

underpin alpha-gal allergy are required to comprehend the true burden of alpha-gal allergy and identify potential therapeutic targets.

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Non-specific lipid transfer protein allergy in United Kingdom



Nonspecific lipid transfer proteins (nsLTPs) are a group of highly conserved, low-molecular-weight proteins that are found throughout the plant kingdom.¹ The nsLTPs are believed to have an important role in plant defense² and are concentrated in the skin of many fruits, including those belonging to the *Rosaceae* family,^{1,3} of which the peach and its nsLTP Pru p 3 is the most well characterized.¹ Nonspecific lipid transfer protein allergy is a common type of food allergy in the Mediterranean, but it is thought to be uncommon in Northern and Central Europe.⁴

Sensitization to nsLTPs is not yet understood, but it is thought to occur through either inhalation or digestion.⁴

We describe 8 patients identified with nsLTP allergy presenting throughout 2017 and 2018 to a tertiary adult allergy department in Preston, in northwestern England. The age range of these patients is 22 to 54 years; 4 are women, and 4 are men. Seven of the 12 patients are of white British heritage, and 1 is of Chinese heritage. All patients are local to northwestern England. Their diagnoses were made by 2 experienced clinicians, based on clinical history and positive blood test, and skin test (skin prick test [SPT] and prick to prick test).

No oral challenges were performed. All of these patients underwent SPTs to a panel of aeroallergen and food extracts (either from ALK Abelló, Horsholm, Denmark, Allergopharma, Reinbeck, Germany, Stallergenes, Antony, France or from Allergy Therapeutics, Worthing, United Kingdom), prick to prick test to fresh/raw foods (when possible), and positive and negative control solutions (histamine dihydrochloride 10 mg/mL and normal saline). All SPTs were performed by experienced operators using standardized techniques. Blood test for specific immunoglobulin E (IgE) testing (whole extract and component testing) was done using the ImmunoCAP assay by Thermo Fisher Scientific in an accredited laboratory.

The clinical phenotype of nsLTP allergy is highly variable, ranging from mild localized reactions to severe systemic reactions, including anaphylaxis.^{4,5} The reason for the variability in clinical expression is not understood; however, co-factors such as exercise, alcohol, fasting, and nonsteroidal anti-inflammatory drugs are often needed for clinical expression of nsLTP hypersensitivity.⁵ Co-factors appear to be

important for several of our patients, as outlined in Table 1. Patients 4 and 7 both describe severe allergic reactions after engaging in strenuous exercise following the consumption of culprit foods. Nonsteroidal anti-inflammatory drugs are implicated in patient 5, who took aspirin 30 minutes before eating a ready-made chicken curry meal, after which she had anaphylaxis.

The nsLTP proteins are pan-allergens, and because of their highly conserved molecular structure, they carry a risk of allergic cross-reactivity.¹ As such, it is not unusual for patients to experience adverse reactions to multiple nsLTP-containing foods.⁶ As described in Table 1, patients 1, 2, 3, 4, 5, and 8 all display allergic reactions to multiple nsLTP-containing foods, whereas patients 6 and 7 display symptoms after the consumption of only 1 type of food.

Nonspecific lipid transfer proteins are highly resistant to heat and enzyme degradation.^{1,4,5} This allows them to retain their allergenicity even after food processing and digestion, explaining their ability to provoke severe and systemic allergic reactions.¹

Although thought to be uncommon in Northern Europe, here we have described 8 cases of nsLTP allergy presenting to a tertiary adult allergy center in northwestern England. The clinical presentations are varied, and these patients are presenting later in life, having tolerated these foods previously. Seven of these patients had LTP component positivity to their implicated food (ie, Ara h 9, Cor a 8, Jug r 3, Mal d3), in which we were able to test for it or for LTP component in peach (Pru p3), when unable to test specifically for LTP in a particular food. Only 1 patient (patient 1) had negative peanut component to LTP, despite reacting to peanuts (with negative results for other peanut components and weakly positive specific IgE to peanuts) but was positive to peach LTP, with a history of also reacting to peach. Peach SPT was only carried out when peach was implicated in the patient's clinical history. All the patients had Pru p3 checked, with the exception of patient 7, because this patient's history was only of having an allergic reaction to peanuts, and it was not expected that this patient would be solely positive to just Ara h9 peanut component. Skin tests (SPT and prick to prick test) or blood test to implicated foods in our patient cohort were always found to be positive.

