Wheat and peanut food allergy in mugwort (*Artemesia vulgaris*) sensitized patients: A case series of four cases

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ABSTRACT

Non-specific lipid transfer proteins (LTPs) are the major food allergens in mugwort-Pollen Food Syndrome and are associated with systemic allergic reactions. We evaluated the relationship between mugwort pollen with peanut and wheat. The diagnosis was based on a convincing history of an allergic reaction after their food consumption and positive skin prick test with elevated food-specific immunoglobulin E (IgE) by Immunocap. We speculate that the causative allergenic protein Art V3 nsLTP in artemisia, Arh 9 nsLTP in peanut, and Tria 14 nsLTP in wheat are the major allergenic epitopes which are thermostable and resistant to peptic digestion, causing for systemic reaction in our cases.

Key words: *Artemisia vulgaris, Non specific Lipid Transfer Protein, Oral Allergy Syndrome, Pollen-Food Allergy Syndrome*

Mugwort (Latin: *Artemisia vulgaris*) is the important representative of the *Asteraceae* family. In India, mugwort pollen flowers appear in late summer and autumn. It is a coarse perennial herb, often reddish, angled stems, having dark green above, and white woolly beneath [1]. The main allergen in mugwort is 80% glycoprotein with a defensive-like domain (Art V1) and has 60% non-specific lipid transfer protein (Ns LTP-Art V3). This Ns LTP has cross-reactivity with peanut, soybean, wheat, and sunflower seeds. In Mugwort-Mustard Allergy Syndrome (MMAS), individuals sensitized to mugwort may develop an allergic reaction (urticaria, angioedema, and anaphylaxis) to mustard [2]. Mugwort pollen may represent the primary allergen source for Ns LTP sensitization. The pathogenesis of Lipid Transfer Protein Syndrome (LTPS) is linked to cross-reactivity between pollens (*A. vulgaris,* etc.) and homologous epitopes contained in food protein (wheat, peanut, etc.). In one study, it was found that 20% of patients allergic to grass and mugwort pollen are suffering from PFAS with symptoms of urticaria, nasal symptoms, angioedema, abdominal symptoms, and even anaphylaxis [3].

We herein describe four cases of mugwort (*A. vulgaris*), peanut, and wheat association confirmed by positive skin prick test (SPT) with positive specific immunoglobulin E (IgE) antibodies (Immunocap system) for mugwort, peanut, and wheat which has not been reported so far to our knowledge. Ns LTPs have a role in the transport of hydrophobic molecules. Nuts group (walnut, hazelnut, and peanut) and cereal (wheat, maize, and rice) have been described as foods eliciting a reaction not only like oral allergy syndrome (OAS) but also severe systemic reaction (anaphylaxis) in LTP-sensitized patients [4,5].

CASE SERIES

Case 1

A 20-year-old male presented with a history of recurrent anaphylactic reactions (urticaria with itching, angioedema, swelling of the tongue, choking sensation, vomiting, and hypotension) after ingestion of peanuts, pizza, and spicy food. There was a history of persistent signs and symptoms of rhinoconjunctivitis in the past (watery nasal discharge, sneezing, lacrimation, itching in the eyelids, and redness in the eyes). The patient was otherwise healthy except during episodes of anaphylaxis. His vitals were within the normal range. Blood tests revealed an elevated level of serum IgE: Total IgE – 612.0 IU/ml (normal range <87.0 IU/ml) and 25-hydroxyvitamin D – total was low – 7.3 ng/ml (normal range 30.0–100.0 ng/ml). SPT was positive to mugwort (*Artemisia vulgaris*) – 8 mm, mesquite (*Prosopis juliflora*) – 6 mm, wheat – 7 mm, peanut – 4 mm, and shrimp – 6 mm (Table 1). Serum-specific IgE was positive for mugwort (*A. vulgaris*) – 0.62 kua/L, wheat – 1.60 Kua/l, peanut – 0.11 kua/l, *Dermatophagoides farinae* – 0.78 kua/l, *Dermatophagoides pteronyssinus* – 0.70 kua/l, cockroach – 0.67 kua/l, and Bermuda grass – 0.44 kua/l. He was recommended the elimination of wheat and peanut from the diet along with allergen immunotherapy (AIT) and Inj Omalizumab (Anti IgE) for *A. vulgaris* with supportive therapy (emergency kit containing injection adrenaline, antihistamine, and oral corticosteroid). He was followed up for 3 years and no new episodes of urticaria/angioedema/anaphylaxis were reported.

