

Case series of seven cases of urticaria, angioedema, and anaphylaxis (LTP syndrome) due to foods (nuts, lentils, and citrus foods) related to tree pollen (*Prosopis juliflora* and *Holoptelea integrifolia*) sensitization

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ABSTRACT

Lipid transfer protein syndrome (LTSP) results from a primary sensitization to LTP belonging to the PR-14 family of pathogenesis-related PR-proteins which are plant food allergens, stable against heat and digestive enzymes, and can induce systemic reactions of urticaria, angioedema, and anaphylaxis. Here, we report a case series of seven patients with nsLTP syndrome. Our six cases of LTSP were significantly sensitized to *Prosopis juliflora* and *Holoptelea integrifolia* and one case was sensitized to *H. integrifolia* only. In our seven cases, we hypothesized that symptoms of hypersensitivity reaction to foods were due to cross-reactivity by IgE reactive protein of ns-LTP as a major allergenic protein in foods.

Key words: Allergy, *Holoptelea integrifolia*, Lipid Transfer Protein Syndrome, Mesquite, *Prosopis juliflora*

The conventional diagnostic workup for IgE-mediated food allergy begins with the clinical history, followed by *in vivo* (Skin Prick Test [SPT]), and/or *in vitro* tests. Specific IgE test against the whole allergen source usually ends with Oral Food Challenge (OFC) which remains the gold standard in diagnosing food allergies. Lipid Transfer Protein Syndrome (LTSP) differs from Pollen Food Allergy Syndrome (PFAS) by having a different family of pan-allergens and clinical characteristics. The principal allergens involved in LTSP are a family of stable allergens (resistant to heat and acid) of non-specific lipid transfer protein (ns LTP) which are abundant, soluble, cysteine (cys) rich, with molecular size usually belonging to 10 kDa, with a rigid tertiary structure formed by four disulfide bridges. These allergens are mainly represented in surface tissue (peel) and are present in apples, peaches, apricots, cherries, plums, pears, raspberries, strawberries, blackberries, weed, and tree pollens, while in PFAS, the allergens belong to Bet v 1 family (PR-10) and profilins, are labile allergens present in fruits, vegetables, and pollens (tree, grass, and weed) which are denatured by high temperatures and gastric enzymes [1,2].

Holoptelea integrifolia is also an important tree pollen allergen of India and sensitizes almost 10% of the atopic population in Delhi as shown by an epidemiological survey carried out on the adult

population of India. This flower has four allergenic components with molecular weights of 50, 60, 66, and 70 kDa [3]. *Prosopis juliflora* is a potent source of naso-bronchial allergy with almost 34.7% of patients being sensitized to *Prosopis juliflora* allergen according to a study [4].


Here, we report a case series of seven patients of nsLTP syndrome in whom the history of urticaria, angioedema, and anaphylaxis was induced by ingested foods such as nuts, lentils, and citrus foods within 30 min in sensitization to tree pollen (*P. juliflora* and *H. integrifolia*) with signs and symptoms of nasobronchial allergy.

CASE SERIES

Case 1

A 60-year-old male, a known case of diabetes mellitus and hypertension on Ramipril, Losartan, and Metformin presented with a history of recurrent urticaria and two episodes of anaphylaxis (swelling of lips, giddiness, choking sensation, and hypotension). He had a history of seasonal allergic rhinitis during February–March for 3 years with a history of urticaria and angioedema following ingestion of walnut and peanut.

His vitals were otherwise normal. Total IgE was normal-54 IU/ml. The SPT was positive for *H. integrifolia* Indian Elm-10 mm, walnut- 4 mm, and peanut-4 mm. Prick-Prick Test (PPT) was

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positive for peach pulp-3 mm and peach peel-4 mm. Specific IgE was negative for all (Table 1). OFC was positive with walnut and peanut. He was given symptomatic treatment with diet elimination of walnut and peanut.

Case 2

A 54-year-old male presented with a history of nasobronchial allergy (rhinorrhea, sneezing, itching, and watering from eyes) during March-May months for 20 years. He had a history of urticaria, angioedema, and anaphylaxis after the ingestion of yellow split gram, nuts (peanut, walnut, and almond), cantaloupe seeds, and sesame seeds for a year. He had a history of repeated courses of oral corticosteroids and antihistamines with no relief.

His vitals were within normal range. Total IgE was raised- 568.5 IU/ml. SPT was positive for *P. juliflora*-10 mm, *H. integrifolia* Indian Elm-6 mm, peanut-4 mm, almond-4 mm, and walnut-4 mm. PPT was positive for peach pulp-4 mm and peach peel-4 mm. Specific IgE test was positive for Mesquite (*P. juliflora*)-3.66 kUA/L, *H. integrifolia* Indian Elm-0.61 kUA/L, peanut-0.80 kUA/L, sesame seeds-3.74 kUA/L, almond-0.96 kUA/L, and walnut-0.65 kUA/L (Table 1). OFC was positive with yellow split gram and peanut. He was given pollen Adoptive Immunotherapy (AIT) and Inj Omalizumab along with diet

elimination of yellow split gram, cantaloupe seeds, sesame seeds, and nuts (peanut, walnut, and almond).