Nonspecific lipid transfer protein allergy has been reported in Germany, Austria, and China.^{7–9} Skypala et al¹⁰ recently published 35 nsLTP allergy patients diagnosed in 2 allergy centers in London, England. Our experience suggests that this condition is more

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Table 1Age, Sex, Ethnicity, Clinical Presentation, Skin Prick, and Specific IgE Results for nsLTP Patients Seen in the Preston Allergy Clinic^a

Ethnicity, age (y), and sex	Clinical presentation & co-morbidities	Skin prick test and prick to prick test results (mm), positive result ≥ 3 mm	Specific IgE blood test results (KUa/L) positive result ≥ 0.35 KUa/L
Pt 1 White British 43M	• Streaming eyes, angioedema, itching of the face & uvula minutes after eating peanut butter (this occurred twice in 1 month) • Angioedema of face after consumption of peaches, plums, apricots, apples, raspberries, nectarines, and strawberries • Tingling of lips after eating honeydew melon • Co-morbidities: Seasonal allergic rhinitis, asthma, mild eczema	Positive: Kiwi (3), strawberry (3), peach (3), almond (3), Timothy grass (5), 6 grasses (6), birch (3) Negative: Peanut, walnut, cashew nut, Brazil nut, hazelnut, pecan, pistachio, pine nut, sesame, mustard seeds, vanilla essence, clove, star of anise, nutmeg powder, cinnamon bark.	Positive: Peanut (0.63), Pru p 3 (1.3), Mald d3 (0.68), Timothy grass (1.54) Negative: Birch, hazelnut, Brazil nut, almond, cashew nut, walnut, Bet v 1, Pru p 1, Pru p 4, sesame seed, Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 8, Ara h 9, Mal d1, Jug r1, Jug r3, pecan, pistachio, pine nut, caraway, mace, cardamom, cloves, mugwort. Total IgE: 49
Pt 2 White British 54F	• Vomiting, shortness of breath, and wheeze after eating hazelnuts • Abdominal pain and diarrhea after consuming peanut • Vomiting and hives on eating lettuce (this happened twice) • Co-morbidities: Asthma, seasonal allergic rhinitis.	Positive: 6 grasses (5), timothy grass (5), birch (3) Negative: Peanut, hazelnut, walnut, Brazil nut, almond, cashew nut, pecan, pistachio, pine nut, sesame, weed mix, <i>Alternaria</i>, <i>Cladosporium</i>, & <i>Aspergillus</i>	Positive: Peanut (1.21), hazelnut (0.64), walnut (1.68), Cor a 8 (1.05), Pru p 3 (2.77), Ara h 9 (2.84), Jug r 3 (0.49), Timothy grass (10.2). Negative: Brazil nut, almond, cashew nut, macadamia nut, horse chestnut, sweet chestnut, hazelnut, Ara h 1, Ara h 2, Ara h 3, Ara h 8, Jug r 1, Cor a 1, Cor a 9, Cor a 14, Pru p 4, Pru p 1. Total IgE: 801
Pt 3 Chinese 23F	• Itchy throat, lip swelling, and nausea immediately after eating peach (this happened twice) • Itchy mouth & throat after eating apple • Wheeze on eating Chinese turtle jelly • Co-morbidities: Perennial allergic rhinitis, mild eczema, asthma	Positive: Peach (8), house dust mite (6), almond (4) Negative: Timothy grass, 6 grasses, birch, weed, cat, dog, apple, kiwi fruit, celery, peanut, hazelnut, Brazil nut, cashew nut, and walnut	Positive: Peach (2.69), Pru p 3 (3) Negative: Birch, apple, Bet v 1, Bet v 2, Cor a 1, Cor a 8, Pru p 1 & Pru p 4. Total IgE: 316
