

Food allergy and oral allergy or pollen-food syndrome

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Purpose of review

This paper reviews current concepts in our understanding of oral allergy or pollen-food syndrome. As technology has improved, much more accurate profiling of food allergic individuals is now possible, resulting in more precise diagnosis, elucidation of cross reactivity patterns and more helpful prediction of risk of anaphylaxis.

Recent findings

The identification and characterization of various ubiquitous plant proteins have led to greater understanding of food cross reactive reactions. Newer diagnostic techniques utilizing purified and recombinant allergens are available for more precise diagnosis and clinical profiling of patients presenting with food allergy.

Summary

In-vitro screening of food allergic patients with large panels of allergens will change the accuracy of diagnosis resulting in better management. Allergens are now available for use in the allergist's office to improve diagnostic accuracy of skin tests in patients presenting with plant-food allergy. Knowledge of the specific sensitization of individual patients has consequences for both risk assessment and dietary management.

Keywords

birch pollen, oral allergy syndrome, pollen-food syndrome, profilin

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Introduction

This review will focus on the most common form of food allergy found in adult populations – oral symptoms induced by eating raw plant-derived foods, originally termed the oral allergy syndrome and now called pollen food syndrome.

Oral allergy symptoms were first recognized in patients with birch pollen allergy where immediate symptoms in the oropharynx occurred following ingestion of certain fruits and vegetables. This clinical syndrome has led to elegant investigations into the immunopathogenesis of this cross reactivity. It is now understood that the nature of the particular proteins responsible for the sensitization profoundly influences the clinical spectrum of the reactions and the range of plant foods involved.

Knowledge of the specific sensitization of individual patients has consequences for both risk assessment for severe reactions and dietary management.

Terminology

The term oral allergy syndrome (OAS) was first coined by Amlot *et al.* [1] in 1987 to describe the most common set of symptoms occurring in individuals reporting food allergy and having positive skin prick tests to the implicated food. In that original report, 45% of patients gave a

history of oral symptoms in response to food ingestion and these symptoms always preceded any other systemic symptoms. The authors documented a characteristic progression of symptoms commencing with oral irritation, throat tightness and lip swelling that then may proceed to more systemic features. These symptoms were described in relation to ingestion of a range of foods including egg, milk, and fish.

In 1988 Ortolani *et al.* [2] described the characteristic cluster of OAS symptoms after fruit and vegetable ingestion and proceeded to describe a relationship between the onset of these symptoms and hay fever and pollen sensitivity. From then, the term OAS was most commonly used to describe this pollen-fruit allergy link but it is now recognized that oral symptoms may occur as a prelude to generalized reactions caused by a variety of foods and not confined to those occurring with fruits and vegetables. There is a need for a more specific term to describe the allergy occurring as a result of cross reactivity between pollen and plant foods. Pollen-food syndrome (PFS) or pollen-food allergy syndrome are terms that have been coined to describe the particular association between pollen-sensitivity and allergy to raw fruits, vegetables and spices caused by cross reactive allergens [3].

Most recently, Konstantinou and Grattan [4] have proposed food contact hypersensitivity syndrome (FCHS) as a more encompassing term for food allergy that results

from cross reactivity, not only with pollen but also with latex, as well as reactivity that may be due to contact urticaria (non-IgE mediated). Thus in their classification, FCHS may be IgE or non-IgE-mediated, and of the IgE-mediated forms, there are pollen-related reactions and pollen-unrelated reactions that include latex fruit, mites-snail and bird-egg cross reactivity [4].

In this review, the term OAS is used as a descriptor for the particular oropharyngeal symptoms elicited following ingestion of an implicated food and PFS is used for the clinical entity of OAS resulting from cross reactive allergens between pollen and plant foods. OAS as a result of other forms of cross reactivity is beyond the scope of this review.

Epidemiology

The prevalence of PFS is difficult to ascertain as many patients experience mild symptoms and simply avoid the offending food without further presentations.

