Title:
The epidemiology, diagnosis and management of Lipid Transfer Protein Allergy in the United Kingdom - a BSACI Clinical Practice Statement

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Author Contributions
The writing group, consisted of Isabel Skypala, Hannah Hunter, Stephen Till, Susana Marinho, Marina Frleta-Gilchrist, Dominika Murgasova and Nandinee Patel. Isabel Skypala and Hannah Hunter organised the BSACI LTP survey and co-wrote the case. Hannah Hunter wrote the section on dietary management and designed Table 1. Marina Frleta-Gilchrist wrote the section on diagnosis. Susana Marinho wrote the section on management excluding dietary management and designed Tables 2 and 3. Dominika Murgasova and Nandinee Patel wrote the section on paediatrics. Stephen Till supported the section on diagnosis and extensively edited the final paper. Isabel Skypala wrote the methodology, introduction, epidemiology and conclusion sections, the key points boxes, and recommendations box. She also designed the figures and put all of the sections together to draft the final paper. All authors commented on subsequent drafts and Isabel Skypala edited the final draft.

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Abstract
Although the most prevalent plant food allergy in the United Kingdom (UK) is pollen food syndrome (PFS), there is increasing evidence that reactions to plant foods could also be due to sensitisation to Lipid Transfer Proteins (LTP). These proteins, highly resistant to heat and processing, are present in raw, cooked and processed plant foods and often provoke moderate to severe symptoms. LTP allergy is common in Mediterranean countries, but reports from Northern Europe are scarce, although data has been published characterising LTP allergy in both England and Scotland. To gather further information and aid the development of a clinical practice statement on LTP allergy, a survey was conducted by the British Society of Allergy & Clinical Immunology (BSACI). The results confirmed that LTP allergy is being diagnosed in both children and adults in all areas of the UK. The survey results, along with published UK data, confirm that tree nuts, peanuts, apples, stone fruits, tomatoes and processed foods, such as pizza or curry, are common food triggers. Anaphylactic reactions are not uncommon and often facilitated by the presence of co-factors such as exercise or alcohol. Unlike LTP allergy in Spain and Italy, UK individuals are also more likely to be sensitised to birch and grass pollen, but this does not appear to reduce the severity of the condition. Diagnosis can be complex; a positive test to LTP allergens, such as the peach allergen Pru p 3, can only be confirmatory of a diagnosis of LTP allergy when accompanied by a typical clinical history. Management can be difficult and individualised advice is vital to avoid the exclusion of multiple foods and minimise the likelihood of co-factors. Given the diverse range of foods, co-factor involvement and highly idiosyncratic nature of LTP allergy, the need for adrenaline autoinjectors should always be assessed.

Key words
Lipid transfer protein, allergy, food allergy, fruit, vegetable, nuts

Introduction

Non-specific lipid transfer proteins (LTP) are present in many plant foods, including tree nuts, legumes, fruits, vegetables, seeds and cereals.[1] They are a common cause of moderate to severe allergic reactions to plant foods in the Mediterranean area.[1] Although previously believed not to occur in Northern Europe,[2] LTP sensitisation and allergy has been reported in both children and adults from London, and adults from Northern England and Scotland.[3-6] Published UK data suggests there are similarities but also some differences between the presentation of this condition in the UK compared to that seen countries with much greater prevalence of the condition such as Italy and Spain.[4] Given the complexities of LTP allergy, it was considered that there was a need for information and guidance for UK clinicians in order to ensure the correct diagnosis and management of this condition.

Methodology

A survey of British Society of Allergy and Clinical Immunology (BSACI) members in 2022 found that LTP allergy is diagnosed in both adults and children in all areas of the UK. Given the lack of published evidence of LTP allergy in a Northern European population, it was not possible to produce a guideline underpinned by a formal systematic review guided by PICO questions. Therefore a narrative review was undertaken to develop clinical recommendations, underpinned by a formal literature search using the following search terms: Lipid transfer protein, allergy, food allergy, fruit, vegetable, nuts.

Epidemiology

Prevalence

The prevalence of sensitisation to LTP allergens is reported to be 9% and 12% in Italian and Spanish adults respectively.[1] A small study on UK children with seasonal allergic rhinitis found that 7% were LTP-sensitised.[3] There are no studies evaluating prevalence in UK adults, but publications have characterised LTP allergy in cohorts of adults in England (London and Preston) and Scotland (Glasgow).[4-6] The results suggest adults with LTP allergy are aged between 30-40 years, and more likely to be female. The BSACI survey results suggest LTP allergy is seen in children and adults in all areas of England and Scotland, with 20% of survey participants seeing more than 50 patients per year. LTP sensitisation and allergy has also been documented in Belgium, Austria, Germany and Poland, with sensitisation to LTP affecting 63% of patients in Poland compared to 12% sensitised to profilins and only 4% sensitised to PR10 allergens.[7-10]

