

Prevalence of Sensitization to Lipid Transfer Proteins and Profilins in a Population of 430 Patients in the South of Madrid

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■ Abstract

Background: Lipid transfer proteins (LTPs) and profilins are the most important panallergens in the management of patients who are allergic to pollen and plant food in our area. LTPs are highly stable proteins that can induce systemic symptoms after ingestion. Profilins are labile proteins that are present in pollens and vegetables. Considered markers of several types of pollen sensitization, they are responsible for cross-reactivity between pollens and vegetables. The objective of this study was to assess the frequency of sensitization to LTP and profilin using skin prick tests (SPTs) in patients referred to our allergy unit for any complaint (not only pollen and plant food allergy).

Methods: The study sample comprised 430 consecutive patients who were evaluated using their medical history and SPTs with pollen, date palm profilin, and peach extract enriched in Pru p 3 (30 µg/mL) as an LTP marker.

Results: We found that 52 (12.1%) patients were sensitized to profilin and 53 (12.3%) to LTP. Pollen allergy was diagnosed in 53% and plant food allergy in 11%. In the LTP-sensitized group and the profilin-sensitized group, 37.7% and 34.6% of the patients had plant food allergy, respectively. Thirty-three patients (62.3%) were sensitized to LTP but had no symptoms after eating vegetables.

Conclusions: To the best of our knowledge, this is the first study to analyze the real rate of sensitization to profilin and LTP in a population sensitized to allergens other than pollens and plant foods. Twelve percent of patients were sensitized to both profilin and LTP. A large proportion of LTP-sensitized patients had no symptoms at the time of the study.

Key words: Allergy. Fruit. LTP. Plant food. Pollen. Profilin. Pru p 3. Sensitization.

■ Resumen

Introducción: Las Proteínas Transportadoras de Lípidos (LTPs) y las Profilinas son los panalergenos más importantes en el manejo de los pacientes alérgicos a polen y frutas en nuestra área. Las LTPs son proteínas muy estables capaces de inducir clínica sistémica tras su ingestión. Las profilinas son proteínas lábiles que se encuentran en pólenes y vegetales; se consideran marcadores de polisensibilización a pólenes, y son responsables de los fenómenos de reactividad cruzada entre pólenes y vegetales. El objetivo del estudio fue investigar la frecuencia de sensibilización a LTP y Profilina, por medio de pruebas cutáneas (PCs), en pacientes que remitidos por cualquier motivo (no sólo alérgicos a pólenes y vegetales) a nuestra Unidad de Alergia.

Métodos: Cuatrocientos treinta pacientes consecutivos fueron evaluados por medio de una historia médica y la realización de PCs con pólenes, profilina de palmera y un extracto de melocotón enriquecido en Pru p 3 (30 µg/ml) (como marcador de LTP).

Resultados: Cincuenta y dos sujetos (12.1%) estaban sensibilizados a profilina y 53 (12.3%) a LTP. Se diagnosticó alergia al polen en 53% de los pacientes, y alergia a vegetales en 11%. En el grupo sensibilizado a LTP y en el grupo sensibilizado a profilina, 37.7% y 34.6% de los pacientes referían alergia a alimentos vegetales respectivamente. Treinta y tres pacientes (62.3%) estaban sensibilizados a LTP pero no presentaban síntomas al comer vegetales.

Conclusiones: Hasta donde tenemos conocimiento, esta es la primera vez que se ha realizado una aproximación a la proporción real de sensibilización a profilina y LTP en una población no solo sensibilizada a pólenes y vegetales, mostrando un porcentaje de sensibilización a ambas proteínas, profilina y LTP, del 12%. Una gran proporción de los pacientes sensibilizados a LTP, tenían una sensibilización asintomática en el momento del estudio.

Palabras clave: Alergia. Fruta. LTP. Polen. Profilina. Pru p 3. Sensibilización. Vegetales.

Introduction

Component-resolved diagnosis of allergic diseases has become essential in the management of allergic patients [1-4]. In recent years, important advances in this field have partly clarified the diagnosis of some pollen and plant food allergies.

Lipid transfer proteins (LTPs) are highly stable during thermal processing and digestion; this makes them potent food allergens that usually induce systemic symptoms after ingestion [5-9]. LTPs are implicated in cuticle formation and defense against pathogens and are present in several plant food sources (fruits, vegetables, nuts). They have been identified as major allergens in fruits belonging to the *Rosaceae* family (eg, Pru p 3 in peach) [10]. Peach is the most frequently involved fresh fruit in allergic reactions in Mediterranean countries [11-14], and more than 60% of patients with peach allergy are sensitized to Pru p 3 in our area [10]. LTPs are the most important family of plant food allergens in Spain [15]. Recent studies have shown the rate of sensitization to LTP to be 10% in pollen-allergic patients [3] and around 8% in pollen-allergic patients with no symptoms of plant food allergy [15].

