



Submitted: 23.3.2022

Accepted: 25.7.2022

Conflict of interest

None.

DOI: 10.1111/ddg.14881

Lipid transfer protein allergy: characterization and comparison to birch-related food allergy

Paula Wolters¹, Thomas Ostermann², Silke C. Hofmann¹

(1) Department of Dermatology, Allergy and Dermatosurgery, Helios University Hospital Wuppertal, University Witten/Herdecke, Wuppertal, Germany

(2) Department for Psychology and Psychotherapy, Faculty of Health, University Witten/Herdecke, Witten, Germany

Summary

Background: Lipid transfer proteins (LTP) are a frequent elicitor of anaphylaxis to plant-derived food allergens in southern Europe.

Patients and methods: 15 German patients with LTP allergy were compared to 17 patients with birch-related food allergy (BRFA) using a detailed anamnesis, serology, skin tests, and the FAQLQ-AF quality of life questionnaire.

Results: While patients with BRFA mainly reacted to tree nuts, and pome and stone fruits, LTP allergic individuals reported vegetables, berry fruits, cereals, and seeds as common additional elicitors. Anaphylaxis was associated with cofactors in 73 % of LTP allergic patients compared to only 6 % in BRFA ($P < 0.001$). Symptoms occurred delayed by more than one hour in 40 % and were triggered by raw and cooked foodstuffs in 86 % of LTP allergic patients, compared to only 6 % and 41 % of BRFA patients, respectively. A peach prick test was positive in all LTP allergic patients, but only in 15 % of BRFA patients ($P < 0.001$). Although patients with LTP allergy reported severe anaphylaxis more frequently, quality of life did not differ between groups.

Conclusions: Anaphylaxis to plant-derived foodstuffs warrants assessment by IgE detection to Pru p 3 and skin tests with peach extract, particularly if cofactors and intolerance to heated foodstuffs are related.

Introduction

With a prevalence of approximately 6 %, food allergy represents one of the most important immediate type allergies in Europe with substantial variation in causative foods across different European areas [1]. Non-specific lipid-transfer proteins (nsLTPs) are ubiquitous proteins in plant-derived foodstuffs and pollen [2]. LTP syndrome was first reported in Italy and Spain, where the 9 kDa LTP of peach (*Prunus persica*), Pru p 3, was identified as marker allergen [3]. In southern Europe LTP allergy is considered the most frequent primary food allergy. Clinical manifestations range from mild contact urticaria to potentially life-threatening anaphylactic reactions [4]. Due to the widespread distribution of LTPs in fruits, vegetables, legumes, nuts, seeds, and cereals LTP allergic individuals often suffer from allergic symptoms after ingestion of various plant-derived foodstuffs [5, 6]. Therefore, health-related quality of life (HRQL) is expected to be reduced.

In central and northern Europe, birch-related food allergy (BRFA) represents the most common form of food allergy

[7] confirmed by IgE detection to the major birch pollen allergen Bet v 1. Patients are primarily sensitized to pollen of birch (*Betula verrucosa*) manifesting as allergic rhinitis or asthma. Sensitization to homologous PR10-proteins in birch-related foodstuffs is associated with secondary food allergy. Affected patients are burdened by contact urticaria of the oropharyngeal sites (oral allergy syndrome) and, less frequently, by systemic allergic reactions after consumption of foodstuffs containing Bet v 1-homologs, for example pome and stone fruits, hazelnut, soy, kiwifruit, or carrot.

Health-related quality of life as assessed by means of the *Food Allergy QoL Questionnaire – Adult Form* (FAQLQ-AF) was shown to be impaired, particularly in women, elderly individuals, and those with multiple relevant food allergies [8].

While nearly 70 % of adults with peanut (*Arachis hypogaea*) allergy in the Mediterranean area react to the LTP Ara h 9, severe peanut allergy in Central Europe is mostly due to sensitization to peanut storage proteins, such as Ara h 2. In contrast, sensitization to the Bet v 1 homolog Ara h 8 is

more common in central Europe, with predominantly mild symptoms [9, 10].

In the last five years, increasing evidence for occurrence of LTP allergy in Central Europe has been published, although the LTP-sensitizing source remains elusive. Faber et al. calculated a prevalence of 25 % in a group of Belgian patients allergic to pollen and/or plant food [11]. However, the majority of these patients showed clinically silent sensitization to the LTPs from peach, apple, peanut, or hazelnut. In contrast, severe food-induced anaphylaxis could be attributed to Pru p 3 sensitization in 10/13 Austrian patients with reactions to plant-derived food such as apricot, raspberry, and peach [12]. Furthermore, cabbage, lettuce, and mustard were additionally identified as LTP-containing foodstuffs in native British patients with LTP allergy [13]. In Germany, only casuistic evidence of LTP allergy has been reported to date [14, 15].

The aim of this study was to characterize all patients with LTP allergy diagnosed in our department in the past five years with regard to eliciting foodstuffs, clinical manifestations, the role of cofactors, and HRQL. To better understand this burdensome condition in a German cohort, LTP allergic patients were compared to patients with BRFA.

