

Hypersensitivity to major panallergens in a population of 120 patients

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Abstract

Introduction: Lipid transfer proteins (LTP), profilin and PR-10 are the most important panallergens in central and southern Italy. Lipid transfer proteins are stable molecules, predominantly present in the fruit peel, which can induce systemic symptoms after ingestion of vegetables. Profilin and PR-10 are randomly distributed in the pulp and peel. Both are labile proteins and usually determine reactions restricted to the oral cavity. Panallergens-specific IgE may cross-react with homologues from different plant sources, due to their conserved structure.

Aim: To assess the pattern of sensitization to panallergens and the correlation with the clinical history and the allergological evaluation of food and aeroallergens.

Material and methods: One hundred and twenty patients with adverse reactions after vegetables ingestion underwent skin prick tests (SPT) with commercial extracts of plant-derived foods and inhalant allergens and commercial extracts of LTP, profilin and PR-10.

Results: Many patients presented positive SPT with different plant-food allergens. We found that 76 patients were sensitized to LTP, 14 to profilin and 5 to PR-10. In the LTP-sensitized group, 64 (84%) patients suffered from systemic symptoms while the patients sensitized only to profilin referred the oral allergy syndrome.

Conclusions: This study shows a high rate of sensitization to LTP in our population according to the literature about food allergy in our geographical area and confirms the literature data about the symptoms referred by patients with sensitization to panallergens. Panallergens should be considered as clinically relevant food allergens.

Key words: food allergy, panallergens, IgE, cross-reaction.

Introduction

Panallergens originate from unrelated organisms that share highly conserved sequence regions and three-dimensional structures and hence can fulfill the requirements for IgE cross-reactions between inhalant, latex and plant-derived food allergens (Table 1) [1].

The most important panallergens are lipid transfer proteins (LTP), profilins and PR-10 (pathogenesis-related proteins). Lipid transfer proteins constitute a proteins family widely distributed through the plant kingdom and they play a role in plant defense for their antifungal and antibacterial activities [1]. Allergenic LTP have been identified in tree and weed pollens of vegetable foods, fruits and latex.

The primary sensitizer agent and the most involved fruit seem to be the peach [2], which belongs to the Rosaceae family. Allergy to Rosaceae fruits linked to LTP

have been mainly described in Italy, Spain and Greece [3] and only exceptionally in central and northern Europe where allergy to Rosaceae fruits is more often associated with Bet v 1, the major allergen of birch [4].

In addition to the geographical area, the allergenic potential of LTP is influenced by their localization and stability to proteolytic and thermal denaturation. Lipid transfer proteins are stable molecules, predominantly present in the fruit peel; this might explain why some LTP-sensitized individuals easily tolerate fruits without peel [5, 6]. Lipid transfer proteins may induce sensitization through the oral route and may determine systemic symptoms also upon oral ingestion of both fresh and processed food as beer, fruit juices, wine, etc. [7].

Profilin, instead, comprises a family of highly conserved proteins, which are present in all eukaryotic cells and are involved in processes related to cell motility

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Table 1. Most important panallergens and their related vegetable foods

PR 10 (Bet v 1 like proteins)	Hazelnut, apple, celery, cherry, peach, carrot, potato etc.
Lipid transfer protein (LTP)	Peach, apple, soy, hazelnut, wheat, lettuce, etc.
Profilin	Kiwi, melon, chestnut, banana, pear, pepper, etc.

[8, 9]. The first allergenic profilin was described in birch pollen and was designated Bet v 2 [10]. Profilin sensitization varies between 5% and 40% among allergic individuals and sensitization to Bet v 2 was observed in about 20% of patients allergic to birch pollen in different studies [10–13].

Allergenic profilins were identified in tree and grass pollens, in weeds, in plant-derived foods, as well as in latex [1]. Due to its conserved structure, profilin-specific IgE may cross-react with homologues from virtually every plant source. Therefore, profilin sensitization is a risk factor for allergic reactions to food allergen sources [14].

Profilin is randomly distributed in pulp and peel and it is labile to heat denaturation and pepsin digestion [15]. So it is unable to cause sensitization via the gastrointestinal tract. In fact, the ingestion of raw fruits in profilin sensitized patients usually determines reactions restricted to the oral cavity (oral allergy syndrome – OAS), despite in the literature systemic reactions to zucchini and litchies are reported [16].

