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CASE REPORT

A case of a 6-year-old boy diagnosed with lipid transfer protein syndrome using the ImmunoCAP and ImmunoCAP Immuno Solid-phase Allergen Chip

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We experienced a rare case of a 6-year-old boy who was suspected of having lipid transfer protein (LTP) syndrome; the patient was diagnosed with LTP syndrome using the ImmunoCAP/ImmunoCAP Immuno Solid-phase Allergen Chip (ISAC) test. LTP syndrome affects patients who are already sensitized to pollens with signs and symptoms of allergic rhinitis with or without bronchial asthma. Its severity is closely associated with the geographical location as well as the level, nature, and duration of the allergen exposure in a susceptible individual with or without cofactors, such as exercise, alcohol, chemicals, or nonsteroidal anti-inflammatory drug. Patients with LTP syndrome may present with diverse manifestations ranging from local symptoms, such as mild contact urticaria, oral allergy syndrome, or gastrointestinal problems, to anaphylaxis and even anaphylactic shock. Our case highlights the usefulness of the ImmunoCAP/ImmunoCAP ISAC test in establishing a diagnosis of LTP syndrome. (*Allergy Asthma Respir Dis 2024;12:31-34*)

Keywords: Child, Food hypersensitivity, Lipid transfer protein, Immunoglobulin E, Allergy and immunology

INTRODUCTION

Lipid transfer proteins (LTPs) were first identified as allergens ubiquitously present in diverse plant species through *in vitro* experiments in 1985.[1] These are a class of low-molecular-weight, hydrophobic proteins that have highly conserved structures composed of 4 intramolecular disulfide bonds and show resistance to proteolysis and harsh food-processing conditions.[2] LTPs are present in plants and plant-derived foods. Plant allergy due to LTP sensitization is commonly associated with polysensitization, with a varying degree of cross-reactivity between diverse fruits, plant foods, and pollen.[3] LTPs share high structural similarity in the amino acid sequences with diverse foods, and they could act as pan-allergens.[4] LTPs act as powerful allergens to which individuals are sensitized through the gut.[3] Further, LTPs might be involved in the immunological cross-reactivity of fruits, vegetables, and nuts with pollens.[5] They are currently known as the primary causes of immunoglobulin E (IgE)-mediated food allergy and food-induced anaphylaxis.[6] As they are resistant to heat and pepsin, they can reach the gut without undergoing modifications.[7] Due to a relatively higher homology between the LTPs of taxonomically unrelated plant foods or pollen, patients who are sensitized to them may show allergic responses to a broad spectrum of vegetables.[8]

An allergic reaction to many plant-derived foods or pollen after LTP sensitization because of the high cross-reactivity of LTP, regardless of plant classification, is called LTP syndrome.[9] Therefore, LTP syndrome can be defined as an allergy that may affect individuals who are sensitive to LTPs and may be sensitive to vegetables, fruits, nuts, or cereals.[10] Notably, LTP syndrome is characterized by the extreme diversity of its clinical presentations. Patients with strong LTP sensitization may remain asymptomatic.[11]

We encountered the rare case of a 6-year-old boy who was suspected of having LTP syndrome. The patient was diagnosed with LTP syndrome using the ImmunoCAP/ImmunoCAP Immuno Solid-phase Allergen Chip (ISAC) (Thermo Fisher Scientific, Uppsala, Sweden) test. Herein, we report our case along with a review of the literature.

CASE REPORT

On December 23, 2013, a 5-month-old boy visited Busan St. Mary's Hospital with a chief complaint of atopic dermatitis and was hos-

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pitalized at Busan St. Mary's Hospital. However, at 26 months, the patient revisited us for further evaluation of allergic reactions to certain foods. Depending on the severity of symptoms for each food and the ImmunoCAP results, we encouraged the patient to avoid squid, egg, sesame, clam, and to carefully consume soy milk in small quantities.