Patients and methods

Patients and data collection

This prospective monocentric study included 15 adult patients with LTP allergy, consecutively diagnosed at the Department of Dermatology, Allergy and Dermatocurgery, Helios University Hospital Wuppertal, Germany, between January 2016 and February 2021.

Diagnosis was confirmed by a history of previous anaphylactic reactions to plant foods and serological detection of IgE antibodies to the peach LTP Pru p 3 ($> 0,35$ kU/l, ImmunoCAP, Thermo Fisher Scientific, Freiburg) or to the wheat LTP Tri a 14.

The control group consisted of 17 consecutive adult patients with BRFA seeking advice in our department between April 2020 and March 2021. Birch-related food allergy was diagnosed in patients with clinical symptoms of an immediate-type allergy after ingestion of birch pollen-associated foodstuffs with sensitization to birch. The latter was confirmed by skin prick test for birch and/or specific IgE to Bet v 1 or its homologs. BRFA patients with IgE antibodies specific to Pru p 3 were excluded from the control group.

All patients gave written informed consent to participate in the study. Ethical approval was obtained by the Ethics Committee of the University of Witten/Herdecke.

The following data was collected from all LTP allergic and BRFA patients: each implicated food remembered by

the patient, severity and symptoms of clinical manifestations upon different occasions, presence of co-factors, delay between food ingestion and start of clinical symptoms, and whether raw foodstuffs only elicited symptoms.

Furthermore, the majority of patients completed the German version of the FAQLQ-AF [8]. It consists of 29 questions with answer possibilities corresponding to an ordinal scale from 1 (no impairment) to 7 (maximum impairment due to the food allergy). Each question relates to one of four subscales (Allergen Avoidance and Dietary Restrictions [AADR], Emotional Impact [EI], Risk of Accidental Exposure [RAE], and Food Allergy Related Health [FAH]).

Allergological work-up

Serum analysis including determination of total IgE (kU/l), IgE to Pru p 3 (kU/l), sx1 (kU/l), and fx5 (kU/l) was performed. Specific IgE to implicated foodstuffs was assessed by use of extracts or component-resolved diagnostics (for example, IgE to apple LTP Mal d 3, walnut LTP Jug r 3, or IgE to banana, grape, chickpea, sesame).

Skin prick-tests were performed with a selection of aeroallergens (birch, ash, grass, and mugwort) and with commercial extracts for wheat flour, soy, peanut, hazelnut, walnut, celery, and an LTP-enriched peach extract (ALK-Abello, Hamburg, Germany). Tests were read after 20 minutes, and a wheal diameter ≥ 3 mm was considered positive. Additional prick to prick tests were performed with fresh foods to confirm the sensitization to implicated foods, for example different berries, tree nuts, legumes, vegetables, seeds, and native flour of different grains. Prick tests were not evaluable in all patients.

Statistical analysis

Data were processed using IBM SPSS Statistics 27 (SPSS, Chicago, Illinois, USA) and visualized using Microsoft Excel 2016 for Windows. For descriptive analysis of continuous variables, medians and interquartile range (IQR) are reported. Differences between LTP allergic and BRFA patients were assessed using the independent sample t-test and Pearson's Chi-Squared test. Results were considered statistically significant at a P value < 0.05 .

Results

Characteristics of patients with LTP allergy and BRFA

The group of LTP allergic patients was younger (median age 33 years, IQR 28–44) than the BRFA patients group (55 years, IQR 36–68), while male:female ratio was nearly

identical. Particularly in the LTP allergy group, a substantial delay between first symptoms of food allergy and a precise diagnosis was reported (median delay 5 years).

Ten out of fifteen LTP allergic patients (67 %) suffered from associated rhinoconjunctivitis. Six of these patients (40 %) presented elevated IgE to both LTP and PR10 proteins, and a positive skin prick test to birch pollen extract. The remaining 9 LTP sensitized patients (60 %) had no birch pollen allergy. Four of these patients showed an isolated sensitization to grass pollen and/or mugwort.

Serological allergy work-up revealed slightly higher total IgE values in the LTP allergy group, but there were no statistically significant differences with regard to total IgE levels, sx1 aeroallergy, and fx5 food allergy screening between LTP and BRFA groups. The patient data are summarized in Table 1.

Allergenic foods

The majority of LTP allergic patients reported clinical manifestations after ingestion of stone and pome fruits (12/15, 80 %) with peach (8/15, 53 %) and apple (7/15, 47 %) being the most frequently reported single foodstuffs within this group (Figure 1, Table 2). Second and third most frequently implicated food groups were vegetables in 11/15 (73 %) LTP allergic patients (with tomato being the most common allergenic food), and tree nuts in 9/15 (60 %). Furthermore, 8/15 (53 %) LTP sensitized patients reported allergic reactions to berry fruits including strawberry, raspberry, and grapes, 5/15 (33 %) each to cereals and legumes, and 3/15 (20 %) to seeds. 9/15 (60 %) LTP allergic patients recalled allergic reactions to other foods containing citrus fruits, exotic fruits (such as bananas), and curry.

