

Causes of Food-Induced Anaphylaxis in Italian Adults: A Multi-Centre Study

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Key Words

Food-induced anaphylaxis • Food allergy

Abstract

Background: Data about food-induced anaphylaxis in Italy are missing. **Objective:** It was the aim of this study to detect the main foods/food allergens causing anaphylaxis in Italy. **Methods:** The frequency of anaphylaxis and the relative importance of many offending foods were assessed in 1,110 adult patients with food allergy diagnosed by common criteria at 19 allergy centres scattered throughout Italy from 1 January to 31 December 2007. **Results:** Fifty-eight of 1,110 (5%) food-allergic patients experienced at least 1 episode of anaphylaxis. On average, they were older than other food-allergic patients (34 vs. 31 years; $p < 0.05$). The majority of

anaphylactic episodes occurred in patients sensitized to lipid transfer protein (LTP; $n = 19$), followed by shrimp ($n = 10$), tree nuts ($n = 9$), legumes other than peanut ($n = 4$), and seeds ($n = 2$); peanut, spinach, celery, buckwheat, wheat, avocado, tomato, fish, meat, and *Anisakis* caused an anaphylactic reaction in single patients. Among LTP-hypersensitive patients, peach caused 13/19 anaphylactic episodes. Shrimp-allergic patients were significantly older than other patients with food-induced anaphylaxis ($p < 0.05$), whereas patients allergic to LTP experienced their anaphylactic episodes at a younger age ($p < 0.001$). The frequency of anaphylaxis among patients sensitized to LTP, shrimp or tree nuts did not differ between northern and central/southern Italy. **Conclusion:** LTP is the most important allergen causing food-induced anaphylaxis in Italy, peach being the most frequently offending food. Peanut-induced anaphylaxis seems very un-

common. Geographic and environmental differences both between Italy and other countries and within Italy seem to play a relevant role in the pattern of sensitization to foods.

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Introduction

Food allergy represents one of the most frequent causes of anaphylaxis [1, 2], and it has been estimated that food-induced anaphylaxis is responsible for hundreds of fatalities worldwide every year [3]. Previous studies show that in most cases of fatal anaphylaxis, the offending food(s) had already caused at least 1 allergic reaction previously [4–6], and that pre-existing asthma represents the main risk factor for fatal anaphylaxis in food-allergic individuals [4].

Peanut and tree nuts are unquestionably 1 main cause of anaphylaxis among both adults and children in the US [4, 5] as well as in some European countries such as Great Britain [2, 7] and the Netherlands [8], as well as in other Anglo-Saxon countries such as Australia [9]. Both past and recent surveys suggest that also crustaceans and shellfish are a main offending food in the US [10, 11], in the Far East [12] and in Australia [13]. Relatively little is known about the prevalence of offending foods in other countries. The lack of such information is relevant because food habits differ from one area to another and this may heavily influence the importance of single foods as offenders in different countries. For instance, in France, along with peanuts, nuts and shellfish, lupine flour, wheat flour and latex-associated fruits seem to represent a relevant cause of food-induced anaphylaxis [14]; in Switzerland, celeriac seems the main offending food [15], and (especially) in Spain, the habit of eating raw or undercooked fish or shellfish has been associated with an 'epidemic' of anaphylactic reactions due to sensitization to the parasite *Anisakis simplex* [16].

In Italy, precise data are missing, although an emergency department survey found that foods (particularly fruits and vegetables) are the most frequent cause of anaphylaxis [17]. During 2006, several clinical allergy centres in Italy, most of whom adhering to the AAITO (Associazione Allergologi Immunologi Territoriali e Ospedalieri) association, gave birth to the EpidemAAITO consortium, a multi-centre study group whose aim was to define the prevalence of food allergy in Italian adults and to detect the prevalence of allergy to different kind of foods. The general results of this survey have been presented elsewhere [18]. Briefly, in more than 1,000 food-allergic adult

patients scattered throughout Italy, the most frequent food allergy was the pollen-food allergy syndrome, which was associated with oral allergy syndrome in 95% of cases and whose frequency decreased southbound. Forty-five percent of patients had primary food allergy that was caused by fruits and/or vegetables in >70% of cases and was generally associated with systemic symptoms. Sensitization to lipid transfer protein (LTP) caused most primary food allergies (60%). In the present study, we focused our attention on severe systemic reactions.