Case 3

A 16-year-old male presented with a history of recurrent rhinoconjunctivitis (rhinorrhea, sneezing, redness, and watering from eyes) and urticaria which aggravates on exposure to dust and after ingestion of peanuts for the past 1 year, which subsided on taking anti-histamines.

His vitals were within the normal limit. Total IgE was 1862 IU/ml. SPT was positive for *P. juliflora*-8 mm, *H. integrifolia* Indian Elm-6 mm, and peanut-4 mm. PPT was positive for peach pulp-3 mm and peach peel-4 mm. Specific IgE was positive for *P. juliflora*-1.13 kUA/L, *H. integrifolia* Indian Elm- 1.54 kUA/L, wheat-0.89 kUA/L, peanut-1.21 kUA/L, and soyabean-0.99 kUA/L. OFC was positive with peanut (Table 2). He was given pollen AIT and Inj Omalizumab along with diet elimination of peanut. Symptoms gradually improved.

Case 4

A 20-year-old female presented with a history of nasobronchial allergy (breathlessness, sneezing, and rhinorrhea) for 1 year. She had a history of recurrent episodes of physical urticaria (on exposure to cold and water) with severe itching and angioedema

Table 1: Clinical characteristics of cases 1 and 2

Case Number	SPT wheal size	Specific IgE	PPT and SPT (Marker of ns LTP)	Oral food challenge
Case 1 Total IgE: 54 IU/ml	Histamine	N/A	Peach peel	Walnut and peanut positive
	<i>Holoptelea integrifolia</i>	<0.01 kUA/l	Peach pulp	
	Walnut	<0.01 kUA/		
	Peanut	<0.01 kUA/l		
Case 2 total IgE: 568.5 IU/ml	Histamine	N/A	Peach peel	Yellow split gram and peanut positive
	<i>Prosopis juliflora</i>	3.66 kUA/L	Peach Pulp	
	<i>Holoptelea integrifolia</i>	0.61 kUA/L		
	Peanut	0.80 kUA/l		
	Almond	0.96 kUA/L		
	Walnut	0.65 kUA/L		

SPT: Skin Prick Test, PPT: Prick-Prick Test

which occurs within 30 min following ingestion of black gram and Peanut. She took repeated courses of oral corticosteroids and anti-histamines with no relief.

Her vitals were otherwise normal. Total IgE was 1949.7 IU/ml, SPT was positive for Mesquite (*P. juliflora*)-6 mm, *H. integrifolia* Indian Elm-5 mm, black gram-3 mm, and peanut-4 mm. PPT was positive for peach pulp-3 mm and peach peel-4 mm. Specific IgE was positive for Mesquite (*P. juliflora*)-0.66 kUA/L, *H. integrifolia* Indian Elm- 0.76 kUA/L, peanut-0.89 kUA/L, wheat-0.45 kUA/L, soyabean- 0.87 kUA/L, cow’s milk-0.42 kUA/L, and egg white- 0.10 kUA/L (Table 2). OFC was positive with black gram and peanut. She was given pollen AIT and Inj Omalizumab along with diet elimination of black gram and peanut.

Case 5

A 32-year-old female presented with a history of recurrent urticaria associated with itching following ingestion of apricot, peanut, and lemon. She gives a history of two episodes of lip angioedema and one episode of periorbital edema following ingestion of apricot.

Her vitals were normal. Total IgE was 181 IU/ml, SPT was positive for *P. juliflora*-6 mm, *H. integrifolia* Indian Elm-6 mm, peanut-4 mm, wheat-4 mm, and chicken-4 mm. PPT was positive for peach pulp-3 mm, peach peel-4 mm, apricot extract-4 mm, and lemon-4 mm. Specific IgE was positive for Mesquite (*P. juliflora*)-3.65 Kua/L, *H. integrifolia* Indian Elm- 3.39 kUA/L, wheat- 3.12 kUA/L, rice-3.45 kUA/L, peanut-3.92 kUA/L, soyabean-2.13 kUA/L, and lemon-2.98 kUA/L. OFC was positive

with apricot, peanut, and lemon (Table 3). She was given pollen AIT and Inj Omalizumab along with diet elimination of apricot, peanut, and lemon.

