Gastrointestinal Symptoms: Under the Tip of the Iceberg in Lipid Transfer Protein Food Allergy

Ruano-Zaragoza M[1,2,3], Araujo-Sanchez G[1,2], Gelis S[1,2], Loli-Ausejo D[1,2], Mir-Ihara P[1,2,3], Mascaró-Hereza B[1,2], Sánchez-Fernández MC[1,2], Pascal M[3,4], Muñoz-Cano R[1,2,3]*, Bartra J[1,2,3]*

[1]*Allergy Department, Hospital Clínic, University of Barcelona, Barcelona, Spain*

[2]*Clinical and Experimental Respiratory Immunoallergy, Institut Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*

[3]*RETIC Asma, Reacciones Adversas y Alergia (ARADyAL) and RICORS Red de Enfermedades Inflamatorias (REI), Madrid, Spain*

[4]*Immunology Department, Centre de Diagnòstic Biomèdic (CDB), Hospital Clínic de Barcelona, Barcelona, Spain*

**Both authors contributed equally to this work.*

J Investig Allergol Clin Immunol 2024; Vol. 34(6): 404-406
doi: 10.18176/jiaci.1006

Key words: Lipid transfer protein (LTP). Gastrointestinal symptoms. Food allergy. Pru p 3. Anaphylaxis.

Palabras clave: Proteína de transferencia de lípidos (LTP). Clínica digestiva. Alergia alimentaria. Pru p 3. Anafilaxia.

Gastrointestinal symptoms (GIS) have been reported to be a manifestation of IgE-mediated food allergy (FA) [1], although epidemiologic data are limited [2]. Patients with FA caused by lipid transfer proteins (LTP-FA) may react to many different plant foods, present a broad spectrum of clinical symptoms (ranging from oral allergy syndrome to anaphylaxis), and develop GIS [3-4]. However, data regarding the epidemiology and triggers of LTP-related GIS are limited [3-4]. Thus, we aimed to analyze the prevalence of GIS in patients with LTP-FA and examine their clinical features. This study was approved by the Hospital Clinic Ethics Committee (HCB/2022/1049) and was conducted according to the Declaration of Helsinki, good clinical practice, and local regulations.

We consecutively recruited 512 peach nsLTP (Pru p 3)–allergic adult patients (Pru p 3 specific IgE [sIgE] ≥0.10 kU/L) (ImmunoCAP, ThermoFisher Scientific) (Detailed methods-Supplementary Material) from the outpatient clinic of the Allergy Department of Hospital Clinic, Barcelona, Spain and grouped them according to the patient-reported presence of GIS (abdominal pain, cramping, bloating, nausea, vomiting, and diarrhea) related to intake of LTP-containing foods (with a maximum of 1 hour between eating the food and experiencing the symptoms). The GIS group (GIS-YES) comprised 228 patients (44.5%) and the non-GIS group (GIS-NO) comprised 284 patients (55.5%). All patients had a positive result in the peach LTP skin prick test.

The GIS-YES group had more women (71.93% vs 54.42%; *P*<.001) and patients were older (43.3 vs 39.7 years; *P*=.001) (Table). Comparison of LTP sensitization profiles revealed no differences (Table S1-Online Repository). Considering only the most severe LTP-related reaction experienced by each patient [5], having GIS was not associated with either more frequent or more severe systemic reactions (generalized urticaria or anaphylaxis) (Table).

Table. Clinical Characteristics.[a]