Table 1 Comparison between patients with LTP allergy and BRFA.

	Parameter	LTP allergic patients (n = 15)	BRFA patients (n = 17)	P value
Epidemiological data	Sex	9 women, 6 men	10 women, 7 men	N.d.
	Age (years)	18–67 (median 33, IQR 28–44)	25–73 (median 55, IQR 36–68)	N.d.
	Latency between first symptoms and diagnosis (months)	2–422 (median 59, IQR 11–117)	0–363 (median 13, IQR 0–143)	N.d.
Most relevant serological findings	Total IgE (kU/l)	222.0 (75.75–350.50)	101.85 (49.88–154)	0.18
	sx1 (kU/l)	2.81 (0.46–20.80)	14.1 (5.19–24.03)	0.37
	fx5 (kU/l)	0.42 (0–0.94)	0.0 (0–0)	0.50
	IgE Pru p 3 (> 0.35 kU/l)	2.21 (0.78–4.85) 14/15 (93 %)	0/17 (0 %)	N.d.
Prick test results	Positive for peach extract (ALK)	15/15 (100 %)	2/13 (15 %)	< 0.001
	Positive for birch pollen extract	6/13 (46 %)	13/13 (100 %)	N.d.
	Positive for any pollen allergen	10/13 (77 %)	13/13 (100 %)	N.d.
Manifestations of immediate type allergy	Oral allergy syndrome	13/15 (87 %)	16/17 (94 %)	N.d.
	Contact urticaria	6/15 (40 %)	4/17 (24 %)	
	Systemic symptoms	15/15 (100 %)	15/17 (88 %)	
Maximum severity of anaphylactic reactions	Grade 1	4/15 (27 %)	9/17 (53 %)	
	Grade 2	3/15 (20 %)	6/17 (35 %)	0.023
	Grade 3	8/15 (53 %)	2/17 (12 %)	
Latency until start of first symptoms	< 15 minutes	5/15 (33 %)	16/17 (94 %)	< 0.001
	15–60 minutes	10/15 (67 %)	1/17 (6 %)	< 0.001
	1–6 hours	6/15 (40 %)	1/17 (6 %)	0.019

Continued

Table 1 Continued.

	Parameter	LTP allergic patients (n = 15)	BRFA patients (n = 17)	P value
Presence of cofactors	At least one cofactor reported	11/15 (73 %)	1/17 (6 %)	< 0.001
Food processing and allergy induction	Raw and cooked food eliciting symptoms	12/14 (86 %)	7/17 (41 %)	0.024
Quality of life as measured by FAQLQ-AF	AADR	3.37 (2.75–5.11)	3.27 (2.27–4.91)	0.68
	EI	4.36 (3.68–5.47)	4.43 (3.1–5.6)	0.46
	RAE	4.07 (3.29–6.07)	4.63 (3.5–5.25)	0.66
	FAH	5.17 (4.25–5.67)	4.67 (3.67–5.67)	0.19
	Total score	4.18 (3.63–5.12)	4.38 (2.66–5.28)	0.51

For continuous variables median and IQR are presented.

sx1 corresponds to a screening for sensitization to inhalant allergens and includes house dust mite, timothy, rye, birch, and mugwort. fx5 is a screening for sensitization to food allergens including egg white, milk protein, cod, wheat flour, peanut, and soy.

Abbr.: LTP, lipid transfer proteins; BRFA, birch-related food allergy; FAQLQ-AF, food allergy quality of life questionnaire – adult form; EI, emotional impact; RAE, risk of accidental exposure; FAH, food allergy related health.

All BRFA patients reported allergic symptoms after ingestion of tree nuts, followed by stone and pome fruits (14/17, 82 %) and other foods (7/17, 41 %) including kiwi and citrus fruits. Allergic reactions due to vegetables, berries, legumes, seeds, and cereals occurred rather rarely in BRFA patients (Figure 1, Table 2).

One LTP allergic patient reported symptoms solely after wheat ingestion, while the remaining 14 LTP allergic patients considered at least three of the aforementioned food groups as elicitors of symptoms (average 4 different food groups). Similarly, BRFA patients referred on average to three causative food groups.

Clinical manifestations

All 15 LTP allergic patients and 15/17 (88 %) BRFA patients had a history of systemic reactions after food ingestion varying from grade 1 to 3 according to Ring and Messmer (Figure 2). Two BRFA patients reported oral allergy syndrome only. Seventy-three percent of LTP allergic patients (11/15) had previously sought medical assistance at least once in contrast to 8/17 (47 %) BRFA patients. While 8/15 (53 %) LTP allergic patients had reported at least one grade 3 anaphylactic reaction in the past, the highest grade of anaphylaxis in the majority of BRFA patients was grade 1

