

Oral Allergy Syndrome

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KEY CONCEPTS

- Oral allergy syndrome is a subset of plant cross-reactivity syndromes.
- Pollen–fruit syndrome explains the relationship between allergic rhinitis and certain fruit allergies through homologous proteins in the plant kingdom.
- Wide regional variability exists in plant cross-reactivity syndromes.
- The diagnosis of plant cross-reactivity syndrome is currently suboptimal, as *in vivo* and *in vitro* tests are poor predictors of clinical reactivity.
- The management of plant cross-reactivity syndromes currently relies on food avoidance, but may evolve to include immunotherapy in the future.

The first report of hypersensitivity to fruits and vegetables in patients with pollinosis occurred in 1942 when Tuft *et al.* described four individuals with hay fever who experienced localized symptoms with fresh fruits and vegetables [1]. In 1970, the observation that ragweed allergy was commonly associated with allergy to melon and banana was described [2]. Ragweed-allergic patients experienced immediate oral symptoms after eating melons or bananas. There were no reports of anaphylaxis and none of the non-pollinosis patients reported symptoms with these fruits. Soon after, similar associations were reported for birch pollen and apple allergy [3] as well as for celery and mugwort allergy [4]. These pollen–fruit–vegetable associations have similar characteristics of localized oropharyngeal symptoms following the ingestion of fresh plant-derived products.

The term oral allergy syndrome (OAS) has been used to describe such symptoms with ingestion of fresh fruits and vegetables in pollinosis patients. This is an IgE-mediated allergy that is generally due to cross-reacting, homologous proteins found in the food proteins and pollens [5]. Since conserved proteins are widely expressed throughout the plant kingdom, it is not surprising that homologous proteins are being identified in a growing number of plant-derived foods. In fact, cross-reactivities between fruits and vegetables and pollens have been increasingly reported in recent

years, coincident with the increased prevalence of allergic rhinitis. There has been tremendous progress in the characterization of these proteins in the last two decades leading to a better understanding of these cross-reacting allergens.

Epidemiology

OAS is the most common form of food allergy in adults, with more than half of food-allergic individuals reporting oropharyngeal symptoms to fresh fruits and vegetables [6,7]. Recently, a study of an unselected adult population in Denmark revealed that 10% of adults have both allergic rhinitis and OAS [8]. Among individuals with allergic rhinitis, the prevalence of OAS ranges from 30% to 70% depending on location, likely due to differences in pollens and dietary habits [8–10]. Osterballe *et al.* [8] found that a higher probability of clinical allergy to plant-derived foods occurs in individuals who have sensitization to multiple pollens (birch, grass, and/or mugwort). Fewer studies have reported the prevalence of OAS in children. However, it appears relatively common in the pediatric population, with 29% of Italian children with allergic rhinitis to grass reporting food allergy symptoms [11].

In addition to regional variations in prevalence, different foods are responsible for OAS in different locations. In a study of 274 adults in England who were allergic to at least one pollen (birch, grass, and/or mugwort), 34% were sensitive to apple, 25% to potato, 23% to carrot, 23% to celery, 22% to peach, and 16% to melon [9]. In contrast, OAS was most commonly due to hazelnut, kiwi, apple (Golden

Delicious), and celery root in Italy [8]. Pollen-allergic adults in Sweden most often reported symptoms with hazelnut, apple, tomato, carrot, and peanut [12]. In Spain, peach is the most common fruit which causes allergy [13].

Regional differences also exist in the patterns of associations. Patients with allergy to apple, but not birch, have not been reported in northern and middle Europe, but are usually seen in Spain [14]. In Spain, Rosaceae fruit allergy is instead associated with grass allergy [15]. Different patterns of kiwi allergen recognition are evident in different parts of Europe as well [16]. Kiwi is associated with grass pollen allergy in Italy, but with birch pollen allergy in Spain [11]. New sensitizations have also been reported when people are exposed to new environments. Two patients who tolerated jackfruit in the Philippines, a birch-free environment, reportedly reacted to jackfruit when they were sensitized to birch in Switzerland [17]. This highlights the role of regional exposures on the development of cross-sensitization.