Prevalence is influenced by many factors including sensitivity patterns in various geographical regions and the rising prevalence of allergic rhinitis. In the original description of OAS [1] 45% of 80 highly atopic individuals had OAS in response to food ingestion. Following a survey of the United States allergists, Ma *et al.* [5] determined that approximately 8% of adults demonstrated PFS – a figure they considered to be an underestimate because of lack of recognition of the syndrome. In other studies in the literature, 47–70% pollen-allergic individuals have OAS with fruit and vegetable ingestion [6–8]. Cross reactivity patterns vary with geographical region. In central and northern Europe, birch, grasses and mugwort pollen are the most common sensitizers in those with FPS. In the Mediterranean region approximately 20% of sensitized individuals have PFS where the most common sensitizers are grasses, ragweed and parietaria [8]. In the rest of Europe this figure is 50% [9].

There are regional differences concerning which foods are responsible for symptoms of PFS. For example, in Central and Northern Europe where birch tree pollen allergy is common, tree nuts and fruits, particularly those of the Rosaceae family, are important food allergens.

In a study [10] conducted in Italy, significant regional differences were described in the overall prevalence of food allergy. PFS was more frequently found among patients from northern and central Italy than in southern Italy whereas latex-fruit allergy syndrome showed the same low prevalence in all three regions. This difference can be explained by the difference in birch pollen sensitization with 51% of those from northern Italy showing sensitization compared with only 2% from southern Italy.

In Japan where Japanese cedar is the major cause of pollinosis, ingestion of fresh tomato has caused OAS with cross reactivity between Japanese cedar and tomato demonstrated by RAST inhibition and immunoblot inhibition [11].

There is little written about PFS in populations in the southern hemisphere.

Immunology

PFS is caused by the wide cross reactivity seen between pollen and plant-derived foods. Cross reactivity occurs when a specific antibody formed in response to one epitope reacts with another similar or identical epitope on another antigen. These pollen and foods are not botanically related but share highly conserved homologous proteins called panallergens that are widely distributed throughout the plant and animal kingdoms. Examples of these include profilin, pathogenesis-related proteins and lipid transfer proteins (LTPs).

Profilin, described as a plant pan allergen in 1992 [12[•]], is a monomeric, actin-binding protein. Profilins are prominent in trees, grasses and weeds and are recognized by 20% of pollen allergic patients [13]. Sensitization to profilins causes reactivity to a wide range of inhalant and food allergens. In birch pollen Bet v 2 is a profilin and those birch-allergic patients sensitized to this particular protein will frequently have OAS symptoms on ingestion of pear, apple, celery, carrot. Grass allergic individuals may react to carrot and celery because of the similarity between the profilins [14].

Pathogenesis-related (PR) proteins, another group of panallergens, are responsible for defence responses in plants and are induced by a variety of stressors. They have been classified into 14 pathogenesis-related protein families with certain ones identified as plant allergens (a more comprehensive description of this family can be found in reference [12[•]]). Of these, the PR protein 10 family is the most important in PFS. Bet v 1, the major birch pollen allergen is a member of this family. In temperate zones of Europe sensitization to Bet v 1 is the major cause of pollen allergy. Between 50 and 90% of birch pollen-allergic individuals develop sensitivity to foods such as apples, carrot, hazelnut and celery and this is due to cross reactive allergens against Bet v1 [15]. Mal d 1, the major apple allergen, shares 64% homology with Bet v1 but there is some discrepancy between serological cross reactivity and onset of clinical symptoms. Whereas IgE of most birch allergic individuals can bind Mal d 1, not all show clinical reactivity. Recently, Klingmeyer *et al.* [16^{••}] have shown this to be due to binding to different B cell epitopes within the Bet v 1 allergen. More detailed knowledge about the structure of the various

cross reactive proteins and B cell epitope recognition patterns will aid our understanding of the various clinical patterns of reactivity that we recognize clinically.