Profilins are ubiquitous labile proteins that are present in pollens and vegetables [16]. They are considered markers of several types pollen sensitization [17,18], thus explaining positive results in SPTs with pollen extracts, although these are not always clinically relevant. Between 10% and 50% of pollen-allergic patients are sensitized to profilin [3,19]. Profilins are also responsible for the so-called pollen-fruit syndrome, in which fruit-allergic patients cosensitized to pollens experience mild oral symptoms (oral allergy syndrome) [19,20]. Around 30% of patients with allergy to pollen and plant food are sensitized to profilin [15]. Bet v 1-like allergens are mainly implicated in the pollen-fruit syndrome in North and Central Europe, but the prevalence of sensitization to these allergens in our area is very low.

LTPs and profilins are the most important panallergens in the clinical management of patients with allergy to pollen and plant food in our area. Nowadays, these panallergens can be used as purified allergens or as whole extract with exact quantities of allergen to perform SPTs at the doctor's office. They are a fast and inexpensive source of valuable information on cross-reactivity, clinical severity, and avoidance.

Rates of sensitization to these allergens in patients who are allergic to pollen and fruit are well known and may depend on geographic area. Knowledge of the prevalence of sensitization to these relevant allergens in the population would be extremely useful. However, the study design required to reach this objective would be too extensive for our group to perform. The present study aimed to provide an approximate assessment of the frequency of sensitization to LTP and profilin using SPTs in patients referred to our allergy unit for any complaint. Although these patients suffer allergic disease more frequently than the general population, this is the first time sensitization to LTP and profilin has been investigated in patients without symptoms of pollen or plant food allergy.

Methods

Patients

The study sample comprised consecutive patients older than 4 years referred from September to December 2008 to the Allergy Unit of Hospital Universitario de Fuenlabrada, Madrid, Spain. Selection was not based on individual diseases, and patients with rhinoconjunctivitis, asthma of any etiology, food allergy, cutaneous symptoms (eg, urticaria, dermatitis), or drug allergy were invited to participate. All the patients—or representatives in the case of children—who agreed and signed the informed consent document were included.

Study Design

The clinical evaluation comprised an exhaustive medical history with data on pollen and plant food allergy. We also performed SPTs with the common panel of pollens in our area (grass mix, olive, *Platanus acerifolia*, *Cupressus arizonica*, mugwort, *Chenopodium album*, plantain, pellitory, *Salsola kali*) and date palm profilin. A peach extract enriched in Pru p 3 was used as the LTP marker (Pru p 3 extract content: 30 µg/mL) (ALK Allergologisk Laboratorium A/S, Horsholm, Denmark). Saline and histamine were used as negative and positive controls, respectively. An SPT result was considered positive if the difference between the mean diameter of the wheal and the negative control was at least 3 mm [21].

Statistical Analysis

Data on continuous variables are presented as median (interquartile range), and crude analyses were performed using the Mann-Whitney test for nonnormally distributed data. Categorical variables were analyzed using the χ^2 test. *P* values <.05 were considered statistically significant. Logistic regression and the Fisher exact test were used to evaluate the risk of suffering plant food allergy and pollen allergy in patients sensitized to LTP or profilin. The statistical analysis was performed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois, USA).

Results

The study population comprised 430 patients, of whom 283 (66%) were referred to our unit for respiratory symptoms, 57 (13.3%) for reactions to drugs, 41 (9.6%) for skin symptoms, 40 (9.3%) with problems after eating foods, and 9 (2.09%) for other reasons. Median age was 27 years (15-41 years), with a gender distribution of 230 females (53.5%) and 200 males (46.5%). Three hundred and ninety-seven patients (92.3%) were born in Spain and 33 patients (7.7%) were foreign, mostly from South America (46.2%).

More than half of the patients (227 [52.8%]) suffered from pollen allergy; 223 (98.2%) of these patients had rhinoconjunctivitis and 149 (65.6%) asthma. Among patients with pollen allergy, grass had the highest sensitization rate (194 patients [85.5%]), followed by olive pollen (170 patients [74.9%]) and *Chenopodium album* (166 patients [73.1%]).

