Received: 20 July 2020 | Revised: 13 September 2020 | Accepted: 5 October 2020

DOI: 10.1111/all.14634

ORIGINAL ARTICLE

Food Allergy and Gastrointestinal Disease

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

Systemic allergic reactions induced by labile plant-food allergens: Seeking potential cofactors. A multicenter study

Riccardo Asero[1] | Renato Ariano[2] | Arianna Aruanno[3] | Claudio Barzaghi[4] | Paolo Borrelli[5] | Moira Busa[6,7] | Giorgio Celi[8] | Massimo Cinquini[9] | Gabriele Cortellini[10] | Francesca D'Auria[11] | Marco De Carli[12] | Camilla Di Paolo[9] | Giulia Garzi[13] | Fabio Lodi Rizzini[14] | Monica Magnani[15] | Giuseppina Manzotti[16] | Alessandro Marra[4] | Stefano Miceli Sopo[17] | Francesco Murzilli[18] | Eleonora Nucera[3] | Elena Pinter[13] | Valerio Pravettoni[19] | Federica Rivolta[19] | Angela Rizzi[3] | Nicoletta Saporiti[20] | Enrico Scala[21] | Danilo Villalta[22] | Mona-Rita Yacoub[20] | Giuliana Zisa[23]

[1]Ambulatorio di Allergologia, Clinica san Carlo, Paderno Dugnano (MI), Italia

[2]Private Practice, Liguria, Italy

[3]Fondazione Policlinico Universitario A. Gemelli- IRCCS Università Cattolica del Sacro Cuore, Roma, Italy

[4]Ambulatorio di Allergologia, UOC Medicina, ASST Rhodenese, P.O Rho, Rho, Italia

[5]SSD Dermatologia e Allergologia - Ospedale Beauregard, Aosta, Italia

[6]Ambulatorio di Allergologia U.O.S. Dermatologia Ospedale di Mirano (VE), Mirano, Italia

[7]Ambulatorio di Allergologia Ospedale di Bassano del Grappa (VI), Bassano del Grappa, Italia

[8]Clinica Villa Pia, Roma, Italy

[9]SSVD Allergologia, Spedali Civili Brescia, Italia

[10]UOD Allergologia, Az Sanitaria della Romagna, Rimini, Italia

[11]ASST Bergamo Ovest, Bergamo, Italia

[12]S.O.C Medicina 2, Presidio Ospedaliero "Santa Maria della Misericordia", Udine, Italy

[13]Ambulatorio di Allergologia, UOC Medicina Interna ed Immunologia Clinica, Policlinico Umberto I, Roma, Italia

[14]Dipartimento Scienze Cliniche e Sperimentali, Università Studi Brescia / SSVD Allergologia, Spedali Civili Brescia, Italy

Abstract

Background: Heat-and-pepsin-sensitive plant food allergens (PR-10 and profilin) sometimes cause systemic reaction.

Objective: To detect the risk factors for systemic reactions induced by labile food allergens.

Methods: A retrospective multicenter study was performed on patients with a documented history of systemic allergic reaction to labile plant food allergens and on age-matched controls with a history of oral allergy syndrome (OAS) induced by the same foods. Offending foods, their amount, and state (solid or liquid), and potential cofactors (nonsteroidal anti-inflammatory drugs, protonic pump inhibitors, exercise, alcohol, and fasting) were considered.

Results: We studied 89 patients and 81 controls. Sensitization to PR-10 or profilin, IgE to Bet v 1 and/or Bet v 2, and foods causing OAS were similar in the two groups. Twenty patients experienced >1 systemic allergic reaction. Tree nuts, Rosaceae, Apiaceae, and soymilk were the main offending foods. Seventeen (19%) patients were taking a PPI when the systemic reaction occurred (vs 5% in controls; $P < .025$). The ingestion of the offending food in liquid form (soymilk) was frequent among patients (15%) but unusual among controls (2%; $P < .025$). Soy milk-induced systemic reactions were independent of PPI treatment. Fasting and excess of allergen, but not NSAID and exercise, were other relevant cofactors for systemic reactions. Systemic reactions occurred without any identifiable cofactor in 39 (44%) cases.

