

Defining the Role of Food Allergy in a Population of Adult Patients with Eosinophilic Esophagitis

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Abstract: The aim of this study was to establish the clinical types of food reactions and the food sensitization profile in an adult cohort of patients with Eosinophilic esophagitis (EoE). We have prospectively analyzed the food allergen sensitization profile using skin prick test (SPT) and atopy patch test (APT) to 22 plant and animal-derived foods in 19 adult patients with biopsy-proven EoE. For each patient the following data was collected: age, sex, atopic disease status, and clinical characteristics of the EoE. A total of 123 food sensitizations were detected by SPT and 45 food sensitizations by patch testing in 18 patients (94.8%). Thirty-five double-positive (SPT+, APT+) responses against the same food were detected in 15 patients (78.9%). We have also identified 11 clinical episodes clearly suggestive of oral allergy syndrome, urticaria and/or anaphylaxis after intake of some specific foods. All cases showed positive SPT to the offending food (Type 1 food reactors). 68 clinically apparent episodes of EoE related with specific foods were detected in our patients. In 40 instances (58.8%) the foods involved in developing EoE symptoms showed a positive SPT and/or APT results (Type 2). 155 food sensitizations were identified in 18 patients (94.7%) using SPT and/or APT neither related with clinically apparent episodes of EoE nor with clinical episodes suggestive of oral allergy syndrome, urticaria and/or anaphylaxis after food intake (Type 3). In conclusion, the patients with EoE can be allocated into 3 different groups of food reactors, with well-defined clinical and biological characteristics.

Keywords: Eosinophilic esophagitis, food allergy.

INTRODUCTION

Eosinophilic esophagitis (EoE) is an emerging inflammatory disease of an unknown etiology which has been affecting an increasing number of children and adults over the last decade [1]. EoE is defined as a clinicopathological disorder characterized by esophageal and/or upper gastrointestinal tract symptoms associated with biopsy-proven eosinophilic infiltration with absence of gastroesophageal reflux disease (GERD) as evidenced by a normal pH monitoring study of distal esophagus or lack of response to proton pump inhibitors drugs [1-3].

The mechanisms for developing EoE are poorly understood. Some lines of evidence have supported a possible role of TH₂-type allergic inflammation in the pathogenesis of EoE [4,5]. Most patients with EoE have shown a wide range of allergic diseases such as atopic dermatitis, and allergic respiratory disease (i.e. rhinitis and/or bronchial asthma associated with allergen sensitization) with highest frequencies that reach 80 percent in pediatric cohorts; and lowest in adulthood with a range from 40% to 70% [2,6].

Food allergy often coexists with EoE and it could be considered as contributory in at least 3/4 parts of the children with EoE [7, 8]; however, little is known about the role of food allergen sensitization in adulthood [9]. In this sense, several case series have determined the yield of a complete allergy evaluation of adult patients with EoE. Roy-Gantha S. *et al.* have disclosed similar figures of prevalence of food

sensitization than those observed in pediatric cohorts, when serum measurement of specific IgE antibodies to common food was used. Patients had serum specific IgE for one or more food allergens, mainly plant-derived food (median, 5 foods). Wheat, tomato, carrot, and onion were the foods more commonly identified [10]. Moreover, when skin prick testing (SPT) was carried out, half of adult patients with EoE demonstrated a positive SPT to at least one food allergen [11]. Peanut, egg white, soybean, cow milk, and tree nuts were the most common food allergens identified. Both studies confirmed the high degree of atopy in adults with EoE, similar to that seen in the pediatric population. EoE patients tend to be polysensitized to several environmental allergens, and the profiles of specific IgE for food allergens suggest that food sensitization may be partly a response to environmental allergens [10].