Clinical features

OAS is an IgE-mediated allergy that is generally mild. It is a contact allergy resulting in local symptoms such as lip/mouth pruritus, swelling, hoarseness, papulae, and in rare cases, blisters [14]. The onset of symptoms is rapid, with most symptoms appearing within 5 minutes of exposure to the food [18]. However, symptoms may be delayed, appearing after 30 minutes in 7% of cases [18]. The degree of clinical reactivity has seasonal variations; birch pollen-allergic individuals were shown to have higher symptom scores to apple during the birch pollen season [19]. This may be due to upregulation of birch pollen allergens (Bet v 1 and 2) in pollen during maturation [20].

Symptoms can occur outside the oropharynx as well (Table 11.1). In a study of 706 patients with plant food allergy, 13.6% had extra-oral gastrointestinal symptoms, 13.9% reported laryngeal edema, and 2.1% of individuals experienced

anaphylaxis [21]. However, only 71% of these patients had evidence of allergic rhinitis, as this study selected for patients with plant food allergy, not OAS. Since symptoms can extend beyond the oropharyngeal area and symptoms are elicited from cross-reactive proteins between pollens and foods, the more inclusive term pollen–food syndrome (PFS) may be more appropriate.

Molecular basis/pathogenesis

IgE-mediated food allergies can be classified according to the route of sensitization [22]. Class I allergy is due to sensitization via the gastrointestinal tract, whereas class II allergy indicates that the primary allergic sensitization is to inhalant allergens. Class I allergy often presents in childhood, while class II allergy is more commonly observed in adults. Complete food allergens, which have the ability to both sensitize and elicit symptoms, induce class I allergy. In contrast, class II allergy is a result of incomplete food allergens, which cannot cause sensitization, but can elicit symptoms because of cross-reactivity to the homologous sensitizer [23]. PFS is classified as class II allergy, since the pollen allergens are the sensitizers and homologous proteins in plant-derived foods elicit symptoms. These food allergens are generally heat labile and susceptible to gastric digestion, thus inducing symptoms limited to the oropharynx.

There are several hypotheses explaining the localized symptoms present in PFS. Amlot *et al.* proposed that the local oral symptoms occur because there is a high concentration of mast cells in oropharyngeal mucosa [5]. Local symptoms may also be due to a high concentration of allergens in the oral mucosa that are rapidly released when in contact with saliva [14]. Alternatively, high concentrations of T-cells in the oropharyngeal lymphoid tissue can have food-specific T-cell responses since cross-reactivity has been found at the T-cell level [24,25].

Allergens

A variety of plant proteins have been identified to play a role in food allergy. These include pathogenesis-related (PR) proteins, proteinase and α -amylase inhibitors, peroxidases, profilins, seed storage proteins, thiol proteases, and lectins [26]. Many of these are distributed throughout the plant kingdom, accounting for the extensive IgE cross-reactivity between taxonomically unrelated plant foods.

Several plant allergens belong to the PR protein family. These are plant defense proteins that are expressed in response to stress from the environment, chemicals, or infection [27]. IgE to the major birch pollen, Bet v 1, cross-reacts with homologous plant food allergens belonging to the PR-10 protein family. Symptoms are often mild, due to the heat lability of these Bet v 1-related proteins [28,29]. The most common fruits causing symptoms in Bet v 1-allergic

Table 11.1 Symptoms of pollen–food syndrome

<i>Oropharyngeal</i>
Lip/mouth swelling
Lip/mouth pruritus
Hoarseness
Papulae
Laryngeal edema
<i>Systemic</i>
Cutaneous – urticaria/angioedema, atopic dermatitis flare
Rhinitis
Conjunctivitis
Wheezing
Gastrointestinal symptoms – abdominal pain/cramps, nausea, vomiting, diarrhea
Anaphylaxis

individuals include members of the order Rosaceae, such as apple, pear, cherry, and apricot (Table 11.2). Homologous proteins are also found in celery, carrot, hazelnut, soy, and peanut.