The results of SPT were positive in 203 patients (65.8%); 66 (23.3%) had no clinical symptoms at inclusion. Thirty-three patients (7.7%) had received specific immunotherapy or were receiving it at inclusion.

Plant food allergy was diagnosed in 48 patients (11.2%). The foods most commonly implicated in symptoms according to the clinical history were peach (20 patients [41.6%]), melon (16 [33.3%]), watermelon (13 [27%]), kiwi (9 [18.7%]), and banana (9 [18.7%]). Approximately 40% of the patients referred symptoms with only 1 food and 60% with more than 1 food.

Pattern of Sensitization to Panallergens

Taking the study sample as a whole (n=430), we found that 40 patients (9.3%) were sensitized to profilin, 41 (9.5%) to LTP, and 12 (2.7%) to both. This is, 52 patients (12.1%) were sensitized to profilin and 53 (12.3%) to LTP. The sensitization profile and the clinical manifestations of these patients are summarized in the Table.

LTP Allergy Group

In the LTP-sensitized group, 37 patients out of 53 (69.9%) suffered pollen allergy ($P<.05$) and 20/53 (37.7%) suffered plant food allergy ($P<.001$): therefore, 33/53 (62.3%) sensitized to LTP did not have symptoms after eating vegetables or other plant foods (eg, nuts) at the time of the study ($P<.001$). No significant associations were observed between sensitization to LTP and the presence of rhinitis or asthma.

Profilin Allergy Group

In the profilin-sensitized group, 49/52 patients (94.2%) had pollen allergy ($P<.001$), 18/52 patients (34.6%) had plant food allergy ($P<.001$), and 18/52 patients (34.6%) had both pollen

allergy and plant food allergy. All the patients in the profilin group were sensitized to more than 1 pollen. Fifty (96.1%) patients sensitized to profilin suffered from rhinitis ($P<.001$) and 40 (76.9%) from asthma ($P=.001$).

Plant Food Allergy Group

When analyzing only the patients with plant food allergy, 20/48 (41.7%) were sensitized to LTP ($P<.001$) and 18/48 (37.5%) to profilin ($P<.001$). Sixteen patients (33.3%) were not sensitized to either of the allergens. Eighteen patients (34.6%) sensitized to profilin developed plant food allergy.

Pollen Allergy Group

Among the 227 pollen-allergic patients, 49 (21.6%) were sensitized to profilin ($P<.001$), 37 (16.3%) to LTP ($P<.05$), and 11 (4.8%) to both; 6 of these 11 patients suffered from plant food allergy.

Severity of Symptoms and Number of Fruits Implicated

In the group of patients with plant food allergy who were sensitized to LTP, we found that 18/21 patients (86%) had only local symptoms and 3/21 patients (14.3%) had local and systemic complaints after eating fruits or vegetables (no data were available for the remaining patients). No patients had systemic involvement only. All the patients sensitized to profilin had local symptoms only.

In the group of patients sensitized to profilin, 30% had symptoms with 1 fruit only and 70% with several plant foods. All the patients sensitized to LTP had symptoms with *Rosaceae* fruits or with *Rosaceae* and other plant foods; 63.9% of the patients reported symptoms with only 1 fruit and 36.4% with more than 1 fruit or vegetable.

Table. Sensitization Profile and Clinical Manifestations^a

Sensitization (Number of Patient)	Pollen		Plant Food		Pollen and Plant Food	
	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic
Profilin (n=40)	38/40 (95%)	2/40 (5%)	12/40 (30%)	28/40 (70%)	12/40 (30%)	NA
LTP (n=41)	26/41 (63.4%)	15/41 (36.6%)	14/41 (34.1%)	27/41 (65.9%)	6/41 (14.6%)	NA
Profilin + LTP (n=12)	11/12 (91.7%)	1/12 (8.3%)	6/12 (50%)	6/12 (50%)	6/12 (50%)	NA
None (n=337)	152/337 (45.1%)	185/337 (54.9%)	16/337 (4.7%)	321/337 (95.3%)	6/337 (1.8%)	NA
Total (n=430)	227/430 (52.8%)	203/430 (47.2%)	48/430 (11.2%)	382/430 (88.8%)	30/430 (7%)	NA

Abbreviation: NA, not available (due to the design of the study).

^aThe data in the text are analyzed for the profilin and the LTP-sensitized groups as a whole. In this table, data are divided into patients sensitized to profilin, patients sensitized to LTP, and patients sensitized to both

Risk Assessment

Using a logistic regression model with LTP as the target variable and pollen and plant food allergy as covariates, we observed an odds ratio (OR) of 6.6 (95% confidence interval [CI], 3.3-13) for plant food allergy and 2.4 (95% CI, 1.25-4.5) for pollen allergy. An identical model with profilin as the target variable and the same covariates yielded an OR of 4.9 (95% CI, 2.3-10.4) for plant food allergy and 14.9 (95% CI, 5.2-42.4) for pollen allergy.

