

ADULT-ONSET FOOD ALLERGIES

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ABSTRACT

While much attention is paid to food allergies in infancy and early childhood, some types of food allergy classically have their onset in later childhood and adulthood. Such allergies can lead to some confusion, especially if foods were previously tolerated. Adult-onset food allergies can be late-onset 'primary' food allergies such as those to seafood, peanut and tree nuts; or they can be secondary to sensitisation to specific proteins in seemingly 'unrelated' allergens such as the pollen food syndromes and lipid transfer protein syndrome. Alpha-gal allergies cause a characteristic allergy to non-primate mammalian red meats, usually in adulthood and typically delayed by 3–6 hours after allergen ingestion. In adulthood, co-factors such as exercise, alcohol, infections, hormonal fluctuations and the use of non-steroidal anti-inflammatory drugs may be necessary for certain food allergies to manifest. A knowledge of adult-type food allergies, including cross-sensitivity patterns and co-factors, is essential to the correct diagnosis and management of adult-onset food allergies.

Keywords: adult-onset food allergies, lipid transfer protein syndrome, alpha-gal syndrome

INTRODUCTION

Much research in the realm of food allergies focuses on childhood-onset food allergies. Adult-onset food allergies represent a sub-set of food allergies which are often unexpected and more complex to diagnose, often involving cross-reactivities and confounding factors.

In the United States, self-reported food allergies are as high as 19%, of which 5% are of adult-onset.¹ The prevalence of challenge-proven food allergies in adults is 2–3%.^{1,2} Some of these are residual allergies from childhood, others are of new onset.

New-onset allergies in adulthood involve most commonly shellfish, finfish, peanuts and tree nuts.^{1–4} Cross-reactivity syndromes such as pollen fruit syndrome (PFS) and lipid transfer protein (LTP) syndrome usually begin in adolescence or adulthood. Other cross-reactivity syndromes such as alpha-gal syndrome manifest more commonly in adults than children. Adult-onset preservative allergies are increasingly described and occupational allergies related to foods – such as baker's asthma with wheat allergy or contact dermatitis in food handlers – typically have their onset in adulthood.^{4,5}

Allergies manifesting only when confounding factors are present are also more commonly observed in adults than in children. One such manifestation is food-dependent exercise-induced anaphylaxis (FDEIA). Confounders other than exercise that can affect food allergy expression include temperature extremes, hormonal influences, stress, intake of alcohol or non-steroidal

anti-inflammatory drugs (NSAIDs).^{4,5} An altered immune response to previously tolerated foods has also been observed in the mast-cell activation syndrome (MCAS),⁶ post-infection; and it has been most recently described as part of the long Covid syndrome (anecdotal evidence – CG). This article describes a series of case reports illustrating and discussing adult-onset food allergies.

TABLE 1: EXAMPLES OF ADULT-ONSET FOOD ALLERGIES

1. Late-onset primary food allergies (most commonly to seafood, peanuts and tree nuts)
2. Preservative allergies
3. Cross-reactivity syndromes, including PFS and LTP syndromes
4. Alpha-gal allergy
5. Allergies associated with co-factors such as FDEIA
6. Occupational allergies related to foods (eg baker's asthma as a reaction to wheat)

CASE 1: NEW-ONSET 'PRIMARY' FOOD ALLERGIES IN ADULTS

Patient MW, a 23-year-old male, fit and well, with no pre-existing food allergies, was enjoying a paella meal at a restaurant with friends when he noticed that his lips were feeling tingly. Shortly afterwards, he experienced swelling of the lips. He mentioned this to his friends, who thought that he was possibly reacting to the spicy chilli sauce he had eaten on the side. A friend gave him an antihistamine and the symptoms soon subsided. Two months

later, he was eating sushi (which he had tolerated many times before) and once again noted lip swelling. This time he also noted itching in the throat. He drove himself to a nearby pharmacy, where he was given an antihistamine–steroid combination tablet and advised to go to the nearest emergency unit, which he duly did. The symptoms had almost subsided by the time he arrived at the ER, and the examining doctor discharged him soon after assessment with a referral to an allergy clinic two weeks later.