Foods Involved (Table 1 and Figure 1)

The structure of LTP allergens is compact and they have high thermic and proteolytic stability.[1] The four conserved immunodominant IgE epitopes of Pru p 3 make it the most likely primary sensitising allergen, although it is unclear whether this applies to UK populations.[11] These epitopes are shared by the LTP of other fruits from the Rosaceae family, but LTP in other foods such as hazelnut or sunflower seed do not contain these conserved sequences.[1] Thus LTP allergens are structurally subtly different, with varying degrees of cross-reactivity depending on the food provoking the index reaction. In Europe, peach is the most commonly reported trigger, alongside other stone fruits, apples, tomatoes, and to a lesser extent peanut and some tree nuts (Table 2).[4,12] In the UK, the trigger foods are most commonly tree nuts, peanuts, apples, stone fruits, and tomatoes, but reactions to composite foods such as curry, pizza, desserts, and snack foods are also reported.[4-6] The BSACI Survey respondents reported the most dominant triggers of symptoms in the UK are peaches, tomatoes, apples, other fruits, peanuts and tree nuts (Figure 1).

Pollen Sensitisation

There are conflicting view and evidence as to whether a pollen LTP could be the primary sensitising allergen in individuals with LTP allergy.[2,13] In Italy and Spain, Pru p 3 is the primary sensitising LTP allergen in individuals with LTP allergy who are also allergic to plane tree pollen.[14,15] However, primary sensitisation to the mugwort (*Artemesia vulgaris*) pollen LTP, Art v 3, has been demonstrated as the

cause of co-sensitisation to Pru p 3 and consequent peach allergy in Chinese adults.[16] A highly significant correlation between Pru p 3 and both Art v 3 (mugwort) and Pla a 3 (plane tree) has been shown in UK LTP-allergic individuals, much greater than that seen in a matched cohort of Italian adults with LTP allergy.[4] Sensitisation to the mugwort pollen LTP Art v 3 was also found to be a precursor of allergic reactions to foods, in a group of patients with LTP allergy from Poland.[8]

Co-sensitisation to birch or grass pollen is considered to be associated with a milder LTP phenotype.[13,17] However, although pollen sensitisation is common in UK adults with diagnosed LTP allergy, over 80% still report systemic symptoms to foods including anaphylaxis, suggesting sensitisation to birch pollen does protect against severe reactions.[4,6,18] Some individuals with LTP allergy who are co-sensitised to birch pollen may experience milder symptoms to some foods due to the co-existence of PFS, which affects up to 70% of birch-sensitised individuals in Northern Europe and has similar food triggers to those provoking LTP allergy.[19]

Co-factors

Allergic reactions to foods may increase in severity, or only occur when food ingestion is associated with co-factors, which may be implicated in up to 30-40% of LTP-food allergic reactions.[20-25] The best characterised co-factors are exercise[21,23,24] and non-steroidal anti-inflammatory drugs (NSAIDs).[21,24,26,27]Allergy to LTP is the most frequent cause of food-dependent exercise-induced anaphylaxis in Mediterranean/Southern European countries, although this is being recognised and reported in other geographical areas.[28-31] Other relevant co-factors include alcoholic drinks and cannabis – both of which may act as co-factors and as sources of LTPs, with one in three cannabis-allergic patients reporting co-factor-mediated reactions to plant foods.[32,33] Consuming a mixture of different plant foods in one meal may be the most likely cause of co-factor related reactions that are severe and systemic.[21]

Other co-factors include concomitant viral infections, menstrual period (also frequently linked to intake of NSAIDs to control menstrual pain), fasting, stress/anxiety, sleep deprivation and anti-acid medication[20,34] Some studies have also shown that more than one co-factor need to be present along with LTP-containing food ingestion, in order to elicit reactions, e.g. a meal with alcohol followed by dancing.[23] Co-factors are relevant causes of reactions in UK patients, potentially affecting up to 70% of patients diagnosed with LTP allergy, with exercise and alcohol being predominant.[4] In the BSACI survey, the most common co-factors clinicians reported were also exertion and alcohol, suggesting that NSAID involvement may be less common in a UK population.