[15]Allergologia U.O.C.P.S. AUSL Bologna, Bologna, Italia

[16]Ambulatorio di Allergologia, Casa di Cura Beato Palazzolo, Bergamo, Italia

[17]Pediatric Allergy Unit, Pediatrics Area, Department of Life Sciences and Public Health, Policlinico Gemelli Fondazione Universitaria IRCCS, Università Cattolica del Sacro Cuore, Roma, Italia

[18]U.O.S.D. di Allergologia, Ospedale S.S. Filippo e Nicola, Avezzano (AQ), Italy

[19]UOC General Medicine Immunology and Allergology – IRCCS Foudation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[20]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milano, Italy

[21]Istituto Dermopatico dell'Immacolata, Rome, Italy

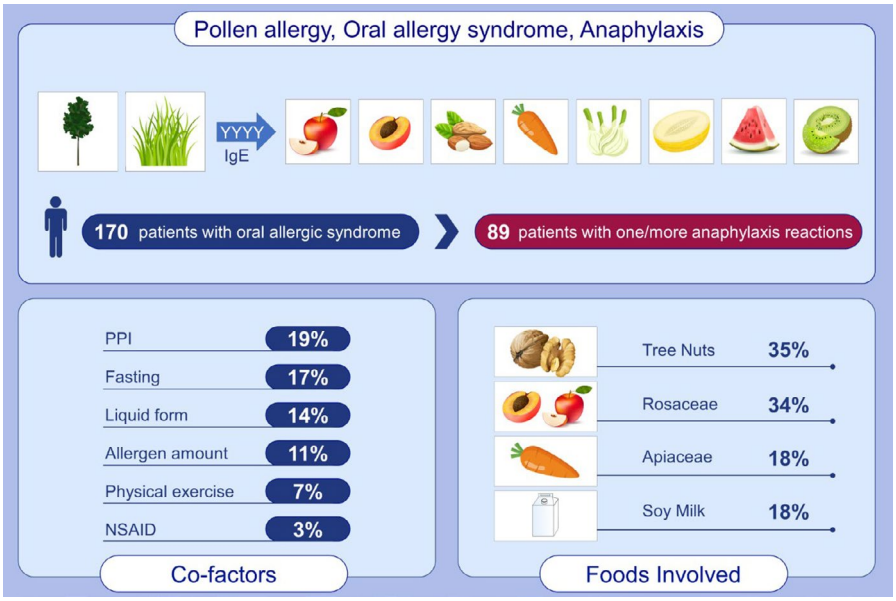
[22]Immunologia e Allergologia, Ospedale S. Maria degli Angeli, Pordenone, Italia

[23]S.S. Allergologia e Immunologia Clinica, S.C.D.U. Medicina Interna I - A.O.U. Maggiore della Carità di Novara, Novara, Italy

Correspondence
Dr. Riccardo Asero, Ambulatorio di Allergologia, Clinica San Carlo, Via Ospedale 21, 20037 Paderno Dugnano (MI), Italia.
Email: r.asero@libero.it

Conclusion: PR-10- and profilin-induced systemic reactions are facilitated by PPI, ingestion of large amounts of unprocessed foods, and fasting. Soybean beverages represent a risk for PR-10 hypersensitive patients and should be avoided.

KEYWORDS
anaphylaxis, food allergy, pollen allergy



GRAPHICAL ABSTRACT

Hypersensitivity to labile plant-food allergens (PR-10 and profilin) secondary to pollen allergy frequently causes oral allergy syndrome. Labile allergens may become dangerous when the raw foods are ingested in excessive amounts or in liquid form. Other cofactors include therapy with proton pump inhibitors and fasting. The most frequently involved foods are as follows: tree nuts, *Rosaceae*, *Apiaceae*, *and* soy milk. Abbreviations: NSAID, non- steroidal anti- inflammatory drugs; PPI, proton pump inhibitors; PR- 10, pathogenesis- related proteins group 10