Discussion

We determined the prevalence and clinical relevance of sensitization to 2 of the main known panallergens (LTP and profilin) in our area.

Since it is known that more than 20% of pollen-allergic patients are sensitized to profilin [19] and more than half of the patients in this study suffered from pollen allergy, we expected a higher rate of sensitization to profilin than to LTP. However, we observed an equal proportion of sensitization to LTP and profilin (12%).

The rate of sensitization to profilin in pollen-allergic patients was almost 22%, which is consistent with previous studies [19], but higher than that observed in a recent Spanish multicenter study [15]. The proportion of profilin-sensitized patients suffering from pollen allergy was very high (94%). As expected, since most of the patients sensitized to profilin had pollen allergy, an association was observed between sensitization to profilin and rhinitis (96%) and asthma (77%). Furthermore, the percentage of food allergy in the profilin-sensitized patients and the rate of profilin sensitization in patients with allergy to plant foods were both around 35%; similar data had been found in previous studies [15]. We observed that an individual who is allergic to plant food is almost 5 times more likely to be sensitized to profilin than one who is not. This proportion increases significantly for pollen allergy, where an allergic individual is almost 15 times more likely to be sensitized to profilin than one who is not. Since previous studies [3,4] had reported that only some profilin-sensitized patients (35% in the present study) develop food allergy, we hypothesized that profilin might simply be a marker for food allergy as a pollen allergen present in vegetables. A similar pattern is observed with Bet v 1-like allergens, which are also present in pollen and plant foods.

Regarding LTP, the rate of sensitization to this protein was 16% in the pollen-allergic group but almost 70% in LTP-sensitized patients with pollen allergy. In addition, 42% of fruit-allergic patients were sensitized to LTP, which is similar to previous findings in the Vegetalia study [15]. However, only 37% of patients sensitized to LTP had symptoms after eating vegetables and 62% reported no food allergy symptoms, indicating that almost two-thirds of the patients had asymptomatic sensitization to LTP at the time of the study. Patients have a 6.6-fold higher probability of being sensitized to LTP when they have plant food allergy than when they do not, supporting the fact that LTP is an important plant food allergen in our area. We also observed that patients have a

2.4-fold greater probability of being sensitized to LTP if they have pollen allergy than if they do not.

As for severity of food allergy symptoms and sensitization profile, the whole group of profilin-sensitized patients had only local symptoms after eating vegetables. In patients allergic to plant food and LTP, 15% had systemic symptoms after eating the food and 85% had only local symptoms. Although it is well known that LTPs are stable allergens capable of inducing systemic and severe reactions, our results support those of previous studies in which most of the LTP-sensitized patients presented only mild symptoms [22].

The main interest of our study lies in the fact that the sample comprised all patients referred to our unit for evaluation, not only those who were allergic to pollen, plant foods, or both. Thus, the study tries to establish the real rate of sensitization to these allergens in the general population. The main limitation of the study is the selection bias generated by the fact that the percentage of allergic diseases in the population referred to our unit is higher than in the general population. Therefore, the above-mentioned results should be considered an approximation.

Our results are generally consistent with those of previous studies on pollen and plant food allergy in our area. Nevertheless, to the best of our knowledge, this is the first attempt to establish the real rate of sensitization to profilin and LTP in a population not only sensitized to pollens and plant foods. A very relevant finding is the large proportion of patients with asymptomatic sensitization to LTP; more than 60% of LTP-sensitized individuals had no symptoms after eating fruits or other plant foods. This is particularly interesting, since LTP (Pru p 3) meets the criteria to be considered a class I food allergen. The percentage of asymptomatic or latent LTP sensitization had been reported before in only one study, and it reached 8% of the pollen-allergic patients studied [15]. We observed that almost 6% of patients were sensitized to profilin without symptoms of pollen allergy.

More studies are necessary to follow patients with asymptomatic sensitization to LTP or profilin, and, in particular, to investigate the development and timing of onset of symptoms with pollens or vegetables.

Although recent research into component-resolved diagnosis has proven useful in the management of allergy, the significance of panallergen sensitization has yet to be determined. The data obtained from such studies could provide us with additional therapeutic tools and a better understanding of the routes of sensitization and clinical relevance of this condition.

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