Key Points

- Lipid Transfer Protein (LTP) allergens are small proteins found in many plants which are highly resistant to heat and processing and present in raw, cooked and processed foods
- LTP allergy, highly prevalent in Mediterranean countries, is an increasing phenomenon in adults in the United Kingdom (UK), but data on LTP allergy in UK children is sparse
- UK food triggers include tree nuts, peanuts, apples, peaches, other stone fruits, tomatoes, and composite foods such as curry and pizza
- Co-factors, e.g. exercise, alcohol or non-steroidal anti-inflammatory drugs (NSAIDs), are a common feature of LTP allergy and may be involved in 30-40% of LTP-food allergic reactions
- Pollens such as mugwort and plane tree also contain LTP allergens and UK adults may be sensitised to these
- Sensitisation to birch or grass pollen does not affect symptom severity in UK individuals with LTP allergy, but they might be more likely to also have pollen-food syndrome (PFS)

Diagnosis

Clinical History (Figure 2)

It is essential to establish the time of symptom onset following ingestion, the presence of potential co-factors, reaction severity, reproducibility, the quantity of food ingested and details of food preparation (e.g. peeled or cooked).[12,35] One of the difficulties of diagnosis is that the foods involved are often very similar to those reported by patients with Pollen Food Syndrome, such as tree nuts, peanuts, apples and stone fruits.[19] However, LTP allergy can involve a wide spectrum of plant food triggers, including vegetables such as lettuce and cabbage, fruits such as raspberries and blueberries, seeds such as linseed and cereals such as corn.[20,36] Also, a wide range of composite foods can be involved due to the ability of LTP allergens to withstand heat.[37] Symptoms associated with LTP allergy can range from mild and localised (e.g. oropharyngeal pruritis, contact urticaria) to generalised (gastrointestinal symptoms, such as nausea, vomiting, abdominal cramps, diarrhoea, angio-oedema, urticaria, anaphylaxis). The relevance of co-factors should be assessed, especially exercise, which can range from walking, through to strenuous exercise at the gym. Co-factors may occur together such as eating out, drinking alcohol and running for a bus, or attending the gym, taking pain relief and eating a snack or protein bar. Other less common co-factors should also be considered including cannabis use, menstruation, illness and fatigue.[38,39]

Allergy Tests

Testing in the absence of a suggestive clinical history is strongly discouraged.[12] Assessing the clinical significance of sensitisation to individual LTPs can be challenging and has important implications for management.[40]

Skin prick and specific IgE tests (Figure 3)

Given the high likelihood of pollen sensitisation it is essential undertake SPT or specific IgE tests to determine sensitisation to grass and birch pollen and enable the correct interpretation of food allergy tests. Positive tests to mugwort and plane tree pollen can also support the diagnosis of LTP allergy. Specific IgE testing to foods has limited utility for investigation of suspected LTP allergy, so, with some limitations, skin prick testing (SPT) is the best first-line diagnostic tool for food triggers. Testing of plant foods can be done with commercially available extracts or by prick-to-prick testing with fresh whole fruits since LTP content is typically higher in the peel of plant foods.[41-43] However, positive results from testing with fresh whole foods or whole extracts may occur due to sensitisation to PR-10 or profilin allergens, rather than LTP allergens, especially in birch or grass sensitised individuals. It is therefore recommended to use an easily available commercial peach skin prick test extract enriched with Pru p 3 (e.g. ALK-Abello, Hoersholm, Denmark and Lofarma S.p.A. laboratories, Milan Italy), which have a relatively low rate of positivity in PR-10 and profilin sensitised individuals.[43-45] Although a negative skin test with these extracts does not exclude sensitisation to LTP proteins from other plant foods, this test provides a useful starting point for investigating patients where the clinical picture is suggestive of LTP allergy.[45]

Component resolved diagnosis (Figure 3)

In cases of suspected LTP allergy, especially if reported triggers include tree nuts, peanuts or composite foods, molecular diagnostics using single allergen LTP components is recommended.[46-48] Due to its high cross-reactivity with other LTP allergens, the peach LTP allergen Pru p 3 is the best marker of potential LTP sensitisation, even if the reported food trigger is not peaches. Although sensitivity is high, a negative Pru p 3 test may not completely exclude LTP allergy, particularly if wheat

is involved because the wheat LTP allergen Tri a 14 shares only 45% sequence homology with Pru p 3.[49] Also, if wheat is a suspected trigger, especially if co-factors are involved, then wheat-dependent, exercise induced anaphylaxis (WDEIA) needs to be ruled out, so testing for both Tri a 14 and Tri a 19 (Omega 5 gliadin) is recommended.[50]