1 | INTRODUCTION

IgE-mediated sensitization to pollen allergens is often associated with a food allergy due to the co-recognition (ie, cross-reactivity) of structurally homologous proteins present in plant-derived foods (Reviewed in 1). In allergology, a cross-reaction is the consequence of the binding of IgE to homologous, linear or conformational, allergen structures conserved among proteins that are characterized by a similar function.[1,2] It has been estimated that up to 60% of food allergies in older children, adolescents, and adults are linked with an inhalant allergy.[1] In effect, the pathogenesis-related proteins group 10 (PR-10), to which the major birch pollen allergen (Bet v 1) belongs, and the plant pan-allergen profilin are two of the most frequent causes of seasonal respiratory and also the most frequent cause of food allergy in Italian adults[3] as well as in several other countries. What characterizes these two allergens is the elevated sensitivity to heat and pepsin digestion. Therefore, food-allergic patients sensitized to PR-10 and/or to profilin experience typically a sort of immediate contact urticaria called oral allergy syndrome (OAS) involving the oral and pharyngeal mucosa following the ingestion of unprocessed fruits, nuts, legumes, and vegetables. In patients sensitized to PR-10, systemic symptoms have been reported mostly following the ingestion of soy products due to the cross-reactivity to the soybean allergen Gly m 4.[4] Other, sparse cases of systemic reactions from tree nuts and apple have been reported from Northern Europe.[5] More recently, some cases of systemic allergic reactions following the ingestion of fresh carrot juice, raw almonds, fresh melon, raw tomato, banana, persimmon, and pesto sauce have been reported in three Italian patients.[6] These episodes appeared to be associated with some conditions facilitating an at least partial by-pass of pepsin digestion (proton pump inhibitors [PPI] treatment, gastric atrophy, excessive amount of allergen, fasting, and/or liquid nature of the food). Based on that preliminary report, we decided to carry out a large retrospective multicenter study of systemic allergic reactions induced by labile allergens with the aim to detect the associated cofactors. The basis for such a study is a proper component resolved diagnosis in plant-food-allergic patients. This can be accomplished by measuring IgE specific for marker allergens such as birch pollen major allergen, Bet v 1, timothy grass pollen profilin, Phl p 12, the peach lipid transfer protein, Pru p 3, Cor a 9 and Cor a 14 as predictors of clinical reactivity to hazelnut, and Jug r 1 as predictor of walnut reactivity.

2 | PATIENTS AND METHODS

2.1 | Patients

A retrospective study was carried out in 22 allergy centers scattered throughout Italy. Participating doctors included the recorded cases of systemic allergic reactions which occurred during the last 8 years (up from January 2013) following the ingestion of plant-derived foods in patients showing the following characteristics:

a. History of oral allergy syndrome (defined as the occurrence of immediate itching and tingling of the oral/pharyngeal mucosa with or without lip angioedema) following the ingestion of fresh, unprocessed vegetable foods.
b. Occurrence of one or more episodes of systemic allergic reaction (including acute urticaria/angioedema, anaphylaxis, hypotension, severe acute gastrointestinal disorders, and/or asthma [defined as wheeze/bronchospasm during the allergic reaction], either alone or variably associated) <2 hours after the ingestion of the putative offending plant-derived food, requiring an intervention by emergency medical service.
c. Hypersensitivity to birch pollen and/or to profilin as shown by both in vivo and in vitro testing (see beyond).
d. No detectable sensitization to stable food allergens by both in vivo and in vitro testing (see beyond).

A similar number of age- and sex-matched subjects showing the same clinical characteristics except a history of systemic reactions to foods were randomly selected and enrolled as controls. The reason why patients and controls were recruited up from 2013 is that in that period diagnostic allergenic components became largely available in different clinical settings.

By analyzing the clinical documents of the patients, participating doctors recorded foods causing either OAS and/or systemic reactions, the amount of food ingested when systemic reactions occurred, the state (solid or liquid) and whether the offending food had been thermally treated, and potential cofactors. These included:

a. contemporary treatment with nonsteroidal anti-inflammatory drugs [NSAID];
b. ongoing treatment with PPI;
c. exercise, defined as sustained running, climbing, or practicing sports within the 2 hours following the food ingestion;
d. alcohol intake, defined as the ingestion of at least 250 mL of wine or one-half glass of super-alcoholics together with plant foods;
e. fasting, defined as ingestion the of fresh plant food alone at least 12 hours after the last meal;
f. fever.

Foods causing OAS in controls as well as current treatment with proton pump inhibitors (PPI) were recorded.