Profilin is another family of allergens involved in many cross-reactivities between pollens and plant foods (Table 11.2) [22]. They are small (12–15 kDa) proteins that bind actin and have an important role regulating the cytoskeleton. Profilins also are sensitive to heat and gastric digestion [30]. The first profilin identified was a minor birch pollen protein, Bet v 2 [31]. Patients with pollinosis and plant food allergy have a high frequency of IgE reactivity to Bet v 2. Patients sensitized to Bet v 2 also had reactivity to latex, grass, olive tree, and mugwort pollens, suggesting that reactivity to Bet v 2 may be a marker for broad aeroallergen sensitization [32]. Wensing *et al.* [33] similarly reported that profilin is responsible for a broader spectrum of cross-reactivity than Bet v 1. The authors found that those sensitized to both Bet v 1 and profilin had significantly more

specific IgE to foods than those sensitized only to Bet v 1. However, this broad sensitization was not always correlated with clinical reactivity. Therefore, the clinical role for profilin remains unclear, since sensitization to profilin is rarely associated with clinical symptoms [34].

A group of high molecular weight allergens (45–60 kDa) has recently been identified in various pollen and foods [35]. These are highly cross-reactive IgE-binding structures, and have been named cross-reactive carbohydrate determinants (CCDs) [35]. They are ubiquitous in pollen and plant-derived foods and have also been identified in hymenoptera venom [35]. Thirty to forty percent of pollen-allergic individuals have evidence of IgE against CCDs. CCDs exhibit broad *in vitro* cross-reactivity [36] and are heat stable [37]. Their immunological activity was demonstrated by Foetisch *et al.* [38] who showed that the tomato glycoprotein, β -fructofuranosidase, could induce histamine release when basophils were sensitized by serum from tomato-allergic patients. However, the role of CCDs in PFS remains uncertain as the *in vivo* relevance has not been demonstrated.

Table 11.2 List of allergens mentioned in this chapter (scientific names in parenthesis)

Bet v 1 homologs

Apple (Mal d 1)
Apricot (Pru ar 1)
Carrot (Dau c 1)
Celery (Api g 1)
Cherry (Pru av 1)
Hazelnut (Cor a 1.04)
Jackfruit (Art i)
Peanut (Ara h 8)
Pear (Pyr c 1)
Soy (Gly m 4) (starvation-associated message 22)
Strawberry (Fra a 1)

Profilin

Almond (Pru du 4)
Apple (Mal d 4)
Banana (Mus xp 1)
Bell pepper (Cap a 2)
Birch (Bet v 2)
Carrot (Dau c 4)
Celery (Api g 4)
Hazelnut (Cor a 2)
Latex (Hev b 8)
Melon (Cuc m 2)
Mugwort (Art v 4)
Peach (Pru p 4)
Ragweed (Amb a 8)
Soy (Gly m 3)
Strawberry (Fra a 4)
Timothy grass (Phl p 12)
Tomato (Lyc e 1)

Adapted from the International Union of Immunological Societies (IUIS) List of Allergens. A complete list can be found at www.allergen.org.

Pollen–food syndromes

Birch–fruit–vegetable syndrome

Foods belonging to the order Rosaceae, which include apple, pear, peach, and almond, most commonly cause symptoms in birch-allergic patients. Bet v 1, the major birch tree allergen, accounts for most of this cross-reactivity [39]. The prevalence birch–fruit syndrome is variable depending on geographic location. A US study reported that 75.9% of birch pollen-allergic patients had clinical symptoms with apple [40]. Lower rates have been reported in Europe, with 34% of birch pollen patients in Denmark reporting symptoms to apple [3], and 9% of birch pollen patients in Italy having symptoms following ingestion of apple [8].

The primary sensitization in birch–fruit syndrome is to birch pollen, and the symptoms elicited by foods is a secondary phenomenon [20]. A Bet v 1 homolog was identified in apple in 1991 (Mal d 1) [40]. Other Bet v 1 homologs have subsequently been identified in various fruits and vegetables, including celery, pear, carrot, apricot, cherry, and hazelnut (Table 11.2) [26]. There is a high degree of homology between Bet v 1 and the plant food allergens. Bet v 1 and Mal d 1 share 64.5% sequence homology [14], and Cor a 1 (hazelnut) is 72% homologous with Bet v 1 [28]. Bet v 1-related proteins have also been identified in peanut [29] and soy [41].

