



Can patients with oral allergy syndrome be at risk of anaphylaxis?

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Purpose of review

Oral allergy syndrome, also known as pollen-food syndrome (PFS), is a condition usually associated with adults and characterized by mild transient oropharyngeal symptoms. The purpose of this review is to determine whether systemic or anaphylactic reactions do occur and if so, who is affected and what are the triggers.

Recent findings

An increasing number of studies demonstrate that PFS occurs all age groups, and a significant number of affected adults do experience systemic and anaphylactic reactions. The upsurge in the adoption of vegan lifestyles, increase in consumption of fruits and vegetables including smoothies and juices, and use of plant foods in nutritional or body-building supplements, could exacerbate this. Changes in pollen and pollution levels, cofactors and sensitization to other plant food allergens may also be involved.

Summary

While the majority of those with PFS will continue to experience mild symptoms, all individuals should be properly advised regarding the dangers of concentrated or unusual forms of plant food allergens such as smoothies, juices, soy/nut milks and nutritional supplements. Further well characterized studies are needed to determine risk factors for severe reactions, and sensitization patterns to pollens and plant food allergens.

Keywords

anaphylaxis, fruits, oral allergy syndrome, pollen, vegetables

INTRODUCTION

Oral allergy syndrome, also known as pollen-food syndrome (PFS) is probably the most common manifestation of cross-reactive food allergy [1]. Those with PFS experience allergic symptoms to fruits, vegetables and nuts linked to pollen sensitization, although other forms of plant cross-reactivity such as latex-food allergy and reactions to nonspecific lipid transfer proteins (nsLTP) have sometimes been included in the PFS family [2^{••}]. The vast majority of studies or reviews of PFS have led to the characterization of PFS as a condition which is generally mild to moderate, with anaphylaxis thought to be rare [3]. However, more recent studies appear to show increasing levels of anaphylaxis to plant foods. This might be linked to changes in diet and lifestyle or increasing levels of sensitization to pollens and plant food allergens. This review will describe the presentation of PFS, the evidence that PFS reactions can be severe, the risks associated with some individual foods, the effect of processing on severity of reactions and whether other factors such as cofactors, medications or other modulating effects can

enhance the likelihood of a more severe reaction in those with PFS.

ALLERGENS INVOLVED IN POLLEN-FOOD SYNDROME

In the early 1990s, the apple allergen Mal d 1 was characterized and demonstrated to have 67.6% identity to Bet v 1, the major allergen of *Betula verrucosa* (birch) pollen [4,5]. A new hierarchy of plant food allergens demonstrated the high level of sequence identity between Bet v 1, and allergens classified as pathogenesis-related 10 (PR10) proteins and present in many different edible plants [6].

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KEY POINTS

- Anaphylactic reactions can occur in people with a diagnosis of oral allergy syndrome, also known as PFS, with up to 10% of adults possibly experiencing systemic reactions.
- Consuming concentrated forms of plant foods such as juices, smoothies, soy/nut milk and soy-based body building powders could increase the likelihood of more severe reactions in those with diagnosed PFS.
- Advice should be given about the consumption of so-called super foods or nutraceutical products, based on plant foods which might cross-react with pollens.
- Changes in atmospheric conditions, leading to increased pollen counts and a rise in ozone levels, could lead to longer pollen seasons and precipitate more severe reactions to foods in those with PFS.
- The correct diagnosis of PFS is essential to confirm that the reaction to the plant food is not due to another plant food allergen such as a nonspecific lipid transfer protein, and ensure the appropriate medical and dietary management is provided.