The PR-10 family consists of the Bet v 1 homologues, a protein with unknown function induced in stress conditions [17].

Bet v 1 is the major allergen of birch and about 50–70% of birch pollen allergic patients, usually after respiratory sensitization, report symptoms after ingestion of a large spectrum of fruits and vegetables such as apple, hazelnut, peach and potato.

PR-10 proteins are randomly distributed in pulp and peel and many vegetable food proteins homologous to Bet v 1, especially belonging to *Rosaceae*, are extremely labile and easily destroyed by heat, oxidation, extraction procedures and pepsin digestion [18, 19]. So the PR-10 allergic patients present a good tolerance for heat-processed foods as well as of commercial fruit juices and their symptoms rarely differ from the oral allergy syndrome.

Aim

The aim of our study was to assess: the pattern of sensitization to lipid transfer proteins, profilin and PR-10 in a patients with clinical history of plant-derived foods hypersensitivity; the correlation between panallergens sensitization and symptoms; the allergological evaluation of food and aeroallergens in patients sensitized to panallergens.

Material and methods

Patients

We studied 120 subjects (39 males and 81 females) with history of adverse reactions after the ingestion of plant-derived foods and sensitized to at least one panallergen. All subjects referred to the Allergy Unit of the Policlinico “A. Gemelli” in Rome between June 2010 and May 2013 underwent a thorough medical interview to identify the food involved in the reactions and the triggered symptoms. Symptoms were divided into the oral allergy syndrome (itching, burning and swelling of lips, tongue, roof of the mouth or throat) and systemic reactions (urticaria-angioedema, respiratory symptoms, gastrointestinal symptoms, anaphylaxis).

Skin test

All the patients underwent skin prick tests (SPT) with commercial extracts (Alk-Abellò, Milan, Italy; Lofarma, Milan, Italy; Stallergenes, Milan, Italy; Allergopharma, Milan, Italy) of plant-derived foods and inhalant allergens present in our geographical area (grass pollen, pellitory, compositae, olive tree, cypress, birch, hazel tree) and with fresh fruit/vegetables (prick by prick method) referred in anamnesis.

Furthermore all the patients underwent SPT with commercial extracts of LTP, profilin and PR-10 (all from Alk-Abellò, Milan, Italy).

All SPTs were performed according to the EAACI guidelines [20], wheal reactions that equalled or exceeded a diameter of 3 mm were considered positive after 15 min. The SPT with histamine (10 mg/ml) and saline solution were carried out as positive and negative control, respectively.

Serological tests

Quantification of specific IgE to the studied panallergens was performed according to the manufacturer's instructions (UniCAP System; Pharmacia, Uppsala, Sweden). We considered some recombinant allergens of LTPs (Pru p 3), profilin (Pru p 4) and PR-10 (Pru p 1). Samples with specific IgE concentrations of ≥ 0.35 KU/l were regarded as positive.

Statistical analysis

Associations were assessed by the Fisher's exact test. Values of $p < 0.05$ were considered statistically significant.

Results

Characteristics of our population

Ninety-five/120 (79%) patients were monosensitized (76 to LTP, 14 to Profilin and 5 to PR-10), instead twenty-five/120 were contemporaneously sensitized to > 1 panallergen (14 LTP + Profilin; 9 LTP + PR-10; 2 LTP + Profilin