Determination of total IgE levels is also helpful; the ratio of total IgE to Pru p 3 is a useful serological marker of clinically relevant disease in the UK and other Northern European countries, with a high total IgE and low level of Pru p 3 suggesting sensitisation may not be relevant.[6,51,52] Given that the ratio of Total IgE/Pru p 3 is important, a low level of Pru p 3, even when below the cut-off of 0.35, could still be relevant if Total IgE is also low, in which case measurement of other relevant LTP allergens may be useful.[53] Sensitisation to multiple LTPs from different foods, especially Mal d 3 (apple), Ara h 9 (peanut), and Cor a 8 (hazelnut), is associated with a higher likelihood of severe reactions.[54,55] Testing to Art v 3 and Pla a 3 may also add weight to a diagnosis of LTP allergy if positive.[4] The BSACI survey showed that 92% of respondents utilise component tests to assess for sensitisation to Pru p 3, and over 70% also test for Ara h 9 (LTP in peanut) and Cor a 8 (hazelnut). Array based IgE assays can be effective at identifying sensitisation to different allergen families, however, the results must be interpreted in the light of clinical context: if LTP sensitisation is an incidental finding, this should only be considered of clinical significance if the history is consistent with past LTP allergic reactions. For example, in one study, 68% of individuals who tested positive to wheat LTP (Tri a 14) were fully tolerant of wheat.[56] This has been confirmed in another study comparing those sensitised to Tri a 14 to those sensitised to Tri a 19 (omega-5-gliadin), with the latter more likely to be older, more likely to react to wheat with more severe reactions and have involvement of co-factors, whereas sensitisation to Tri 1 14 was associated with sensitisation to other foods.[57] Despite this, it is still important to test for both Tri a 14 and Tri a 19 if reactions to wheat have been reported, especially if co-factors are reported, being as they are a feature of both wheat allergy and LTP allergy.[56]

Other tests

The Basophil activation test (BAT) may help distinguish clinically relevant positive IgE results to LTPs from asymptomatic sensitisation,[58,59] although the test is not widely available, and its diagnostic effectiveness in clinical settings is variable.[52,60]

Food Challenge

Although food challenges (FC) are generally considered the gold standard in food allergy diagnosis, there are some significant pitfalls in the context of LTP allergy. LTP allergic reactions may be difficult to reproduce, due to varying quantities of LTPs in foods and the effect of co-factors, and so there is a high potential for a false negative result.[61-63] Also, a positive FC cannot identify an LTP as a causative allergen, without component testing, and such tests may not be available for all known LTP food triggers.[63] These factors could explain why only one third of BSACI respondents in the UK survey would use food challenge as a diagnostic test.[64]

Key Points

- Allergy history should include symptom type, severity and speed of onset, presence of co-factors, plant food(s) involved, whether raw or processed, or if a composite food is suspected
- Diagnosis is facilitated with prick-to-prick skin prick tests (PPT) to suspected trigger foods plus skin prick testing (SPT) using an LTP-enriched peach extract, although if the history is strong, a negative peach SPT does not preclude LTP allergy
- Specific IgE tests using whole food extracts are not helpful; if the history cannot be confirmed with peach SPT, then testing with the peach LTP allergen extract (Pru p 3) is recommended
- A diagnosis of LTP allergy can be made in someone sensitised to LTP allergens, and reporting moderate/severe symptoms to typical LTP foods
- Sensitisation to Pru p 3 in the absence of a convincing history does not confirm a diagnosis; low levels of Pru p 3 may not be clinically relevant, especially in the context of an elevated total IgE, and a differential diagnosis of pollen food syndrome should be considered
- Co-sensitisation to other LTP (Mal d 3 (apple), Cor a 8 (hazelnut), Jug r 3 (walnut) Art v 3 (mugwort) and Pla a 3 (plane tree)) can support diagnosis
- Testing to the major nut allergens is useful if reactions to nuts are reported e.g. seed storage proteins in peanut (Ara h 2/Ara h 6), hazelnut (Cor a 9/Cor a 14), cashew nut (Ana o 3), walnut (Jug r 1) and Brazil nut (Ber e 1)

Management (Table 3)

General considerations

The management of patients with LTP allergy is complicated by the widespread distribution of these proteins throughout the plant kingdom, with high homology between taxonomically unrelated plants.[1] Furthermore, the clinical expression of LTP allergy can be complex and variable, with several aspects remaining poorly defined. These include the development and progression of LTP sensitisation, why only a proportion of sensitised individuals exhibit symptoms upon ingestion of LTP-containing foods, and why some will require concomitant presence of co-factors to elicit reactions to these foods.[1,12] Therefore a pragmatic and personalised approach, tailored for each patient and their lifestyle, is recommended. This should include individualised dietary management, advice on non-food sources of LTP such as cannabis, pharmacological support including rescue medications, and the avoidance or management of co-factors.[33,65-67]

Patient education and support

LTP allergy is complex and requires regular follow-up. Support from an experienced dietitian is beneficial to aid education, identify which foods to avoid, what to replace them with and achieve nutritional balance and adequacy. Because of the paucity of specialised allergy dieticians in the UK , this task also involves the commitment of trained allergy specialists. Monitoring is supportive for this group who may develop reactions to new foods after diagnosis including foods which have been tolerated previously.[65,68] People with LTP allergy may have high levels of anxiety, possibly due to the unpredictable nature of this food allergy and because it can be alarming or confusing to have reactions to previously tolerated foods, as well as having inconsistent reactions to the same food.[4] Some patients can become very anxious or remove foods from their diets unnecessarily. Support from a psychologist is recommended for individuals experiencing high levels of anxiety.

