



Should patients with pollen fruit syndrome be prescribed an automatic epinephrine injector?

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Purpose of review

The review outlines recent insights into our understanding of the complex relationships between pollen and plant food sensitization patterns resulting in the pollen fruit syndrome and the possible risk, upon ingestion, of generalized symptoms rather than localized oropharyngeal reactions. Appreciation of this risk will inform management strategies, which include epinephrine prescription.

Recent findings

In recent times, the ability to examine molecular components of foods and pollen has allowed further delineation of reactivity patterns. These reveal complex patterns of IgE reactivity and sensitization pathways. More precise definition of these patterns will allow a more accurate analysis of risk of severe food reactions following ingestion.

Summary

Despite improvement in diagnostic tests, there remains no completely reliable way to determine whether an individual with pollen fruit syndrome is at risk of a systemic reaction. The decision to prescribe an epinephrine autoinjector must be based on a risk assessment for the individual patient.

Keywords

epinephrine autoinjector, lipid transfer protein, pathogenesis-related proteins, pollen fruit syndrome, profilin

INTRODUCTION

Many different associations and symptom patterns are described resulting from cross-reacting allergens in pollen and certain foods. Ortolani *et al.* [1] first described this phenomenon in a publication in 1988 using the term oral allergy syndrome (OAS) to describe pollen-allergic individuals who experienced oral symptoms on ingestion of certain fresh plant-derived food.

A year before, Amlot *et al.* [2] had used the term OAS to describe any oral symptoms that occurred as a prelude to any food-induced allergic reactions. Since then, there has been much confusion generated by the various terminologies used to describe symptoms of lip tingling with or without mild swelling, oral itching or tingling, and pharyngeal symptoms that result from contact with certain foods. This symptom complex may be experienced in certain individuals who are pollen-allergic, when they ingest specific plant-derived foods in the fresh (not cooked) state. In this group, it is generally a self-limited reaction that does not progress. However, similar symptoms may be experienced by some patients as a prelude to a more serious, systemic reaction to the food in question. Two terms – pollen

fruit syndrome (PFS) (also called pollen food allergy syndrome and pollen food syndrome) and OAS – are in common use. The former term should be restricted to pollen-allergic individuals who have the abovementioned symptoms following ingestion of a fresh plant-derived food such as fruit or vegetable where sensitization has resulted from cross-reactive allergens present in the pollen and the food. OAS, on the other hand, is a general term applied to the occurrence of any oropharyngeal symptoms following ingestion of any food and may herald progression to a systemic reaction. Individuals in this category usually have a type 1 food allergy where sensitization to the particular food has occurred via the gut and not via cross-reactivity with an inhalant allergen.

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KEY POINTS

- There remains confusion between the terms 'OAS' and 'PFS' and this results in incorrect assignment of risk for systemic reactions.
- Even with the advent of component-resolved diagnosis, there is no definitive way in which to recognize patients with PFS who are at greater risk of a systemic allergic reaction.
- Prescription of an epinephrine autoinjector is based on risk assessment considering the pattern and target of specific IgE reactivity, comorbidities such as asthma and previous systemic reactions.

Thus, oral allergy symptoms may be exhibited by those with PFS, by individuals with latex allergy who react to certain foods (latex-food syndrome) and by those with bird-egg syndrome and mite-shrimp syndrome. Finally, individuals with type 1 food allergy can have their reaction begin with oral allergy symptoms.

The clinician must use precision in delineating the difference between the two syndromes (i.e. OAS and PFS) to properly advise patients about outcomes, risks, and treatment of reactions.

Molecular-based diagnosis will help clarify this messy situation but at this time, this is not widely available so rational thought has to be applied to decision-making for patient safety.

The following discussion will address PFS.

CAUSES OF POLLEN FRUIT SYNDROME

PFS is the most common type of food allergy seen in adolescents and adults as it follows the development of respiratory allergy. Various studies suggest between 47 and 70% of those with pollen allergy have concomitant PFS [3].

Based on few studies from Europe [4] and the United States [5], PFS has been regarded as uncommon in children with a reported prevalence of 1–5%. However, one European study [6] suggested that it may be more prevalent in childhood than previously recognized. In an Australian cross-sectional study [7], 12% of children aged 4–17 years with allergic rhinitis and pollen sensitization had PFS.

