

Advances in the understanding of the *cofactor effect* in lipid transfer protein food allergy: From phenotype description to clinical management

To the Editor,

Cofactors may explain why in some cases food ingestion leads to anaphylaxis while in others elicits a milder reaction/tolerance.^{1,2} Cofactors have also been related to a complex food allergy (FA) phenotype such as Lipid Transfer Protein (LTP)-FA,³ although limited data regarding the epidemiology and clinical profile of these patients are available.

Five hundred and twenty-eight peach nsLTP (Pru p 3)-sensitized adult patients (Pru p 3 specific IgE (sIgE) ≥ 0.10 kU/L (ImmunoCAP[®],

ThermoFisher Scientific) were selected and grouped according to the presence of cofactor (physical exercise, non-steroidal anti-inflammatory drugs (NSAIDs), alcohol, menstruation and/or sleep deprivation). 194 (37%) patients were included in the cofactor group (CG) and 302 (57%) in the non-cofactor group (NCG). Thirty-two (6%) patients were asymptomatic, and therefore, were not included in any of the groups. All patients had a positive peach LTP skin-prick test. (*Detailed methods-Supplementary Material*).

TABLE 1 Clinical characteristics

	Cofactor group (194 patients)	Non-cofactor group (302 patients)	p value
Female n (%)	129 (66.5)	174 (57.6)	.04
Age (years)	40.8 $\pm$ 11.6	41.8 $\pm$ 11.6	ns
Age at food allergy onset (years)	27 $\pm$ 17.6	16.1 $\pm$ 11.7	.001
Rhinitis (%)	150 (77.3)	250 (82.8)	.017
Asthma (%)	50 (25.8)	110 (36.4)	.002
Sensitization:			
Pollen ^a (%)	133 (68.6)	221 (73.2)	ns
Dust mites (%)	95 (49)	165 (54.6)	ns
Dog/cat (%)	57 (29.4)	101 (33.5)	ns
Fungi (%)	11 (5.7)	38 (18.9)	ns
Pru p 3 skin-prick test (%)	194 (100)	302 (100)	N/A
PR-10 (Pru p 1, %) ^b	0 (0)	0 (0)	N/A
Profilin (Pru p 4, %) ^b	15 (7.7)	16 (5.3)	ns
Total IgE (kU/L)	241.5 $\pm$ 343.4	293.4 $\pm$ 483.7	ns
Peach sIgE (kU/L)	7.3 $\pm$ 10	7.0 $\pm$ 9.7	ns
Pru p 3 sIgE (kU/L)	10.2 $\pm$ 16.2	7.7 $\pm$ 10.9	ns
Pru p 3/peach	1.3 $\pm$ 0.9	1.3 $\pm$ 1.1	ns
Pru p 3/tIgE	0.08 $\pm$ 0.1	0.05 $\pm$ 0.7	<.001
Local reactions (%)		105 (34.8)	
OAS	N/A ^c	61 (20.2)	N/A
Gastrointestinal symptoms		16 (5.3)	
Contact urticaria		28 (9.3)	
Systemic reactions:	194 patients	197 patients	
Grade 1: mild (%)	54 (36.5)	94 (63.5)	<.001
Grade 2: moderate (%)	118 (55.1)	96 (44.9)	<.02
Grade 3: severe (%)	22 (75.9)	7 (24.1)	.003

Note: A p value <.05 was considered statistically significant.

Values are expressed as mean $\pm$ standard deviation.

Abbreviations: N/A, non-applicable; ns, non-statistically significant.

^aPollen sensitization includes plane tree, grass, mugwort, olive tree, wall pellitory, and cypress.

^b Profilin sensitization was analyzed by positive sIgE to Pru p 4. PR-10 sensitization was analyzed by positive sIgE to Pru p 1. Positive results were considered ≥ 0.10 kU/L.

^c All patients in CG had a systemic reaction.

TABLE 2 Foods involved in systemic reactions in cofactor and non-cofactor patients

	Cofactor group (194 patients)			Non-cofactor group (197 patients)			p value [*]
	N° of patients (%)	N° of reactions	Mean reactions per patient	N° of patients (%)	N° of reactions	Mean reactions per patient	
Plant-food mix ^a	147 (75.8)	245	1.7	71 (36.6)	88	1.2	<.0001
Nuts	59 (30.4)	94	1.6	84 (43.3)	131	1.6	.01
Peach	56 (28.9)	63	1.1	68 (35.1)	76	1.1	ns
Rosaceae ^b	53 (27.3)	68	1.3	32 (16.5)	44	1.4	.008
Other fruits	32 (16.5)	36	1.1	41 (21.1)	59	1.4	ns
Other vegetables	29 (14.9)	44	1.5	23 (11.9)	31	1.3	ns
Lettuce	23 (11.9)	24	1.0	11 (5.7)	13	1.2	.03
Seeds	15 (7.7)	16	1.1	17 (8.8)	17	1	ns
Cereals	14 (7.2)	16	1.1	12 (6.2)	17	1.4	ns
Other plant-food	4 (2.1)	4	1	2 (1)	3	1.5	ns

