ORAL ALLERGY SYNDROME – WHAT’S NEW?

Harris Steinman, MB ChB, DCh(SA)
Food & Allergy Consulting Services, Milnerton, Cape Town, South Africa

ABSTRACT
Oral allergy syndrome/pollen-food syndrome (OAS/PFS) affects up to 70% of patients with birch-pollen allergy. Prevalence is likely to continue to increase as the prevalence of inhalant allergies rises. Homologous proteins in fruits, vegetables, and pollen of grasses, trees, and weeds are responsible for PFS. Component-resolved diagnosis (CRD) with recombinant allergens may assist with the diagnosis of this condition in the future. As there is currently no proven therapy for this syndrome, cooking and avoidance of offending foods and vegetables are the only options.

INTRODUCTION
Individuals with pollen allergy often report adverse effects after the ingestion of a wide variety of foods from plants. This association has in recent years gained greater recognition because of the increasing prevalence of pollen allergy. The clinical effects are usually restricted to the oral cavity and include oral pruritus, swelling of the lips, tongue and throat, hoarseness, pharyngitis, and laryngeal oedema. These localised symptoms, caused by fruit, vegetables and spices, have been termed oral allergy syndrome (OAS). Immunoglobulin E (IgE) antibodies to the aeroallergen cross-react with the proteins in fresh fruit and vegetables to cause symptoms. Symptoms that patients experience are usually mild and do not require immediate medical attention. However, some patients experience more severe systemic reactions, such as severe laryngeal oedema, urticaria, asthma, or even food-induced anaphylaxis, though this is quite rare except in mugwort-celery-spice syndrome. This variation has resulted in a debate over whether such reactions may be considered a severe form of OAS or whether, as other authors contend, OAS includes only mild symptoms.

Further, whereas the term OAS has been used by some authors to describe oral symptoms caused by any food allergen, and not necessarily related to pollen allergy, others have argued that the term pollen-food syndrome (PFS) should be used to highlight the association between pollen-sensitisation and oral symptoms, therefore similar clinical effects may be seen locally. Further, allergenic weed sources can be found in the botanical families of Asteraceae (mugwort, ragweed, sunflower, feverfew), Amaranthaceae (goosefoot, Russian thistle), Urticaceae (wall nettle), Euphorbiaceae (castor bean, mercury pollen, latex tree), Plantaginaceae (plantain), and Cannabaceae (Japanese hop pollen), with mainly plants of the Asteraceae family giving rise to OAS/PFS, particularly in Europe. In Australia and Mediterranean countries, 20-40% of pollen-allergic patients are found to be allergic to plantain (Plantago lanceolata).

ASSOCIATIONS
Although individuals may experience oral symptoms following ingestion of fruit and vegetables without underlyging pollen allergy, in the majority of cases the initial event is sensitisation to pollen, and then there is subsequent development of cross-reactivity to food allergens, so that patients often develop pollen allergies before the development of oral symptoms. In Europe, sensitisation to birch pollen is a very common contributor. The association of oral symptoms and pollen allergy results from cross-reactivity of pollen-specific IgE with homologous food allergens. Prior to the identification of these proteins, the association between different families of plants was not well understood. The pollens and foods involved are usually not botanically related but contain conserved homologous proteins, as there are shared epitopes (binding sites) in the primary and tertiary structures of pollen and food allergens. Several clinical syndromes have been described as resulting from these associations, e.g. between birch pollen and fruit, in particular apple; between ragweed pollen and melon and/or bananas; between birch and/or mugwort pollen and celery (the so-called ‘mugwort-celery-carrot-spice syndrome’); between latex and fruit (latex-fruit syndrome); between plantain and cocks-foot (orchard) grass (Dactylis glomerata) pollen and melon; and a number of other associations among aeroallergens and plant proteins, depending on the particular cross-reactive allergens.

The plant proteins involved in OAS and PFS have been shown to belong to plant protein families, including those of profilins, pathogenesis-related proteins (PRs), and lipid transfer proteins (LTPs). There are a few well-described associations between aeroallergens and the fruits that elicit OAS symptoms. Appreciating the pattern of sensitisation to these foods and to pollen may assist in the deduction of the responsible panallergen, and thereby assist with predicting the range of food that may affect an individual. Only the most common relevant panallergens are reviewed below, and it should be kept in mind that other allergen families, e.g. calcium-binding proteins (polcalins), are occasionally responsible for PFS. With the development of recombinant allergens, component-resolved diagnosis (CDR) may assist in the prediction and management of OAS/PFS.