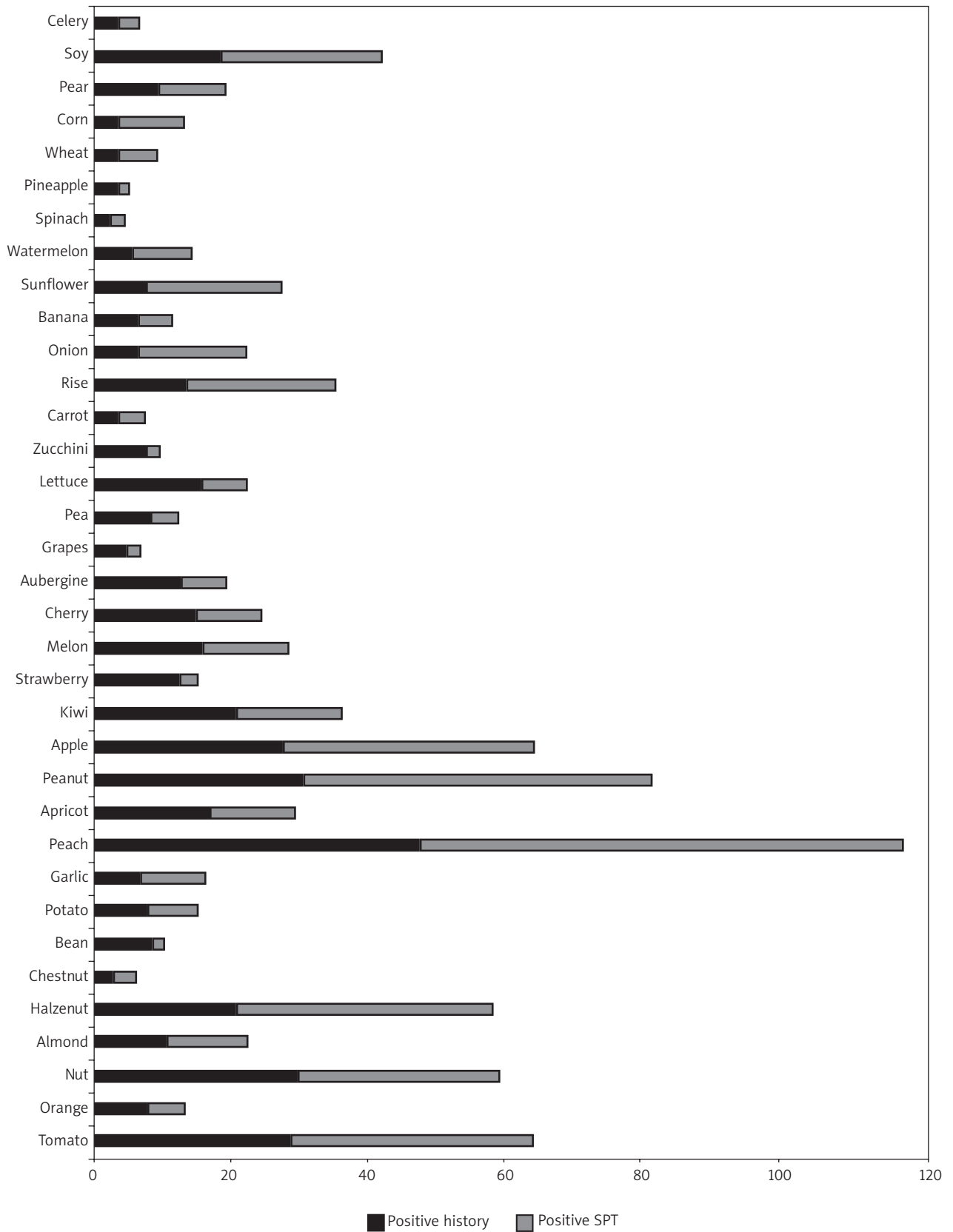


Figure 1. Offending foods and skin reactivity in the total population

Table 2. Offending foods and statistical associations

Food	nsLTP (N = 76)	Value of p	Profilin (N = 14)	Value of p	PR-10 (N = 5)	Value of p
Tomato	20	NS	3	NS	2	NS
Orange	5	NS	0	NS	1	NS
Nut	23	0.04	1	NS	1	NS
Almond	6	NS	0	NS	0	NS
Hazelnut	12	NS	2	NS	3	0.03
Chestnut	2	NS	0	NS	0	NS
Bean	5	NS	0	NS	0	NS
Potato	5	NS	1	NS	0	NS
Garlic	4	NS	0	NS	0	NS
Peach	30	NS	5	NS	4	NS
Apricot	5	NS	3	NS	1	NS
Peanut	23	NS	2	NS	1	NS
Apple	11	NS	6	NS	3	NS
Kiwi	10	NS	4	NS	3	NS
Strawberry	4	NS	0	NS	2	NS
Melon	3	NS	6	0.002	0	NS
Cherry	5	NS	0	NS	4	< 0.01
Aubergine	7	NS	2	NS	1	NS
Grapes	2	NS	0	NS	1	NS
Pea	5	NS	1	NS	0	NS
Lettuce	13	0.04	1	NS	0	NS
Zucchini	4	NS	2	NS	0	NS
Carrot	1	NS	0	NS	2	NS
Rice	10	NS	2	NS	0	NS
Onion	5	NS	0	NS	0	NS
Banana	5	NS	0	NS	0	NS
Sunflower	7	0.04	0	NS	0	NS
Watermelon	3	NS	0	NS	0	NS
Spinach	2	NS	0	NS	0	NS
Pineapple	3	NS	0	NS	0	NS
Wheat	2	NS	1	NS	0	NS
Corn	3	NS	0	NS	0	NS
Pear	5	NS	0	NS	2	NS
Soy	14	0.01	0	NS	0	NS
Celery	3	NS	0	NS	0	NS