Dietary management

The common food triggers in the UK are shown in Table 1 and individuals may react to one single food or multiple LTP-containing foods.[12] LTPs are generally heat stable allergens i.e. resistant to cooking or processing, and so education on sources of LTP in cooked or composite foods is essential.[1] The amount of LTP in a fruits and vegetables is affected by varietal origin, ripeness, or processing such as peeling or concentration (juice, puree), because LTPs are more abundant in the peel and pips/ seeds. [12,69,70] For example, the LTP content of peach peel extracts is approximately seven times greater than in pulp[43] Also, organic fruits and vegetables have the same LTP content than non-organic fruit varieties.[71] If a patient reacts to a fruit in the Rosaceae family (e.g. peach, cherry, plum, almond, apricot) they should monitor for reactions to other fruit in the same family. If tolerated, then they should be encouraged to keep them in their diet.

Patients should be advised to exclude only those foods which have triggered previous systemic reactions and follow an individualised approach for foods that have caused only localised oral reactions, based on their dietary habits and preferences and assessment of co-factors. Education should also include an explanation of the unpredictability of LTP food reactions; many people find that a food can be tolerated on one day but not the next, due to the variable LTP content between different varieties and the influence of co-factors.[21] They should also be aware that they are unlikely to react to trace amounts of the trigger food(s). Unfortunately, many LTP-allergic individuals exclude numerous foods from their diet due to unfounded concerns, misconceptions, or multiple positive tests. Typical issues include the exclusion of all tree nuts and peanuts after having reacted only to peanuts or walnuts, and being advised to avoid all LTP-containing foods to which they are sensitised, including those not associated with any reactions.

In these cases, attempts should be made to assess tolerance of foods not implicated in any reactions, or those considered to be less likely to provoke symptoms, through the use of FC. The challenge should aim for a portion size of the food being assessed as a minimum cumulative dose, although larger doses could be considered to increase sensitivity. For example, it has been demonstrated that individuals with co-factor related reactions will react without co-factors when given a high enough dose of wheat.[72-74] Food challenges can help improve the variety and nutritional quality of the diet. Plant foods are an essential part of a healthy and immune-supportive diet, and avoiding them risks nutritional deficiencies and reduces diet diversity.[75]

Plant foods that are safest to consume, especially if co-factors are involved, include potato, carrot/ root vegetables, beans, peas, melon (avoiding pips and skin), cashew and pistachio nuts.[67,76-80] Banana's may also be tolerated, although, an LTP isolated from banana has been implicated in reactions, so may not always be a safe option.[65,81] Strict avoidance of LTP-containing foods is not only difficult, given their ubiquitous presence in plant foods, it is also inappropriate and unnecessary, given many of these foods will be tolerated and it is desirable that they continue to be included to ensure a healthy, nutritious diet. Patients should be encouraged to continue to consume previously tolerated foods, due to concerns over loss of tolerance following prolonged elimination.[82] However, a small number of long-term studies have shown that reactions to previously tolerated foods do occur, even with continued consumption.[65,68] Therefore, advice should be individualised to minimise chance of reactions whilst aiming to avoid over-restriction, as well as broaden and improve patients' diet, ensure adequate nutritional intake, and improve quality of life. Advice for different scenarios is given in Table 3.

Co-factor management

A key element of management is education on the role of co-factors in LTP allergy. It may be advisable for individuals to avoid concentrated or mixed sources of LTP-containing foods such as smoothies and

juices in association with co-factors such as exercise. To identify the influence of exercise, the initial evaluation should focus on the type and intensity of activity, timing of onset of symptoms and food consumption[38] and a clear assessment of patients' exercise preferences and routines. From a long-term management perspective, every effort should be made to avoid limiting exercise activity and a shared plan should be agreed with patients to achieve this, although some modifications in the patients' choice of activities may be needed. Several precautions with exercise are advised, including having emergency medication for anaphylaxis, stopping immediately if any symptoms develop, avoiding the causative foods and other LTP-containing foods to which they are sensitised for 4-6h before exercise (which can be reduced to a usual minimum of 2h in most patients), avoid other possible co-factors, exercise with other informed individuals[38] Patients should also be alerted to the influence of other recreational co-factors such as alcohol and cannabis, with the potential risk that two or more co-factors are much more likely to occur in an evening out, such as exercise and alcohol, and potentially NSAID intake.