Profilin
Profilin is a monomeric, actin-binding protein that regulates the organisation of the actin filaments to form the actin cytoskeleton in plants. Profilins are present in a...
Pathogenesis-related proteins (PRs)

PR proteins are involved in the defence systems of higher plants and are induced upon infection, wounding or environmental stresses (e.g., drought, flooding, freezing temperature, and ozone).27 They are classified into 14 families based on similarities such as in their amino acid sequence or enzymatic activities.27 Importantly, these proteins are stable at low pH and resistant to proteolysis. Not all PR families contain allergens: plant-derived allergens have sequence similarities to PR families 2,3,4,5,8,10, and 14.28,29 Approximately 25% of characterised allergens are PRs.29 As PR proteins are influenced by a number of factors, they may vary depending on the environmental conditions in which the plant grows, and on the particular cultivar of the plant. Even ripeness and storage conditions affect PR content, with more mature plants having more.23 Geographical and dietary factors also play a role in sensitisation to fruit or vegetables containing PRs.21 For example, allergy to Rosaceae family fruits is attributed to grass pollen sensitisation in southern Europe and to birch pollen sensitisation in northern Europe.20,30,31

The PR family consists of, among others, the beta 1,3 glucanases (the PR-2 family), the class I, II, and IV chitinases (the PR-3 family), thaumatin-like proteins (PR-5), class III chitinases (PR-8), Bet v 1 homologues (PR-10), and LTPs (PR-14).

The PR-2 family consists of beta 1,3 glucanases, which catalyse the hydrolytic cleavage of 1,3 beta-D-glucosidic beta 1,3 glucans, abundant components of the plant cell wall.28 These allergens have been isolated from banana, potato, tomato and latex (Hve b 2), and are thought to be responsible for the cross-reactivity between these foods and latex in the latex-fruit syndrome seen in some patients.18,21

The PR-3 family consists of the class I, II, and IV chitinases. However, only class I chitinases have been associated with allergy.28 These proteins hydrolyse chitin found in the exoskeletons of insects and the cell walls of fungi. Banana, avocado and chestnut have allergens with sequence similarity to the class I chitinases, and the class I chitinases have an N-terminal hevein domain that is shared by latex prohevein (Hve b 6.01).17,23,34 The PR-3 allergens are thought to be responsible for the cross-reactivity between the above foods and latex in latex-fruit syndrome.34

The PR-5 family contains the thaumatin-like proteins. Although not fully understood, thaumatin-like proteins are thought to have antifungal properties, to rapidly accumulate in high levels during stress on the plant, and to give plants resistance to freezing and drought.1 The PR-10 family consists of the Bet v 1-homologues, i.e. proteins that have an amino acid sequence homology with the allergen Bet v 1 from birch pollen, a protein with unknown function.28 As with other PRs, their expression is induced upon environmental stress, wounding or infection.28 They are probably the most important PR proteins involved in OAS/PFS, with approximately 70% of birch-pollen-allergic individuals being affected by OAS/PFS as a result of IgE cross-reactivity between Bet v 1 and its food homologues.18,28

The PR-8 family of allergens includes 14 families based on similarities such as in their amino acid sequence homology. Some of these have been shown to have antifungal properties and to act as a barrier to the entry of pathogens.28

The PR-14 family comprises the LTPs. LTPs transfer phospholipids from liposomes to mitochondria and have antimicrobial activities.2 LTPs are important allergens of the Prunoideae family (peaches, apricots, plums, cherries) and the Rosaceae family (apples, pears), and are usually found in the peel.29 Significantly different from the protein families involved in OAS/PFS where a pre-existing pollen allergy sensitisation is found, LTPs often cause food allergy to fruit in the absence of pollen allergy. For example, hypersensitivity to peach, the most frequent fruit allergy in Spain, is clinically not associated with any kind of particular pollen allergy,31 even though there seems to be a higher prevalence of asthma in pollen-allergic patients with peach allergy.31 There are exceptions. For example, the LTP from mugwort pollen has been shown to cross-react with peach LTP and may be involved in the mugwort-peach allergy association frequently seen in the Mediterranean. Mugwort is not found in South Africa. Individuals who are allergic to LTPs in fruit have been shown to have a higher rate of anaphylaxis (36%) than those sensitised to PR-10 fruit allergens (18%).2,20,29
Cross-reactive carbohydrate determinants

The role of cross-reactive carbohydrate determinants (CCDs) remains controversial. Glycoproteins contain N-linked carbohydrate groups, which induce IgE, leading to cross-reactivity between foods and pollens. CDDS are found in, among others, celery, potato and peanut, and in ragweed, timothy grass and birch pollen. However, debate continues over whether these CCDs can cause clinical symptoms. For example, in a study of patients with grass-pollen allergy who are clinically asymptomatic to ingested peanut but have positive serum IgE to peanut but negative reactions to a skin-prick test for peanut, the patients were found to have IgE to the CCDs of peanut. The cross-reactive IgE had low biological activity. In contrast, in a study of celery-allergic patients, 25% were shown to have IgE to CCDs. In a study of the sera of 10 tomato-allergic patients, 4 with IgE to CCDs showed biological activity in the basophil histamine release assay with tomato glycoproteins only but failed to react to nonglycosylated recombinant tomato proteins.