An excess of allergen was defined as a quantity of triggering food much superior than a normal serving for an adult.

2.2 | Skin tests and in vitro tests

Patients and controls underwent SPT with a large series of commercial extracts of both seasonal and perennial airborne allergens including SPT with a profilin-enriched extract of date palm pollen (ALK/Abello, Horsholm Denmark). These included grass, mugwort, ragweed, pellitory, plantain, birch olive, cypress, Alternaria, house dust mites, dog dander, and cat dander for all participating centers.

The single centers used SPT extracts from different producers. Further, SPT with an array of commercial food extracts (ALK/Abello) was performed, including a peach extracts containing uniquely stable allergens (ie, Lipid transfer protein and peamaclein). Skin tests with the offending foods by the prick-prick technique were carried out as well. The relevance of performing SPT with whole birch pollen, date palm profilin, and peach lipid transfer protein relies in the possibility to discriminate at a first sight plant food-allergic patients, before measuring IgE specific for single components.

Patients' and controls' sera were assessed for IgE specific for Bet v 1, Bet v 2 and/or Phl p 12, and Pru p 3. Patients with a history of systemic reactions to tree nuts underwent in most cases also the detection of IgE to stable allergens present in these foods such as Cor a 9, Cor a 14, and Jug r 1 in order to rule out the sensitization to these allergens. Ara h 1, Ara h 2, and Ara h 3 IgE were measured in patients reporting a peanut-induced systemic reaction. IgE to all components was measured by ImmunoCAP (Thermo Fisher, Uppsala, Sweden). IgE levels < 0.1 kU/L were considered negative.

2.3 | Statistics

The findings in patients and controls were compared by Student's *t* test and chi-square test with Yates' correction. Probability values < 5% were considered statistically significant.

Multiple logistic regression was performed for the clinical variables with dichotomous scores (present/absent) to investigate whether associations between clinical symptoms and cofactors were present after simultaneously adjusting for other variables of interest. Separate modeling was performed for each condition including all cofactors, in addition to sex and age. *P* values < .05 were considered significant.

2.4 | Ethics

Since the study was strictly retrospective, based on routine investigations, and observational, it was not formally submitted to an external ethical committee and was approved by the internal review board of the principal investigator's clinic.

3 | RESULTS

3.1 | Study population

One hundred and seventy subjects were eventually enrolled in the study. Of these, 89 with a recorded history of at least one episode of systemic reaction following the ingestion of plant-derived foods were included as patients, and 81 with a clinical history of OAS only were included as controls. The in vivo and in vitro tests showed that both patients and controls were sensitized uniquely to labile food allergens, that is, PR-10, profilin, or both. The two populations are compared in Table 1. Patients and controls did not differ in the prevalence of sensitization to PR-10 (83 [93%] vs 74 [91%], respectively; p = NS) or profilin (29 [32%] vs 31 [38%], respectively; p = NS). Similarly, patients and controls hypersensitive to birch showed similar levels of IgE specific for Bet v 1 (mean 24.5 kU/L [median 15.8 kU/L], range 0.35->100 vs 30.5 kU/L [median 17.8 kU/L], range 0.31->100, respectively; p = NS). Also profilin reactors of the two groups showed similar levels of IgE specific for Bet v 2 (mean 5.63 [median 2.93 kU/L], range 0.21-54.9 for patients vs 3.56 [median 3.2 kU/L], range 0.25-12.0 for controls; p = NS). Further, the sensitization profile in terms of co-sensitization to different allergen sources (poly-sensitization) did not differ between patients and controls. In no patient or control, primary mugwort reactivity was detected.