Celery–birch–mugwort–spice syndrome

Celery has been found to have cross-reactivity with both birch and mugwort pollens. In areas where birch trees are prevalent, celery allergy is due to Bet v 1 homologs. However, celery allergy does exist in birch-free areas; in these cases, mugwort pollen allergens may be the primary

sensitizer [22]. Wuthrich *et al.* [42] reported that patients with celery–birch allergy had negative or low specific IgE to cooked and uncooked celery. In contrast, patients with celery–mugwort association had positive IgE to cooked and uncooked celery, suggesting that different allergens are involved in these two associations. Similarly, Hoffmann-Sommergruber *et al.* [43] examined two groups of celery-allergic individuals from two different geographic locations, one from Switzerland (birch trees present) and one from southern France (birch free). The authors found that in Switzerland, all the patients had positive skin testing to birch and commercial celery extract. In contrast, only 25% of patients in southern France had positive skin testing to birch pollen and commercial celery extract, but all had sensitization to mugwort pollen. Immunoblots from these patients revealed IgE against high molecular weight proteins in the range of 28–69kDa and two had IgE reactivity to a 12–13kDa protein, suggesting that CCDs and profilin may be playing a role, rather than Bet v 1 homologs.

Bet v 1 and profilins have also been identified in various spices, including anise (Pim a 1 and 2), coriander (Cor s 1 and 2), cumin (Cum c 1 and 2), fennel (Foe v 1 and 2), and parsley (Pet c 1 and 2) [44]. Cross-reactivity between mugwort and mustard has been demonstrated recently [45]. Thus, the term celery–birch–mugwort–spice syndrome has been used to describe these cross-reactivities.

Ragweed–melon–banana association

Up to 50% of ragweed-allergic patients have specific IgE to at least one member of the gourd family (Cucurbitaceae, e.g. watermelon, cantaloupe, honeydew, zucchini, cucumber) [46]. In fact, this association was the first report linking pollen and fruit allergy [2]. Melon allergy occurs mainly in association with pollinosis, even in ragweed-free locations [47].

Profilin has been identified in both melon [22] and banana [48]. Melon profilin is highly susceptible to pepsin digestion [49], and therefore melon allergy usually causes oropharyngeal symptoms. However, one study reported that almost 20% of melon-allergic individuals experienced symptoms outside the mouth [50], and in another study, 11% had anaphylaxis [51], suggesting that other more stable allergens such as lipid-transfer proteins (LTPs) may be involved as well. It has also been reported that pollen-allergic patients with melon allergy have higher rates of asthma than pollen-allergic individuals without melon allergy [50].

Other associations

PFS are becoming more complex as new associations are being described. Additional associations include mugwort–peach association, plantain–melon association, pellitory–pistachio association, goosefoot–fruit association, and Russian thistle–saffron association. With this continually expanding knowledge, allergen-based classification has been proposed as a more appropriate categorization [22].

Other cross-reactivity associations

Latex–fruit syndrome

The first report of an allergic reaction to banana in a latex-allergic patient was published in 1991 [52]. Soon thereafter, cross-reactivity between latex and various fruits was demonstrated, and this was termed latex–fruit syndrome [53]. Significant cross-reactivity between the latex and fruit allergens was demonstrated by Blanco *et al.* [53] who reported that 13 of 25 patients (52%) with latex allergy had specific IgE (prick skin test or *in vitro* test) to fruits. Similar studies have reported up to 88% of latex-allergic adults have evidence of specific IgE to plant-derived foods [54,55]. Although there is a high degree of immunological cross-reactivity between the latex and fruit allergens, the clinical significance appears to be much lower. A study from Germany of 136 latex-allergic patients showed that although 69% had specific IgE to fruits, only 32% had clinical symptoms [56]. Similarly, among melon-allergic patients, 68% had detectable latex-specific IgE, but only 26% were clinically reactive [51].

The primary sensitization is believed to be due to latex, generally via inhalation. In a study of children with atopic dermatitis, all of the children who had latex-specific IgE also had IgE to various foods, mostly potato, tomato, sweet pepper, and avocado [57]. However, none of the children with elevated IgE to avocado, chestnut, and kiwi ever had exposure to these foods.

Several latex allergens have been implicated in the latex–fruit syndrome (Table 11.3). Class I chitinases (Hev b 11) belonging to the PR-3 protein family have been identified in chestnut, avocado, and banana [58]. The *N*-terminal region of Hev b 11 is related to hevein (Hev b 6.02), which is an important latex allergen that has several cross-reactive epitopes.