Patients and Methods

Patients

One thousand one hundred and 10 (4%) adult patients (mean age 31 years, range 12–79; males 391, females 719) diagnosed with IgE-mediated food allergy out of 25,813 subjects who first visited 1 of 19 allergy outpatient clinics scattered throughout Italy from 1 January to 31 December 2007 were included in the study. Fourteen centres (Paderno Dugnano, Torino, Verona 1, Verona 2, Milano, Udine, Casatenovo, Brescia, Treviglio, Desenzano, Genova, Giussano, Domodossola and Reggio Emilia) are located in northern Italy, 2 (Ancona and Avezzano) in central Italy, and 3 (Messina, Vibo Valentia and Caltanissetta) in the south.

Food allergy was diagnosed only in the presence of an unequivocal history of adverse reactions occurring some minutes up to 2 h after the ingestion of the offending food(s) confirmed by a clear-cut positive skin prick test (SPT) and/or by elevated circulating food-specific IgE. Clinical symptoms suggesting food allergy included oral allergy syndrome (defined as the rapid onset of itching of the oral mucosa with or without angio-oedema of the lips and tongue) [19], acute generalized urticaria with or without angio-oedema [20] and/or anaphylaxis [21].

Definition of Anaphylaxis

The doctors of participating centres reviewed the medical recordings of patients reporting suspect anaphylaxis. Following previously published clinical criteria [22], an anaphylactic reaction was considered highly likely when any of the following 3 criteria were fulfilled:

- (1) Acute onset of an illness involving skin, mucosal tissue or both, plus at least 1 of the following: respiratory compromise; reduced blood pressure or associated symptoms of end-organ dysfunction (collapse, syncope, incontinence).
- (2) Rapid onset after exposure to a likely allergen for that patient of 2 or more of the following: involvement of skin or mucosal tissue; respiratory compromise; reduced blood pressure or associated symptoms; persistent gastrointestinal symptoms.
- (3) Systolic blood pressure <90 mm Hg or >30% decrease from baseline blood pressure for that patient.

In vivo and in vitro Tests

Hypersensitivity to food allergens was detected by commercial food extracts (ALK-Abello, Madrid, Spain). The series tested in all patients with suspect food allergy in all participating centres included egg white, egg yolk, cow's milk, shrimp, codfish, wheat,

maize, soybean, peanut, sunflower seed, bean, walnut, hazelnut, tomato, carrot, orange, peach, celery, almond, sesame seed, kiwi, and banana.

In the case of suspect allergy to foods not included in this series, commercial extracts from the same or other companies (where available) and/or fresh foods were used for skin testing. A *simplex* SPT (ALK-Abello) was performed on patients reporting systemic allergic symptoms following the ingestion of raw or underdone fish and scoring negative on a SPT with fish extract. Fresh foods were tested by the prick-prick technique. All SPTs were carried out on the volar side of the forearm using disposable prick lancets (ALK-Abello). SPTs with saline and histamine 10 mg/ml were used as negative and positive control, respectively. Readings were taken at 15 min; wheals with a mean diameter >3 mm were considered positive [23].

In several centres, hypersensitivity was confirmed by specific IgE measurements (Uni-CAP, Phadia, Uppsala, Sweden). In these cases, specific IgE levels >0.35 kU/l were regarded as positive.

Although a recent study on patients sensitized to stable food allergens, namely LTP, showed that double-blind, placebo-controlled food challenges can be carried out quite safely [24], in view of the severity of reported allergic reactions, due to the fear of possibly severe adverse reactions, diagnosis of food-induced anaphylaxis was not confirmed by double-blind, placebo-controlled food challenges.

Classification of Patients Sensitized to Plant Food Allergens

In view of the extremely large variety of plant-derived foods possibly involved in allergic reactions, in order to uniform the recording of clinical data by participating centres, patients with plant food allergy were divided into 2 main groups.

Group 1: Type 1 (Primary) Food Allergy

This category included the following subgroups of patients with primary sensitization to plant-derived foods.

Lipid Transfer Protein. This group included all patients allergic to LTP irrespective of the offending food(s). LTP hypersensitivity was diagnosed in the presence of a positive SPT with commercial peach extract (ALK-Abello). Previous studies showed that this peach extract virtually contains only LTP at a concentration of 30 µg/ml, and that a positive SPT with this extract may be used as a clinical marker of sensitization to this protein [25, 26], with only minor exceptions [14]. Offending foods for LTP-allergic patients included all *Rosaceae* (apple, pear, peach, cherry, plum, apricot, medlar, almond, strawberry), tree nuts, maize, rice, beer, and grapes [27].