Foods causing oral allergy syndrome showed a similar distribution in the two groups (Table 1). *Rosaceae* (including apple, pear, peach, plum, cherry, loquat, and almond) represented by far the

TABLE 1 Comparison between patients and controls

	Patients	Controls	*P*
No.	89	81	
Mean Age (Range)	41.6 (5-80)	35.2 (6-71)	
M/F	19/70	19/62	
Type of sensitization			
PR-10	60	50	
PR-10+ Profilin	23	24	
Profilin	6	7	
IgE levels in positive patients			
Median Bet v 1 (kU/L) (range)	15.8 (0.35->100)	17.8 (0.32->100)	NS
Median Bet v 2 (kU/L) (range)	2.93 (0.67-54.9)	3.2 (0.31-12.0)	NS
Foods causing OAS			
Rosaceae	55 (62%)	57 (70%)	NS
Tree nuts (walnut, hazelnut)	27 (30%)	33 (41%)	NS
Apiaceae	14 (16%)	13 (12%)	NS
Kiwi	13 (15%)	10 (12%)	NS
Melon, Watermelon	13 (15%)	4 (5%)	NS
Tomato	9 (10%)	3 (4%)	NS
Peanut	6 (7%)	5 (7%)	NS
Pineapple	5 (6%)	1 (1%)	NS
Banana	5 (6%)	3 (4%)	NS
Fig	3 (3%)	1 (1%)	NS
Soy milk/Soybean	2 (2%)	2 (2%)	NS
Citrus fruits	2 (2%)	0 (0%)	NS
Eggplant	1 (1%)	2 (2%)	NS
Persimmon	0 (0%)	1 (1%)	NS
Grapes	0 (0%)	1 (1%)	NS

Note: Rosaceae include: Apple, pear, peach, cherry plum, loquat, strawberry, almond.

Apiaceae include: Celery, carrot, fennel, parsley.

most frequently reported cause of OAS both in patients and in controls (62% vs 70%, respectively), followed by tree nuts (30% vs 41%), *Apiaceae* (including carrot, celery, fennel, and parsley), kiwi, and *Cucurbitaceae* (melon and watermelon).

3.2 | Systemic reactions

Systemic allergic reactions that occurred in the patients' group are shown in Table 2. Urticaria/angioedema, anaphylaxis, asthma, and gastrointestinal reactions occurred in 41, 38, 5, and 5 cases, respectively. Twenty patients experienced more than one episode of systemic allergic reaction. In this case, tree nuts were the most frequent triggers, causing 35% of events, although Rosaceae still represented a relevant causative food (34%). Interestingly, *Apiaceae* and soymilk products were two further, relevant causes of systemic reactions (18% of cases each). Comparing the foods inducing OAS in the patients' group (Table 1) with those responsible for systemic reactions (Table 2), it turned out that soymilk was a negligible cause of local reactions (reported by only 2% of patients) but a relevant cause of systemic reactions (18% of patients: $P < .005$). IgE to Gly m 4, Gly m5, and Gly m 6 were measured in 8 soybean reactors. In all 8 cases, specific IgE to Gly m 4 (range 2.17-84.0 kU/L) in the absence of IgE to Gly m 5 and Gly m 6 was found. *Apiaceae* were also surprisingly frequent inducers of systemic reactions in some patients that did not report OAS from these vegetables.

The research of possible cofactors (Table 2) showed that 17 patients (19%) were taking a proton pump inhibitor when they experienced the systemic reactions; this proportion was significantly higher than that recorded among controls (5%; $P < .025$). One of the patients taking regularly a PPI experienced 5 distinct episodes of asthma after the ingestion of Kiwi, fennel, tomato, celery, and carrot, respectively; 2 other patients experienced two distinct episodes of urticaria/angioedema following the ingestion of almonds and hazelnuts in one case, and of melon and lettuce in another case. Systemic reactions induced by unusual allergen sources such as eggplant and persimmon occurred uniquely in patients treated with PPI.

The ingestion of the potentially offending food as a drink (ie, soymilk or soymilk ice cream) was rather frequent among patients (15%) but very unusual among controls (2%; $P < .025$). Systemic reactions following the ingestion of soya drinks were strongly associated with hypersensitivity to PR-10 (11 patients were PR-10+/Profilin− and 2 PR-10+/profilin+). In contrast, interestingly, soy milk-induced systemic reactions were independent on PPI treatment; in fact, these occurred in only 1/17 (6%) of patients that were taking a PPI vs 15/72 (21%) who were not, although the difference did not reach the statistical significance.

Fasting and excess of allergen were two other relevant cofactors associated with systemic reactions. The 10 patients experiencing a systemic reaction after ingesting what was recorded as an overload of allergen reported the following: 25 almonds, >30 almonds, carrots + celeries + pear, carrots + celeries, 2 apples + 20 hazelnuts, "many hazelnuts" (3 cases), 7 figs, and 5 slices of melon, respectively. One patient who experienced an episode of severe urticaria after eating one apple and one persimmon was not classified among patients who ingested an excess of allergen but was taking a PPI.