	GIS-NO (284 patients)	GIS-YES (228 patients)	*P* Value
Age, y	39.7 (11.78)	43.31 (11.63)	.001
Female, No. (%)	154 (54.42)	164 (71.93)	<.001
Rhinitis, No. (%)	222 (78.2)	195 (85.5)	NS
Asthma, No. (%)	87 (30.6)	89 (39)	NS
Sensitization to pollen[b], No. (%)	218 (77.04)	186 (81.58)	NS
Local reaction[c], No. (%)	42 (14.79)	38 (16.67)	NS
Systemic reactions[d], No. (%)	242 (85.21)	190 (93.33)	NS
Grade 1	91 (37.60)	68 (35.79)	NS
Grades 2 and 3	151 (62.40)	122 (64.21)	NS
tIgE	292.81 (613.52)	275.32 (473.43)	NS
Peach sIgE	7.55 (12.24)	7.65 (11.28)	NS
Pru p 3 sIgE	8.8 (15.34)	9.72 (14.57)	NS
Pru p 3 sIgE/tIgE	0.06 (0.10)	0.07 (0.10)	NS
Pru p 3 sIgE/peach sIgE	1.28 (0.85)	1.37 (1.13)	NS
Mal d 3 sIgE	7.67 (14.61)	6.16 (11.51)	NS
Jug r 3 sIgE	5.31 (13.25)	4.3 (8.52)	NS
Ara h 9 sIgE	6.64 (14.85)	4.73 (8.66)	NS
Cor a 8 sIgE	3.61 (9.01)	3.22 (6.03)	NS
Tri a 14 sIgE	2.14 (5.50)	1.93 (4.06)	NS

Abbreviations: GIS, gastrointestinal symptoms; NS, non significant.
[a]Values are expressed as mean (SD) unless otherwise indicated. tIgE and sIgE are expressed as kU/L.
[b]Pollen sensitization includes plane tree, grass, mugwort, olive tree, wall pellitory, and cypress.
[c]Local reaction includes oral allergy syndrome, contact urticaria, and/or gastrointestinal symptoms as the most severe reaction experienced.
[d]Local or systemic reactions with foods containing lipid transfer proteins.

Cofactors are considered risk factors for both systemic and more severe LTP-related reactions [6]. Compared with the GIS-YES group, we found that patients in the GIS-NO group experienced more cofactor-dependent anaphylaxis episodes (grade 2/3 of the Brown severity classification) [5] (117/286 [41%] vs 76/249 [31%]; *P*=.013, respectively), suggesting that gastrointestinal discomfort may be associated with avoidance of these foods, prevention of potential interactions with a cofactor, and development of a systemic reaction. However, the possibility of a differential clinical profile depending on factors such as the specific food or the quantity of food cannot be ruled out.

Finally, we analyzed the top 10 foods involved in GIS and in classic allergy symptoms, and although similar (Figure S1), some foods seem to be more frequently related to GIS. A total of 85 foods were reported by patients to induce GIS, with lettuce being the most frequent trigger (93 [40.8%]), followed by plant food mix (45 [19.7%]) and tomato (26 [11.4%]). Plant food mix was defined as the combination of several LTP-containing plant foods consumed in the same meal [7], which makes it impossible to identify whether the trigger is merely one of the plant foods or the cumulative dose of LTPs from different sources (Figure S1A). We identified only a few foods (cashew, coconut, pomegranate, sesame) not reported to induce GIS by any of the patients (Figure S2). On the other hand, we identified 88 foods related to classic allergy symptoms (urticaria/angioedema, oral allergy syndrome, anaphylaxis), with the most frequent triggers being peach (177 patients [62.3%]), plant food mix (110 [38.7%]), and walnut (89 [31.3%]) (Figure S1B).

Some foods may induce GIS by mechanisms other than allergy, thus potentially limiting the results of our study. Some patients, particularly women, may have so-called functional gastrointestinal disorders (FGIDs), such as irritable bowel syndrome or functional dyspepsia [8]. FGIDs affect 5%-30% of the general population and have a considerable impact on quality of life, although there are almost no data on the prevalence of FA in FGIDs [9-10]. With 44% of FA patients experiencing symptoms that can mimic FGIDs, our findings point to a potential relationship between these 2 entities that requires further investigation.

Our study is limited by its single-center design: while the overall findings may be broadly applicable, the reported sensitization profiles may differ substantially in other areas. Similarly, we did not perform oral challenges (considered the gold standard) in all patients. However, it is worth noting that all reactions were related to the consumption of LTP-containing foods and that sensitization to the food involved in each reaction was confirmed using a commercial skin prick test, sIgE, and/or prick-by-prick testing. Indeed, the relevance of foods inducing GIS was confirmed by the improvement in symptoms when the specific food was removed from the diet.