IgE antibodies directed toward glycans appear to show the widest pattern of cross-reactivity among allergenic extracts and are often responsible for observed in vitro cross-reactions within PFS. Further research may elucidate the reasons for conflicting evidence and the causes of the variability of biological activity of CCDs. Importantly, many glycoproteins carry only one IgE-binding glycan and therefore cannot cross-link IgE bound to receptors; nor can they induce activation of mast cells and basophils, whereas other glycoproteins have been identified that contain more than one N-linked glycan.

As plant proteins are characterised in more detail, it will become easier to identify potential cross-reactions. However, not all patients with cross-reactive antibodies will actually experience symptoms; i.e. the IgE cross-reactivity will be either clinically manifest or irrelevant. Clinical manifestations seem to be influenced by a number of factors, including the host’s immune response, allergen exposure, and the individual allergen itself. For example, and importantly, amino acid sequence homology among members of each protein family group varies, which influences the cross-reactivity patterns seen and the likelihood of symptomatic cross-reactivity. For example, in the PR-14 family of LTPs, there is in general a high sequence homology among the allergen members, suggesting a high probability of cross-reactivity among members, and this is confirmed clinically, whereas in the profilin protein family a much wider range of homology exists among members, and therefore cross-reactivity among some plants containing profilin is not certain. Other factors that influence cross-reactivity among family members are the degree of ripeness of the fruit or vegetable, storage conditions, and a number of other factors that influence the expression of the allergen; levels of cross-reactivity may even vary among cultivars.

Food-allergic patients may be sensitised to more than one allergen found in a specific food, complicating cross-reactivity. For example, a high prevalence of OAS/FPS occurs to ingestion of apple in birch pollen-sensitised individuals as a result of the cross-reactivity between Mal d 1 from apple and Bet v 1 from birch pollen; however, apple-allergic individuals may be monosensitised or polysensitised to any number of apple allergens, e.g. to Mal d 1 (PR-10), Mal d 2 (PR-5), Mal d 3 (PR-14), Mal d 4 (profilin), or any other apple allergen or combination of allergens.

Clinical manifestations

The clinical effects are usually restricted to the oral cavity and include oral pruritus, swelling of the lips, tongue and throat, hoarseness, pharyngitis, and laryngeal oedema. The most common complaint among patients is an itching or tingling of the mouth after ingestion of fresh fruit or vegetables. Patients may also experience angio-oedema localised to the mouth. Some studies have shown that a few patients will develop some abdominal cramping or discomfort after ingestion, but rarely vomiting or diarrhoea. Anaphylaxis may uncommonly occur in association with OAS/FPS (as opposed to anaphylaxis without this association). Anaphylaxis is particularly more likely with LTP-containing foods. Almost all patients will have some degree of allergic rhinitis or conjunctivitis because the IgE antibodies to an aeroallergen are cross-reacting with the fruit or vegetable proteins.

Reactions may vary depending on the allergen responsible for symptoms. Patients allergic to profilin may report that ingesting a cooked fruit or vegetable does not elicit symptoms, whereas cooked fruit or vegetables containing heat-stable allergens, e.g. LTPs, may still result in symptoms.

Diagnosis

The diagnosis is based almost entirely on the patient’s history. A history of allergy to aeroallergens and then tingling or itching of the mouth after eating fresh fruits or vegetables is enough to make the diagnosis of OAS in almost all cases. The OAS reaction is usually immediate and can occur as soon as the fruit or vegetable is put into the mouth. The reactions are usually the same if the patient eats the same fruit or vegetable again, but there may be a dose threshold. Most symptoms should be confined to the oropharynx.
Although commercial extracts of most fruits and vegetables are available for tests, these extracts are highly heat-labile and easily degradable, often losing their potency and sensitivity by the time they are used in skin-prick tests. This has led to the use of the prick-to-prick method, in particular if initial skin-prick tests are negative despite a persuasive clinical history. The procedure is to prick the fresh fruit with the lancet and then immediately use the same lancet for the skin-prick test. Studies have confirmed that commercial extracts are not as good as fresh fruit in skin-prick testing.

Skin-prick tests and histamine release is a diagnostic alternative. However, if a skin-prick test with fresh nut or apple cannot be performed, then atypical clinical patterns may occur to a food without oral symptoms, and cross-reactivity may not be related to a cross-reactive allergen (with the exception of mugwort). However, systemic reactions such as urticaria, wheezing, and anaphylaxis occur in association with OAS/FPS, this suggests the involvement of an LTP allergen. Potential cross-reactivity with other LTP-containing foods should be explored, and in this instance coexisting pollen allergy may not be related to a cross-reactive allergen (with the exception of mugwort). However, systemic reactions may occur to a food without oral symptoms, and if an individual is polysensitised to a number of allergens in a food, then atypical clinical patterns may emerge.