In the six patients who were mono-sensitized to profilin (ie, not reactive to PR-10), the foods causing systemic reactions were tomato, fennel + melon, hazelnut, watermelon, banana, and carrot + lettuce, respectively. In four cases, no associated cofactor was

TABLE 2 Systemic reactions

	PATIENTS	CONTROLS	P
No.	89	81	
Adverse reaction (%)			
Urticaria/angioedema	41 (46%)	N/A	
Anaphylaxis	38 (43%)	N/A	
Asthma	5 (6%)	N/A	
Gastrointestinal	5 (6%)	N/A	
>1 episode of systemic reaction	20 (22%)	N/A	
Foods causing systemic reactions (%)			
Rosaceae	30 (34%)*		
Tree nuts (walnut, hazelnut)	31 (35%)**		
Soy milk/Soybean	16 (18%)		
Apiaceae	16 (18%)		
Melon, Watermelon	6 (7%)		
Tomato	4 (4%)		
Kiwi	3 (3%)		
Citrus fruits	2 (2%)		
Fig	2 (2%)		
Eggplant+	1 (1%)		
Banana	1 (1%)		
Persimmon	1 (1%)		
Peanut	1 (1%)		
Lettuce	1 (1%)		
Grapes	0 (0%)		
Cofactors:			
PPI	17 (19%)	4 (5%)	<0.025
Atrophic gastritis	1 (1%)	0 (0%)	NS
Exercise	6 (7%)	N/A	
NSAID	3 (3%)	N/A	
Fasting	15 (17%)	N/A	
Excess of allergen	10 (11%)	N/A	
Liquid food	13 (14%)	2 (2%)	<0.025
Any one cofactor	50 (56%)		
>1 cofactor	12 (13%)		
No cofactor	39 (44%)		

Note: Offending foods exceed the number of patients because several patients experienced more than one episode of systemic reaction.
N/A, not applicable; NS, Statistically not significant.

recorded, while in two cases, exercise and PPI treatment were associated with each of the allergic reactions, respectively.

Exercise or NSAID intake was reported as cofactors only by a minority of cases (7% and 3%, respectively). In 12 cases (13%), more than 1 putative cofactor was present when the adverse reaction occurred. In contrast, 39 cases (44%) of systemic reactions occurred apparently without any identifiable cofactor.

In multivariate analysis, these risk factors remained statistically significant also after multiple adjustments for age and sex (OR_{adj} for treatment with PPI = 3.4, 95% CI 1.1-10.7, $P = .036$; OR_{adj} for fasting = 8.5, 95% CI 2.1-34.1, $P = .002$; OR_{adj} for Excess of allergen = 10.3, 95% CI 1.2-86.6 $P = .032$).

4 | DISCUSSION

The present study shows that, albeit uncommon, systemic allergic reactions may occur in patients sensitized uniquely to labile plant food allergens. All systemic reactions recorded in this study occurred following the intake of plant-derived foods known to contain the allergenic protein(s) the patients were sensitized to. Although in patients reacting to tree nuts hypersensitivity to a stable allergen, such as seed storage proteins or oleosins cannot be fully ruled out as IgE to other components such as Jug r 2 and Cor a 11 were not measured and patients' sera did not undergo an immunoblot analysis,[7] we are quite confident that this was not the case. No patient reacting to tree nuts showed IgE to Cor a 8, Cor a 9, Cor a 14, or Jug r 1, and peanuts were a negligible inducer of systemic reactions in our population. These findings virtually rule out the sensitization to tree nuts stable allergens. Regarding fresh fruits, Pru p 3 IgE scored negative in all patients, thus excluding the reactivity to the main stable allergen in these foods. We must also admit that the final proof of a causal relationship is missing as, due to the severity of most of the allergic reactions, confirmative oral challenges were not carried out. However, it should be considered that oral challenges with the offending food might have probably produced only an oral allergy syndrome in most cases due to the different conditions of the challenge (dosage, timings, etc) and the lack of some of the cofactors such as allergen excess, PPI treatment, fasting, and others, that were present when the systemic allergic reaction occurred.