Another class of allergens, the profilins, are also involved in plant food cross-reactions; thus, sensitization to the profilin allergens in *Phleum pratense* (grass), *Artemisia vulgaris* (mugwort) and *Ambrosia artemisiifolia* (ragweed) could also cause PFS symptoms to a wide range of foods [7–9]. Recent studies have demonstrated that this cross-reactivity provides markers of for the likely development of PFS in children. Cipriani *et al.* [10[•]] reviewed the results from 1120 children and reported that sensitization to the grass pollen profilin Phl p 12, was a reliable biomarker of PFS. A follow-up study of 401 children (10.4 ± 3.4 years) at baseline and 6 years later (16.2 ± 3.6 years) and reported Bet v 1 to be the best marker of persistence of PFS [11[•]].

Both PR10 proteins and profilins are generally thermolabile in nature and susceptible to digestion by proteases, although studies have demonstrated that not all T-cell epitopes are destroyed during digestion and cooked food allergens could provoke T-cell-mediated late-phase reactions [12]. This was demonstrated clinically in a study by Wassmann-Otto *et al.* [13] who undertook double-blind oral food challenges in 182 children and adults with PFS and atopic dermatitis, 36% of whom were positive, with just under half of these also experiencing objective worsening of their atopic dermatitis symptoms. In a more recent study of 186 Korean children with atopic dermatitis and allergic rhinitis, 43.5% were diagnosed with PFS, and the predominant

symptom was skin itching and rash, especially in the younger age groups [14].

Reactions to fruits and vegetables, can also involve other plant food allergens such as nsLTP proteins, which unlike PR10 and profilin allergens are stable due to their compact folded structure [15]. It is considered that sensitization and reactions to nsLTP in foods may come about not only through exposure to nsLTP allergens in foods, but possibly also because of sensitization to pollens such as *A. vulgaris* and *Platanus acerifolia* [16,17,18[•]]. Other plant food allergens include thaumatin-like proteins most recently identified in tomato and wine [19[•],20[•]]. Also, another plant food allergen, gibberellin-regulated protein or peamaclein, has been identified as the causative allergen in 13/100 patients with reactions to peaches [21].

POLLEN-FOOD SYNDROME SYMPTOM TYPE AND SEVERITY

Pollen-related food allergy has highly characteristic symptoms and speed of onset, with symptoms typically appearing 5–10 min after eating, and frequently resolving within 30 min of onset, often without recourse to medications [3,22]. These symptoms are usually localized in the oropharynx and can involve paraesthesia of the lip or tongue, labial, pharyngeal, gingival and palatal pruritis, ear itching, rhinoconjunctivitis and occasionally laryngeal tightness [2^{••}]. More severe symptoms such as anaphylaxis are considered to be rare in those with PFS; a 2019 review of PFS reported that 1.7% of those with PFS are likely to suffer from anaphylaxis, this figure being derived from a 2005 questionnaire survey of 226 US allergists by Ma *et al.* [23[•],24].

More recent data confirms severe reactions to plant foods may be more prevalent than previously suggested. Cho *et al.* [25^{••}], who reviewed 1021 cases of anaphylaxis in Korean children and adults, reported that fruits and vegetables, key triggers of PFS, caused anaphylaxis in 19% of children and 12% of adults. Utilizing clinical data and allergy test results, Kim *et al.* [26] reported that of the 270 patients with PFS, 8.9% were considered to have experienced anaphylaxis. Another article from the same study reported that sensitization to hazel, grass or ragweed, the number of culprit foods and the presence of atopic dermatitis were all potential risk factors for the development of anaphylaxis in those with PFS [27^{••}]. A study on PFS in Turkish adults stated that 49/254 pollen sensitized patients had self-reported PFS, 10% of whom experienced systemic symptoms including one with anaphylaxis [28]. Regarding children, Guvenir *et al.* [29[•]] reported that 22/672 children sensitized to pollen

were diagnosed with PFS, and mainly reported isolated oropharyngeal symptoms, although two subjects (9%) did experience anaphylaxis. Studies on PFS involving oral food challenges have reported severe symptoms due to both PR10 allergens and profilins [30,31].