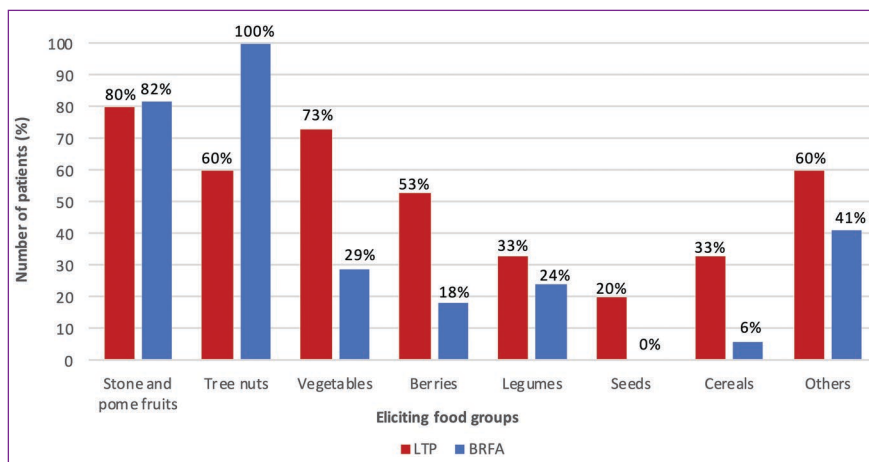


Figure 1 Food groups eliciting allergic manifestations in patients with lipid transfer protein (LTP) allergy and birch-related food allergy (BRFA).

Table 2 Comparison of most common eliciting foods between LTP allergic and BRFA patients.

Food group	Plant food	LTP allergic patients (n = 15)	BRFA patients (n = 17)
Stone and pome fruits	Peach	8	5
	Apple	7	13
	Plum	3	1
	Cherry	6	7
	Nectarine	2	1
	Pear	3	0
	Apricot	0	2
Tree nuts	Hazelnut	5	15
	Walnut	5	6
	Cashew nut	1	1
	Pistachio	2	0
	Pecan	0	1
	Brazil nut	0	1
	Macadamia nut	0	1
	Almond	2	3
Vegetables	Paprika	3	0
	Tomato	4	0
	Celery	1	4
	Fennel	0	1
	Zucchini	1	0
	Lettuce	2	0
	Arugula	1	0
	Cucumber	2	0
	Potato	3	2
	Carrot	3	5
	Cabbage	1	1
	Beetroot	1	0
	Radishes	1	0
Berries	Strawberry	5	3
	Blackberry	2	0
	Blueberry	2	0
	Raspberry	3	0
	Grape (Raisin)	4	2

Table 2 Continued.

Cereals	Cranberry	1	0
	Currant	1	0
	Wheat	4	1
	Spelt	1	0
	Rye	1	0
	Corn	2	0
	Barley	1	0
	Rice	1	0
Seeds	Sesame	1	0
	Mustard	1	0
	Sunflower seed	1	0
Legumes	Chickpea	1	0
	Lupine	1	0
	Soy	1	2
	Peanut	2	1
Others	Pineapple	1	0
	Banana	4	1
	Kiwi	4	5
	Passion fruit	0	1
	Coconut	0	1
	Orange	1	3
	Tangerine	1	0
	Curry	2	1

anaphylaxis in 9/17 (53 %) patients ($P = 0.023$) (Figure 2, Table 1).

A vast majority of LTP allergic individuals (13/15, 87 %) reported additional contact urticaria of the oropharynx after ingestion of plant derived foods. Furthermore, 6/15 LTP syndrome patients (40 %) suffered from contact urticaria when peeling potatoes or cucumber, touching strawberries, or kneading a wheat-containing bread dough. Similarly, 4/17 BRFA patients (24 %) reported contact urticaria related to potatoes and fruits, but not to cucumber.

Significant differences were identified with regard to the delay between food ingestion and appearance of first symptoms. While most BRFA patients (16/17, 94 %) developed clinical manifestations within 15 minutes after food intake, a delay of 15–60 minutes or even 1–6 hours was not uncommon in LTP allergic patients ($P \leq 0.019$) (Figure 3, Table 1).

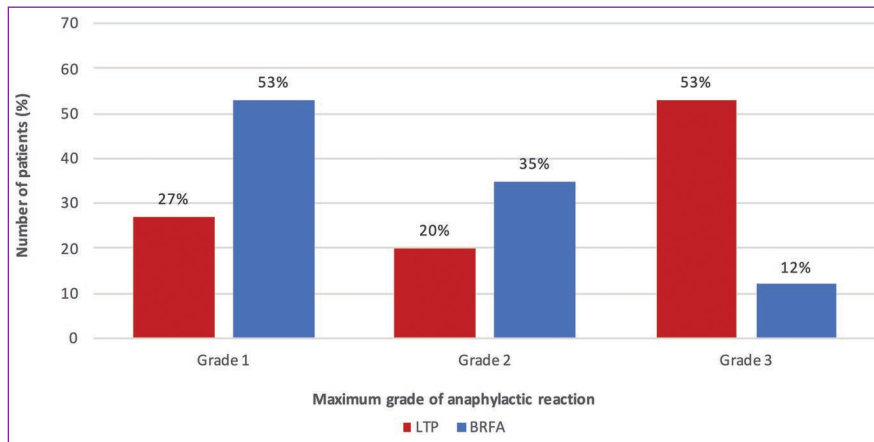


Figure 2 Severity of anaphylactic reactions as recalled by the patients. For analysis, the highest reported grade of anaphylaxis according to the Ring and Messmer classification was used for each LTP and BRFA allergic patient.