Table 11.3 Latex allergens involved in latex–fruit syndrome and the plant foods that have homologous proteins

<i>Hev b 2</i> (β -1,3-glucanase)
Bell pepper
<i>Hev b 11</i> (class I chitinase)
Avocado (Prs a 1)
Banana
Cherimoya
Chestnut (Cas s 1)
Kiwi
Mango
Papaya
Passion fruit
Tomato
<i>Hev b 8</i> (profilin)
Banana
Bell pepper
Celery
Pineapple

Low-level inhibition of IgE binding to hevein, a major latex allergen, can be demonstrated with class I chitinases from several fruits [59], suggesting that these two allergens share some IgE-binding epitopes. In fact, Hev b 11 and hevein share 58% sequence identity at the chitin-binding domain [59]. Another major latex allergen, Hev b 2 (β -1,3-glucanase, PR-2 protein family), is also involved in the latex–fruit syndrome and has been identified in bell peppers [60]. Furthermore, Hev b 8 (profilin), a minor latex allergen, has been demonstrated to have cross-reactivity with some fruits [61]. Thus, many latex allergens may contribute to food allergies in latex-sensitive individuals.

Individuals with latex–fruit syndrome can experience more generalized symptoms in addition to oral symptoms, distinguishing this from OAS [62]. These more severe symptoms may be due to the stability of some latex allergens. Hevein has been demonstrated to be stable in simulated gastric fluid [23]. In addition, although class I chitinase in avocado is extensively degraded in simulated gastric fluid, the peptides have been shown to retain their IgE-binding epitopes, and can induce positive skin test results [63].

Differences have been observed between patients allergic to latex (without fruit allergy) and those with allergy to both latex and fruit. Blanco *et al.* [58] showed that chestnut and avocado class I chitinases were able to induce positive prick skin test responses in more than 60% of patients with latex–fruit allergy, but did not result in positive tests in control subjects who were latex, but not fruit allergic. Pooled serum from latex-allergic and not fruit-allergic individuals also do not detect class I chitinases in several fruit extracts [58]. In addition, different human leukocyte antigen (HLA) associations have been identified for those with latex–fruit syndrome as compared to those with only latex allergy, suggesting a genetic basis for the latex–fruit syndrome [64].

Lipid-transfer protein syndrome

Approximately 15–20% of patients with allergies to fruits and/or vegetables have no reported symptoms of allergic rhinitis and negative skin tests to pollens [18,65]. In fact, up to 20% of peach allergy is not associated with pollinosis [13]. Since sensitization is found in patients who do not have pollinosis, this suggests that the primary sensitization in this group may occur via the gastrointestinal tract (class I allergy) [17,66].

Individuals with allergies to plant-derived foods without associated pollinosis were found to have several features distinguishing them from those with OAS-associated pollinosis [15]. In a study comparing the two groups, individuals without pollinosis had significantly more systemic symptoms (82% versus 45%), including anaphylaxis (73% versus 18%) and had fewer oral symptoms (64% versus 91%) when compared to those with pollinosis. Individuals without pollinosis were older at the onset of symptoms to fruits and vegetables (19 years of age versus ~12 years). In

addition, those without pollinosis mainly reacted to fruits in the order Rosaceae whereas those with pollinosis had more diverse sensitizations to different families of fruits and had reactions to a greater number of foods in general. Although the non-pollen-allergic group is more likely to have systemic reactions, those with pollinosis appear to have a higher risk of asthma [22].

LTPs, belonging to the PR-14 family [66], have been identified as major allergens involved in non-pollinosis plant food allergies; the term LTP syndrome has since been used to describe these patients. LTPs comprise a family of polypeptides that have the ability to transfer phospholipids from liposomes to mitochondria and are found throughout the plant kingdom [22]. They are defense proteins upregulated by some plants in response to fungal infection [67].

They were first identified as the major allergen in peach as well as an allergen for apple in 1999 [68,69], and have since been discovered in other related foods, including apricot [70], plum [71], and cherry (Table 11.4) [72]. LTPs have also been identified in various unrelated plant products such as corn, asparagus, grape, lettuce, sunflower seeds, latex, and mugwort [17,73].