Case 6









A 63-year-old male, presented with a history of repeated sneezing, rhinorrhea, nose block, loss of smell on and off for 20 years. He underwent polypectomy 8 times and was given Inj avil, Inj dexona, and autohemotherapy in 1999 with no relief. He has a history of breathlessness and cough during acute upper respiratory tract infections. His quality of life was affected because of nasal congestion due to insufficient airflow through the nose with repeated episodes of nose block. In 2007, he developed urticaria with itching after ingestion of peanut and walnut, which responded to symptomatic treatment.

His vitals were normal. Total IgE was 270 IU/ml, SPT was positive for *H. integrifolia* Indian Elm-10 mm, *P. juliflora* -7 mm 5 mm, and peanut-4 mm. PPT was positive for peach pulp-4 mm and peach peel-4 mm. Specific IgE was negative for all. OFC was positive with peanut and walnut (Table 3). He was given pollen AIT with diet elimination of peanut and walnut.

Case 7























A 51-year-old male presented with recurrent episodes of nasobronchial allergy (rhinorrhea, sneezing, nose block, watering from eyes, and itching in eyes and ears) on and off for 10 years. Symptoms aggravate during August-September and November-January months. He has a

Table 2: Clinical characteristics of cases 3 and 4

Case Number	SPT wheal size	Specific IgE	PPT and SPT (Marker of ns LTP)	Oral food challenge
Case 3 Total IgE: 1862 IU/ml	Histamine	N/A		Peanut positive
	<i>Prosopis juliflora</i>	1.13 kUA/L	 8 mm	
	<i>Holoptelea integrifolia</i>	1.54kUA/L	 6 mm	
	Peanut	1.21kUA/L	 4 mm	
Case 4 Total IgE: 1949.7 IU/ml	Histamine	N/A	Peach peel  4 mm	Black gram and Peanut positive
	<i>Prosopis juliflora</i>	0.66 kUA/L	Peach Pulp  3 mm	
	<i>Holoptelea integrifolia</i>	0.76 kUA/L	 5 mm	
	Peanut	0.89 kUA/L	 4 mm	
	Black gram	N/A	 3 mm	

SPT: Skin Prick Test, PPT: Prick-Prick Test

Table 3: Clinical characteristics of cases 5, 6, and 7

Case Number	SPT wheal size		Specific IgE	PPT and SPT (Marker of ns LTP)		Oral food challenge
Case 5 Total IgE: 181 IU/mL	Histamine	 5 mm	N/A	Peach peel	 4 mm	Aprico, peanut and lemon. positive
	<i>Prosopis juliflora</i>	 6 mm	0.66 kUA/L	Peach Pulp	 3 mm	
	<i>Holoptelea integrifolia</i>	 6 mm	0.76 kUA/L	Apricot extract	 4 mm	
	Peanut	 4 mm	0.89 kUA/L	Lemon	 4 mm	
Case 6 Total IgE: 270 IU/mL	Histamine	 5 mm	N/A	Peach peel	 4 mm	Peanut and walnut positive
	<i>Prosopis juliflora</i>	 7 mm	<0.1 kUA/L	Peach Pulp	 4 mm	
	<i>Holoptelea integrifolia</i>	 10 mm	<0.1 kUA/L			
	Peanut	 4 mm	<0.1 kUA/L			
Case 7 Total IgE: 321IU/mL	Histamine	 5 mm	N/A	Peach peel	 4 mm	
	<i>Prosopis juliflora</i>	 4 mm	0.66 kUA/L	Peach Pulp	 3 mm	
	<i>Holoptelea integrifolia</i>	 6 mm	0.47 kUA/L	Orange	 4 mm	
	Peanut	 6 mm	0.28 kUA/L	Lemon	 4 mm	

SPT: Skin Prick Test, PPT: Prick-Prick Test

history of urticaria and peri-orbital edema following ingestion of citrus foods (lemon and orange) and peanuts.

Vitals were normal. Total IgE was 321 IU/ml, SPT was positive for *H. integrifolia* Indian Elm-6 mm, Mesquite (*P. juliflora*)-4 mm, and peanut-6 mm. PPT was positive for peach pulp-3 mm, peach peel-4 mm, lemon-4 mm, and orange-4 mm. Specific IgE was positive for *H. integrifolia* Indian Elm-0.47 kUA/L and peanut-0.28 kUA/L (Table 3). OFC was positive with citrus foods. He was given pollen AIT with supportive therapy and diet elimination of citrus foods and peanuts.