The patient exhibited skin rashes after ingesting pork at 28 months and red fish at 31 months. As the symptoms were mild and intermittent, the patient was advised to consume these foods cautiously. At 35 months of age, the patient exhibited abdominal pain and rashes in the eyes after the ingestion of walnuts. The patient also presented with symptoms suggestive of angioedema and dyspnea, leading to the diagnosis of anaphylaxis. For further evaluation, the patient underwent an ImmunoCAP test.

At 3-year-old, the patient developed swelling in the neck after ingesting soy milk. The patient again experienced angioedema and dyspnea and was diagnosed with anaphylaxis. Therefore, the patient was advised not to consume soy milk.

At 6-year-old, the patient was advised not to consume eggs, walnuts, soy milk, or squids. The patient voluntarily limited himself to shrimp, bananas, and eggplants. However, the patient could eat meat and fish but complained of coughing while eating pork. As the diet was not well followed and the causative food was often unclear, the patient underwent the ImmunoCAP test again.

When the patient was 8-year-old, the patient presented with a cough with itching on the tongue when eating an unknown type of nut-enriched milk. However, the patient had no problems eating meat. The patient was unable to eat seafood, particularly shrimp or shellfish. Therefore, the patient was advised to be careful while eating nuts and shellfish and was asked to accurately keep a record of the food he consumed and the associated symptoms.

In conclusion, 1 year later, the patient experienced itching when eating eggplant. The patient experienced a tickling sensation, even while looking at the eggs. The patient developed anaphylaxis to squid. The patient had no history of ingesting shrimp, lobsters, or crabs in the past year. The patient also experienced anaphylaxis to walnuts but had no problems eating peanuts or almonds.

To check the possibility of consuming shrimp and eggs, which have ambiguous allergy symptoms, the patient underwent an oral food challenge (OFC), which was negative for shrimp and eggs. Therefore, the patient was allowed to eat these foods. Thereafter, the patient underwent an ImmunoCAP ISAC test, which established the diagnosis of LTP syndrome. The clinical course of this patient is currently being monitored. Patient's profile, clinical presentations, and ImmunoCAP test results are summarized in Tables 1–3.

Table 1. Results of the ImmunoCAP test

Age at the time	Eosinophil counts (/μL)	Total IgE (U/mL)	Trigger foods	ImmunoCAP (class)
26 Months	1,300	356.70	Squid	39.50 KU/L (4)
			Sesame	12.10 KU/L (3)
			Egg	40.20 KU/L (4)
			Soy bean	6.17 KU/L (3)
			Clam	14.60 KU/L (3)
35 Months	820	970.07	Walnut	34.40 KU/L (4)
			Pork	4.80 KU/L (3)
			Shrimp	13.20 KU/L (3)
6 Years	2,390	1,099	Egg	3.15 KU/L (2)
			Shrimp	5.74 KU/L (3)
			Almond	3.02 KU/L (2)
			Peanut	8.01 KU/L (3)
			Banana	3.13 KU/L (2)

IgE, immunoglobulin E.

Table 2. LTP sensitization on ImmunoCAP Immuno Solid-phase Allergen Chip assay

Allergen source	Allergen component	Level of aslgE (ISU-E)	Level
Peanut	Ara h 9	0.7	Low
Hazelnut	Cor a 8	0.6	Low
Walnut	Jug r 3	1.4	Moderate/High
Peach	Pru p 3	3.8	Moderate/High
Mugwort	Art v 3	0.4	Low
Plane tree	Pla a 3	2.4	Moderate/High

The patient exhibited sensitization to diverse LTP components and showed the highest response to peach LTP (Pru p 3).
aslgE (ISU-E) <0.3 undetectable, 0.3–0.9 low, 1–14.9 moderate/high, ≥15 very high.
LTP, lipid transfer protein; aslgE, allergen-specific immunoglobulin E; ISU-E, ImmunoCAP/ImmunoCAP Immuno Solid-phase Allergen Chip standardized units.