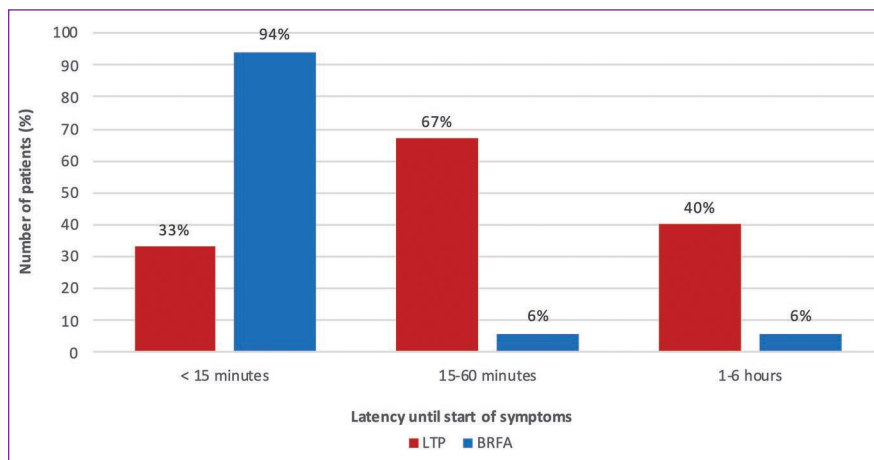


Figure 3 Delay of symptom onset after ingestion of triggering food-stuffs. Multiple answers were possible since patients reported different intervals between food ingestion and start of symptoms on various occasions.

Cofactors and relevance of food processing

While cofactors were relevant in eliciting allergic reactions in 11/15 (73 %) LTP allergic patients, only 1/17 (6 %) BRFA patients recalled associated cofactors ($P < 0.001$). The most common cofactor in LTP allergy was physical activity in 47 %, followed by consumption of alcohol or non-steroidal anti-inflammatory drugs (NSAIDs) in 27 %, respectively (Figure 4).

Eighty-six percent of the patients with LTP allergy (12/14) reported clinical symptoms after ingestion of raw and cooked plant foods, while one patient was unsure about this question. In contrast, only 7/17 (41 %) BRFA patients reported allergic reactions after eating cooked food ($P = 0.024$). In the majority of BRFA patients heating of the foods led to a better tolerance (Figure 5, Table 1). The processed foods that elicited allergic reactions in LTP patients were most commonly cherry and black currant jam or cake with walnut, hazelnut, apple, or raisins.

Diagnostic features

All but one LTP allergic patient demonstrated elevated specific IgE antibodies to the peach LTP Pru p 3 (93 %, median 2.21 kU/l, IQR 0.78–4.85). One patient showed an isolated sensitization to wheat LTP Tri a 14 in accordance with the clinical history.

By skin prick test using peach extract, all LTP allergic patients showed a positive reaction corresponding to a sensitivity of 100 % although only 8/15 (53 %) patients reported clinical symptoms after ingestion of peach. Interestingly, even the patient with isolated IgE to the wheat LTP reacted to the peach prick test. In the BRFA group, only 2/13 patients (15 %) had a positive skin prick test to peach extract.

Quality of life

Most patients had self-completed the FAQLQ-AF questionnaire and quality of life was clearly impaired in both

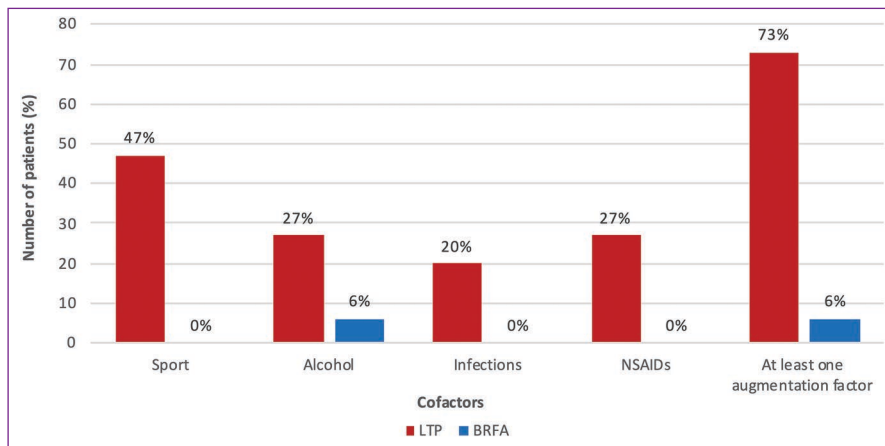


Figure 4 Relevance of cofactors in the development of allergic reactions.