Moreover, atopy patch test (APT) with foods has been used for the diagnosis of food allergies in several studies published by Spergel. *et al.* in pediatric cohorts [7, 8, 12]. The APT has been used for the diagnosis of non-IgE, cell-mediated immune responses in which T cells are thought to play a prominent role [13]. Using a combination of APT and SPT identified certain foods which were, apparently, a potential stimuli of acute episodes of intermittent dysphagia, impaction or GERD-like symptoms and/or could have a contributory role in the pathogenesis of EoE as confirmed by means of elimination or reintroduction of specific single foods [12, 14]. However, the role of APT for detecting food allergy in the subset of EoE adult patients cohorts as well as its diagnostic predictive values, its specificity or its sensitivity is largely unknown.

The purpose of this study was to identify the foods involved in clinically apparent, acute episodes of EoE and the sensitization profile in an adult cohort of patients with

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EoE using both SPT and APT. Beyond this initial allergy evaluation, we have tried to identify different types of food allergy syndromes that might occur in these EoE patients. Recognizing and defining clinical food allergy phenotypes might be crucial in order to establish its importance in the diagnosis and management of EoE [1].

PATIENTS AND METHODS

Patients

Nineteen consecutive adult patients who have been previously diagnosed of EoE were referred to the Allergy Unit for study. The disease definition of EoE fulfilled all the following criteria: i) clinical: dysphagia, food impaction and other non swallowing-associated symptoms such as retrosternal pain, regurgitation and pyrosis; ii) histologic, with 15 eosinophils in at least one high-power field; iii) exclusion of GERD, lack of response to high-dose proton pump inhibitors or normal pH monitoring; and iv) exclusion of other conditions that cause esophageal eosinophilia [1,3]. A complete medical questionnaire was recorded for each patient where the following data was collected: age, sex, atopic disease status, and clinical characteristics of the EoE (i.e., EoE symptoms, clinically apparent acute episodes of EoE and their relationship with the ingestion of specific foods, and type and number of foods involved). Plant or animal-derived food allergy was diagnosed on the basis of a clear history of allergic reactions (oral syndrome, urticaria or systemic anaphylaxis), and a positive SPT with the offending food. Written informed consent from the patients (or their parents if younger than 18 years) was obtained for participation in the study. The protocol was approved by the Investigation and Ethic Committee of the Hospital.

Atopy Patch Testing with Foods

Patch testing using 22 different plant or animal-derived foods was performed in accordance with the modified protocols established by Niggemann *et al.* [15] and Spergel *et al.* [7]. Briefly, a mixture of each food was diluted with saline solution at a concentration of 1 gm of food per ml. Every single food mixture was placed into 12 mm aluminum cups (Finn Chambers on Marti Tor, Barcelona, Spain) and adhered to the patient's back. Patch cups were removed after 48 hours and the results were read at 48, 72 and 96 hours. Clinical assessment of the intensity of the reaction was carried out according to the methods previously described. Reactions were classified as follows: – negative, doubtful reaction (faint erythema), + weak positive (erythema, slight infiltration), ++ strong positive reaction (erythema, infiltration, papules), +++ extreme positive reaction (intense erythema, infiltration, vesicles) [7].

Skin Prick Testing

SPT with the mixture of each food used in APT (as described above) were performed according to the recommendations of the EAACI [16].

The patients were also tested with a panel of common aeroallergens, including *Dermatophagoides pteronyssinus*, *Glycyphagus domesticus*, *Tyrophagus putrescentiae*, *Blattella*

germanica, dog and cat dander, *Alternaria alternata*, *Olea*, *Phleum pratense*, *Cupressus sempervirens*, *Platanus acerifolia*, *Artemisia vulgaris*, and *Salsola kali* (Bial SA, Bilbao, Spain). Patients were regarded as being sensitized to a specific food or environmental allergen if the wheal had a surface area of at least 9 mm².

RESULTS

Demographics, Clinical Data and Skin Testing Results

Nineteen patients with biopsy-proven EoE were referred on an ad hoc basis by the Department of Gastrointestinal Diseases of our Hospital and not based on a prior identification of an allergic diathesis. The demographic and atopic data are summarized in Table 1.

All EoE patients underwent skin prick and patch testing with 22 animal and plant-derived foods. The skin test results as well as their relationship with the clinical episodes after food intake is summarized in Table 2.