The PR 14 family comprises lipid transfer proteins (LTPs) that have antimicrobial properties and transfer phospholipids from liposomes to mitochondria. They are important allergens in the Rosaceae fruits (apples, pears) and the Prunoideae fruits (peaches, apricots, plums, cherries) where they are found in greatest concentration in the peel of the fruits. They may be responsible for fruit allergy in the absence of pollen allergy. Allergy to LTPs confers a higher risk of the possibility of anaphylaxis than is seen with PR10 reactivity. Unlike profilins and PR10, LTPs are very heat stable so cooking does not destroy the allergen thus rendering the particular food well tolerated [17].

Recently, Cudowska *et al.* [18] have carefully investigated the relationship between birch pollen allergy and apple allergy in children. The major cause of cross reactivity between birch and apple is similarity between Bet v1 and Mal d 1 heat-labile PR 10 proteins. Some individuals demonstrate allergy to fruits such as apple and peach with no prior history of pollen allergy. They have been found to have specific IgE directed to Mal d 3 (apple), Pru p 3 (peach) or Pru ar 3 (apricot) which are LTPs. These individuals show strong skin test reactivity to extracts of the fruit peel and are more likely to suffer severe systemic reactions [14]. In their study, Cudowska *et al.* [18] demonstrated strong reactivity against Mal d 3 in children who were not reacting to birch pollen allergens and these children demonstrated different clinical symptoms to those reacting to Mal d 1, with severe systemic symptoms more likely with Mal d 3 sensitivity.

Cross reactive carbohydrate determinants (CCDs) can induce IgE and are present on the glycoproteins of vegetables such as celery, tomato, peanut and potato and are also found in ragweed, timothy grass and birch pollen. Whether reactivity to CCDs can cause clinical symptoms is still a matter of investigation [12*].

Clinical features

Almost all patients presenting with PFS will have a background of allergic rhinoconjunctivitis because the specific IgE antibody response to pollen allergens is the source of cross reactivity with proteins in fruits and vegetables. This syndrome is rarely seen in the very young but prevalence of PFS increases with age becoming the most common manifestation of food allergy in adolescents and adults [19].

The relative importance of different plant foods varies among countries depending on geography, pollen exposure and dietary patterns [19].

OAS symptoms are characterized by the presence of oropharyngeal pruritis, usually beginning with tingling and itching of the lips immediately on contact with the food. There may be some angioedema involving the oral mucosa, tongue, palate or throat. In the original description of the condition, Ortolani [2] also described some abdominal cramping and discomfort following ingestion of the food occurring in a minority of patients. Vomiting or diarrhoea was rarely seen. Anaphylaxis may occur in association with initial OAS symptoms; this is seen more often with LTP-containing foods [20].

Cooking usually renders the food safe and this is particularly so if the offending allergen is profilin. LTPs, being heat stable, may still cause symptoms when the food is ingested in the cooked state [12*].

Although symptoms may occur at any time on exposure to the offending plant food, often symptoms are more pronounced if the exposure occurs during the pollen season.

Patients who have atopic dermatitis and PFS may experience an exacerbation in eczema symptoms after ingesting the food in the cooked state even though the OAS symptoms are eliminated [21–23].

Differential diagnosis

Severe systemic reactions or absence of pollen sensitization is suggestive of classic type 1 food allergy.

Eosinophilic oesophagitis may result in complaints about throat symptoms but this is usually more consistent with food impaction, dysphagia or other gastrointestinal symptoms. A recent interesting case report [24] has described a patient with confirmed eosinophilic oesophagitis and OAS with a variety of fruits and vegetables who continued eating the foods despite oral symptoms. Eosinophilic oesophagitis remitted completely when the implicated raw fruits and vegetables were eliminated from his diet.

Non IgE-mediated reactions may be involved in symptoms related to the lips or oral cavity. For example, spices, or food additives may cause an allergic or irritant contact dermatitis [4].

Diagnosis

Although diagnosis relies heavily on the clinical history, testing is required to elucidate the nature of the sensitization.

History

A positive history of typical symptoms on immediate contact with the implicated food on the oral mucosa in those with pollen allergy is, of course, essential for the

diagnosis of PFS. Characterizing the specific IgE-mediated sensitivity and elucidating cross reactivity patterns are more problematic.