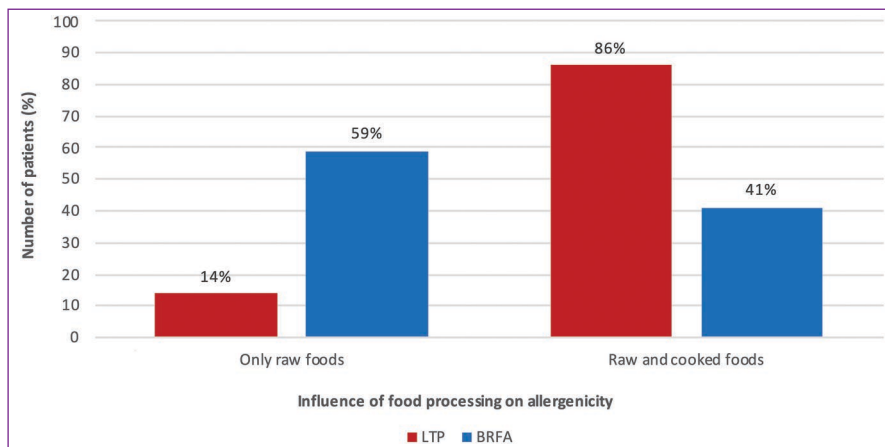


Figure 5 Relevance of the cooking condition of plant-derived foods for allergy induction.

groups. The median overall FAQLQ-AF score was slightly higher in BRFA patients while the median value for Food Allergy Related Health (FAH) was higher in LTP allergic patients. There were no statistically significant differences between BRFA and LTP allergic patients (Table 1).

Discussion

In our department, 15 patients with LTP allergy were diagnosed in the past five years corresponding to 1.5 % of all outpatients in the allergy clinic. Therefore, this condition may be more important in Germany than previously reported.

Diagnosis of LTP allergy may be impeded by the fact that cofactors such as physical exercise, intake of NSAIDs, or acute infections are often required for elicitation of allergic symptoms after ingestion of plant-derived food allergens. This may explain the longer delay between food intake and onset of symptoms as demonstrated by 40 % of our LTP allergic patients, who reported a delay by more than one hour,

significantly longer than in BRFA. Only 6 % BRFA patients reported cofactors in contrast to 73 % LTP allergic patients in line with previously published studies indicating that cofactors are associated with LTP allergy in a majority of patients [13, 16].

Wheat-dependent exercise-induced anaphylaxis (WDEIA) in central and northern Europe represents to date the most common variant of food-dependent exercise-induced anaphylaxis (FDEIA) [17]. It is usually triggered by sensitization to omega-5-gliadin (Tri a 19), but some patients react to other wheat allergens, for example γ -gliadin [18]. The wheat LTP, Tri a 14, however, is a major allergen in baker's asthma and has only rarely been identified as causative allergen of WDEIA [16, 19, 20]. Our LTP patients group included one patient with isolated sensitization to Tri a 14, but not to Pru p 3, manifesting in repetitive urticaria and angioedema occurring several hours after wheat ingestion in relation to cofactors. In line with this finding, it has been shown that Tri a 14 is only rarely subject to co-sensitization with other LTPs [21].

In the Mediterranean area, LTP syndrome was found to be the most common elicitor of FDEIA [16, 22] with peach and apple being the most important eliciting foodstuffs [5, 23]. In our study, only 8/15 patients reported peach as eliciting food, indicating that other, LTP containing food sources are likely to be relevant as causative allergens. According to our LTP allergic patients' medical history, vegetables (including tomatoes, cucumber and lettuce), all types of red berries and grapes, legumes (for example, peanut, lupine, chickpea), seeds (for example, sesame, mustard, sunflower seeds), and cereals (for example, wheat, maize, rice) were elicitors of food allergy. In contrast, tree nuts (for example, hazelnut, walnut), and pome and stone fruits (for example, peach, apple, cherry) were mentioned as frequent causes of clinical manifestations in patients with both BRFA and LTP allergy. These findings confirm the published knowledge about relevant LTP allergens in other countries and demonstrate once more that LTP syndrome patients often react to a multitude of different plant-derived foodstuffs [12, 13, 24–26]. However, it is conceivable that the broad spectrum of foods leading to symptoms in our LTP allergic patients may be influenced by the co-sensitivity to birch or other pollen in part of the studied group.

Since component-resolved diagnostics is to date only commercially available for peach LTP Pru p 3, peanut Ara h 9, hazelnut Cor a 8, walnut Jug r 3, and wheat Tri a 14, extension of the panel of LTPs for molecular allergy diagnostics is desirable [6]. Fortunately, our data show that the diagnostic utility of skin prick tests with Pru p 3 enriched peach extract is excellent, reaching high specificity and a sensitivity of 100 %. Similarly, Skypala et al. reported positive peach prick tests in 91 % of their LTP allergic patients [13], and Asero et al. demonstrated a diagnostic accuracy of even 98 % [27]. Therefore, routine skin prick tests with peach extract in patients with suspected food allergy may enable an early diagnosis of this burdensome condition.