A thorough history should be obtained to ensure that the patient has no signs of a more serious IgE-mediated food allergy. Patients should be questioned about what foods were ingested around the same time; excluding those foods as the cause of the reaction would be appropriate. This may include skin-prick testing, specific IgE antibody testing, and food challenge.

The development of recombinant allergens representative of cross-allergenic allergens has resulted in the evolution of component-resolved diagnosis (CRD), in which sensitisation to single allergens can be tested, enabling improved evaluation of OAS/FCS and cross-reactivity. Table I lists examples of useful recombinant allergens that have been developed.

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<th>Table I. Diagnostic recombinant allergens</th>
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<tr>
<td>rBet v 1 PR-10</td>
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<td>rAra h 8 PR-10</td>
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<td>rApi g 1.01 PR-10</td>
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<td>rCor a 1 PR-10</td>
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<td>rGly m 4 PR-10</td>
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<tr>
<td>rPru p 1 PR-10</td>
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<tr>
<td>rBet v 2 Profilin</td>
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<td>rPhl p 12 Profilin</td>
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<td>rAra h 9 LTP</td>
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<td>rCor a 8 LTP</td>
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Double-blind, placebo-controlled food challenges (DBPCFC) are considered the gold standard in the diagnosis of food allergy. However, using DBPCFC to diagnose OAS/FPS has various constraints, including the fact that storage ripening processes affect the level of allergen present, and that levels of the same pan-allergen vary between varieties. Food-in-a-capsule challenges are also problematic, as the food bypasses the oral mucosa and the allergen may be degraded in the stomach by digestion.

TREATMENT

Most patients with OAS will avoid the fruit(s) or vegetable(s) eliciting their symptoms. If the patient wishes to tolerate the localised symptoms and there is no suggestion of systemic symptoms, it is safe to continue eating the food. A survey of allergists concern management of OAS found no consensus: some recommended complete avoidance of the offending foods, others did not advocate food restrictions, and 38% personalised recommendations according to the individual, sometimes advocating the avoidance of cross-reactive foods.

However, since cross-reactivity may depend on the heat-stability of the responsible cross-reactive allergen, cooking alone may be sufficient to deactivate the responsible panallergen. However, in patients with concomitant eczema, ingestion of cooked birch-pollen-related foods, while not inducing OAS, still caused atopic eczema to worsen, suggesting that T-cell cross-reactivity between Bet v 1 and related food allergens occurs independently of IgE cross-reactivity in vitro and in vivo. Therefore, ingestion of cooked fruits and vegetables may cause perennial activation of pollen-specific T cells and B cells, leading to maintenance of perennially increased allergen-specific IgE levels, and thereby symptoms, in pollen-allergic patients outside the pollen season.

Although the same panallergen may be present in a range of foods, homology may still vary, resulting in clinical cross-reactivity between some members and not others. Studies assessing cross-reactivity in the Rosaceae family of fruits found that from 46% to 63% of patients with confirmed PFS to one fruit had clinical reactivity to other Rosaceae fruits; the authors recommended that if a reported reaction is confirmed, tolerance to other Rosaceae fruits, particularly apricot, apple, and plum, should be evaluated, unless the patient has eaten them without symptoms after the initial reaction.

It is inappropriate to take an antihistamine prior to eating a culprit food, as this would mask symptoms beyond the OAS (although in certain circumstances, this may be acceptable, i.e. if the symptom pattern is established and is not variable). Additionally, patients should be made to understand that if the food ever causes symptoms beyond the oropharynx, they should avoid the food as if they have classic IgE-mediated food allergy.

The hypothesis that immunotherapy for pollen allergy may reduce or abolish symptoms of OAS/FPS, as a result of cross-reactivity among panallergens, has been addressed in a number of studies, with varying results. A study of birch-pollen-allergic individuals with symptoms to apple who were treated with subcutaneous immunotherapy reported a significant reduction or disappearance of oral symptoms to apples (84%), with a concomitant reduction in reactivity to skin-prick tests to apple. Similarly, a study reported that immunotherapy resulted in birch-allergic patients being able to eat significantly more apple or hazelnut with no resulting symptoms. However, the amount of apple or hazelnut tolerated remained small. In contrast, other studies have demonstrated no improvement following immunotherapy (except for pollen-related symptoms of rhinoconjunctivitis). Results of an immunotherapy...
study of birch subcutaneous immunotherapy for apple allergy reported the possible induction of OAS in 2 of 12 study participants as a result of immunotherapy.\textsuperscript{53}

**Disclosure of interest**

Consultant to Phadia, Sweden.

**REFERENCES**