Table 3. Detection of pathogenesis-related protein family 10 and profilin molecules on the ImmunoCAP Immuno Solid-phase Allergen Chip assay; only positive results have been mentioned

Allergen source	Profilin		
	Allergen component	Level of aslgE (ISU-E)	Level
Birch	Bet v 2	2.1	Moderate/High
Latex	Hev b 8	1.7	Moderate/High
Annual mercury	Mer a 1	2.5	Moderate/High

The patient only responded positively to profilin.
aslgE (ISU-E) <0.3 undetectable, 0.3–0.9 low, 1–14.9 moderate/high, ≥15 very high.
aslgE, allergen-specific Immunoglobulin E; ISU-E, ISAC standardized units.

This study was approved by the Institutional Review Board (IRB) of Busan Saint Mary's Hospital (IRB subject number: BSM 2023-02), and the requirement for informed consent was waived.

DISCUSSION

LTPs belong to the prolamin protein superfamily; their structure is closely associated with 2S-albumins and α-amylase/protease inhibitors. They are present in diverse phylogenetic plant families, some of which originate from different plant species, and are characterized by < 30% amino acid sequence identity. Nevertheless, their tertiary structure serves as a determinant of conformational IgE epitopes and is highly conserved. Moreover, they are characterized by conserved expression in phylogenetically distantly-related plant species and strong cross-reactivity with IgE between LTPs. Therefore, these compounds are referred to as pan-allergens.[10]

LTP syndrome affects patients who are already sensitized to pollen and have signs and symptoms of allergic rhinitis with or without bronchial asthma.[12] The severity of LTP syndrome is closely associated with the geographical location as well as the level, nature, and duration of allergen exposure in a susceptible individual, with or without the presence of cofactors such as exercise, alcohol, chemicals, and nonsteroidal anti-inflammatory drugs.[13,14] Patients with LTP syndrome may present with diverse manifestations, ranging from local symptoms such as mild contact urticaria, oral allergy syndrome (e.g., itching in the oral mucosa and swelling of the lips), or gastrointestinal problems to anaphylaxis and anaphylactic shock.[12,15] Of these, anaphylaxis is a fatal condition due to hypersensitivity to an allergen that occurs within minutes or hours and involves at least 2 body areas, such as the skin and mucosae, airways, gastrointestinal tract, and cardiovascular system.[16]

At our medical institution, we perform a skin prick test (SPT) on selected foods. Then, we measure the IgE levels against selected food allergens using the ImmunoCAP and establish IgE specific to allergen components using the ImmunoCAP ISAC, for which we consider the IgE levels ≥ 0.35 kUA/L as positive, as previously described.[17] Thus, we routinely perform the ImmunoCAP ISAC test for patients with sensitization to LTP antigens, such as Jug r 3 (walnut), r Arah 9 (peanut), and Pru p 3 (peach), based on the ImmunoCAP test, to establish a diagnosis of LTP syndrome.

Our patient had a history of an allergic disease. As demonstrated in the current case, LTP syndrome may have a long-term and variable clinical course. Clinicians should also note that the onset of symptoms is not an indicator of LTP syndrome, and time-dependent changes in the course of the symptoms may occur. Additional sensitization may also lead to the onset of LTP syndrome. However, estimating the time of onset of LTP syndrome is difficult. Therefore, considering the possibility of LTP syndrome as the first diagnostic clue for patients with persistent nonspecific symptoms is essential. The ImmunoCAP/ImmunoCAP ISAC test is a useful modality for accurately analyzing the LTP components in patients with suspected LTP syndrome.

The patient in the present study initially showed positive results for the ImmunoCAP test. This indicates that negative ImmunoCAP results cannot be interpreted as a lack of a food allergy. Therefore, identifying the causal relationship between foods and symptoms based on the SPT or OFC is mandatory. Moreover, repeated ImmunoCAP tests at certain periods must be performed in patients with persistent food allergies.

In conclusion, our case highlights the usefulness of the ImmunoCAP/ImmunoCAP ISAC test for establishing a diagnosis of LTP syndrome.