Tree Nuts. This group included all patients allergic to tree nuts (including hazelnut, walnut, Brazil nut, pine nut, almond, pistachio, chestnut, and cashew) but not allergic to LTP. Diagnosis was based on a positive SPT with commercial extract (when available) or with fresh offending nut in the absence of skin reactivity to both commercial peach extract and birch pollen extract. Previous studies showed that commercial walnut extract contains only stable allergens and can therefore be used as a means to discriminate between patients sensitized to labile allergens homologous to pollen proteins only and patients sensitized (also or uniquely) to stable allergens [26]. Further, in Mediterranean countries, hypersensitivity to tree nut LTP, particularly hazelnut [28] and walnut [29] LTP, is always associated with (and most probably secondary to) peach LTP hypersensitivity.

Seeds. Patients allergic to 1 or more seeds (such as sesame, sunflower, poppy, or other seeds) but not sensitized to tree nuts were included in this group.

Legumes. This group included subjects allergic to 1 or more legumes including peanut, bean, string bean, pea, chickpea, lupine, and lentil.

Cereals. This subgroup included patients with a clinical allergy to cereals (wheat, barley, maize, rice, rye) not sensitized to LTP, as shown by negative SPT with commercial peach extract.

Kiwi. This category included subjects with single kiwi allergy.

Allergy to Single Vegetable Foods. This category included all remaining foods that caused isolated allergic reactions in single individuals.

Group 2: Type 2 (Secondary) Food Allergy

This category included patients with plant food allergy caused by cross-reactivity to a primary sensitizer, divided into the following subgroups.

Pollen-Food Allergy Syndrome. This subgroup included patients either mono-sensitized to birch pollen (Bet v 1) or showing sensitization to all seasonal airborne allergens (and hence, possibly sensitized to profilin). Since both Bet v 1 homologous proteins and profilin are heat- and pepsin-labile allergens, a pollen-food allergy syndrome was diagnosed if patients reported good tolerance of the offending foods if these were cooked or otherwise processed, and/or in the presence of positive SPT with fresh offending foods, but a negative SPT with commercial extract of the same foods.

Latex-Fruit Allergy Syndrome. Patients primarily sensitized to natural rubber latex with a history of allergy to foods known as being potentially cross-reacting, such as chestnut, avocado, kiwi, papaya, and banana, were included.

Mugwort-Celery-Spice Syndrome. Patients primarily sensitized to mugwort with a history of allergy to potentially cross-reacting vegetables such as celery, fennel, anise, bell pepper, and other spices, were included in this group.

Patients sensitized to non-plant foods were grouped by allergen. For instance, patients allergic to shrimp, squid, octopus or shellfish were considered as possibly sensitized and grouped together (group 'shrimp'); similarly, those allergic to different fishes were grouped together, as were those allergic to different meats, and so on.

Statistics

Proportions were compared by the χ^2 test with Yates' correction. Means were compared by the 2-tailed Student's t test. Probability levels <5% were considered statistically significant.

Results

In total, 58/1,110 (5%) patients diagnosed with food allergy during 2007 in participating centres experienced at least 1 episode of food-induced anaphylaxis. Thirty-four of 58 (59%) patients were visited by the participating centres 2–24 months after the anaphylactic event, whereas 24 patients had experienced their anaphylactic episodes >2

years before the visit. All patients had been visited and cared for in an emergency department when anaphylaxis occurred. The mean age of patients with a history of anaphylaxis (34 years, range 12–72) at the time of the first visit was higher than the mean age of the general population with food allergy (31 years; $p < 0.05$), whereas the gender distribution (males 16, females 42) showed the same female prevalence.

The largest number of anaphylactic episodes was recorded among patients allergic to LTP ($n = 19$), followed by patients allergic to shrimp ($n = 10$), tree nuts ($n = 9$), legumes other than peanut ($n = 4$), and seeds ($n = 2$); peanut, spinach, celery, buckwheat, wheat, avocado, tomato, fish, meat, and *Anisakis* caused anaphylactic episodes in single patients. Four patients with type 2 food allergy experienced anaphylaxis from hazelnut ($n = 2$), carrot ($n = 1$) and bell pepper ($n = 1$). The frequency of anaphylaxis by single food allergen is shown in table 1. The most frequently offending foods caused anaphylaxis in a proportion ranging between 9 (LTP) and 44% (legumes other than peanut) of allergic individuals.

LTP hypersensitivity is analysed in more detail in table 2. Among LTP-hypersensitive patients, anaphylactic episodes were caused by peach in 13 cases, by apple in 2 cases, and by apricot, grapes, maize, walnut, hazelnut and peanut in 1 case each; 2 patients experienced 2 anaphylactic episodes each caused by peach and peanut, and by peach and maize, respectively. With the exception of maize and wine/grapes that were rather seldom reported as offending foods, in the LTP-allergic group, single vegetable foods consistently caused anaphylaxis in $<10\%$ of sensitized individuals.