A total of 123 food sensitizations were detected by SPT in 18 patients (94.8%). Patients were positive to an average of 8.3 skin prick tests (ranged from 0 to 17 positives SPT). The foods more commonly identified by SPT were (in order of frequency): potato, wheat, walnut, rice, banana, pepper, melon, milk and egg.

Eighteen patients (94.8%) had a positive patch test result. A total of 45 food sensitizations were detected by patch testing. Patients were positive to an average of 4.4 atopy patch tests (ranging from 0 to 8 positive APT). Foods more commonly identified by APT were (in order of frequency): clam, chicken, peanut, shrimp and kiwi.

Table 1. Demographics and Environmental Allergen Reactivity of Patients with Eosinophilic Esophagitis

	EoE Patients
Age in years (range)	35.7(14-71)
Sex (male/female)	15/4
Environmental allergen reactivity (patients/percent)	17 (89.4%)
<i>Dermatophagoides pteronyssinus</i>	10 (52.6)
<i>Glycyphagus domesticus</i>	4 (21.1)
<i>Tyrophagus putrescentiae</i>	2 (11.1)
<i>Canis familiaris</i>	6 (31.6)
<i>Felis domesticus</i>	3 (15.8)
<i>Olea europaea</i>	15 (78.9)
<i>Phleum pratense</i>	14 (73.7)
<i>Platanus acerifolia</i>	7 (36.8)
<i>Artemisia vulgaris</i>	9 (36.8)
<i>Salsola kali</i>	8 (42.1)

EoE, eosinophilic esophagitis.

Thirty-five double-positive (SPT+, APT+) responses against the same food was detected in 15 patients (78.9%). Seafood (shrimp, clam, and squid) and cereals (wheat and

rice) were the most frequent animal and plant-derived food groups in which we detected this combined skin response.

Clinically Apparent Episodes After Food Intake in Patients with EoE and their Relationship with Food Skin Testing

A careful history seeking clinically apparent episodes of symptoms after food intake and potentially causative foods was obtained.

We have firstly identified 11 clinical episodes clearly suggestive of oral allergy syndrome, urticaria and/or anaphylaxis after intake of some specific foods. Eight of them had also presented clinically apparent episodes of EoE (Table 3). Six patients presented oral allergy syndrome mainly induced by seafood and nuts, one had oral allergy syndrome and urticaria by fruits and finally, one presented an anaphylaxis by soybean. All cases showed positive SPT to the offending food.

We have also identified 68 clinically apparent episodes of EoE related with specific foods in our patients (Table 3).

The most common symptoms referred by the patients were simultaneous acute dysphagia and impaction in 28 episodes (41.1%), GERD-like symptoms in 16 (23.5%), isolated impaction in 12 (17.6%), intermittent dysphagia in 11 (16.1%) and finally, dysphagia and GERD-like symptoms in one patient.

The foods involved in EoE episodes and the results of skin tests are detailed in Tables 2 and 3. In 40 instances (58.8%) the foods involved in developing EoE symptoms showed a positive SPT and/or APT results. No skin test responses were found in the remaining 28 episodes (41.2%), in spite of a positive clinical history of EoE symptoms followed by the ingestion of the offending foods.

SPT was positive in 25 instances to foods involved with apparent EoE symptoms in 10 patients (52.3%). Patients were positive to an average of 2.1 skin prick tests (ranged from 0 to 3 positives SPT). The foods more commonly identified by SPT were (in order of frequency): walnut, potato, banana and wheat (in 3 cases for each one) followed by pepper, rice and egg (in 2 cases).