Note: Foods were depicted in order of frequency of involvement: Plant-food mix; Nuts (walnut, hazelnut, peanut, almond, cashew, pistachio, chestnut, or a combination of nuts); Peach; *Rosaceae* (apple, pear, plum, cherry, strawberry, nectarine, apricot); Other fruits (kiwi, banana, grape, melon, pineapple, watermelon, orange); Lettuce; Cereals (wheat, corn, rice, oats); Seeds (sunflower seed, mustard, soy); Other vegetables (tomato, green bean, lentils, chickpeas, peas, zucchini, mushroom). 'Other plant food' included: honey, cocoa, peppers, parsley, lemon verbena, pepper, or cinnamon.

Abbreviation: ns, non-statistically significant.

^aPlant-food mix: reactions where several LTP-containing plant foods were involved, but no a particular food was identified as a single trigger.

^b*Rosaceae*: other *Rosaceae* apart from peach.

^{*}p value has been calculated comparing the number of patients reacting with each food group using the Chi² test. A p value <.05 was considered statistically significant.

Cofactor group had more women (66.5% vs. 57.6%; $p = .04$), a later disease onset (27 vs. 16.1 years; $p = .001$) and a higher Pru p 3 sIgE/tIgE ratio (0.08 ± 0.1 vs. 0.05 ± 0.7 ; $p < .001$) (Table 1).

In the overall cohort, 391 patients had a history of at least one systemic reaction (SR). Considering only the most severe reaction experienced by each patient, 29 (5.5%) suffered grade 3, 214 (40.5%) grade 2, and 148 (28%) grade 1 reactions.⁴ Considering only patients with SR, CG showed a higher risk of either a G2 or G3 (OR 1.97; $p < .05$) and G3 reactions (OR 3.5; $p = .003$) compared with NCG (Table 1). Plant-food mix (55.8%), nuts (36.6%), and peach (31.7%) were the most frequent culprit foods (Figure S2). Among nuts, walnut (25%), peanut (18%), hazelnut (16%), and almond (8%) were the most frequent. Indeed, when comparing both groups, plant-food mix was significantly more involved in CG, as well as lettuce and other *Rosaceae* fruits apart from peach (Figure S2 and Table 2).

Noteworthy, 185 out of 194 patients in CG presented reactions both with and without cofactors, related to different foods (Table S3). Interestingly, cofactor-induced reactions were more severe (G2 and G3) than non-cofactor ones (OR 3.2; $p < .001$). Exercise (41.7%) and NSAIDs (37.8%) were the most frequent cofactors and cofactor type did not correlate with reaction severity (Figure S1).

In summary, patients with cofactor-related reactions are mostly female, with a delayed onset of disease and a higher Pru p 3 sIgE/tIgE ratio. So far, sIgE levels in LTP allergy have not been correlated with severity,⁵ and there is no data regarding the relevance of the

ratios. Female predominance in the CG may be related to hormone factors; estrogen levels have been related to higher risk of anaphylaxis.² Indeed, NSAID intake to control menstrual pain is a frequent practice that may explain the frequent involvement of these drugs in our series.

We have also shown that the same patient may have a systemic reaction both with and without a cofactor. Thus, the *cofactor effect* may not depend on the intrinsic characteristic of the individuals and may be considered a potential universal effect, as also shown in the wheat allergy model.⁶ In our study, cofactor-related reactions were also more severe, and as far as we know, this is the first description in LTP-FA.

Plant-food mix was the group most frequently involved in SR, meaning that a mix of different plant-foods was consumed in the same meal, most of them containing LTP.³ Thus, it was not possible to identify whether the trigger was just one of the plant-foods, or the cumulative dose of LTPs from different sources.

In conclusion, more than 30% of the LTP-sensitized patients of this large cohort have cofactor-related reactions, frequently severe, although the individual culprits cannot usually be identified. Thus, dietary advice is extremely complicated, leaving the patients at high risk of developing anaphylaxis. This observation may suggest that, following the guidelines,¹ the prescription of adrenaline autoinjectors may be based not only on the history of a previous anaphylaxis, but also on a previous mild-to-moderate reaction to foods known to

be associated with anaphylaxis in the patient's region, which in ours, is any LTP-containing food.

KEYWORDS

anaphylaxis, cofactor, lipid transfer protein, Pru p 3, risk factors

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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