Lipid transfer proteins are heat resistant allergens as reflected by the finding that 86 % of our LTP allergic patients reacted to raw and cooked foodstuffs in contrast to only 41 % BRFA patients. Similar observations have been published for British and Austrian patients [12, 13]. Although 53 % of our LTP allergic patients had reported at least one grade 3 anaphylactic reaction in the past compared to only 12 % BRFA patients, the range of clinical manifestations was broad in both groups. Several patients reported both mild oral symptoms or contact urticaria when peeling potatoes or cucumber, and on other occasions anaphylactic reactions to LTPs.

We also assessed the impairment of HRQL of LTP allergic patients in comparison to patients with BRFA, for two reasons: First, BRFA represents the most common form of food allergy in Europe. Second, the FAQLQ-AF was

previously used to assess HRQL in German-speaking adults with BRFA [8] and it has proven to be a suitable instrument. Beyer et al. calculated a mean overall FAQLQ-AF score of 3.7 ($\pm$ 1.6) corresponding to a mild to moderate impairment of HRQL in BRFA patients. Our analysis revealed similar values without a significant difference between LTP allergic and BRFA patients. In contrast, a statistically significant decrease in HRQL compared to BRFA patients was reported in British patients with LTP syndrome [13]. This is likely due to the fact that all patients in this British cohort had a history of severe reactions. However, this does not necessarily represent the usual spectrum of mild to severe allergic manifestations occurring in LTP allergy [4]. Taken together, LTP allergy clearly affects HRQL because of the high number of potential food triggers and the relevance of cofactors. The latter renders prediction of allergic reactions to foodstuffs difficult [28, 29].

Limitations of this study are that the diagnosis of food allergy was based on patients' personal accounts, on skin and serological tests, but not on oral food provocation. It is conceivable that eliciting foodstuffs were affected by recall bias, since culprit foods may vary and cofactors may hamper identification of causative foods. Moreover, given its monocentric design larger studies with age- and sex-matched controls are recommended.

The increasing geographical spread of LTP sensitization highlights the growing impact of LTP allergy and a need for prevention and therapy. The latter is currently mainly based on avoidance of causative foods and use of rescue medication in case of accidental exposure. The difficulty in predicting which foodstuffs may provoke reactions, however, render avoidance difficult. Therefore, patients may benefit from sublingual immunotherapy with Pru p 3 [30, 31].

In conclusion, this systematic analysis demonstrates the importance of prick tests with peach extract and IgE detection to Pru p 3 for diagnosis of LTP allergy in German patients. In addition to tree nuts, and pome and stone fruits as in BRFA, various vegetables, berry fruits, cereals, legumes, and seeds are frequent causes of LTP related food allergy. Delayed clinical reactions, presence of cofactors, and reactions to raw and cooked plant derived foodstuffs are indicative of LTP allergy.

Acknowledgment

The authors thank the German Allergy and Asthma league for providing us with the German version of the FAQLQ-AF. Furthermore, we thank Jenny Schönrock-Ersfeld, Cornelia Scheu, and Andrea Gabler for performing skin prick tests.

Open access funding enabled and organized by Projekt DEAL.

Correspondence to

Silke C. Hofmann, MD
 Department of Dermatology, Allergy and Dermatosurgery
 HELIOS University Hospital Wuppertal
 University Witten/Herdecke

 Heusnerstrasse 40
 42283 Wuppertal, Germany
 E-mail: silke.hofmann@helios-gesundheit.de