PFS occurs in those with respiratory allergy who have been sensitized via the respiratory route to pollen allergens and then shows symptoms on ingestion of certain plant-derived foods as a result of cross-reacting allergens shared between the pollen and the foods. These class 2 food allergens are heat

labile and susceptible to digestion so do not cause sensitization via the gastrointestinal route as do class 1 food allergens. In PFS, the respiratory allergy appears first, followed by the development of oropharyngeal symptoms on ingestion of the relevant plant foods. Cross-reactivity develops as a consequence of shared epitopes in the primary and tertiary structures of pollen and food allergens. Pollen-specific IgE antibodies are able to recognize homologous dietary allergens that share the same epitopes [8]. These proteins are referred to as pan allergens because of their ubiquitous nature in the plant kingdom. A number of these including profilins, pathogenesis-related protein family, and lipid transfer proteins (LTPs) are important in PFS. A detailed description of all the pan allergens and their various reactivity patterns is beyond the scope of this study but this has been addressed in detail by Popescu [9¹¹].

Profilin is a protein that has a role in formation of the actin cytoskeleton. Bet v 2 is a profilin; profilins are widespread in all pollen and stimulate specific IgE reactivity in many pollen-allergic people.

In the Mediterranean area, in patients allergic to the Rosaceae fruits, the frequency of sensitization to profilins is approximately 40% and is higher in those sensitized to the pollen of grass, weed, and trees. The most frequently cross-reacting foods are melon, watermelon, tomato, banana, and citrus fruits [10]. Sensitization to profilin mostly is associated with mild symptoms although Vieira *et al.* described a patient with a systemic reaction following ingestion of tomato and another patient experiencing a systemic reaction who was cosensitized to both LTP and profilin. Similarly, Gomez *et al.* [11¹²] reported some patients sensitized to profilins having more severe reactions.

The PR-10 family is the most important pathogenesis-related family of proteins in PFS. It is widespread and highly conserved throughout the plant kingdom. Approximately 70% of Birch pollen-allergic people develop PFS most frequently to apple, hazelnut, celery, and carrot. Bet v 1, a PR-10 protein is responsible for these symptoms, being cross-reactive with its homologues in these foods [9¹³].

LTPs belong to the PR-14 family and are plant defence proteins located in the outer layers of the plants such as in the peel and they are especially abundant in the peels of Rosaceae fruits (apples and pears) and the Prunoideae fruits (peaches, apricots, plums, and cherries) [12]. Reactivity to LTP in fruit predisposes to a greater risk of anaphylaxis than sensitization to other pan allergens [11¹⁴,13]. LTPs may be a cause of fruit allergy in the absence of pollen allergy.

Confusion surrounds the entity of plant food reactions and as stated, this stems in a large part from the confused terminology used to describe these reactions. Whether a reaction to a fresh fruit will be localized to the oropharynx with no progression or whether it will progress to a systemic reaction depends on a number of factors. Reaction type is primarily determined by sensitization pattern and reaction severity is related to the nature of the sensitizing allergen. Pollen sensitization patterns also contribute to the sensitization to certain plant foods. Where sensitization occurs to labile proteins (e.g. PR-10 and profilin), the associated clinical syndrome is usually oropharyngeal alone. When sensitization occurs to a stable protein such as LTP then the reaction is more likely to be a systemic one.

It is hoped that component-resolved diagnosis may be of assistance in stratifying the risk of a systemic reaction based on the particular pan allergen sensitization profile [10].

This question has been addressed recently by Gomez *et al.* [11[■]]. They take the example of apple allergy to explore the complexities of this situation. It is known that in Northern Europe, apple allergy is associated with PFS and initial sensitization to Birch pollen, in particular to Bet v 1. Patients who were so sensitized also responded to Mal d 1 because of the strong homology between the two molecules. In Southern Europe, apple allergy is a cause of systemic reactions and frequently is observed without pollen allergy. Cross-reactivity to other fruits, in particular, peach, is observed. This linkage is explained by sensitization to peach LTP, Pru p 3.