Table 2. Skin Test Results of Patients with Eosinophilic Esophagitis

Food	Food Involved in Clinical Episodes			Food not Involved in Clinical Episodes of EoE			Total
	SPT + APT -	SPT - APT +	SPT + APT +	SPT + APT -	SPT - APT +	SPT + APT +	
Milk				8			8
Egg	2			6	1	1	10
Shrimp	2	1	3	2	2	2	12
Squid	1			1	8	2	12
Clam	1	1		4	4	1	11
Codfish					1	1	2
Chicken		1	1	2	3		7
Walnut	5	1	1	4		1	12
Peanut	1	2		4	2		9
Pepper	2		1	6	2	1	12
Tomato				3		1	4
Potato	3			7		2	12
Onion	1	1		6	1	1	10
Soy			1	5	1	2	9
Lentil				3	2	2	7
Carrot	1						1
Peach	2			5	1	1	9
Kiwi				4	3		7
Melon	1		1	6	2	1	11
Banana	4	1		4		2	11
Wheat	3			7	2	2	14
Rice	2		1	5	2	3	13
	31	8	9	92	37	26	203

SPT, Skin Prick Test; APT, Atopic Patch Test.

Table 3. Food Sensitizations and Clinical Episodes of Eosinophilic Esophagitis

Case	Food Involved in Episodes of EoE		Food Not Involved in Episodes of EoE	Food Allergy (Oral Syndrome, Urticaria and/or Anaphylaxis)
	Positive SPT and/or APT Results	Negative Skin Test Results	Positive SPT and/or APT Results	Prick Test Only
1	D (squ), I (pot) G (ban, mel)	D, I (chi)	mil, egg, cla, tom, whe, ric, soy, len	OAS/ wal, squ mel
2	D, I, (shr, wal)	D (pch, pea)	squ, cla, chi, pep, len	
3	G (pea, oni)	G (mel) I (chi)	shr, cla, squ, wal, pot, whe, pep, kiw, egg	
4	D, I (shr, mel, ban) ; I (wal)		mil, egg, squ, pea, pep, tom, pot, pch, kiw, ric, whe, soy, len, oni	
5	D (pot, whe)	D, I (chi)	pea, oni, pch, mel, ric, len	Anaphylaxis/soy
6	D, I (shr, cla) I (chi); G (pep)	D, I (tom, ric) G (oni)	egg, cod, pot, len	OAS/shr, cla
7	D, I (wal, car) I (ban)	D, I (pea)	pep, squid, kiw, mel, whe, ric, soy, shr, cla	
8		I (chi)	tom, mel, shr, squ, cla, pea	
9		I (mel, chi)	Mil, squ, cla, pea, ban, whe, ric,	OAS/shr
10		D (wheat, I (chi)	shr	
11	D, I (shr, chi, pep, ric)		mil, egg, wal, pot, pch, kiw, mel, ban, whe, soy, len, cla	
12		D (chi)	mil, egg, shr, wal, pep, pot, pch, mel, ban, ric, oni, whe, squ	
13	D, G (pep)	D, I (len, wal, tom, cla)	mil, egg, shr, ban, whe, cod, chi, squ	
14	I (ric); G (cla, whe, pch, peat, egg)	I (pot); G (mil, shr, len)		
15	D, I (wal) G (pea)	I (chi)	pep, pot, oni, kiw, ban, whe, soy, squ, mel, ric	OAS/wal
16	D, I (whe, pot)	D, I (pch, mel)	milk pep, oni, kiw, ric, soy, len. squ, chi	OAS/wal
17	D, I (Ban)		egg, squ, cla, chi, wal, pea, pot, oni, pch, kiw, mel, whe, ric, soy.	OAS/shr
18	D (ric egg, wal)		mil, chi, pea, pepper, tom, pot, oni, pch, mel, ban, whe, soy	
19		D (chi)	cla, wal, pep, pot, oni mel, ric, pea	OAS/ban Urticaria/pch

D, dysphagia; I, impaction; G, GERD-like symptoms; OAS, oral allergy syndrome.

Mil, milk; squ, squid; cla, clam; wal, walnut; tom, tomato; pot, potato; mel, melon; whe, wheat; ric, rice; soy, soybean; ban, banana; len, lentil; shr, shrimp; chi, chicken; kiw, kiwi; pea, peanut; oni, onion; pep, pepper; pch, peach; cod, codfish; car, carrot.