Skin tests

Pollen sensitization can be confirmed by the performance of a battery of skin prick tests with the relevant pollen allergens.

Skin testing with commercial fruit and vegetable extracts is problematic because these extracts are heat labile and very easily degraded, thus often resulting in negative results. Skin testing by the prick-prick method has been shown to be very reliable in patients with a confirmed history of PFS [25]. More recently this was confirmed by Ballmer-Weber *et al.* [26] who examined 64 birch pollen-sensitized individuals with OAS to a number of cross reactive foods using both commercial and in-house prepared extracts. Skin testing with commercial extracts of celery, hazelnut and carrot had a sensitivity of 85, 80 and 29%, respectively, whereas the in-house extracts yielded corresponding sensitivities of 100, 80 and 100%.

Another recent study [27**] has demonstrated the usefulness of performing skin tests with purified allergens. The authors used skin testing with purified natural date palm profilin (Pho d 2) in 200 pollen allergic individuals 30% of whom showed skin test reactivity to this. More than half the profilin reactors had food allergy, the large majority reporting OAS symptoms and tolerance to the food in the cooked state.

Availability of purified natural allergens and development of recombinant allergens representative of cross-reactive allergens has resulted in what is termed component resolved diagnosis (CRD). Using this, sensitivity to single allergens can be categorized resulting in a more accurate prediction of cross reactivity patterns.

Commercially available extracts (ALK Abello) with known allergen content such as apple, Mal d1 (Bet v1 homologue), peach, Pru p 3 (LTP) and a profilin extract from date palm pollen (Pho d 2) allow performance of CRD in routine allergy practice utilizing skin testing [27**].

In-vitro tests

Commercially available in-vitro tests for specific IgE have also been limited by poor sensitivity and specificity. In the study by Ballmer-Weber *et al.* [26], specific IgE determinations were performed on the same group of patients using CAP-FEIA. Sensitivities for celery, hazelnut and carrot were 71, 73 and 57%, respectively, whereas the respective specificities were 67, 73 and 60%.

CRD can also be performed using ImmunoCap (Phadia). By the use of a panel of recombinant allergens, patients

may be shown to react to either the PR10 family of proteins or to profilins. By using individual peach allergens, Pru p1 (Bet v1 homologue), Pru p 3 (LTP), and Pru p 4 (peach profilin), careful profiling of a patient's reactivity can be obtained [19]. One of the important consequences of such careful profiling is the ability to offer some prediction regarding severity of a food allergic reaction. Those reactions resulting from profilin sensitivity tend to be at the milder end of the PFS spectrum and usually have OAS symptoms alone, whereas sensitivity to LTP is associated with severe systemic reactions necessitating provision of adrenaline devices as first aid.

A number of studies have been conducted exploring the usefulness of tests other than measurement of specific IgE.

Cellular allergen stimulation test-ELISA

This test has been shown to be of interest in diagnosis of IgE-mediated allergies to inhalant allergens, venom, latex and some drugs [28]. Raap *et al.* [29] have shown high sensitivity and specificity in certain food allergies. Cellular allergen stimulation test (CAST)-ELISA was shown to be more predictive of PFS than specific IgE determinations [26]. This study demonstrated that the usefulness of the test is dependent on allergen concentration used and the authors defined a concentration of 20 ng/ml of total protein for the foods tested as the optimal concentration to discriminate prospectively between challenge positive and challenge negative patients.

Using natural purified food allergens or recombinant allergens, Gamboa *et al.* [30**] have shown excellent sensitivity and specificity for the CAST-ELISA when compared with the results of food challenges in peach-allergic individuals. Furthermore, there was excellent agreement between the results with this test and specific IgE determinations with the same allergens.

A number of investigators have obtained high sensitivity and specificity for basophil activation measured by flow cytometry when compared with results of challenges and skin tests. These figures are improved using recombinant or purified native allergens [31]. By contrast, histamine release assays have not proven to be very useful [30**].

