

## Allergy in frequent travelers: the alpha-gal story and the first UK case series



Galactose- $\alpha$ -(1,3)-galactose (alpha-gal) is found in most non-primate mammalian cell membranes.<sup>1</sup> Humans, apes, and Old World monkeys lack alpha-1,3 galactosyltransferase required for the synthesis of this carbohydrate.<sup>2</sup> It is therefore highly immunogenic to humans and implicated in alpha-gal syndrome/allergy—the first noninfectious tickborne disease in humans.<sup>3</sup> Alpha-gal moiety has been found in tick salivary proteins, and primary immunoglobulin E (IgE) sensitization to alpha-gal is thought to occur through inoculation of saliva during a tick bite.<sup>2,4</sup> Recurrent tick bites induce high levels of anti-alpha-gal IgE antibodies, which in some individuals results in hypersensitivity reactions on consumption of red meat, innards, dairy, and gelatin.<sup>2</sup> Different tick species seem responsible: lone star tick (*Amblyomma americanum*) (United States), *Ixodes ricinus* (Europe), and *Ixodes holocyclus* and *I. australis* (Australia), *Amblyomma variegatum* (Africa—Ivory coast), *Haemaphysalis longicornis* (Korea), *H. longicornis* and *Amblyomma testudinarium* (Japan), *Amblyomma cajennense* (Panama, Costa Rica), *Amblyomma sculptum* (Brazil).<sup>2,5,6</sup> In the United Kingdom, a culprit tick species is yet to be identified, but *I. ricinus* is likely given its distribution in Europe.<sup>6</sup> Hypersensitivity reactions of varying severity. They can present with cutaneous (pruritus, urticaria, angioedema), gastrointestinal, and systemic symptoms, including anaphylaxis, and are often delayed (3–8 hours post food).<sup>1</sup> Alpha-gal also might be responsible for hypersensitivity reactions to cetuximab, snake anti-venom, and *Varicella zoster* vaccine.<sup>2,7</sup>

Population studies showed high prevalence of alpha-gal sensitization, but not allergy.<sup>7</sup> Amongst 300 high-risk forestry employees in Germany, 58 were sensitized but only 5 were allergic.<sup>7</sup> The allergic individuals appeared to mount a reaction to red meat more quickly than reported in US studies.<sup>7</sup> Alpha-gal epitopes in red meat are exposed and readily accessible to IgE, but the quality and quantity of the IgE repertoire might not be adequate to mount an allergic response in all sensitized individuals.<sup>4,8</sup>

The pathogenesis of the delayed presentation of alpha-gal allergy is poorly understood. The kinetics of lipid metabolism and long transit/metabolism of alpha-gal-containing glycoproteins and glycolipids (4–5 hours) may be implicated.<sup>1,5</sup> Venison, a lean meat, seldom triggers allergic reactions in alpha-gal-allergic patients compared with fatty red meat such as lamb.<sup>8</sup> The dose of antigen ingested appears important; offal is richer in alpha-gal epitopes than lean meat.<sup>3</sup>

We report the first UK case series of 5 nonatopic adult female patients with alpha-gal allergy induced by prior multiple tick bites. Three of 5 patients had a background history of autoimmunity (Hashimoto's thyroiditis), polycystic ovarian syndrome, and Parkinsonism syndrome, and 1 patient had chronic spontaneous urticaria. Interesting findings (Table 1) include that 80% (4/5) presented with accelerated hypersensitivity, 30 to 120 minutes after red meat ingestion, and only 20% (1/5) with delayed-onset anaphylaxis (3–6 hours). The main red meats implicated included beef, pork, and lamb. In patients who had IgE testing to both beef and pork (3/5), the beef sIgE titer was considerable higher than the pork sIgE. Our findings also

indicated sensitization to cat dander in 2 of 5 cases with positive sIgE to beef and lamb (pork sIgE was not done). Gelatin was not implicated, and none received cetuximab. No identifiable cofactors were present (alcohol, exercise, opiates or nonsteroidal anti-inflammatory drugs). Urticaria was the most common symptom, followed by gastrointestinal (3/5), angioedema (2/5), and respiratory symptoms (1/5). All patients had previously tolerated red meat. All reported multiple tick bites outside the United Kingdom (Europe, Africa, United States, Latin America, Asia, Australia). Suspected culprit tick species are shown in Table 1.