Table 1: Total IgE, SPT, and specific IgE for mugwort (*Artemisia vulgaris*), wheat, and peanut for case number 1 and 2

	Case 1		Case 2		
Total IgE	612.0 IU/ml		187.0 IU/ml		
SPT wheal size		**Specific IgE**			**Specific IgE**
Histamine	6 mm		6 mm		
Mugwort	8 mm		0.62 kua/L	8 mm		<0.01 kua/L
Wheat	7 mm		1.60 kua/L	6 mm wheal/12 mm erythema		<0.01 kua/L
Peanut	4 mm		0.11 kua/L	5 mm		<0.01 kua/L

Case 2

A 37-year-old male presented with a history of repeated episodes of nasobronchial allergy (rhinorrhea, sneezing, nose block, and cough) with recurrent urticaria/angioedema/anaphylaxis associated with itching after ingestion of mango, wheat, spicy, food, watermelon, and peanuts. He has had history of severe urticaria/angioedema/anaphylaxis after ingestion of NSAIDS. His vitals were normal. Blood tests revealed an elevated level of serum IgE: Total IgE – 187.0 IU/ml (normal range <87.0 IU/ml) and low 25-hydroxyvitamin D – Total – 13.7 ng/ml (normal range 30.0–100.0 ng/ml). SPT was positive to mugwort (*A. vulgaris*) – 8 mm, Bermuda grass (*Cynodon dactylon*) – 6 mm, wheat – 6 mm, and peanut – 5 mm (Table 1). Serum-specific IgE was negative for all allergens. The patient was advised diet elimination of wheat and peanut combined with AIT of *A. vulgaris* and Inj Omalizumab (Anti IgE) [150 mg once a month for 6 months] along with supportive therapy (emergency kit containing injection adrenaline, antihistamine, and oral corticosteroid) to which he responded well. He was followed up for 3 years with no episodes of urticaria/anaphylaxis.

Case 3

A 37-year-old male presents with a history of recurrent rhinoconjunctivitis and urticaria/angioedema/anaphylaxis after ingestion of pizza, spicy food, dry fruits, and eggs. His vitals were normal. Blood tests revealed: Serum IgE was elevated, total IgE – 104.0 IU/ml (normal range <87.0 IU/ml), and 25-hydroxyvitamin D – total was low – 26.38 ng/ml (normal range 30.0–100.0 ng/ml). SPT was positive for mugwort (*A. vulgaris*) – 8 mm, mesquite (*P. juliflora*) – 6 mm, Bermuda grass (*C. dactylon*) – 6 mm, wheat – 4 mm, and peanut – 4 mm (Table 2). Serum-specific IgE was positive for mugwort (*A. vulgaris*) – 0.74 kua/L, common silver birch (*Betula verrucosa*) – 0.75 kua/L, wheat – 0.40 kua/L, peanut – 0.18 kua/L, goosefoot (*Chenopodium album*) – 1.13 kua/L, Bermuda grass (*C. dactylon*) – 2.41 kua/L, elm (*Ulmus americana*) – 0.95 kua/L, common pigweed (*Amaranthus retroflexus*) – 2.46 kua/L, and common ragweed (*Ambrosia elatior*) – 0.37 kua/L. The patient was advised wheat and peanut avoidance with AIT of artemesia and Inj Omalizumab (Anti IgE) [150 mg once a month for 6 months] along with supportive therapy (emergency kit containing injection adrenaline, antihistamine, and oral corticosteroid) there was an improvement in his symptoms in follow up for 3 years and responded well to therapy.

Case 4

A 43-year-old female presented with recurrent episodes of rhinoconjunctivitis, periorbital edema, angioedema of the face, and generalized urticaria with itching in the palate and nose, 30 min after the ingestion of peanuts, beetle nut, wheat, and broccoli. She also gives a history of periorbital edema following aspirin intake (NSAIDS). Her vitals were within the normal range. Blood tests revealed: Serum IgE was elevated: Total IgE – 162.0 IU/ml (normal range <87.0 IU/ml) and 25-hydroxyvitamin D – total was low – 18.7 ng/ml (normal range 30.0–100.0 ng/ml). SPT was positive for mugwort (*A. vulgaris*) – 9 mm,

Table 2: Total IgE, SPT and specific IgE for mugwort (*Artemisia vulgaris*), wheat, and peanut for case number 3 and 4

	Case 3		Case 4	
Total IgE	104.0 IU/ml		162.0 IU/ml	
SPT wheal size		**Specific IgE**		**Specific IgE**
Histamine	6 mm		6 mm	
Mugwort	8 mm	0.74 kua/L	8 mm	1.09 kua/L
Wheat	6 mm wheal/12 mm erythema	0.40 kua/L	6 mm	0.42 kua/L
Peanut	5 mm	0.18 kua/L	5 mm	0.22 kua/L

mesquite (*P. juliflora*) – 6 mm, wheat – 4 mm, peanut – 4 mm, and fish – 4 mm (Table 2). Serum-specific IgE was positive for mugwort (*A. vulgaris*) – 1.09 kua/L, goosefoot (*C. album*) – 0.25 kua/L, Bermuda grass (*C. dactylon*) – 0.21 kua/L, elm (*U. Americana*) – 0.24 kua/L, common pigweed (*A. retroflexus*) – 0.17 kua/L, common ragweed (*Ambrosia elatior*) – 0.22 kua/L, wheat – 0.42 kua/l, and peanut – 0.22 kua/L. She was advised with wheat and peanut elimination from her diet and was given AIT of Artemesia and Inj Omalizumab (Anti IgE) [150 mg once a month for 6 months] along with supportive therapy (emergency kit containing injection adrenaline, antihistamine, and oral corticosteroid) to which she is responding well. She was followed up for 2 years and her symptoms of anaphylaxis and angioedema have reduced markedly.