Food challenges

In other instances of food allergy, DBPCFC are considered to be the 'gold standard' test for confirming the presence of allergy to a particular food. This procedure is problematic for the confirmation of diagnosis in PFS. Often reactivity in PFS depends on the stage of ripeness of the particular plant food. Lyophilization, commonly used to prepare foods for double blind challenge, may destroy relevant allergens resulting in a false negative challenge. Whether or not the fruit peel is included may also affect results with peel being a source of LTP

allergen. Using capsules as part of the blinding process eliminates direct mucosal contact that is considered essential in initiating the reaction in PFS. The degree of processing of an individual food may determine how much allergen is found within the food product and this may affect reactivity. Despite these difficulties, DBPCFC have elicited OAS in individuals. In a study by Ballmer-Weber *et al.* [31], soy flour was successfully masked in a chocolate base. Masking may be more difficult with foods having a stronger flavour.

In some cases it may be necessary to perform challenges cautiously with other possible cross reactive foods to which the patient has not yet been exposed although with increasing use of CRD, this may be less frequently performed.

Management

At this time there are no universally agreed management strategies for patients presenting with PFS and indeed there is dispute regarding the level of care needed.

Avoidance

Although most patients with significant symptoms of PFS will choose to avoid the implicated foods, there is no agreement among clinicians as to the best way to manage this clinical problem. Ma *et al.* [5] demonstrated a diversity of opinion among the United States allergists regarding management ranging from strict avoidance of the implicated food to not applying any particular restrictions. Another area of uncertainty is what advice to give about potentially cross reactive foods. In the earlier survey, 4% of clinicians advocated avoidance.

Clinical cross reactivity, particularly among members of the Rosaceae fruits has been shown to be significant 46–63% [32], leading these authors to recommend that tolerance to other members of the family should be specifically investigated unless the patient has eaten them without symptoms. Open food challenges with potentially cross reactive foods must be considered for patients who have had a systemic reaction.

Patients who have experienced more significant or generalized symptoms should be treated in the same manner as any other food allergic patient with instructions regarding strict avoidance and first aid measures including provision of a self-injectable adrenaline device.

Many patients with PFS tolerate the food in the cooked state. Cooking causes denaturation of the relevant proteins and loss of conformational structure [21] resulting in loss of IgE-binding ability. However, these cooked foods retain their ability to stimulate Bet v 1 specific-T cells which may explain why patients with PFS and

atopic dermatitis may experience a flare although they do not experience OAS on ingestion.

Immunotherapy

The role of immunotherapy in management of PFS remains controversial as published studies report conflicting results. All studies have involved use of birch pollen extract in patients with birch pollen-induced allergic rhinoconjunctivitis who also have PFS. In the most successful study, Asero [33] reported that 84% of patients undergoing immunotherapy with birch pollen extract had disappearance or significant reduction of apple allergy. In most patients, this was associated with disappearance of skin test reactivity to fresh apple. In a subsequent paper, he attempted to evaluate the long-term efficacy of immunotherapy with a pollen extract on a pollen-related food allergy [34]. Some patients who had become skin test-negative to apple and who could tolerate eating it still showed a negative skin test and tolerance 30 months after the immunotherapy course. In many cases, however, apple allergy showed a tendency to recur after cessation of immunotherapy.

Another study [35] also demonstrated improvement in food-related symptoms following birch pollen immunotherapy. Eighty-seven percent of patients with PFS could tolerate significantly more apple or hazelnut after immunotherapy although the amount tolerated remained small.

In contrast to these encouraging findings, a number of studies have failed to demonstrate improvement in any food-related symptoms following immunotherapy, subcutaneous or sublingual [36], although there was improvement in the respiratory allergy symptoms [36,37]. One study [38] reported induction of OAS in 2/12 study individuals during immunotherapy.

Conclusion

Understanding the nature of cross reactivity between pollen and plant foods has resulted in greater understanding of the various presentations seen in clinical practice. With the advent of purified and recombinant allergens and micro-array technology, rapid and accurate diagnosis is possible resulting in characterization of an individual's sensitivities.

For patients with PFS, knowledge of specific sensitization patterns has consequences for both risk assessment and dietary management.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 270).

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