Skin prick tests (SPT) with commercial meat extracts yielded low positive results in 80% of patients (mean diameter, 3-mm weal; range, 3–4 mm). Red meat sIgE serology was positive in all patients (range, 0.51–2.03 kua/L). Alpha-gal IgE serology was undertaken in 4 of 5 patients, coinciding with the availability of alpha-gal assay in the hospital, with positive results (mean, 6.5 kua/L; range, 1.74–14.3 kua/L). Alpha-gal sIgE titers were higher than sIgE to red meat(s). Patients were advised to avoid red meat, wear protective clothing to reduce further tick bite risk, and carry emergency medicines (oral antihistamines, adrenaline auto-injector). All patients reported recurrence of symptoms on reintroduction of red meats after a period of avoidance.

Most cases in our series had accelerated hypersensitivity similar to findings in the German cohort.<sup>7</sup> In non-endemic areas such as England, most cases of alpha-gal allergy could be considered travel-related illness. Positive alpha-gal sIgE is diagnostic in the correct clinical context.

The prevalence of alpha-gal allergy is increasing, but no comprehensive epidemiological data are available yet.<sup>8</sup> Since the first case of alpha-gal allergy was reported a decade ago, more cases have been reported worldwide, with the highest number in the United States and Australia.<sup>2</sup> The reported prevalence of asymptomatic alpha-gal sensitization is 10% to 20%, with higher estimates in the southeastern United States.<sup>3,7</sup>

There is considerable lack of awareness of this novel food allergen, with an average of 7.1 years from presentation to diagnosis and only 21% of patients correctly diagnosed within a year of symptoms.<sup>9</sup> Many are misdiagnosed as acute urticaria or idiopathic anaphylaxis. A thorough allergy, medical and travel history, and previous tick bite history is therefore paramount. Once the diagnosis has been made, patients must be alerted to the presence of alpha gal in offal and gelatin. The differential diagnosis needs to include meat allergy unrelated to tick bites (eg, to bovine serum albumin), pork-cat syndrome, chronic urticaria, mastocytosis/mast cell activation syndrome, and idiopathic anaphylaxis. Only 2 cases of successful desensitization to alpha-gal have been reported.<sup>10</sup> Complete avoidance of red meat and related products is advised.<sup>10</sup> An anaphylaxis management plan should be provided.

In summary, this first British case series raises awareness of alpha-gal as a novel food allergen that is potentially missed. Certain patient groups can be considered at risk of alpha-gal allergy: frequent travelers, agricultural/forestry workers, and countryside residents. Establishing a correct diagnosis is life saving for patients at risk of life-threatening anaphylaxis; improves quality of life, and saves cost for health services. Further studies on the epidemiology, pathophysiology, molecular allergology, and the immunological responses that