A recent study reported that apple allergy in Spain (birch-free area) is more severe (>35% systemic reactions) than apple allergy in other locations, and the major allergen in these cases has been identified as Mal d 3, a LTP [74]. The authors proposed that apple allergy in Spain is a result of cross-reactivity with peach proteins rather than with birch pollen proteins because peach is introduced in early childhood in that country and consumed in large quantities. Peach allergy develops at a younger age than apple allergy; therefore, the primary sensitization is likely to peach LTP, Pru p 3. This is consistent with the hypothesis that LTP syndrome is a class I allergy.

The reactions that occur with LTP syndrome are more systemic, and are likely due to the stability of LTPs in acidic and proteolytic conditions of the gastrointestinal tract [75] as well

Table 11.4 LTPs found in plant foods and pollens

Asparagus (Aspa o 1)
Apple (Mal d 3)
Apricot (Pru ar 3)
Cherry (Pru av 3)
Grape (Vit v 1)
Hazelnut (Cor a 8)
Lettuce (Lac s 1)
Maize, corn (Zea m 14)
Mugwort (Art v 3)
Parietaria (Par j 1 and 2)
Peach (Pru p 3)
Strawberry (Fra a 3)
Tomato (Lyc e 3)
Walnut (Jug r 3)

as their resistance to heating [28,37]. For example, celery-allergic patients have been shown to have positive food challenges to cooked celery under double-blind, placebo-controlled conditions [37]. The heat resistance of LTP has also been demonstrated for hazelnut, maize, and cherry [28,66,76]. Thus, commercial foods that have been thermally processed may still cause symptoms in some sensitized individuals.

Recent reports have indicated that LTPs may sensitize via the inhalation route as well, thus suggesting that LTP syndrome may be a class II allergy in some cases. Lombardero *et al.* [77] demonstrated that in some mugwort-allergic individuals, mugwort LTP (Art v 3) is the primary sensitizing agent since these patients were sensitized to Art v 3, but demonstrated no sensitization to Pru p 3 (peach LTP). In a subset of these patients, Art v 3 was able to partially inhibit IgE binding to Pru p 3; however, Pru p 3 was not able to inhibit IgE binding to Art v 3, suggesting that Art v 3 was the primary allergen.

Diagnosis

The primary diagnostic tools for food allergy are prick skin tests and serum-specific IgE levels. However, these tests are not very reliable for the diagnosis of PFS. The results may be variable depending on which food is being tested since there can be a great deal of cross-reactivity between allergens that have common epitopes in different foods.

Skin tests and *in vitro* tests are poor predictors of clinical reactivity. Skin tests rely on extracts that may not contain all of the relevant allergens. Some plant food allergens are heat labile [28,29] and lose potency, and thus sensitivity, during processing of the extracts. Proteases from the fruits themselves can play a role in allergen degradation, as has been demonstrated for pineapple. The pineapple protease bromelain destroys pineapple profilin in extracts prepared without protease inhibitor [61]. In addition, low yield of protein for extracts has been a problem for some exotic fruits [61].

Skin testing with fresh fruits and vegetables is generally a better predictor of clinical reactivity when compared to commercial extracts, but this type of testing is not standardized [78,79]. A study by Anhoej *et al.* [80] showed that the negative predictive value for skin testing with fresh hazelnut, apple, and melon was greater than 90%. The positive predictive value was more variable, ranging from 50% to 85%. Sensitivity was high for all three (89–97%) and the specificities were greater than 70%. Of note, ripeness of the plant food can affect the sensitivity of *in vivo* tests, since allergenicity has been demonstrated to increase with ripening in banana [81] and peach [82]. Additionally, differences in storage and different cultivars (e.g. Golden Delicious apples, Granny Smith apples) can lead to variations in allergenicity [83,84]. Apples in prolonged cold storage under controlled atmosphere conditions are less allergenic than apples stored at 2°C in normal air, and Golden Delicious apples are generally more allergenic than Santana apples [83].

Skin and *in vitro* testing can indicate allergic sensitization, but positive results do not always correlate with clinical reactivity. Therefore, double-blind, placebo-controlled food challenge remains the gold standard for the diagnosis of food allergy. However, there are no standardized protocols for oral food challenges for PFS, and issues such as adequate blinding of fresh foods are a concern.

Management

There are currently no consensus guidelines for the management of PFS. A survey of allergists revealed that there is tremendous variation in management strategies used [85]. These authors suggest that this may be due, in part, to the imprecise definition of PFS and lack of accurate and standardized diagnostic tests.