Anaphylaxis to plant foods may also be due to other plant food allergens such as nsLTP, although many with sensitization and clinical symptoms to nsLTP experience oropharyngeal symptoms comparable with those of PFS [32,33]. However, the speed of onset may be different; a study comparing subjects with PFS to those sensitized and symptomatic to nsLTP allergens reported that a significantly larger proportion of those with PFS experienced symptoms when the trigger food touched the lips or when biting and chewing it, and they were also more likely to recover within an hour [34].

DIETARY FACTORS WHICH AFFECT SYMPTOM SEVERITY IN POLLEN-FOOD SYNDROME

The triggers of PFS are key constituents of a healthy diet, being protective against hypertension, metabolic syndrome, diabetes [35,36,37]. The very important promotion of fruits and vegetables has resulted in an increase in their consumption across many different countries [38]. This includes a rise in popularity of fruit smoothies and fresh fruit/vegetable juices, which have been linked to adverse effects on both the kidneys and the teeth [39,40]. These concentrated forms of unheated fruits and vegetables also have the potential to provoke much more severe reactions than would occur from eating the fruit in its natural state. The same is true for tree nuts, with handfuls of raw nuts anecdotally provoking very severe reactions of the oropharynx, whereas processed hazelnuts and almonds rarely provoke more than mild transient reactions [41]. Nut milks are also becoming increasingly commonly consumed but there is currently no published evidence to determine whether they are causing an increase in more severe reactions in those with PFS.

Superfoods, nutrient-rich plant foods considered to be especially beneficial for health and well being, have also been demonstrated to be causes of anaphylaxis [42]. Martini *et al.* [43] published a case report on a case of anaphylaxis following the consumption of a vegan snack bar containing baobab, a plant heavily promoted as having health-giving properties. A recent review of severe reactions to mulberries suggested that due to their increasing use in dietary supplements or nutraceuticals, it was important to consider them as the cause of reactions in those sensitized to birch, parietaria or olive

pollen, due to close homology between the species [44]. Takaoka *et al.* [45] evaluated 15 patients who had local or systemic reactions to loquat and concluded that these reactions were caused by a Bet v 1 homologue with a sequence similar to that of the apple PR10 allergen Mal d 1, but with a different immunoblot pattern.

Some foods are being increasingly consumed due to the rise in the popularity of vegetarianism and veganism, linked to the increased awareness and perception that this is more than just a dietary change [46]. It is against this backdrop that a much more diverse range of foods have become mainstream in the diets of many. One example is the increase in the use of jackfruit in vegan cuisine; jackfruit is a known cause of PFS and has previously reported to cause anaphylaxis so its increased consumption may result in more cases being seen [47,48]. The other food which has seen a rise in consumption linked to changes in diet and lifestyle is soy. An early study determined that around 10% of those sensitized to Bet v 1 had clinical symptoms to soy, with the allergen responsible, Gly m 4, being present in widely varying amounts in different foods, ranging from 0 ppm in soy sauce, miso and roasted soy beans, 2 ppm in textured soy protein, 6 ppm in soy drinks such as soy milk, 9 ppm in tofu and 70 ppm in dietary powders containing soy [49]. Although published in 2004, this study has assumed an increasing importance, given the rise in veganism and interest in fitness supplemented by body building dietary products. Another more recent study from Japan reported very similar results, with 10% of 167 patients with birch sensitization and PFS reporting reactions to soymilk, 92% of whom had a positive test to Gly m 4 [50].

PROCESSING AND OTHER FACTORS WHICH MIGHT AFFECT THE PREVALENCE OR SEVERITY OF POLLEN-FOOD SYNDROME

Both PR10 and profilin allergens are susceptible to degradation on digestion, heating and processing [23]. However, this may not apply to all foods equally, with the Bet v 1 homologous allergen in celery Api g 1 appearing to be stable even when heated, compared with other plant foods such as apples, peaches and hazelnuts [51,52]. Rib-Schmidt *et al.* [53] found that the IgE recognition of the Bet v 1 homologue Api g 1 during heat treatment was strongly dependant on the pH of the matrix. A review of dietary interventions in PFS by Lyons *et al.* [54] gave an excellent overview of the evidence demonstrating regarding the thermal effects on PR10 and profilin allergens, concluding that the safety of