DISCUSSION

Mugwort-related PFAS and LTPS is classified as celery-mugwort-spice syndrome (CMSS), mugwort-peach association (MPA), Mugwort-Mustard Allergy Syndrome (MMAS), and mugwort-chamomile association (MCA). In India, sensitization has been reported to *A. vulgaris* (mugwort) in Aligarh (28%), Bhopal (23%), Kanpur (22%), Delhi (19%), Mumbai (8%), and Bangalore (5–7%) [6].

The presence of a convincing history of respiratory symptoms (rhinoconjunctivitis) linked to pollen exposure (*A. vulgaris,* etc.) with immediate symptoms (urticaria, angioedema, and anaphylaxis) following ingestion of certain food items (peanut, wheat, etc.) and positive specific IgE test to the relevant allergens (artemisia, wheat, and peanut) is enough to make the diagnosis of LTP syndrome. All our four cases have Vitamin D3 deficiency. A high degree of IgE cross-reactivity is observed among different weed pollens like Artemisia species (mugwort pollen; Art V3, Ns LTP) to homologous molecules in plant food (peanut and wheat, etc.) containing LTP. Primary sensitization to *A. vulgaris* (major allergen; Art V1) can induce symptoms of rhinoconjunctivitis and/or asthma only.

Positive SPT and specific IgE are indicative of primary sensitization. Component resolved diagnosis of Art V1, Art V6, and Art V3 would be the diagnostic marker for PFAS and LTP which is not yet available in India for routine diagnosis. Ns LTP-specific IgE antibody is an important marker of true food allergy with a high risk of severe systemic reaction and is found in the peel of the fruit more than the pulp and has been recognized in tree and weed pollens and in vegetable food allergen sources. Sensitivity to LTP is expressed in variable ways: (a) Patients can tolerate certain food even when SPT or specific IgE is positive, indicating sensitization. (b) Some patients will react only in the presence of associated cofactors (exercise, nonsteroidal anti-inflammatory drugs, or alcohol) as in case number 2 and 4. (c) Patients can get severe allergic reaction despite low or negative specific IgE value as observed in our case number two. The clinical reactivity of the individual associated with sensitivity to pollen (*A. vulgaris,* etc.) and food (wheat/peanut, etc.) depends on the amount of the allergen ingested, the affinity of IgE antibodies in the blood, coexposure to other allergens, and the degree of processing and storage of foodstuff [7,8].

The peanut allergen belongs to a diverse group of protein families leading to immunochemical IgE-mediated cross-reactions

among different members of the legume families. According to a study, Arh 9 (Ns LTP type I) is considered as a secondary food allergen. It possesses thermal and digestive stability. Peanut, hazelnut, and walnut not only induce OAS but also severe systemic reactions (urticaria, angioedema, and anaphylaxis) in LTP-sensitized patients as seen in our four cases who have shown significant immunological positivity to *A. vulgaris* by both SPT and specific IgE except in case number two where the specific IgE is negative. Cereal such as wheat, maize, and rice can also cause systemic reactions in various degrees of severity in LTP allergic patients. Sensitization to omega-5 gliadin is the most specific marker for Wheat Dependent Exercise Induced Anaphylaxis (WDEIA). Wheat Ns LTP Tria cross-reacts with weed pollen (*A. vulgaris*: Art V3) can induce severe systemic reaction as per history in our four cases [9,10]. In our four cases, SPT and specific IgE were found positive against mugwort, peanut, and wheat which need further confirmation to rule out cross-reactivity or cosensitization by immunoblotting inhibition assay and Immunocap ISAC test which were not done in our patients because of their non-availability in India. Whether Art V3 (Ns LTP) in Artemisia may have cross-reactivity to peanut (Arh 9) and wheat (Tria 14) food or independent Ns LTP syndrome needs further studies [11].

CONCLUSION

The true prevalence of PFAS/LTP syndrome is difficult to determine because of wide geographic variability. By appropriate recognition, diagnosis, and management, one can prevent allergic reaction after discussion with the patient which includes the risk of the reaction, severity of the reaction, and potentially cross-reactive foods. Our four cases demonstrate that suspected LTP syndrome with significant sensitization to *A. vulgaris* has marked improvement in symptoms of allergic Rhinoconjunctivitis and urticaria/angioedema/anaphylaxis from AIT of *A. vulgaris* combined with Inj Omalizumab (Anti IgE) along with complete diet elimination of wheat and peanut. Further studies are needed to confirm the causative allergen epitopes in mugwort-sensitized patients because of the cross-reactivity between Art 3 Ns LTP of *A. vulgaris* with Ns LTP-Arah 9 of peanut and Ns LTP-Tria 14 of wheat for the possible diagnosis of LTP syndrome in our four cases.

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