Recommendations range from avoidance of only the offending fruits or vegetables to eliminating the entire botanical family. Allergy to one food, however, does not necessarily indicate allergy to all members of the botanical family. For example, 63% of peach-allergic individuals react to more than one Prunoideae fruit [86], and 46% have clinical cross-reactivity with other Rosaceae fruits [87]. A study of 65 adults in Madrid with PFS revealed that only 8% of the positive *in vivo* and *in vitro* tests for cross-reacting foods resulted in positive food challenges [88]. This supports the recommendation not to eliminate entire families of cross-reactive foods, which would be unnecessarily restrictive. However, the authors noted that in this series, patients reacted to an additional 18 allergens, which were previously unknown to the patients and were detected only because of further testing and food challenges. Therefore, they suggest that oral challenges be performed to related foods that the patients have not eaten since the most recent allergic reaction in order to rule out other sensitivities to related foods.

Allergenicity can vary between different cultivars of fruits (Table 11.5). For example, Golden Delicious and Gala apples are highly allergenic, whereas Santana apples have been found to have low allergenicity [83]. Therefore, it may be possible that some individuals can tolerate lower allergenic cultivars. In addition, this information may be useful in breeding novel, lower allergenic cultivars. Allergen distribution within the fruit has also been investigated. Mal d 1 (Bet v 1 homolog) is present in both the peel and pulp of

Table 11.5 Allergenicity of different apple cultivars

Golden Delicious, Jonagold, Gala – high allergenic
Elstar, Fuji, Granny Smith – moderate allergenic
Santana, Elize, Braeburn – low allergenic

Ranking from nine Dutch patients (northern Europe) – based on prick-prick testing and double-blind, placebo-controlled food challenges. (Adapted from Bolhaar ST *et al.* [83].)

apples, however, Mal d 3 (LTP) is most abundant in peel. This suggests that some patients may be able to tolerate certain parts of each fruit.

For individuals with PFS due to heat-labile proteins, such as Bet v 1 homologs, cooked versions of the fruits and vegetables can denature the relevant proteins, thus allowing symptom-free consumption. Anecdotal evidence has suggested that briefly heating apples (e.g. by microwaving) may be sufficient to denature Mal d 1 allergens, without compromising the integrity of the fruit, however, this has not been investigated by controlled studies.

Risk factors for systemic reactions to plant-derived foods include a history of systemic reactions to the food, reactions to cooked forms of the food [37,66], positive skin test results to the food extract [89], lack of pollen sensitization [15], and peach allergy/LTP syndrome (Table 11.6) [68]. Therefore, self-injectable epinephrine should be prescribed for such individuals, and patients should be educated on the management of severe reactions.

In addition, physicians should be aware of whether their patients use antihistamines. This may mask mild symptoms, prompting increased consumption of the triggering foods, which may lead to more severe systemic symptoms. This may be a concern for patients who are already taking allergy medications for their allergic rhinitis symptoms [90].

Future directions

More research is needed to characterize the various allergens and clinical cross-reactivity syndromes. An alternative classification of associations based on the major allergens, rather than botanical relationships has been suggested, and this may facilitate the identification of individuals for different forms of therapy [91]. This classification would also encompass the other cross-reactivity syndromes, including latex–fruit allergy and LTP syndrome.

It would also be helpful to understand why individuals are increasingly experiencing these cross-reactivity syndromes. Since many of the allergens are PR proteins and are induced when plants undergo stress, it is possible that pollution and chemicals may be inducing novel proteins (PR family) or upregulating allergenic proteins [62]. Breeding and genetic modification of plants may also lead to the development of novel allergens, potentially contributing to the recent increase in prevalence of affected individuals.

Table 11.6 Risk factors for severe symptoms of cross-reactivity syndromes

- History of systemic reaction to the food.
- Reaction to cooked forms of the food [37,66].
- Positive skin test result to the food extract [89].
- Lack of pollen sensitization [15].
- Peach allergy/LTP syndrome [68].