In some instances, in order to determine whether reactions only occur in the presence of co-factors, it may be helpful or necessary to undertake a FC with co-factors, especially since some individuals may have a systemic reaction both with and without co-factors.[21] Exercise challenges are fraught with difficulties from a logistic perspective (being time-consuming and staff intensive), and due to variability in vigour and duration of exercise used and tolerated by patients. Extrapolating from data for WDEIA, NSAIDs (aspirin) appear to have a stronger "co-factor effect" compared to exercise in lowering the allergen threshold for reactions and leading to reactions in a significant proportion of patients.[72,74] Unlike for omega-5-gliadin (Tri a 19), asymptomatic sensitisation to wheat LTP (Tri a 14) is frequent, highlighting the importance of food challenges preferably with co-factors (in an attempt to minimise the likelihood of false-negative results) to assess tolerance and provide tailored dietary advice with regards to this staple food.[74]

Pharmacological Management

Rescue medication should include non-sedating antihistamines for mild reactions. Also, although LTP allergy may present without a prior history of anaphylaxis, this does not exclude the future risk of such an event, especially because reaction severity may be driven by allergen concentration and the unpredictable effects of co-factors.[83,84] Other factors to consider when assessing the need for pharmacological management include the number and variability of food triggers, the degree of cross-reactivity between foods, the different clinical expressions in sensitised patients and development of new sensitisations/allergy over time, which make it virtually impossible to predict which foods the patients will react to. Given this, together with the potential for severe reactions (itself leading to increased patient anxiety and reduced quality of life), all patients with LTP allergy should be risk assessed to determine the need for Adrenaline Autoinjectors (AAI) even if systemic reactions have not been reported.[83,85-87] The BSACI survey results demonstrated that 50% of participants always prescribed an adrenaline autoinjector for LTP allergy and for others it would depend on factors such as severity of reactions and concomitant asthma.

Immunotherapy

Sublingual immunotherapy (SLIT) using Pru p 3, and oral immunotherapy using commercial peach juice have both been used to good effect to treat LTP allergy in Spain and Portugal.[20,88-96] Recently a new therapy consisting of peach SLIT, followed by oral immunotherapy with peach juice has been shown to be effective in facilitating tolerance to food triggers other than peach.[97] This suggests such treatments may be effective in UK individuals with LTP allergy, most of whom have food triggers other than peach. However, the products utilised in these studies are not available or licensed for use in the UK, so immunotherapy is currently not a viable treatment option for LTP allergy in the UK

Follow-up

Individuals with LTP allergy are at a high risk of experiencing further reactions after their initial diagnosis.[98] Given this, together with the complexity of LTP allergy and possibility for progression, patients with LTP allergy/syndrome should ideally have a period of regular follow up in allergy/immunology services, and when discharged advised to seek timely re-referral if symptoms are becoming more severe or the number of foods involved have increased.[99] Regular visits should focus on reactions since their last review, dietary management and nutritional adequacy, and to assess and re-train on the use of adrenaline auto-injectors. These assessments should be conducted at least annually, with patients offered a review sooner should there be any new concerns, particularly with unexpected systemic reactions/anaphylaxis with new/previously tolerated foods.

Key Points

- When providing advice on the treatment of reactions, strong consideration of prescription of adrenaline autoinjectors should be given, especially where co-factors are involved or triggers are difficult to identify
- Dietary advice must be tailored to the individual, ensuring that only known personal food triggers are avoided
- If co-factors are involved, advice on how to manage these within the context of food triggers is essential
- Food challenges, usually not required to confirm diagnosis, are useful to demonstrate tolerance to common LTP triggers not implicated in an individual's reactions

Paediatric considerations

Sensitisation to Pru p 3 is common in Spanish and Italian children, often being the first sensitising allergen, with higher levels liked to early onset of sensitisation and peaking in late teenager or early adult life.[1] Recent evidence suggests that over 50% of Italian children seen in the allergy clinic are sensitised to one or more LTP, although it is also known that many children sensitised to LTP allergens including those in peanut and hazelnut, may tolerate the food.[100,101] In fact hazelnut allergy is thought to be driven by seed storage proteins Cor a 9 and Cor a 14, even in Spanish children.[102] However, LTP allergy can provoke reactions in children, with severe symptoms including anaphylaxis, and also the presence of co-factors.[103] There is minimal data published on LTP allergy in paediatric patients in the UK.[3] Prevalence may vary by UK region and over time, as a consequence of changing environmental allergen profiles, migration patterns and diets (e.g. increased vegan diets). It would be a reasonable initial assumption that those clinical features reported in UK adult LTP allergy patients may be similar in paediatric presentations, in terms of the most common food triggers and spectrum of symptoms. It is unknown whether co-factors are also relevant in paediatric LTP allergy, but this should be explored in the clinical history. Clinical investigations should follow those recommended for adult patients irrespective of patient age. In respect to subsequent dietary advice or management, dedicated dietary support is essential to minimise dietary restriction and therefore avoid any adverse effects on growth and nutritional intakes through over-restriction.