At the allergist, a thorough history deciphered the ingredients that he had consumed during the two reactions. Accordingly, skin-prick tests (SPTs) were performed, with results as follows:

- Salmon 0 mm
- Hake 0 mm
- Soya 0 mm
- King prawn 6 mm
- Crayfish 5 mm
- Mussel 0 mm
- Squid 0 mm
- Positive control 4 mm
- Negative control 0 mm.

He was diagnosed with an allergy to crustaceans, advised to eliminate crustaceans from his diet and on the emergency management of reactions. He was advised to wear a MedicAlert® bracelet and an adrenaline auto-injector was prescribed in view of the fact that the last reaction had led to itching and clearing of the throat.

BRIEF DISCUSSION

Foods which can cause new allergies with onset after childhood include shellfish, fin fish, peanut and tree nuts. These can occur after a prolonged period of preceding tolerance. Fish and shellfish allergies in adults in the United States have a prevalence of 2–3%.⁴

A recently published study from the United States found that 2.9% of US adults have a peanut allergy, which is a greater percentage than in children. One in six adults with peanut allergy developed it after 18 years of age.⁷

Severe reactions to seafood and nuts can occur in adults with a similar frequency to those in children, hence identification, strict elimination and thorough emergency plans are needed.⁷

CASE 2: POLLEN–FOOD SYNDROME

A 38-year-old female patient, who had spent her childhood and adolescence in Germany, presented with an itchy mouth and lip swelling after ingesting apples on one occasion and praline chocolates on another. She had no previous history of food allergies. On further questioning, she had a longstanding history of allergic rhinitis (AR), which was particularly severe when she was in Germany during the spring. She did not have asthma. She used to love apples but could no longer eat them fresh. She mentioned that, confusingly, apple sauce was still tolerated. She could eat bananas, melons and peanuts without any problem. She had not eaten other tree nuts in a while, apart from the hazelnut contained in praline chocolates. SPTs were tailored to her history, with results as follows:

- Birch tree pollen 8 mm

- Rye grass pollen 0 mm
- Bermuda grass pollen 0 mm
- Apple prick-to-prick test 5 mm
- Pear prick-to-prick test 2 mm
- Hazelnut 8 mm
- Almond 0 mm
- Walnut 5 mm
- Cashew nut 0 mm
- Pistachio nut 0 mm
- Macadamia nut 0 mm.

A diagnosis of PFS was made with a likely *PR-10 cross-reactivity*. The initial sensitiser was probably the birch pollen (a prominent pollen in the European spring). She was advised to avoid fresh apples (peeled apples may be tolerated), but that she could consume cooked apples as the PR-10 protein is destroyed by heat. She was advised to avoid hazelnuts and walnuts. Birch pollen desensitisation was discussed.

BRIEF DISCUSSION

Cross-reactivity syndromes between pollens and certain fruits, vegetables and nuts can manifest in later childhood, adolescence or adulthood. A variety of proteins found in certain pollens, including the PR-10 protein, profilins and LTPs, can be responsible.^{8,9}

Symptoms are frequently confined to the oral cavity and lips, with the PR-10 and profilin-related cross-reactivities, as these are heat- and protease-labile allergens; nonetheless, more severe reactions can occur in a small percentage (1–3%) of patients. LTP-related cross-reactivities, on the other hand, lead to systemic reactions more commonly, as this allergen is heat- and acid-stable.^{8,9}

The patient typically does not react to all fruits and vegetables with the particular cross-reactive allergen but has an array of causative foods which can increase over time.¹⁰ In the PR-10-related syndromes and profilin-related syndromes, peeling or cooking the food may reduce symptoms. Apart from avoidance and emergency management, a possible option for the PFSs is desensitisation to the pollen initially responsible for the sensitisation, which may also reduce the food-allergic reactions.¹⁰

CASE 3: FOOD-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS (FDEIA)

