration used by Turjanmaa et al.¹⁷ However, we were not able to identify the foods in all of our patients; one patient was negative on prick and patch testing but clinically positive to milk on history. In addition, one patient was positive to milk on history but negative on testing. This would suggest that either the testing material is nonideal or alternative testing is needed.

In our study, 81% of patients (21/26) had an atopic background; this is similar to the high incidence of atopy (77%) that has previously been reported.⁸ The high incidence of atopy in this population was not due to a selection bias, inasmuch as patients were initially referred by gastroenterologists. Given that most of these patients have an atopic background, it is possible that systemic atopic sensitization might play a role in the overall pathogenesis of the disease. Recent evidence from a murine model suggests that exposure to aeroallergens can lead to EE.²³ In this model, intranasal exposure of *Aspergillus fumigatus* or ovalbumin led to significant eosinophilia in the esophagus and in bronchoalveolar lavage fluid. Sensitization via the oral or intragastric route led to significant fewer eosinophils per HPF in the esophagus. This result suggests that the patients' asthma and allergic rhinitis might play a role in the pathogenesis of EE. Sixteen patients (62%) in our study had asthma and 13 (50%) had allergic rhinitis, which is consistent with this hypothesis.

In this investigation, we cannot separate the role of environmental allergies from that of food allergies in EE, inasmuch as asthma and allergic rhinitis were also treated by medication and environmental controls when indicated. The inhalation of aeroallergens might sensitize the esophagus, similarly to what is seen in oral allergy syndrome, in which fresh fruits and vegetables cross-react with pollens. However, if respiratory allergens were directly causative antigens in human beings, one would not expect the improvement on elimination diets that has been consistently reported in previous studies.^{10,11} Nevertheless, it is possible that patients with EE might benefit from simultaneous treatment of their food allergy, asthma, and allergic rhinitis.

Our recommendation for the identification of causative foods in patients involves both skin prick testing and patch testing to relevant foods. If elimination of the positive foods leads to resolution of symptoms, then positive foods should be added back at a rate of 1 new food every 5 to 7 days. If elimination of the positive foods does not lead to resolution of symptoms in 4 weeks, complete elimination of foods through use of Neocate 1+ for 4 weeks, followed by the addition of individual foods every 5 to 7 days, is called for.

In sum, we have identified potential food antigens in EE by a combination of skin prick testing and patch testing. Elimination of the causative foods led to symptom resolution in 18 of 26 cases, and challenge in selected cases led to a recurrence of symptoms. Most of the patients had atopy, which suggests that an overall atopic background might play a role in the pathogenesis of this disease.

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REFERENCES

- Kelly K. Eosinophilic gastroenteritis. *J. Pediatr Gastroenterol Nutr* 2000;30:S28-S35.
- Moon A, Kleinman R. Allergic gastroenteropathy in children. *Ann Allergy Asthma Immunol* 1995;74:5-9.
- Brown K. Eosinophilic enteritis. In: Altschuler S, Liacouras C, editors. *Clinical pediatric gastroenterology*. Philadelphia: Churchill Livingstone; 1998.
- Katz A, Twarog F, Zeiger R, Falchuk Z. Milk-sensitive and eosinophilic gastroenteropathy: similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol* 1984;74:72-8.
- Landres R, Kuster G, Strum W. Eosinophilic esophagitis in a patient with vigorous achalasia. *Gastroenterology* 1978;74:1298-301.
- Dobbins J, Sheahan D, Behar J. Eosinophilic gastroenteritis with esophageal involvement. *Gastroenterology* 1977;72:1312-6.
- Matzinger M, Daneman A. Esophageal involvement in eosinophilic gastroenteritis. *Pediatr Radiol* 1983;13:35-8.
- Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993;38:109-16.
- Vitellas K, Bennett W, Bova JG, Johnson JC, Greenston JK, Caldwell JH. Radiographic manifestations of eosinophilic gastroenteritis. *Abdom Imaging* 1995;20:406-13.
- Kelly K, Lazenby A, Rowe P, Yardley JH, Perman J, Sampson H. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;109:1503-12.
- Liacouras CA, Wenner WJ, Brown K, Ruchelli E. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;26:380-5.
- Walsh SV, Antonioli DA, Goldman H, Fox VL, Bousvaros A, Leichtner AM, et al. Allergic esophagitis in children: a clinicopathological entity. *Am J Surg Pathol* 1999;23:390-6.
- Orenstein SR, Shalaby TM, Di Lorenzo C, Putnam PE, Sigurdsson L, Kocoshis SA. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol* 2000;95:1422-30.
- Majamaa H, Moisiu P, Holm K, Kautiaianen H, Turjanmaa K. Cow's milk allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 1999;54:346-51.
- Majamaa H, Miettinen A, Laine S, Isolauri E. Intestinal inflammation in children with atopic eczema: faecal eosinophil cationic protein and tumour necrosis factor- α as non-invasive indicators of food allergy. *Clin Exp Allergy* 1996;26:181-7.
- Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996;97:9-15.
- Kekki O, Turjanmaa K, Isolauri E. Differences in skin-prick and patch-test reactivity are related to the heterogeneity of atopic eczema in infants. *Allergy* 1997;52:755-9.
- Majamaa H, Moisiu P, Holm K, Turjanmaa K. Wheat allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 1999;54:851-6.
- Sicherer S, Eigenmann P, Sampson H. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr* 1998;133:214-9.
- Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985;107:669-75.
- Grewe M, Walther S, Gyufko K, Czech W, Schopf E, Krutmann J. Analysis of the cytokine pattern expressed in situ in inhalant allergen patch test reactions of atopic dermatitis patients. *J Invest Dermatol* 1995;105:407-10.
- Bruijnzel-Koomen C, van Wichen D, Spry C, Venge P, Bruijnzel P. Active participation of eosinophils in patch test reactions to inhalant allergens in patients with atopic dermatitis. *Br J Dermatol* 1988;118:229-38.
- 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.