Conclusion

Although there are few publications on LTP allergy in the UK, it is clear this food allergy exists, not only in the UK but in other Northern European countries. It is becoming a more frequent diagnosis in UK adults, but has the potential to affect children, although there is little published evidence for this. Given the potential for the involvement of multiple foods, severe reactions, and co-factors, it is most important that LTP allergy is correctly diagnosed and managed. This can be complex due to the high cross-reactivity between LTP allergens, with some positive tests possibly only reflecting sensitisation rather than allergy. Diagnosis is achieved by taking a very careful clinical and dietary history, supported by a positive peach extract and/or Pru p 3, and positive tests to the reported food triggers. A positive test to the LTP in mugwort and plane tree pollen can also support a diagnosis of LTP allergy. Given the possibility of severe reactions, and the uncertain nature of triggers, which may only cause symptoms when combined with a co-factor, pragmatic individualised medical and dietary management is vital.

Recommendations

1. Increase knowledge of paediatric presentations of LTP allergy through presentations of paediatric LTP allergy shared within networks to increase understanding of regional phenotypes
2. Gather more data on the foods and symptoms involved in LTP allergy to better utilise the clinical history to make a diagnosis
3. Gain a clearer picture of the effect of pollen sensitisation on symptom severity, and whether sensitisation to pollen LTP can ever be primary sensitising allergens
4. Develop algorithms for the use and interpretation of allergy tests to support the diagnosis of LTP allergy in a UK population
5. Develop patient education materials to support dietary and co-factor management

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Tables and Figures

Table 1 Foods most likely to provoke reactions

Food category	Typical food items
Fruit	Apple, cherry, peach, plum, raspberry, strawberry, grapes, kiwi
Fruit drinks	Juices or smoothies with the above fruit, cordials, wine, cider, fruit tea, cocktails, sangria
Products with dried fruit	Fruit cake, bread & butter pudding, pastries with raisins, Eccles cakes, biscuits, cookies, sweets, breakfast cereals and protein bars
Jams and preserves	Made with the above fruits
Vegetables	Tomato (especially puree), cabbage, onion, lettuce, pepper, aubergine
Composite foods	Pasta sauce, curry, pizza, ready meals and soups
Cereals and grains	Wheat, barley, corn (maize)
Nuts	Walnut, almond, hazelnut, peanut, macadamia
Seeds	Mustard, sunflower seed

Table 2 Food triggers which may be related

Brassicaceae (Cruciferae) (commonly known as the mustards, the crucifers, or the cabbage family)	Cabbage, turnip, black and white mustard seed, rape seed, horse-radish, watercress, mustard cress, rocket, pak choi, kale, Brussel sprout, cauliflower, broccoli, kohlrabi, radish, swede
Musaceae	Banana, plantain
Rosaceae	apples, pear, strawberry, stone fruit (cherry, apricot, peach, plum, nectarine), almond, quince, sloe, damson, greengage, loquat, raspberry, blackberry, loganberry, boysenberry, dewberry, cloudberry
Rutaceae	orange, lemon, grapefruit, tangerine, kumquat, clementine, ugli
Solanaceae (nightshade)	Tomato, bell pepper, potato, aubergine, chili, goji berry, tobacco

Table 3 Management advice for different scenarios

1-5 clearly identified LTP food triggers	Only reacted when co-factors are present	Unknown or multiple suspected triggers	Sensitisation to LTPs but no history of reactivity
1. Avoid only those identified trigger foods 2. Advise that reactions to further foods is possible, especially those that are closely related (see Table 2)	1. Only avoid the specific food 4 hours pre-exercise/other co-factor and 2 hours post exposure to the co-factor 2. Avoid very large or concentrated forms of trigger foods without co-factors, particularly if liquidised in fresh juices or smoothies Advise on safe foods to consume alongside co-factors	1. Provide detailed education on LTP allergy and common food triggers but strongly advise not to eliminate all LTP foods 2. Consider restriction of foods from the same botanical family if there is one clear known trigger 3. Advise caution with consuming LTP-containing foods around co-factors, especially if previous reactions include co-factors or if reactions have been severe 4. Advise on safe foods to consume alongside co-factors	1. Education on LTP allergy 2. No dietary changes 3. Clinical review if reactions occur, with documentation of foods eaten prior to symptom onset as well as involvement of co-factors.