A 47-year-old man presented with a history of two episodes of anaphylaxis, both occurring during prolonged exercise sessions. He was an elite triathlete. Both episodes occurred after 90 minutes of vigorous exercise. During the first episode, he was cycling indoors; he developed urticaria and angioedema of his bottom lip, accompanied by dizziness, which resolved when he discontinued the exercise. The second episode occurred after he had completed a 90-minute cycle and was at the start of a run. He presented with lip swelling, generalised urticaria, shortness of breath and an altered level of consciousness. He was training on his own in a remote area, therefore did not get to seek medical attention, and luckily recovered after lying down and resting. He had not taken NSAIDs before or during the exercise sessions.

TABLE II: PROTEINS INVOLVED IN POLLEN-FOOD SYNDROME^{10,11,12}

PROTEIN FAMILY	SENSITIVITY TO HEAT AND PROTEASES	EXAMPLES OF PLANT FOOD ALLERGEN SOURCES	COMMON POLLEN SOURCES OF SENSITISATION	CLINICAL EXPRESSION
PR-10 proteins (Betv1 analogues)	Sensitive	Hazelnut Apple, peach, cherry Carrot, celery, fennel, parsley Peanut, soyabean	Birch tree pollen (BetV1 protein)	Mainly oral allergy syndrome
Profilins	Sensitive	Citrus fruit, melons, banana, tomatoes	Timothy grass Bermuda grass Zea maize (<i>Zea m 12</i>) Rye grass	Mainly oral allergy syndrome
Non-specific LTPs	Stable	Peach, apple, cherry Hazelnut, almond, walnut Peanut, maize, barley, grape, cabbage	Plane tree Olive tree Mugwort Zea maize (<i>Zea m 14</i>)	Systemic reactions common

He was generally fit and well but suffered from seasonal AR and cat and dog allergy. He also had mild eczema on his shins and in his armpits that flared up seasonally and when he ate ice cream or chocolates. He was under treatment for major depression.

Apart from the possible eczema flares with dairy, he had not noted any symptoms of pre-existing IgE-mediated food allergies. A more detailed dietary history revealed that on training days his breakfast comprised egg whites, oats, almonds, dates, gluten-free bread and jam. While he was cycling, he would eat dates, almonds and a whey-based protein bar. Blood for specific IgE was taken, with results as follows (in kU/L):

- Bermuda grass 5.9
- Rye grass 0.48
- Dog 68.9
- Cat >100
- Cow's milk 43.9
- Casein 0.1
- Wheat 0.76
- Omega-5 gliadin 0.1
- Peanut 0.78
- Almond 0.34

In addition, mast cell tryptase was normal at 6 ng/mL.

An exercise challenge after eating wheat was passed. A diagnosis of possible cow's milk protein-related exercise-induced anaphylaxis was made. On both occasions, a whey protein bar had been consumed during training and, coupled with a high specific IgE to cow's milk, this confirmed the diagnosis. A diet free of cow's milk led to an excellent improvement in the eczema and his general health and depression. On a diet free of cow's milk, exercise at an elite level could continue without symptoms. He was advised to carry an adrenaline auto-injector and to train together with a partner at all times.

BRIEF DISCUSSION

FDEIA is a rare condition with a prevalence of 0.048% reported in the largest epidemiological study among 76 229 adolescents

in Japan.¹³ Anaphylaxis occurs when a patient consumes a certain food and exercises within 4–6 hours of consumption. Usually, the exercise follows the food ingestion, but on occasion anaphylaxis has been described when the patient ate a specific food *after* exercise. The patient is able to consume the food safely in the absence of exercise. Increased gut permeability during exercise with the absorption of larger allergen particles is postulated as a possible trigger mechanism. Anaphylaxis typically occurs within 30–60 minutes of moderate-intensity exercise. Episodes vary and will not always be the same or have the same intensity.¹⁴

The most commonly reported food trigger is wheat – specifically the components omega-5 gliadin or, less commonly, high-molecular weight glutenin. Other trigger foods described include apple, cow's milk, hazelnut, maize, shellfish, tree nuts, beef, pork, peanut, egg, chickpeas and peaches.¹⁴