**Table 1**  
Patient Characteristics and Results of the Investigations for the Alpha-gal Case Series

| Case no. | Gender | Age (yrs) | Meat             | Time at onset of reaction | History of tick bites | Location of tick bites     | Suspected tick species                                 | Index reaction                                                                                     | SPT (weal/flare [mm]) |      |      |      |     | slgE, ref range <0.35 kua/l |      |      |            |                  | tlgE (ku/l) | Tryptase (ng/ml) | Comorbidities |                                                        |
|----------|--------|-----------|------------------|---------------------------|-----------------------|----------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------------------|-----------------------|------|------|------|-----|-----------------------------|------|------|------------|------------------|-------------|------------------|---------------|--------------------------------------------------------|
|          |        |           |                  |                           |                       |                            |                                                        |                                                                                                    | Beef                  | Pork | Lamb | Milk | Cat | Beef                        | Pork | Lamb | Alpha gal  | Turkey & gelatin |             |                  |               | Gluten, wheat, omega-5-gliadin                         |
| 1        | F      | 35        | Pork, Beef       | 30-60 mins                | Multiple bites        | Poland                     | <i>Ixodes ricinis</i>                                  | Lip tingling; facial & tongue swelling; itch; urticaria; nausea; throat tightening; DIB; diarrhoea | 3/6                   | 4/20 | Nd   | Neg  | Neg | 2.03                        | 1.73 | Nd   | Nd         | Nd               | Neg         | 86               | 3.9           | Hashimoto's thyroiditis, iron deficiency anaemia       |
| 2        | F      | 44        | Pork, Beef, Lamb | 1-2 hrs                   | Multiple bites        | Sri Lanka                  | ?                                                      | Abdominal pain; diarrhoea; urticaria                                                               | 3/14                  | Nd   | Nd   | Nd   | 3/0 | 0.57                        | Nd   | 0.51 | 1.74       | Nd               | Nd          | 353              | <1            | Endometriosis, chronic physical urticaria & angioedema |
| 3        | F      | 43        | Beef, Lamb       | 30 mins                   | Multiple bites        | USA (WA), Tanzania, Uganda | <i>Amblyomma americanum</i> , ?                        | Generalised urticaria                                                                              | 3/0                   | Nd   | Nd   | Nd   | 3/0 | 1.37                        | Nd   | 0.58 | 7.86       | Nd               | Nd          | 77               | 7             | Polycystic ovary syndrome                              |
| 4        | F      | 57        | Beef, Pork, Lamb | 3-6 hrs                   | Multiple bites        | Kenya, Namibia, Brazil     | ?<br>?<br><i>Amblyomma sculptum</i>                    | Urticaria; angioedema, nausea, vomiting, abdominal pain                                            | 4/0                   | 4/0  | 4/0  | Neg  | Neg | 0.51                        | 1.67 | 1.28 | 14.3, 6.71 | Neg              | Nd          | 140              | 6.1           | Wasp venom-induced anaphylaxis, anaemia, Loaloa        |
| 5        | F      | 47        | Beef, Lamb, Pork | 1-2 hrs                   | Multiple bites        | Australia                  | <i>Ixodes holocyclus</i> , <i>Ixodes australiensis</i> | Intense pruritus; urticaria                                                                        | Neg                   | Neg  | Neg  | Neg  | Neg | 1.88                        | 1.43 | 1.55 | 2.21       | Nd               | Nd          | 52               | 2             | Filarial disease<br>Atypical Parkinsonism              |

Abbreviations: DIB, Difficulty in breathing; Nd, test not done; neg, Negative; slgE, specific immunoglobulin E; SPT, skin prick test; tlgE, total immunoglobulin E; WA, Washington; ?, unknown.

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.<sup>1</sup> The nsLTPs are believed to have an important role in plant defense<sup>2</sup> and are concentrated in the skin of many fruits, including those belonging to the *Rosaceae* family,<sup>1,3</sup> of which the peach and its nsLTP Pru p 3 is the most well characterized.<sup>1</sup> 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.<sup>4</sup>

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

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.<sup>4,5</sup> 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.<sup>5</sup> 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.<sup>1</sup> As such, it is not unusual for patients to experience adverse reactions to multiple nsLTP-containing foods.<sup>6</sup> 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.<sup>1,4,5</sup> This allows them to retain their allergenicity even after food processing and digestion, explaining their ability to provoke severe and systemic allergic reactions.<sup>1</sup>

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.<sup>7–9</sup> Skypala et al<sup>10</sup> 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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