cooked foods for those with PFS will depend on the food. Insect damage in the cultivation of foods may also increase the risk of those foods provoking more severe PFS; one study reported that attack by insects and worms on soybean crops increased the level of Gly m 4 in both green and mature soybeans [55]. A comprehensive review by Wang *et al.* [56[■]] concluded that varietal differences, cultivation conditions, maturity at harvest, storage conditions and the structural stability of allergens can all affect the allergenicity of fruits and vegetables.

Cofactors such as exercise, alcohol and NSAIDs are typically associated with wheat allergy in adults, and those sensitized to nsLTP allergens [57[■],58]. Cofactors have not previously been considered to occur in PFS; however, Senders *et al.* reported that a 16-year-old girl sensitized to Bet v 1 and describing oropharyngeal symptoms to almonds on rest, experienced anaphylaxis on two occasions when commencing exercise 20 min after eating marzipan, a processed almond sweet. Oral food challenges performed with incremental doses of almond and one with almond followed by exercise confirmed a diagnosis of FDEIA to almond [59]. They suggested that high pollen counts may have also exacerbated the reaction.

Atmospheric pollen levels might also affect symptom severity. A review by Biedermann *et al.* [60[■]] in 2019 reported that in recent years the atmospheric burden of birch pollen has increased, in part due to increase in air temperature. The findings of a 10-year retrospective analysis of pollen counts from 2010 to 2018 were consistent with the assumption that increased pollen concentrations occur in areas of increased carbon dioxide, the primary driver of climate change [61[■]]. Berger *et al.* [62[■]] evaluated the relationship between pollen, air quality and meteorological data (temperature, relative humidity) in the birch, grass and ragweed pollen seasons, and found that ozone was associated with symptom scores. They concluded that air quality was an important marker of symptom severity in seasonal allergic rhinitis, and those with more severe symptoms could experience more severe reactions to foods. Thus, changes due to global warming and pollution might increase the likelihood of higher pollen counts and a longer birch season. More severe PFS reactions have been reported to occur during the birch season, so a longer birch season increases the likelihood of this occurring. Kosma *et al.* [63] reported four cases of children who were birch-sensitized, all of whom had severe reactions to soy milk in the birch pollen season.

Other factors that might lead to a more severe reactions in those with PFS, including gastric acid suppression, fasting, the consumption of liquid sources of allergen or the rapid consumption of large

quantity of allergen, were discussed in a article by Asero *et al.* [64[■]], using a review of three cases of PFS. An intervention which could lead to escalation of PFS symptoms due to changes in gastric acid is bariatric surgery; a case report from Blockhuys *et al.* [65] reported that a 48-year-old woman with known PFS suffered urticaria, angioedema and dyspnoea immediately after eating a fresh peeled peach, following gastric bypass surgery. The authors hypothesized the hypoacidity of the stomach caused the change from mild PFS to a generalized allergic reaction. This accords with other speculations regarding the effect of acid suppressant medication; one early study found 15% of 152 patients showed de novo sensitization to labile allergens in potato, celery, apple and orange, after antacid therapy [66].

CONCLUSION

There is ample evidence that PFS can result in severe symptoms including anaphylaxis, and present across a wide range of ages. The prevalence of pollen-related food allergy is likely to increase, with rising pollen counts and pollution making more severe reactions to foods a possibility. Those with diagnosed PFS should be advised to avoid obvious sources of concentrated allergen such as raw nuts, soy milk, smoothies, fresh fruit/vegetable juices or soy-based protein powders. More research is needed to characterize the patients who experience severe reactions, including the trigger event, sensitization patterns to pollen and plant food allergens, and current diet and lifestyle.

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Conflicts of interest

There are no conflicts of interest.

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