External factors which affect the expression of the allergy in FDEIA include heat, cold, humidity, hormonal fluctuations (eg menstruation) and concurrent use of NSAIDs.¹⁵

A food and exercise challenge is the most accurate way to diagnose FDEIA if the allergenic trigger is unclear. Food and exercise challenges are difficult to perform and can yield false negative results in 30% of cases due to the difficulty in reproducing environmental factors such as heat and humidity and other co-factors.^{13–15} There is no standardised protocol for FDEIA, but challenges should include a negative exercise test, a negative challenge to the food in the absence of exercise, and a food allergen–exercise challenge for 30–60 minutes (administering the suspected food allergen and then getting the patient to exercise for 30–60 minutes, or less if symptoms occur prior to this period).¹⁶ All food challenges must be done under strict observation and adequate available resuscitation equipment and adrenaline must be available.

Management consists of both allergen and co-factor avoidance within 4–6 hours before and after exercise. Until the allergen

has been identified, the patient must exercise on an empty stomach, fasting for 4–6 hours. Training first thing in the morning tends to be the easiest solution. Once the allergen has been identified, the patient can resume exercise without consuming the offending food within 4–6 hours before or after exercise. If exercise is part of the patient's occupation or they are doing multiple training sessions a day, the triggering food is best avoided altogether.^{14–16}

Patient education includes recognising the symptoms early and stopping exercise in addition to administering adrenaline as soon as the symptoms progress to anaphylaxis. A written plan must be given and customised to suit the patient's individual needs. All concomitant allergic conditions must be optimised. Co-factors must be explained and identified: NSAIDs, alcohol, menstruation and the pollen season in the case of pollen-allergic patients.

CASE 4: ALPHA-GAL ALLERGY

Mr HS, a 63-year-old male from George, South Africa, who was generally fit and well apart from psoriasis, started to experience some unexpected anaphylactic reactions, typically a few hours after dinner. He grew up on a cattle farm and had in the past spent a significant amount of time in the 'veld'. He had no past history of food allergy apart from a single episode suggestive of MSG-syndrome after a Chinese meal 15 years previously. New-onset symptoms had been occurring for the preceding two years. During the first such episode, he had eaten out for dinner and unexpectedly experienced an urticarial rash three hours later, with no clear trigger. The rash had occurred mainly at active psoriasis sites. Subsequently, similar symptoms started occurring repeatedly, especially if he had eaten out, always about three hours later. On two occasions he experienced a severe attack with diffuse urticaria and tightening of the throat three hours after eating, for which he required hospitalisation and intravenous antihistamines.

After a few episodes, HS started recognising that he had always eaten red meat before such symptoms occurred. The main cause was beef; lamb caused milder symptoms, which could usually be minimised by taking an antihistamine before eating the lamb. He was able to eat pork.

HS discussed the symptoms with his family practitioner and after discussion with an allergist the diagnosis of allergy to red meat as a result of alpha-gal sensitisation (so-called 'midnight anaphylaxis', as symptoms often occur several hours after

the evening meal) was entertained. Blood tests showed the following results:

- Specific IgE to beef: 1.26 kU/L
- Specific IgE to mutton: 0.34 kU/L
- Specific IgE to alpha-gal: 29.6 kU/L

The diagnosis of alpha-gal allergy was confirmed, and HS was advised to avoid meat of mammalian origin, especially beef, which caused more severe symptoms in his case. He was also given an emergency treatment plan in case of reactions and an adrenaline auto-injector for severe reactions.