Total 8 food sensitizations were detected by patch testing in 5 patients (26,3%). Patients were positive to an average of 1.6 atopy patch tests (ranging from 1 to 3 positive APT). Peanut was the food more commonly identified by APT in this subset of patients.

Nine double-positive (SPT+, APT+) responses against the same food were detected in 7 patients (36,8%). Shrimp was the most frequent food, in which we detected this combined skin response.

Food Sensitizations Not Involved in Clinically Apparent Episodes of EoE

We have also identified 155 food sensitizations in 18 patients (94.7%) using SPT and/or APT neither related with

clinically apparent episodes of EoE nor with clinical episodes suggestive of oral allergy syndrome, urticaria and/or anaphylaxis after food intake (Tables 2 and 3).

Positive SPT were detected in 92 instances, positive APT in 37 instances and a combined skin response were identified in the remaining 26 instances (Table 2).

A total of 92 food sensitizations were detected by SPT in 17 patients (89,4%). Patients were positive to an average of 6.3 skin prick tests (ranged from 1 to 13 positives SPT). The foods more commonly identified by SPT were (in order of frequency): milk (in 8 cases) potato and wheat (in 7), melon, onion, pepper and egg (in 6) and soybean and rice (in 5).

A total of 37 food sensitization were detected by patch testing in 14 patients. Patients were positive to an average of

2.6 atopy patch tests (ranging from 1 to 5 positive APT). Foods more commonly identified by APT were (in order of frequency): squid (in 10 cases), clam (in 4), and chicken and kiwi (in 3 for each one).

Twenty six double-positive (SPT+, APT+) responses against the same food were detected in 15 patients (78.9%). Seafood (shrimp, clam, and squid) and cereals (wheat and rice) in 5 cases and Solanaceae family (pepper, tomato and potato) in 4 cases were the most frequent animal and plant-derived foods respectively, in which we detected this combined skin response.

The most relevant findings of patients with acute EoE episodes with proved food sensitization and those with sensitization to food allergens without any apparent clinical manifestations after food ingestion were analyzed are: first, a positive SPT, to at least one of the species from the Solanaceae family (potato, tomato or pepper), were found in 15 patients (78.9%); second, when seafood (shrimp, clam and squid) was tested, a positive SPT and/or APT response was observed in 14 patients (73.6%) and, finally, 78.9% of the patients had displayed a positive SPT and/or APT to at least one of the members from legumes (soybean, peanut and lentils). Therefore, combining SPT and/or APT with allergens from Solanaceae family or legumes with shrimp, we were able to detect at least one specific food sensitization in any patient with EoE.

DISCUSSION

The need to identify safe foods in EoE is a common problem in clinical practice. How can we better identify offending food allergens? Our study tried to approach this issue. We have studied 19 adult patients with biopsy-proven EoE in whom we have described the existence of positive SPT and/or APT to foods which were potential cause of disease, either inducing immediate reactions or triggering clinically apparent episodes of EoE.

An array of IgE mediated disorders which typically include oral allergy syndrome, urticaria and/or anaphylaxis after intake of specific foods [2, 6, 17, 18], were definitely present in 42% of our patients with EoE (Type 1 food reactors). Up to 45% of patients had an initial episode of

immediate oral syndrome after food intake which was followed by a clinically apparent episode of EoE. Food more frequently involved comprised nuts and seafood. The reactions were immediate and they could be only detected by skin prick testing (Table 3). However, combined positive SPT and APT to food involved in immediate clinical episodes were detected in half of type 1 reactors, mainly in those, who referred some digestive symptoms afterwards.

The type 2 food reaction (or food-triggered EoE reaction) appeared in those 14 patients (73%) who identified the food involved in clinically apparent episodes (dysphagia, acute impaction or GERD-like symptoms) and had a positive skin test to the specific food. Of 68 clinically apparent episodes of EoE studied, it was possible to detect a positive cutaneous test to food in 40 episodes (almost 60%). Interestingly, the foods which had a positive SPT did not induce the typical immediate symptoms associated to EoE type 1 reactors in 78% of episodes. In the remaining 28 episodes, no evidence of skin responses was found, despite clear clinical implication referred by the patient. Chicken meat was the most frequent food involved in clinically apparent episodes of EoE with negative skin test. Possibly, the closed interaction between solid foods with certain physical characteristics (for example, those which are dry and rough) with an previously inflamed esophageal mucosa could be one of the factors involved in this clinical observation, rather than other mechanisms based on an immunologic recognition.