Shrimp-allergic patients were significantly older than other patients with food-induced anaphylaxis both at the first visit (average 42.8 vs. 29.5 years; $p < 0.05$) and at the time when they had the anaphylactic episode (38.1 vs. 22.1 years; $p < 0.005$); in contrast, patients allergic to LTP experienced their anaphylactic episodes at a significantly younger age than all other patients ($p < 0.001$; table 3). In all subgroups, there was a consistent prevalence of female patients.

In view of the markedly higher prevalence of LTP allergy in the southern part of Italy observed in our previous survey [18], the prevalence of anaphylaxis for the 3 major offending foods was analysed separately by geographical area (table 3). This comparison did not show any difference in the frequency of anaphylaxis between northern and central/southern Italy among patients sensitized to LTP, shrimp or tree nuts.

Table 1. Offending foods and prevalence of systemic reaction and anaphylaxis in 1,110 food-allergic Italian adults

Allergen	Allergics		U/A		Ana-phylaxis	
	n	%	n	%	n	%
Fish	22	2	18	82	1	5
Shrimp	68	6	61	90	10	15
Milk	13	1	9	69	0	
Egg	17	2	13	76	0	
Meat	4	<1	3	75	1	25
Snail	2	<1	2	100	0	
<i>Anisakis</i>	3	<1	3	100	1	33
Wheat	11	1	9	82	1	11
LTP (see also table 2)	216	18	130	60	19	9
Sesame/sunflower seeds	6	<1	6	100	2	33
Peanut	19	2	16	84	1	5
Tree nuts	64	6	51	80	9	14
Kiwi	23	2	7	30	0	
Brazil nut	1	<1	1	100	0	
Soybean	9	1	5	56	0	
Legumes	9	1	7	78	4	44
Pineapple	3	<1	2	67	0	
Avocado	1	<1	1	100	1	100
Pine nut	12	1	10	84	0	
Fig	1	<1	1	100	0	
Eggplant	2	<1	0		0	
Buckwheat	4	<1	3	75	1	25
Spinach	2	<1	2	100	1	50
Mango	1	<1	1	100	0	
Boletus mushroom	1	<1	0		0	
Tomato	2	<1	1	50	1	50
Watermelon	2	<1	0		0	
Fennel	1	<1	0		0	
Garlic	1	<1	0		0	
Type 2 food allergy	631	57	41	6	4	<1

U/A = Urticaria with or without angio-oedema. Type 2 food allergy includes subjects with pollen-food allergy syndrome, latex-fruit allergy syndrome and mugwort-celery-spice syndrome. Proportions indicate the prevalence of allergy to a specific food (Allergics), the prevalence of urticaria/angio-oedema induced by a specific food (U/A), or the prevalence of anaphylaxis induced by a specific food (Anaphylaxis).

Discussion

The present study included more than 1,100 adults with food allergy diagnosed by specialist doctors in 19 allergy centres in Italy. So far, most studies of food-induced anaphylaxis have been carried out in English-speaking countries where certain foods, particularly peanut, are very popular and widely present on the market

both in their original form and as processed ingredients. Such studies highlighted the importance of peanut and tree nuts as the main foods causing the most severe and frequent allergic reactions, and the allergy scientific community took it for granted that these results were valid irrespective of the region of origin of the patients. Our results show a quite different picture in that although some foods known worldwide as ‘anaphylactogenic’, such as shrimp and tree nuts, were in effect involved in severe systemic reactions, more than one third of anaphylaxis cases in our population occurred in patients sensitized to LTP. Although LTP is a widely cross-reacting plant pan-allergen (allergy to *Rosaceae*, tree nuts, peanut, beer, maize, rice, mustard, grapes, tomato, spelt, pineapple, and many other foods has been reported in the literature), the food responsible for most cases of anaphylaxis in our patients was peach. However, although peach was by far the most frequently reported offending food in LTP-allergic patients, the prevalence of peach-induced anaphylaxis did not exceed that of other plant-derived foods.