+ PR-10). Ninety-one out of 120 patients referred systemic symptoms after ingestion of different plant foods while only 29 described the oral allergy syndrome. Foods most commonly implicated in symptoms were peach, tomato, nut, peanut, apple, hazelnut (Figure 1). A large part of the patients (98/120 (82%)) suffered from pollen allergy:

grass had the highest sensitization rate, followed by pelitory pollen, compositae pollen and birch pollen.

Clinical history

Sixty-four out of 76 (84%) patients of the LTP group suffered from systemic symptoms, while only 12/76 of them (16%) referred the oral allergy syndrome ($p < 0.01$).

On the other hand, the oral allergy syndrome prevails in patients sensitized only to profilin (57%; $p < 0.005$) and also in those belonging to the PR-10 group (80%; $p < 0.01$). We did not find any significant association between referred symptoms and sensitization to more than one panallergen.

The most commonly foods involved in the reactions are described in Table 2. In this table we observed a significant association between the sensitization to LTP and adverse reaction to nut, lettuce, sunflower and soy, between profilin and melon and finally between PR-10 and hazelnut and cherry.

Skin prick tests with pollen extracts

Concerning pollen sensitization we did not observe any significant association in the LTP group with pollen; on the contrary, the profilin group showed to be significantly positively related to SPT to Grass pollen (12/14 patients; $p < 0.01$), and Birch pollen (4/14; $p < 0.01$). The last one pollen was significantly higher not only in the PR-10 group but also in the LTP + PR-10 group ($p < 0.01$).

Skin prick tests with plant-derived foods

When we analyzed the LTP-sensitized patients, we found a statistically significant association between almond, peanut, rice, onion, sunflower and soy ($p < 0.05$). Further, LTP reactors showed a higher prevalence of sensitization to peach, tomato and nut. As to the profilin group, there was a significant association with kiwi, melon and banana ($p < 0.05$). Finally, the food allergological evaluation in patients sensitized to PR-10 showed a significant association between PR-10 and sensitization to hazelnut, apple, strawberry and pear ($p > 0.05$) (Table 3).

Discussion

Plant-derived food allergy is an increasing and emerging problem of public health; its prevalence is hard to determine as valid tests and standard testing procedures are lacking [21].

As to fruit allergy, in a review by Zuidmeer *et al.*, 2.2–11.5% of children aged 0–6 years and 0.4–6.6% of adults worldwide based on self-reported data seem to be allergic to these foods. As to the vegetable allergy epidemiology, the data are confused, limited and fragmentary. The wide ranges in occurrence determination probably reflect differences in fruit and vegetable allergy prevalence between countries [22].

This epidemiologic and clinical complicated scenario could be resolved by the study of major panallergens sensitization, which role is always more emerging in the literature. So the LTP, PR-10 and profilin seem to be the causal agents of reaction such as the oral allergic syndrome, urticaria, gastrointestinal diseases (abdominal pain, diarrhoea, vomiting), anaphylaxis.

In the present study we are going to analyze the frequency and features of plant-derived food allergy on the basis of panallergens sensitization in 120 subjects of the central and southern Italy.

In the literature, other studies about the component-resolved diagnosis (CRD) of plant-derived food allergy are present [23]; otherwise our study is a further attempt to characterize the correlation between the patients' clinical features and the allergological evaluation, using also the sIgE assay.

We enrolled 120 Italian patients with symptoms after eating plant-derived foods. The majority of the patients (about 68%) were females as confirmed by other studies [24]. The main offending foods reported by patients were peach, tomato, nut, peanut, apple, hazelnut. We related this observation to the studied geographical area, where prevails LTP sensitization.