If a positive SPT suggests an IgE mediated mechanism, the APT has been used for the diagnosis of disorders in which cell-mediated immune responses are thought to play a prominent role. We have detected in 90% of patients a double positive response (immediate SPT and late APT responses) to different foods which could be suggesting that both mechanism might have influence in the disease activity of EoE in the majority of the patients [2]. Moreover, up to 20% of the foods involved for each episode would not have been identified if APT was not used for evaluating this food-triggered EoE phenotype.

Acute esophageal symptoms related to food ingestion were a frequent clinical complaint in EoE patients and offered us a unique opportunity to assess the influence of

Table 4. Clinical Features of Food Allergy Phenotypes in Patients with Eosinophilic Esophagitis

Phenotype	Clinical Features	Clustering of Phenotypes	Main Food Sensitizations Found*	Rate of Positive SPT/APT Reaction (in%)
Type 1	Oral syndrome, urticaria and anaphylaxis after intake specific foods	45% of patients had also clinically apparent episodes of EoE with the same food	Shrimp walnut	100/50
Type 2	Dysphagia, acute impaction or GERD-like symptoms after intake specific foods	An association with foods not involved in EoE episodes were found up to > 90 percent of cases.	Walnut shrimp, banana wheat potato	65/35
Type 3	Nil	This food response was an incidental finding in 15% of patients with EoE	Wheat Squid Clam Pepper Potato	

*In order of frequency

SPT, skin prick test; APT, atopy patch test.

Nil denotes that no relationship among foods with clinically apparent episodes of EoE or with immediate food allergic reactions could be established.

foods in the clinical activity of the disease. Thus, we have observed that the rate of skin reactors to animal or plant-derived foods was unexpectedly high involving the entire population. We have, firstly, examined a subset of patients in whom we could definitely confirm by skin testing the foods that were causing disease activity (Type 2 food reactors). All patients with immediate reactions to foods (type 1 food reaction) and, up to 94.7% of patients with food-triggered EoE phenotype had a clear skin reactivity with other foods which had no apparent correlation with immediate and/or EoE symptoms. It can be argued that no effort was made in this subset of patients in order to identify the clinical importance of these positive skin tests with dietary procedures (elimination diets or food challenges). Therefore, the prevalence of this type of asymptomatic food sensitization may be overestimated. However, our study was initially not designed for this purpose but, rather, to assess the diagnostic value of a large common food allergen battery present in the Mediterranean area in 19 patients who presented 68 clinically apparent episodes of EoE.

There is some evidence that food sensitization with no clinical relevance can occur in children and adults with EoE. Spergel, and *et al.* demonstrated that a positive skin test does not always imply clinical symptoms [7]. They used a wide food allergen elimination diet and, then subsequent food challenges with specific food with positive skin response were carried out. Twenty four negative challenges with several animal or food derived foods were detected in 6 children (23% of the population) with EoE. In adults, the prevalence of this particular food response in EoE is largely unknown, but there is a previous clinical observation where two adult EoE patients tolerated rye and wheat in spite of positive skin test [19]. We propose that this poorly understood food response could be named type 3 food reaction.

CONCLUSION

Now, it is clear to us that, the term food allergy in an adult cohort of EoE patients embraces several distinct phenotypes that can be defined on grounds of clinical features and skin testing results (Table 4). Skin testing in EoE seems to be, not only a low cost method, but also very reliable to examine food allergies in adult EoE patients. The importance of identifying these phenotypes in order to design specific exclusion therapies of food allergens in adult patients for an effective approach to obtain long lasting remission of the disease still has to be elucidated.

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