Patients and controls showed similar clinical characteristics in terms of age, sex, sensitization profile, and foods causing local reactions (OAS) which allowed to compare the two populations for the presence of cofactors. Such analysis showed that different conditions, all facilitating the arrival of the pepsin-labile allergen in the gut in an unmodified form, were largely prevalent in the patients' group. The most important of these were therapy with proton pump inhibitors, fasting, the ingestion of an elevated amount of offending foods, and the liquid status of the food. The protective effect of a proper pepsin digestion was clearly shown by comparing the prevalence of PPI therapies in patients and controls and confirms the observations of our previous study.[6] Interestingly, HCl and pepsin secretion inhibition were associated with systemic allergic reactions following the ingestion of unusual allergen sources such as eggplant and persimmon. The results of this study might suggest warning patients hypersensitive to PR-10 and/or profilin who are taking PPI to avoid the ingestion of large amounts of offending foods, particularly if these are eaten alone. Fasting has been associated with severe allergic reactions in patients sensitized to stable food allergens,[8] and this study confirmed this condition as a potential risk factor for systemic reactions also in patients hypersensitive to labile plant-food allergens.

Soybean-based drinks, such as soy milk, milk shakes, and ice cream, clearly caused a relevant part of the systemic allergic reactions that occurred in our patients, confirming previous studies.[4] In contrast, soybean sprouts eaten in salads did not induce systemic reactions and caused only OAS in some cases. Interestingly, allergic reactions to soy milk and ice cream were not prevalent in patients taking a PPI, suggesting that drinks containing a high amount of allergenic protein not processed thermically represent a risk for allergic patients per se, as liquids may reach rapidly the intestine bypassing, at least in part, the gastric digestion. Further, Schulten and coworkers[9] provided evidence of the rapid increase of the stomach pH after drinking. The risk represented by fresh foods in a liquid form for birch pollen-allergic patients was noticed recently also for other foods such as fresh carrot.[6] Further, soy beans (that are known as adamame in Chinese cuisine) may potentially cause allergic reactions as such because both boiling and microwave oven cooking procedures are unable to denature the PR-10 proteins due to the interaction of membrane phospholipids that increase their heat resistance.[10,11]

Some pure profilin reactors experienced systemic reactions following the ingestion of unprocessed plant-derived foods. These events, albeit rare, seem to contradict the idea that this allergen is virtually harmless[12,13] and confirm that profilin may be a relevant food allergen in patients showing elevated specific IgE levels[14] or following the ingestion of high amounts of foods containing this allergen (eg, melon).[6] The offending foods in these patients were those that have typically been associated with sensitization to this pan-allergen, such as tomato, melon, watermelon, and banana.[15,16]

In more than 40% of our patients, participating doctors were not able to detect any potential cofactor in association with the systemic reactions. While we cannot exclude that some of these events may occur in the absence of a facilitating factor, one should keep in mind that this was a retrospective study and that several of the allergic reactions occurred long time ago. Therefore, it cannot be excluded that some of the potential cofactors were not recorded in patients' documents. Alternatively, other cofactors may exist that we did not consider in the present study.

Tree nuts were the most frequent offenders in patients with systemic allergic reactions followed by *Rosaceae*, *Apiaceae*, and soy milk. This is perfectly in keeping with previous studies,[16] although ex vivo digestion experiments did not find relevant differences between the different members of the PR-10 in terms of pepsin resistance.[17,18] However, possibly some differences in stability of Bet v 1-homologue allergens in respective food items exist.[9,16]

In conclusion, clinicians should be aware that also allergy due to pollen cross-reactive allergens, such as PR-10 and profilin, may be associated with systemic reactions.[19] Such reactions appear to be facilitated

by PPI treatments, by the ingestion of large amounts of unprocessed foods, and by fasting. This information should be provided to PR-10 and profilin-sensitized patients. Further, soy milk and other soybean-based beverages represent a risk for the PR-10 hypersensitive patients and should be avoided. This study highlights once more the relevance of a proper diagnostic procedure in food-allergic patients.