In the most cases, allergens originate from pollen source, which cross-react with allergens from fruits due to similarities in protein structures [25, 26]. In our population, a large part of patients present pollen allergy, suggesting the relevance of the increased prevalence of airborne allergies as a trigger of pollen-food allergy [27]. Analyzing the single panallergens, only the PR-10 and profilin sensitized patients showed a significant correlation respectively with the birch tree pollen for the first one and birch tree and grass pollen for the last one. As expected, the majority of these subject-reported mild local symptoms such as the oral allergy syndrome due to the lability of these two proteins to heat denaturation and pepsin digestion.

On the contrary, in keeping with the previous study, we did not observe a correlation between pollens and LTP sensitization [22].

Focusing on the symptoms referred by LTP-sensitized patients, we observed a prevalence of systemic manifestations such as urticaria-angioedema, respiratory (asthma, rhinitis) and gastrointestinal (abdominal pain, diarrhea, vomiting) diseases. In the literature these data are confirmed [1].

As to the culprit foods involved in reactions, we were going to analyze the correlation between the panallergen sensitization and the plant-derived food allergological evaluation outcomes. An accordance between the trigger foods described in anamnesis and the food allergological tests was observed in all the subjects.

Analyzing in detail the sensitization pattern of each panallergen, we observed a prevalence of sensitization to vegetables and fruits belonging to Rosaceae (particularly

Table 3. Positive allergological findings and statistical association

Food	nsLTP (N = 76)	Value of p	Profilin (N = 14)	Value of p	PR-10 (N = 5)	Value of p
Tomato	21	NS	5	NS	1	NS
Orange	5	NS	1	NS	0	NS
Nut	22	NS	0	NS	2	NS
Almond	4	0.03	2	NS	2	NS
Hazelnut	22	NS	2	NS	5	0.01
Chestnut	2	NS	1	NS	1	NS
Bean	2	NS	0	NS	0	NS
Potato	1	NS	3	NS	1	NS
Garlic	8	NS	1	NS	0	NS
Peach	46	NS	3	NS	5	NS
Apricot	7	NS	2	NS	1	NS
Peanut	41	< 0.01	2	NS	0	NS
Apple	19	NS	5	NS	5	< 0.01
Kiwi	5	NS	4	< 0.001	3	NS
Strawberry	1	NS	0	NS	1	0.03
Melon	2	NS	7	< 0.001	1	NS
Cherry	4	NS	0	NS	3	NS
Aubergine	3	NS	1	NS	0	NS
Grapes	2	NS	0	NS	0	NS
Pea	4	NS	0	NS	0	NS
Lettuce	5	NS	1	NS	0	NS
Zucchini	1	NS	1	NS	0	NS
Carrot	2	NS	1	NS	1	NS
Rice	19	0.01	0	NS	0	NS
Onion	16	< 0.01	0	NS	0	NS
Banana	1	NS	3	0.01	0	NS
Sunflower	17	0.04	1	NS	0	NS
Watermelon	2	NS	3	NS	1	NS
Spinach	2	NS	0	NS	0	NS
Pineapple	2	NS	0	NS	0	NS
Wheat	2	NS	3	NS	0	NS
Corn	6	NS	2	NS	0	NS
Pear	5	NS	1	NS	3	0.003
Soy	20	< 0.01	0	NS	0	NS
Celery	2	NS	0	NS	0	NS

to peach) in all the groups although without a significant role; we believe that this result is due to the fact that the peach contains all the panallergens studied.

Similarly to what has been shown by other authors, we noticed a significant association between LTP and

sensitization to all the seed groups, between profilin and sensitization to kiwi, melon and banana and between PR-10 and positive tests to hazelnut, peach and pear [23].

Conclusions

Because allergic patients to panallergens present a poor quality of life for possible metabolic imbalance and problems to manage their diet without restriction, it is important to identify them with an appropriate allergological evaluation in order to treat them permanently with desensitization therapy such as described in the literature [28–31].

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Eleonora Nucera and Simona Mezzacappa equally contributed.

Conflict of interest

The authors of this manuscript state that the article is original and has not yet been published either wholly or in part. They state that they are responsible for the research that they have designed and carried out; that they have participated in drafting and revising the manuscript submitted, whose contents they approve. They also state that the research reported in the paper was undertaken in compliance with the Helsinki Declaration. They agree to inform the editors of any conflict of interest that might arise, particularly any financial agreements they may have with pharmaceutical or biomedical firms whose products are pertinent to the subject matter dealt with in the manuscript.

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