Figure 1 BSACI survey results - Proportion of foods most often cited as the top trigger

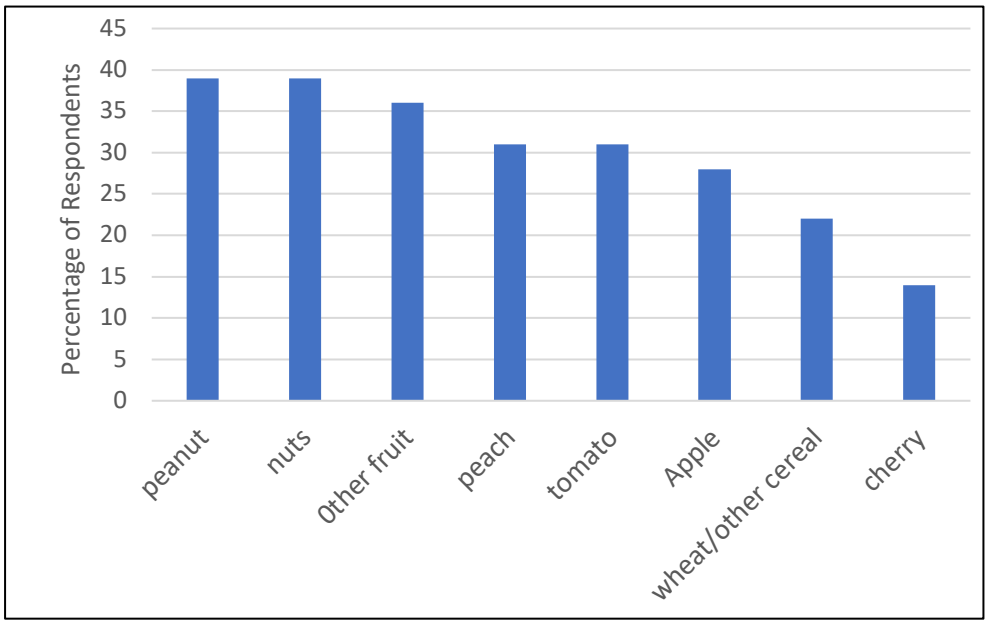

Figure 2 **Key features a clinical history suggestive of LTP allergy**

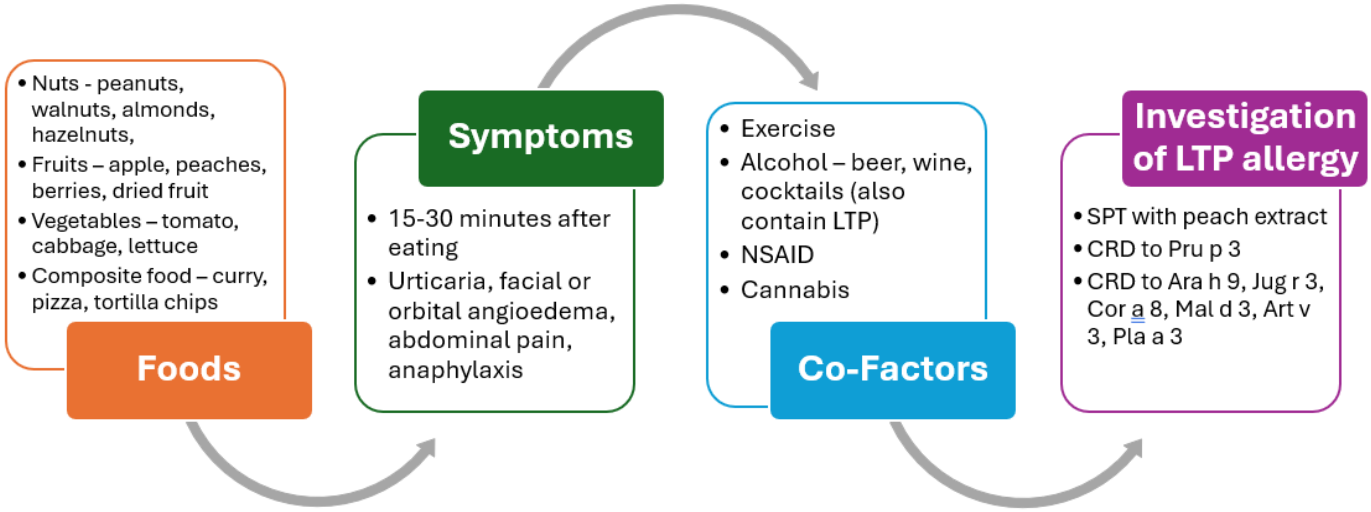

Figure 3 BSACI survey results - Tests used in the diagnosis of LTP allergy