References

- Lyons SA, Burney PGJ, Ballmer-Weber BK et al. Food allergy in adults: substantial variation in prevalence and causative foods across Europe. *J Allergy Clin Immunol Pract* 2019; 7(6): 1920–8 e11.
- Kader JC. Lipid-Transfer Proteins in Plants. *Annu Rev Plant Physiol Plant Mol Biol* 1996; 47: 627–54.
- Pastorello EA, Ortolani C, Farioli L et al. Allergenic cross-reactivity among peach, apricot, plum, and cherry in patients with oral allergy syndrome: an in vivo and in vitro study. *J Allergy Clin Immunol* 1994; 94(4): 699–707.
- Asero R, Piantanida M, Pinter E, Pravettoni V. The clinical relevance of lipid transfer protein. *Clin Exp Allergy* 2018; 48(1): 6–12.
- Asero R, Mistrello G, Roncarolo D et al. Immunological cross-reactivity between lipid transfer proteins from botanically unrelated plant-derived foods: a clinical study. *Allergy* 2002; 57(10): 900–6.
- Petersen A, Kleine-Tebbe J, Scheurer S. Stable Plant Food Allergens I: Lipid-Transfer Proteins. In: Kleine-Tebbe J, Jakob T, editors. *Molecular allergy diagnostics: innovation for a better patient management*. Berlin: Springer International Publishing, 2017: 57–75.
- Geroldinger-Simic M, Zelniker T, Aberer W et al. Birch pollen-related food allergy: clinical aspects and the role of allergen-specific IgE and IgG4 antibodies. *J Allergy Clin Immunol* 2011; 127(3): 616–22. e1.
- Beyer S, Franke A, Simon JC, Treudler R. Measurement of health-related quality of life in adult patients with birch pollen-associated food allergy. *J Dtsch Dermatol Ges* 2016; 14(4): 397–404.
- Lange L, Klimek L, Beyer K et al. White paper on peanut allergy – part 1: Epidemiology, burden of disease, health economic aspects. *Allergo J Int* 2021; 30(8): 261–9.
- Ballmer-Weber BK, Lidholm J, Fernandez-Rivas M et al. IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. *Allergy* 2015; 70(4): 391–407.
- Faber MA, Van Gasse AL, Decuyper II et al. IgE-reactivity profiles to nonspecific lipid transfer proteins in a northwestern European country. *J Allergy Clin Immunol* 2017; 139(2): 679–82. e5.
- Mothes-Luksch N, Raith M, Stingl G et al. Pru p 3, a marker allergen for lipid transfer protein sensitization also in Central Europe. *Allergy* 2017; 72(9): 1415–8.
- Skypala JJ, Cecchi L, Shamji MH et al. Lipid transfer protein allergy in the United Kingdom: characterization and comparison with a matched Italian cohort. *Allergy* 2019; 74(7): 1340–51.
- Gulsen A, Jappe U. Lipid transfer protein sensitization in an apple-allergic patient: a case report from northern Europe. *Eur Ann Allergy Clin Immunol* 2019; 51(2): 80–3.
- Gebhardt C, Vieths S, Gubesch M et al. 10 kDa lipid transfer protein: the main allergenic structure in a German patient with anaphylaxis to blueberry. *Allergy* 2009; 64(3): 498–9.
- Cardona V, Luengo O, Garriga T et al. Co-factor-enhanced food allergy. *Allergy* 2012; 67(10): 1316–8.
- Scherf KA, Brockow K, Biedermann T et al. Wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2016; 46(1): 10–20.
- Hofmann SC, Fischer J, Eriksson C et al. IgE detection to alpha/beta/gamma-gliadin and its clinical relevance in wheat-dependent exercise-induced anaphylaxis. *Allergy* 2012; 67(11): 1457–60.
- Palacin A, Bartra J, Munoz R et al. Anaphylaxis to wheat flour-derived foodstuffs and the lipid transfer protein syndrome: a potential role of wheat lipid transfer protein Tri a 14. *Int Arch Allergy Immunol* 2010; 152(2): 178–83.
- Palacin A, Quirce S, Armentia A et al. Wheat lipid transfer protein is a major allergen associated with baker's asthma. *J Allergy Clin Immunol* 2007; 120(5): 1132–8.
- Palacin A, Gomez-Casado C, Rivas LA et al. Graph based study of allergen cross-reactivity of plant lipid transfer proteins (LTPs) using microarray in a multicenter study. *PLoS One* 2012; 7(12): e50799.
- Romano A, Scala E, Rumi G et al. Lipid transfer proteins: the most frequent sensitizer in Italian subjects with food-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2012; 42(11): 1643–53.
- Gomez F, Aranda A, Campo P et al. High prevalence of lipid transfer protein sensitization in apple allergic patients with systemic symptoms. *PLoS One* 2014; 9(9): e107304.
- Asero R, Antoniceilli L, Arena AB et al. EpidemAITO: features of food allergy in Italian adults attending allergy clinics: a multi-centre study. *Clin Exp Allergy* 2009; 39(4): 547–55.
- Azofra J, Berroa F, Gastaminza G et al. Lipid transfer protein syndrome in a non-Mediterranean area. *Int Arch Allergy Immunol* 2016; 169(3): 181–8.
- Basagana M, Elduque C, Teniente-Serra A et al. Clinical profile of lipid transfer protein syndrome in a Mediterranean area. *J Investig Allergol Clin Immunol* 2018; 28(1): 58–60.
- Asero R, Aruanno A, Bresciani M et al. Evaluation of two commercial peach extracts for skin prick testing in the diagnosis of hypersensitivity to lipid transfer protein. A multicenter study. *Eur Ann Allergy Clin Immunol* 2021; 53(4): 168–70.
- Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A et al. Development and validation of the Food Allergy Quality of Life Questionnaire – Adult Form. *Allergy* 2009; 64(8): 1209–17.
- Goossens NJ, Flokstra-de Blok BM, Vlieg-Boerstra BJ et al. Online version of the food allergy quality of life questionnaire-adult form: validity, feasibility and cross-cultural comparison. *Clin Exp Allergy* 2011; 41(4): 574–81.
- Beitia JM, Vega Castro A, Cardenas R et al. Pru p 3 sublingual immunotherapy in patients with lipid transfer protein syndrome: is it worth? *Int Arch Allergy Immunol* 2021; 182(5): 447–54.
- Moura AL, Pereira C, Regateiro FS et al. Pru p 3 sublingual immunotherapy ultra-rush protocol is safe and clinically effective. *Eur Ann Allergy Clin Immunol* 2019; 51(5): 206–12.