ORCID

Riccardo Asero https://orcid.org/0000-0002-8277-1700
Enrico Scala https://orcid.org/0000-0002-9391-9168

REFERENCES

1. Werfel T, Asero R, Ballmer-Weber BK, et al. Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. *Allergy*. 2015;70:1079-1090.
2. Ferreira F, Hawranek T, Gruber P, Wopfner N, Mari A. Allergic cross-reactivity: from gene to the clinic. *Allergy*. 2004;59:243-267.
3. Asero R, Antonicelli L, Arena A, et al. EpidemAAITO: Features of food allergy in Italian adults attending allergy clinics: a multi-centre study. *Clin Exp Allergy*. 2009;39(4):547-555.
4. Kleine-Tebbe J, Vogel L, Crowell DN, Haustein UF, Vieths S. Severe oral allergy syndrome and anaphylactic reactions caused by a Bet v 1- related PR-10 protein in soybean, SAM22. *J Allergy Clin Immunol*. 2002;110:797-804.
5. Le TM, van Hoffen E, Lebens AF, Bruijnzeel-Koomen CA, Knulst AC. Anaphylactic versus mild reactions to hazelnut and apple in a birch-endemic area: different sensitization profiles? *Int Arch Allergy Immunol*. 2013;160:56-62.
6. Asero R, Celi G, Scala E. Labile plant food allergens: really so harmless? Case series and literature review. *Allergy*. 2020;75:1517-1518.
7. Geiselhart S, Hoffmann-Sommergruber K, Bublin M. Tree nut allergens. *Mol Immunol*. 2018;100:71-81.
8. Arena A. Anaphylaxis to apple: is fasting a risk factor for LTP-allergic patients? *Eur Ann Allergy Clin Immunol*. 2010;42:155-158.
9. Schulten V, Lauer I, Scheurer S, Thalhammer T, Bohle B. A food matrix reduces digestion and absorption of food allergens in vivo. *Mol Nutr Food Res*. 2011;55:1484-1491.
10. Shibasaki M, Suzuki S, Tajima S, Nemoto H, Kuroume T. Allergenicity of major component proteins of soybean. *Int Arch Allergy Appl Immunol*. 1980;61:441-448.
11. Vieths S, Jankiewicz A, Aulepp H, Haustein D. Allergy to heated and processed foods. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M*. 1997;(91):250-62.
12. Santos A, van Ree R. Profilins: mimickers of allergy or relevant allergens? *Int Arch Allergy Immunol*. 2011;155:191-2014.
13. Wensing M, Akkerdaas JH, van Leeuwen WA, et al. IgE to Bet v 1 and profilin.: cross-reactivity pattern amd clinical relevance. *J Allergy Clin Immunol*. 2020;110:435-442.
14. Alvarado MI, Jimeno L, De la Torre F, et al. Profilin as a severe food allergen in allergic patients overexposed to grass pollen. *Allergy*. 2014;69:1610-1616.
15. Asero R, Mistrello G, Roncarolo D, et al. Detection of clinical markers of sensitization to profilin in patients allergic to plant-derived foods. *J Allergy Clin Immunol*. 2003;112:427-432.
16. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. Molecular allergology. User's guide. *Pediatr Allergy Immunol*. 2016;27(Suppl 23):1-250.
17. Schimek EM, Zwölfer B, Briza P, et al. Gastrointestinal digestion of Bet v 1-homologous food allergens destroys their mediator-releasing, but not T cell-activating, capacity. *J Allergy Clin Immunol*. 2005;116:1327-1333.
18. Sancho AI, Wangorsch A, Jensen BM, et al. Responsiveness of the Major Birch Allergen Bet v 1 Scaffold to the Gastric Environment: Impact on Structure and Allergenic Activity. *Mol Nutr Food Res*. 2011;55:1690-1699.
19. Nucera E, Aruanno A, Buonomo A, Mezzacappa S, Rizzi A, Schiavino D. Difficult management of a patient with PR-10 related anaphylaxis. *Postepy Dermatol Alergol*. 2016;33:386-388.

How to cite this article: Asero R, Ariano R, Aruanno A, et al. Systemic allergic reactions induced by labile plant-food allergens: Seeking potential cofactors. A multicenter study. *Allergy*. 2021;76:1473–1479. https://doi.org/10.1111/all.14634