Immunotherapy

Immunotherapy is an effective treatment for allergic rhinitis. Since pollen–fruit syndrome is, in many cases, due to cross-reactivity with pollens, immunotherapy would seem to be a logical treatment for PFS. A study of birch immunotherapy for apple allergy in adults found a reduction of oral symptoms in 11/14 and decreased skin test sizes in 12/14, but an increase in apple-specific IgE was observed in 6/14 [92]. This study was limited by the self-reported symptoms and lack of placebo controls. Another study of birch subcutaneous immunotherapy (SCIT) found decreased symptoms (based on double-blind, placebo-controlled food challenges) and skin test sizes in the treated group, but there was no placebo SCIT group for comparison [93]. Instead, the comparison was made with a group of patients who used medication for symptomatic treatment. A case report of a patient with improved oral symptoms to fennel, cucumber, and melon after 3.5 years of SCIT with grass, mugwort, and ragweed has also been reported [94].

In contrast, several studies have not shown similar efficacy of immunotherapy for PFS. Bucher *et al.* [95] placed 15 adults on SCIT for birch to treat PFS to apple and hazelnut. Open challenges were performed before and after SCIT. The authors found limited benefit of immunotherapy with birch for PFS. Similarly, another study found no benefit of subcutaneous and sublingual immunotherapy to birch for PFS to apple [96]. A pediatric study from Sweden indicated no beneficial effect of birch SCIT or oral immunotherapy for food-allergic symptoms [97]. In addition to difficulties in objective evaluations for improvement in symptoms, there is no consensus for target doses and thus immunotherapy remains an unproven therapeutic approach for PFS.

Purified or recombinant allergens

Improved diagnostic tools may facilitate diagnosis and management of PFS. Purified or recombinant allergens are being developed for several foods and have shown potential. Pauli *et al.* [34] found that individuals with PFS to cherry, apple, or hazelnut reacted to recombinant Bet v 1 (rBet v 1), thus concluding that rBet v 1 is specific for birch and Rosaceae allergy. Mittag *et al.* [41] showed that 45% of 22 patients with pollen–soy allergy had IgE to soy extract, but 96% were positive to the recombinant allergen, rGly m 4, a Bet v 1-related protein. In a study of peanut and birch-allergic patients, 17 of 20 had specific IgE to recombinant Ara h 8 (Bet v 1 homolog) [29]. Interestingly, six of these did not have detectable IgE to the major peanut allergens, Ara h 1–3. The development of new recombinant allergens may thus help standardize the diagnosis of PFS.

T-cell cross-reactivity

PR-10 proteins have been shown to have cross-reactivity at the T-cell level [24,25]. Reekers *et al.* [98] reported that some patients with hypersensitivity to birch pollen and

atopic dermatitis developed worsening of their eczema after oral challenge with birch pollen-related foods. The authors also found birch pollen-specific T-cell responses in the eczematous skin of these patients. The C-terminal end of Bet v 1 (142–156) has been identified as an immunodominant T-cell epitope in many patients with birch–fruit–vegetable syndrome [99]. Bet v 1 (142–156)-specific T-cell clones cross-reacted with Rosaceae fruit allergens in apple and cherry, but less cross-reactivity occurred with vegetables of the Apiaceae family, celery and carrot. Interestingly, celery and carrot allergens were more potent activators of the T-cell clones than apple and peach allergens.

A recent study showed that in patients who have birch allergy and atopic dermatitis, worsening of skin lesions without oral symptoms can be observed when eating cooked fruits and vegetables (i.e. apple, carrot, and celery) [100]. These authors suggest that eating birch related fruits and vegetables outside the birch season can lead to pollen-specific T-cell activation (high IL-4 and thus elevated IgE) and maintenance of the allergic immune response perennially. This raises the question of whether patients should continue to consume the related plant food products outside of the pollen season despite lack of immediate symptoms.

Conclusions

The term oral allergy syndrome was first coined in 1987 [5], but has since evolved to encompass a larger family of cross-reactivity syndromes, including pollen–fruit syndromes, latex–fruit syndrome, and LTP syndrome. The literature on this topic has suffered from an evolving definition and a lack of reliable diagnostic tools. The common unifier to these cross-reactivity syndromes is the presence of a plant-derived food allergy, which can often be attributed to homologous plant proteins. Cross-reactivity syndromes will pose an ongoing challenge as allergens are continually being identified in plant foods and demonstrate regional variability. Finally, effective treatments have yet to be identified as immunotherapy remain unproven.

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