Pt 4 White British 21M	• Hives, chest tightness, and wheeze after consumption of blueberries and strawberries • When on holiday in Spain, the patient consumed a pizza and a peach, after which he went swimming. Shortly after he complained of shortness of breath, rash, and cough. • Co-morbidities: Seasonal allergic rhinitis	Positive: Prick to prick to raw peach (14), kiwi (8), peanut (8), almond (8), timothy grass (8), 6 grasses (8), birch (8) Negative: Apple, celery, strawberries, hazelnut, Brazil nut, cashew nut, walnut, pecan, pistachio, and pine nut	Positive: Peanut (2.81), hazelnut (10), Brazil nut (1.19), almond (3.15), walnut (7.82), cashew nut (0.36), Pru p 1 (10.5), Pru p 3 (2.54), Ara h 9 (0.37), Jug r 3 (1.08), Bet v 1 (3.19), birch (1.92) Negative: Bet v 2, Pru p 4, Ara h 2, Jug r 1. Total IgE: 291
Pt 5 White British 34F	• Anaphylaxis to 'ready-made' chicken curry meal, with raised tryptase at 18.5 ug/L. Aspirin consumed 30 minutes before meal (currently eating chicken). Baseline tryptase normal at 7.1 μg/L. • Itchy skin after eating a hazelnut candy. Itching and urticaria covering the whole body after eating a hazelnut praline (patient is avoiding all nuts) • Tomatoes results in a funny sensation in mouth when cooked or in a sauce, but when eaten raw is associated with nausea. • Swelling of face and hands 1.5 hours after carving a pumpkin • Urticaria and angioedema of the face minutes after eating a fruit salad containing strawberry, blueberry, blackberry, and raspberry. Itchy mouth with peaches • Nasal congestion, urticaria, and difficulty in breathing with corn tortilla chips	Positive: Almond (5), hazelnut (6), prick to prick to raw blackberry (5), prick to prick to raw raspberry (4), prick to prick to raw blueberry (3) Negative: Grass pollen, birch, weed mix, latex, apple, Brazil nut, cashew nut, peanut, and sesame	Positive: Blueberry (0.92), banana (0.73), peanut (0.66), hazelnut (1.62), almond (2.75), walnut (4.51), pumpkin (0.42), pumpkin seed (1.61), raspberry (1.71), strawberry (1.63), Cor a 8 (8.62), Pru p 3 (12.7), Ara h 9 (3.57), sesame seed (1.63), maize (11.10), tomato(7.02), Timothy grass (1.6) Negative: Bet v 1, birch, Brazil nut, cashew nut, Cor a 1, Cor a 14, Cor a 9, Ara h 2, Ara h 1, Ara h 3, Ara h 8 Total IgE: 53
Pt 6 White British 51M	• Itchy palms and angioedema of the face, neck, tongue, and lips and hypotension 5 minutes after eating black currant conserve. The patient was treated with adrenaline and chlorphenamine by paramedics, after which his symptoms immediately improved.	Positive: Prick to prick to black currant conserve (8) Negative: Timothy grass, weed mix	Positive: Pru p 3 (5.16) Negative: Blackcurrant, Pru p 1, Pru p 4, birch, timothy grass, omega-5-gliadin. Total IgE: 57
Pt 7 White British 30M	• Consumed peanut butter and peanuts then went on a run. Shortly afterwards complained of facial swelling and difficulty breathing. Treated with adrenaline and steroids at hospital. Previously no problems with eating peanuts. • Co-morbidities: Mild eczema	Positive: Peanut (5), hazelnut (4), almond (5), walnut (4) and pecan (3), Timothy grass (3), birch (3) Negative: Brazil nut, cashew nut, pistachios, pine nuts, sesame and wheat flour	Positive: Ara h 9 (9.67), almond (1.65), hazelnut (5.37), peanut (5.05), walnut (9.05) Negative: Ara h 1, Ara h 2, Ara h 3, Ara h 8, Ara h 6, Brazil nut, cashew nut. Total IgE: 49