DISCUSSION

Both LTPS and PFAS have unique peculiarities. LTPS differs from PFAS by having a different family of pan-allergens and clinical characteristics: (a) Onset of symptoms is within 30 min in LTPS while it is 5 min in PFAS; (b) severity of symptoms varies from oropharyngeal pruritus to urticaria, angioedema, and anaphylaxis in LTPS while mild to moderate symptoms

of oro-pharyngeal pruritus and swelling in PFAS; (c) common trigger foods are raw, cooked and processed fruits, vegetables, nuts and cereals in LTPS while raw fruits, vegetables, and nuts in PFAS; and (d) co-factors are commonly involved or required for allergic reaction in LTPS, while not involved in PFAS. There are three nuts-ns LTP (Peanut-Ara h 9, Hazelnut-Cor a 8, Walnut-Jug r 3), one cereal flour-ns LTP Wheat (*Triticum aestivum*- Tri a 14), two citrus foods ns LTP-Lemon-Cit I 3, Orange-Cit s 3, and four pollen-ns LTP [Mugwort (*Artemisia vulagris*)-Art v 3, Olive (*Olea europoea*)- Ole e 7, Plane (*Planatus acerifolia*)- Pla a 3, *Parietaria judaica* Par j 1] [5].

H. integrifolia and *P. judaica* belong to the family *urticacea* and share cross-reactive proteins of the molecular weight in the range of 14-95 kDa (14kDa cross-reactive protein in both allergens seems to be profilin). Cross-reactive proteins in *H. integrifolia* and *P. judaica* strongly reacts to Indian allergic patients, while major allergen of *P. judaica*, (Par j 1) is absent in *H. integrifolia* [6].

All our seven patients were positive to peach (peel and pulp) by SPT and PPT, which seems to reflect the presence of IgE

targeting common allergenic determinants of ns LTP which may have cross-reactivity to peanuts, lentils, and citrus foods related to tree pollen sensitization of *P. juliflora* and *H. integrifolia*. Among seven cases, case 1 had a history of two episodes of anaphylaxis after ingestion of food containing walnut and peanut. He was immunologically positive to *H. integrifolia* by SPT (10 mm wheal). We hypothesized that *H. integrifolia* has its own unique epitopes or has ns-LTP which cross-reacts with peanut (Ara h 9) and walnut (Jug r 3) associated co-factors (ACE inhibitor-Ramipril) which could explain the symptoms of urticaria, angioedema, and anaphylaxis due to LTPS. In this case, there may be two distinct patterns of sensitization to *H. integrifolia* and LTP sensitization (positive to peach extract) which needs further tests of LTP of peanut and walnut by CRD to strengthen our diagnosis and management. Moreover, quantitative CRD analysis of ns LTP in foodstuff will guide the clinician for the identification and production of low-LTP foods which can decrease the risk to patients with LTPS. Case 2-7 of nasobronchial allergy were immunologically sensitized to both *P. juliflora* and *H. integrifolia* SPT-10 mm, positive to peach extract by PPT and SPT, and positive specific IgE with positive OFC in consistent with a history of patients. Whether peach-(PruP 3) LTP has been sensitizer in these cases, needs further identification of homologous ns LTP in both tree pollen allergens and also to investigate immunological ns LTP of nuts, lentils, and citrus fruits. The authors have published four cases of LTP cross-reactivity between Wheat (Tri a 14) and Peanut (Ara h 9) in prior sensitization to *Artemisia vulgaris* (Mugwort) [7].

In our cases to discriminate against primary food allergens versus secondary, sensitization by CRD of tree pollen and food pollen was not done due to the non-availability. Moreover, in India, there is a geographic diversity of different exposure of airborne allergens and food allergens in climate zones of different populations. None of the identified Specific IgE cutoff have shown a specificity and sensitivity profile as accurate as OFC which is still the gold standard to diagnose food allergy up until now [8].

Our seven cases continued to have recurrent and frequent reactions to these foods despite diet elimination and anti-histamine prophylaxis with the use of adrenaline injection as per need. Their equality of life was significantly affected. Case 1 could not tolerate AIT and was given symptomatic treatment with diet elimination. In four patients (Cases 2-5), the treatment was initiated with Omalizumab (150 mg once a month) and could tolerate the trigger foods after six months of Omalizumab and AIT for 1 year with *P. juliflora* and *H. integrifolia*. Since then, they have not experienced the systemic reactions of urticaria, angioedema, and anaphylaxis. Other two patients (Cases 6 and 7)

took only AIT for 1 year with *P. juliflora* and *H. integrifolia* and achieved tolerance to trigger foods.

CONCLUSION

We have hypothesized that both sensitizations to peach peel and pulp by PPT and SPT are surrogate markers of LTP and clinical allergy of urticaria, angioedema, and anaphylaxis due to peanuts, lentils and citrus foods related to tree pollen (*P. juliflora* and *H. integrifolia*) are due to ns LTP. Allergists should inform their patients that ns-LTP tree pollen sensitization (*P. juliflora* and *H. integrifolia*) related foods (nuts, lentils, and citrus foods) can cause urticaria, angioedema, and anaphylaxis and such patients should be prescribed self-injection of Epinephrine. Further studies of inhibition and CRD testing are required to distinguish between cross-reactivity {ns-LTP, defensins, PR-10 and storage proteins} and genuine sensitization.

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