REFERENCES

1. Abbey M, Bastiras S, Calvert GD. Immunoprecipitation of lipid transfer protein activity by an antibody against human plasma lipid transfer protein-I. Biochim Biophys Acta 1985;833:25-33.
2. Clare Mills EN, Gao C, Wilde PJ, Rigby NM, Wijesinha-Bettoni R, Johnson VE, et al. Partially folded forms of barley lipid transfer protein are more surface active. Biochemistry 2009;48:12081-8.
3. Ruano-Zaragoza M, Somoza ML, Jiménez-Rodriguez TW, Soriano-Gomis V, González-Delgado P, Esteban-Rodriguez A, et al. Lipid transfer protein sensitization: risk of anaphylaxis and molecular sensitization profile in Pru p 3-sensitized patients. Int Arch Allergy Immunol 2021;182:425-32.
4. Kang JB, Hwang YH. A case report of recurrent anaphylaxis in a 36-year-old female: lipid transfer protein syndrome. Allergy Asthma Respir Dis 2021;9:109-12.
5. Gomez F, Bogas G, Gonzalez M, Campo P, Salas M, Diaz-Perales A, et al. The clinical and immunological effects of Pru p 3 sublingual immunotherapy on peach and peanut allergy in patients with systemic reactions. Clin Exp Allergy 2017;47:339-50.
6. Skypala IJ, Asero R, Barber D, Cecchi L, Diaz Perales A, Hoffmann-Sommergruber K, et al. Non-specific lipid-transfer proteins: allergen structure and function, cross-reactivity, sensitization, and epidemiology. Clin Transl Allergy 2021;11:e12010.
7. Asero R, Piantanida M, Pinter E, Pravettoni V. The clinical relevance of lipid transfer protein. Clin Exp Allergy 2018;48:6-12.
8. Ridolo E, Pucciarini F, Kihlgren P, Barone A, Nicoletta F, Peveri S, et al. Lipid transfer protein syndrome: how to save a life through careful education. World Allergy Organ J 2022;15:100683.
9. Werfel T, Asero R, Ballmer-Weber BK, Beyer K, Enrique E, Knulst AC, et

al. Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. Allergy 2015;70:1079-90.
10. Scheurer S, van Ree R, Vieths S. The role of lipid transfer proteins as food and pollen allergens outside the mediterranean area. Curr Allergy Asthma Rep 2021;21:7.
11. Cuesta-Herranz J, Lázaro M, de las Heras M, Lluch M, Figueredo E, Umpierrez A, et al. Peach allergy pattern: experience in 70 patients. Allergy 1998;53:78-82.
12. Calamelli E, Liotti L, Beghetti I, Piccinno V, Serra L, Bottau P. Component-resolved diagnosis in food allergies. Medicina 2019;55:498.
13. Mastrorilli C, Cardinale F, Giannetti A, Caffarelli C. Pollen-food allergy syndrome: a not so rare disease in childhood. Medicina 2019;55:641.
14. Alessandri C, Ferrara R, Bernardi ML, Zennaro D, Tuppo L, Giangrieco I, et al. Molecular approach to a patient's tailored diagnosis of the oral allergy syndrome. Clin Transl Allergy 2020;10:22.
15. Deng S, Yin J. Mugwort pollen-related food allergy: lipid transfer protein sensitization and correlation with the severity of allergic reactions in a chinese population. Allergy Asthma Immunol Res 2019;11:116-28.
16. Bilò MB, Martini M, Tontini C, Corsi A, Antonicelli L. Anaphylaxis. Eur Ann Allergy Clin Immunol 2021;53:4-17.
17. Ukleja-Sokołowska N, Gawrońska-Ukleja E, Żbikowska-Gotz M, Socha E, Lis K, Sokołowski Ł, et al. Analysis of feline and canine allergen components in patients sensitized to pets. Allergy Asthma Clin Immunol 2016;12:61.