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Table 1 (continued)

Ethnicity, age (y), and sex	Clinical presentation & co-morbidities	Skin prick test and prick to prick test results (mm), positive result ≥ 3 mm	Specific IgE blood test results (KUa/L) positive result ≥ 0.35 KUa/L
Pt 8 White British 28F	- Itchy scalp, widespread hives, facial swelling, and difficulty breathing after drinking red wine and eating nonspecific snacks - Itchy palms, periorbital angioedema, and urticaria 10 minutes after consuming a chocolate bar with nuts - Itchy palms, tight throat, and rash after eating melon and red grapes - Lip swelling after eating spicy chicken nuggets and paprika-flavored potato snack Co-morbidities: Mild Seasonal allergic rhinitis	Positive: Peanut (3), almond (3), pecan (3), strawberry (3), peach (3), hazelnut (5), paprika (6), prick to prick to raw red pepper (4), prick to prick to raw yellow pepper (3), prick to prick to raw chilli (3) Negative: Melon, kiwi, apple, pine nuts, pistachio, sesame, walnut, cashew nut, Brazil nut.	Positive: Ara h 9 (0.44), Pru p 3 (0.72), grape (0.39), Mal d 3 (0.85), hazelnut (0.68), almond (0.74), walnut (0.35) Negative: peanut, cashew nut, Brazil nut, paprika (0.31), Mal d 1, Cor a 1, Cor a 8, Cor a 9, Cor a 14, Pru p 1, Pru p 4, Jug r 1, Jug r 3 (0.34). Total IgE: 25

F, female; IgE, immunoglobulin E; M, male; nsLTP; non-specific lipid transfer protein; Pt, patient.

^aHazelnut components = Cor a 1, Cor a 8, Cor a 9, Cor a 14. Peach components = Pru p 1, Pru p 3, Pru p 4. Peanut components = Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 8, Ara h 9. Walnut components = Jug r 1, Jug r 3. Apple components = Mal d 1, Mal d 3. Total IgE range = 0–81 KU/L. Tryptase normal range = 2–14 μ g/L.

widespread, not geographically restricted, and also is seen in the north of England. Interestingly the patients described by Skypala et al only had reactions to tree nuts, peanuts, apples, stone fruits, and tomatoes.⁸ The patients in this case series reacted to peanuts, tree nuts, stoned fruits, raspberry, strawberry, blueberry, tomatoes, pumpkin, blackberry, grape, melon, lettuce, apple, honeydew melon, paprika, corn, and blackcurrant.

The prevalence of this condition in adults based on the Preston experience is 0.6 adult cases per 100,000 adults in the United Kingdom, although this maybe an underestimation. This is based on the catchment population served by the Preston Adult Allergy Department, which is 1.3 million adults. We believe that this is the first report of cases of nsLTP allergy in the most northern part of Europe.

In conclusion, these findings highlight the importance of investigating patients who present with multiple severe and systemic food allergies for nsLTP allergy regardless of geography. The patients described here were counseled about allergen avoidance and were given a specific leaflet designed in-house for patients with nsLTP allergy, highlighting safe and at-risk foods. These patients were also prescribed adrenaline pens, and each was provided with a tailored anaphylaxis action plan on how to deal with allergic reactions.

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Association of atopic dermatitis with increased risk of anaphylaxis to egg and milk

Although atopic dermatitis (AD) has been associated with increased risk of food allergy (FA), this association is not fully understood, and the predictors of severe reactions to foods are not clear. In a review of 18 population-controlled studies, the rate of food sensitization

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was up to 6 times higher in patients with AD vs healthy controls.¹ A recent study identified a potential physiologic mechanism by demonstrating increased skin barrier dysfunction, measured by increased transepidermal water loss and reduced skin filaggrin levels, in patients with AD and FA.² These defects are hypothesized to facilitate penetration of food proteins through the skin and induce sensitization.² Although the development of FA is associated with more severe AD, it is not well known how the presence of AD