From a statistical point of view, the overall frequency of anaphylaxis among LTP-sensitized individuals (9%) was lower than that observed in patients sensitized to peanut, tree nut or crustaceans; nonetheless, the much higher prevalence of allergy to LTP in Italy eventually resulted in a much larger number of anaphylactic episodes induced by this protein than by other allergens. The reasons for the high prevalence of LTP sensitization in Mediterranean countries are still unclear. Sensitization to certain pollens containing LTP has been suggested as a possible cause [30, 31], but clear evidence is still missing. Skin contact with or inhalation of particles of peach fuzz containing large concentrations of the protein have been suggested as an alternative hypothesis to explain the geographical differences of this type of allergy [32, 33]. Notably, previous studies did not observe significant differences in the amount of peaches consumed in European countries where allergy to LTP is frequent or virtually absent [34]. Irrespective of factors facilitating LTP sensitization, the relevance of LTP as a cause of anaphylaxis seems very high in countries where this type of allergy is common. On average, LTP-allergic patients experienced their anaphylactic episodes at a significantly younger age than other patients with food-induced anaphylaxis. This might be due to the fact that excluding milk and egg allergy which tend to be outgrown by most allergic children, in Mediterranean countries, allergy to LTP seems to occur at a younger age than all other kinds of primary food allergy as observed in our survey [18]. Doctors should be aware that LTP-containing plant-derived foods

Table 2. Offending foods and foods causing anaphylaxis in 216 LTP-hypersensitive patients

	Reactors	Anaphylaxis	
		n	%
Peach	184	13	7
Apple	74	2	3
Walnut	44	1	2
Hazelnut	44	1	2
Cherry	38	0	
Peanut	22	1	5
Plum	17	0	
Apricot	16	1	6
Almond	12	0	
Maize	8	1	12
Pear	7	0	
Kiwi	6	0	
Tomato	5	0	
Lettuce	3	0	
Strawberry	3	0	
Fig	3	0	
Orange	2	0	
Pineapple	2	0	
Chestnut	2	0	
Wine/grapes	3	1	33
Lupine	1	0	
Celery	1	0	
Garlic	1	0	
Bean	1	0	
Lentil	1	0	
Cauliflower	1	0	
Soybean	1	0	
Broccoli	1	0	
Artichoke	1	0	

LTP hypersensitivity was detected by SPT with a commercial (ALK-Abello) peach extract containing uniquely LTP. The total number of reactors exceeds that of allergic individuals due to the cross-reactive nature of the allergen causing co-sensitization to botanically unrelated foods.

Table 3. Prevalence of anaphylaxis among patients sensitized to the 3 most frequently offending foods in 2 geographic areas in Italy

	North		Central + south		p
	n	%	n	%	
Shrimp	9/55	16	1/13	8	NS
LTP	11/127	9	8/89	9	NS
Tree nuts	9/50	18	9/26	35	NS

NS = Not significant.

(particularly peach and nuts) may represent a danger for people sensitized to this protein, even when these patients present with a history of oral allergy syndrome as the only clinical expression of their food allergy. One further point that deserves to be discussed is the possibility that some patients included into the 'tree nut' group were also sensitized to LTP. In fact, a recent study [35] found that children with hazelnut allergy living in non-Mediterranean, birch-endemic areas are sensitized to hazelnut LTP in the absence of peach LTP reactivity. However, this fact has never been observed in Mediterranean countries where peach is the primary sensitizer [28]. Thus, although theoretically possible, we think that none of our patients with 'tree nut' allergy were sensitized to hazelnut LTP, and even if this were the case, it would only strengthen our conclusions that LTP is the main cause of food-induced anaphylaxis in Italy.

Another interesting aspect is the relative infrequency of primary peanut allergy (and hence, of peanut-induced anaphylaxis) among Italian adults. The reasons for this marked difference from Anglo-Saxon countries are all but clear, since peanuts are quite popular in Italy. One possible explanation might be that only roasted peanuts are consumed in Italy and that peanut butter is totally

absent from the market. There are studies showing that the way peanuts are processed may profoundly influence the sensitization process [36].

Further, patients with shrimp-induced anaphylaxis were significantly older than patients with other kinds of food-induced anaphylaxis. The reasons for this difference are unclear; although indirect, these data seem to suggest that sensitization to shrimp occurs at an older age than sensitization to other foods.

Finally, while data from our previous survey [18] showing different prevalences of allergy to specific foods in different areas of Italy seem to confirm that sensitization is, at least in part, a matter of geography (i.e. food habits) [37], the fact that the frequency of anaphylaxis does not change in different areas, irrespective of the number of sensitized individuals, is intriguing. One is tempted to speculate that in sensitized individuals, the external trigger (i.e. the offending food) is a necessary but not sufficient condition to induce anaphylaxis, which might require other factors to occur. The possible role of a specific genetic background associated with a defective synthesis of platelet-activating factor acetylhydrolase in severe anaphylaxis has recently been highlighted [38] and might represent one of these factors.

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