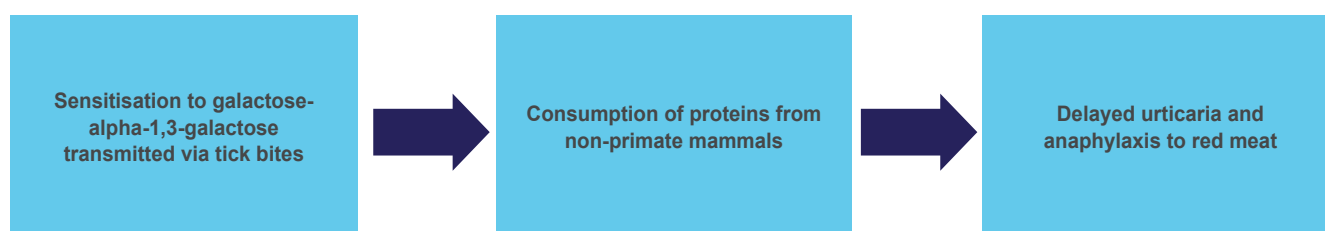
DISCUSSION

ALPHA-GAL SENSITISATION AND REACTIONS TO RED MEAT

The syndrome of 'midnight anaphylaxis' to red meat describes a delayed-onset allergic reaction 3–6 hours after eating mammalian food products. Patients typically react to beef, mutton or pork, but have no trouble with chicken or fish.^{17–19} The responsible IgE antibody for this type of reaction is not to a major protein allergen specific to the meat; rather, it is to the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal). Alpha-gal is found in all mammalian cells, but not in the tissues of human beings and old-world monkeys. The kidneys seem to be particularly rich in alpha-gal.

Most reports of delayed meat allergy due to alpha-gal cross-reactivity have been described in adults, who classically present with an acute onset of delayed anaphylaxis and urticaria. However, recently, a few cases have been described in the paediatric population.^{18,19} Unlike their adult counterparts, it seems that the majority of children with alpha-gal syndrome present with urticaria rather than anaphylaxis. A South African study in the rural Transkei identified 85 subjects with alpha-gal allergy, at a median age of 12 years.²⁰ This cohort showed a more rapid onset of symptoms than in cohorts previously described in the United States and Europe, and a high prevalence of gastrointestinal symptoms.

Sensitisation to alpha-gal may occur through tick bites, possibly via parasitic infection¹⁹ or through exposure to cetuximab. Cetuximab is a chimeric IgG1 monoclonal antibody against the epidermal growth factor receptor and is used in treating colon and squamous carcinomas. SPTs with commercial extracts to meat are often equivocal, and specific antibodies to red meat extracts often show low positive results only, despite a severe reaction, as seen in this case. Specific IgE to alpha-gal, however,



Epitope cross-reactivity Syndrome

Figure 1: Typical pathogenesis of alpha-gal-related delayed reaction to meat

is clearly positive in this type of allergy. Moreover, patients with this syndrome also classically test positive to cat on SPT and specific IgE, as cat IgA has an alpha-gal epitope.

Patients with anaphylaxis to red meat due to alpha-gal sensitisation typically present 3–6 hours after ingestion, which is a far longer interval than classic IgE-mediated reactions.²¹ Because of this delay in symptoms, the allergy often goes undiagnosed for some time or is ascribed to idiopathic anaphylaxis before the pattern is recognised. Other nuances of this type of reaction are that the dose, temporal relation to tick bites and fatty content of the meat seem to influence the allergic reaction. Frequently, a small amount of mammalian meat is tolerated, but larger amounts lead to a reaction, and the more meat that is consumed, the more severe the reaction tends to be. Reactions to red meat and even dairy are more easily elicited if the patient has recently had a tick bite (in the preceding 1–4 weeks). The IgE to alpha-gal can decrease over time but symptoms can worsen again with subsequent tick bites. It also

seems that fattier meats provoke episodes more consistently and more severely.^{21,22}

CONCLUSION

Several types of allergy can have their initial onset in late childhood or adulthood. The clinician should be well versed in the types of food that can cause late-onset allergies, and also the patterns of reactivity according to the groupings of allergens and mode of presentation.

Knowledge of the cross-reactivity syndromes can help with recognising and diagnosing adult-onset allergies. This can help guide targeted avoidance strategies and treatment plans. Co-factors such as exercise, alcohol and NSAID use are important to enquire about to try to understand the underlying risk factors.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

This article has been peer reviewed.

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