In conclusion, almost half of LTP-allergic patients in this large cohort reported GIS as a manifestation of their FA. GIS were more frequent in women and the elderly. The symptoms are not specific and may mimic other gastrointestinal disorders that should be ruled out. Thus, considering that patients may not spontaneously provide this information because GIS are not classically identified as allergic symptoms, we suggest taking a targeted clinical history. Finally, nonidentification of GIS may complicate clinical management and limit the quality of life of food-allergic patients.

Funding

The present study was supported by the Institute of Health Carlos III of the Ministry of Economy and Competitiveness (grants cofunded by European Regional Development Fund (ERDF) (RETIC ARADyAL RD16/0006/0007, RICOR-REI RD21/0002/0058, AES PI16/00696, PI19/01861, and PI22/01572).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Spergel JM. Rise of gastrointestinal-based food allergy. Ann Allergy Asthma Immunol. 2023 Dec;131(6):692-3. doi: 10.1016/j.anai.2023.04.020.
2. Chan JCK, Peters RL, Koplin JJ, Dharmage SC, Gurrin LC, Wake M, et al. HealthNuts Study. Food Challenge and Community-Reported Reaction Profiles in Food-Allergic Children Aged 1 and 4 Years: A Population-Based Study. J Allergy Clin Immunol Pract. 2017;5(2):398-409.e3. doi: 10.1016/j.jaip.2016.12.021.
3. Pascal M, Muñoz-Cano R, Reina Z, Palacín A, Vilella R, Picado C, et al. Lipid transfer protein syndrome: clinical pattern, cofactor effect and profile of molecular sensitization to plant-foods and pollens. Clin Exp Allergy. 2012;42(10):1529-39. doi:10.1111/j.1365-2222.2012.04071.x
4. Skypala IJ, Asero R, Barber D, Cecchi L, Diaz Perales A, Hoffmann-Sommergruber K, et al. European Academy of Allergy; Clinical Immunology (EAACI) Task Force: Non-specific Lipid Transfer Protein Allergy Across Europe. Non-specific lipid-transfer proteins: Allergen structure and function, cross-reactivity, sensitization, and epidemiology. Clin Transl Allergy. 2021;11(3):e12010. doi: 10.1002/clt2.12010.
5. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114(2):371-6. doi: 10.1016/j.jaci.2004.04.029.
6. Ruano-Zaragoza M, Casas-Saucedo R, De la Cruz Martinez CA, Araujo-Sanchez G, Gelis S, González MF, et al. Advances in the understanding of the cofactor effect in lipid transfer protein food allergy: From phenotype description to clinical management. Allergy. 2022;77(6):1924-6. doi: 10.1111/all.15291.
7. Casas-Saucedo R, de la Cruz C, Araujo-Sánchez G, Gelis S, Jimenez T, Riggioni S, et al. Risk Factors in Severe Anaphylaxis: Which Matters the Most, Food or Cofactors? J Investig Allergol Clin Immunol. 2022;32(4):282-90. doi: 10.18176/jiaci.0698.
8. Oshima T, Miwa H. Epidemiology of Functional Gastrointestinal Disorders in Japan and in the World. J Neurogastroenterol Motil. 2015;21(3):320-9. doi: 10.5056/jnm14165
9. Koloski N, Jones M, Walker MM, Veysey M, Zala A, Keely S, et al. Population based study: atopy and autoimmune diseases are associated with functional dyspepsia and irritable bowel

syndrome, independent of psychological distress. Aliment Pharmacol Ther. 2019;49(5):546-55. doi: 10.1111/apt.15120
10. Zuo XL, Li YQ, Li WJ, Guo YT, Lu XF, Li JM, et al. Alterations of food antigen-specific serum immunoglobulins G and E antibodies in patients with irritable bowel syndrome and functional dyspepsia. Clin Exp Allergy. 2007;37(6):823-30. doi: 10.1111/j.1365-2222.2007.02727.x.

Manuscript received December 19, 2023; accepted for publication March 22, 2024.

Rosa Muñoz-Cano
Allergy Department
Hospital Clinic
C. de Villarroel, 170
08036 Barcelona, Spain
E-mail: rmunoz@clinic.cat