By studying a group of apple-allergic patients, they were able to characterize the various sensitization patterns that were seen after profiling with skin prick tests, specific IgE measurement by ImmunoCAP, and by the performance of ELISA to the specific allergens in apple, namely Mal d 1, Mal d 2, Mal d 3, and Mal d 4, as well as ELISA results using Pru p 3 (a measure of LTP) and Bet v 1 and Pho d 2 (measures of PR-10 and profilin). They identified a high percentage of pollen reactivity in this group of patients. Patterns of sensitization were examined according to the clinical presentation of isolated oral symptoms (PFS) or the occurrence of generalized symptoms with apple ingestion. They demonstrated that the apple-allergic population showed a variety of sensitization patterns, including LTP alone, profilin alone, or dual sensitization to both LTP and profilin and that all these reactivity patterns were seen across both groups of patients. Thus, even with detailed analysis of patterns of allergen reactivity, it was not possible to predict with complete certainty whether an individual would experience PFS or a systemic reaction.

Therefore, overall sensitization patterns may be extremely complex, reflecting geographic differences in pollen exposure, certain genetic differences between populations, various patterns of IgE reactivity such that an individual may have both LTP and profilin reactivity demonstrated with the same fruit allergy. Even a detailed analysis of specific IgE reactivity cannot predict with certainty whether a particular individual will experience local or generalized symptoms.

MANAGEMENT OF POLLEN FRUIT SYNDROME IN CLINICAL PRACTICE

Little is known of the approach taken by specialists or generalists to managing patients with PFS. Two surveys, conducted a decade apart have attempted to explore specialist attitudes and prescription patterns in the treatment of PFS.

In 2003, Ma and colleagues [5] surveyed allergists who were members of the American Academy of Allergy, Asthma and Immunology in the United States. They were asked questions about prevalence of the condition, the advice they gave to patients regarding food avoidance and whether an epinephrine autoinjector was prescribed. Approximately half the allergists who returned the questionnaire advised total avoidance of the food causing PFS, whereas 9% did not. Total 20% of this group reported that some of their patients had progressed to systemic symptoms. A third prescribed an epinephrine autoinjector to their patients with only 3% stating they always did while the remainder did so on the basis of individual assessment of risk. When given three cases to categorize as PFS or as OAS representing type 1 food allergy, there were a number of misdiagnoses, confirming the prevailing opinion that terminology and categorization remain confused. More disturbingly, only approximately 75% would have prescribed an epinephrine autoinjector for patients at risk of a systemic reaction.

Over a decade later, Turner *et al.* [14[■]] conducted a similar survey among health professionals in the United Kingdom. Of the 193 health professionals who participated, 139 (72%) were doctors, of whom 61 (44%) were allergists. Most advised avoidance of the foods causing PFS (80%) but only 13% had ever recommended an epinephrine autoinjector. Of those that did prescribe one, the factors aiding their decision included previous reaction with lower airway symptoms, a current diagnosis of asthma, facial angioedema, generalized urticarial, and throat tightness. Turner *et al.* also demonstrated confusion with the terms OAS and PFS and that incorrect thinking around this led to misdiagnosis of the potential

severity of a reaction that may commence with oral symptoms but may then progress to a systemic reaction.

General advice

Classically, PFS presents with oropharyngeal symptoms alone but approximately 10% of PFS presentations are associated with systemic symptoms and 1–2% with anaphylaxis [15,16]. It is clear that at this time, identifying those with PFS at greatest risk of reaction progression is an imprecise science and a clinician's approach to this must be individualized for the particular patient. It appears as common sense that the food or foods producing significant oropharyngeal symptoms be avoided and that this avoidance is best advised to be year-long and not restricted to a pollen season. Patients must be given information about the safety of ingestion of well cooked or tinned forms of the foods in question and the possibility of the reaction spreading to include other cross-reactive foods. If known cross-reacting foods have not been ingested, then conducting a challenge to demonstrate presence or absence of symptoms is worthwhile. Occasionally, an individual may be reactive to a wide range of fresh fruits and vegetables and in this circumstance advice from a dietician may be worthwhile. Advice regarding avoidance of drinks from fresh juice bars and ingestion of fresh smoothies containing the particular fruits or vegetables is important to avoid ingestion of a large amount of allergen very quickly.

EpiPen prescription

Prescription of an epinephrine autoinjector to those with PFS remains an issue for debate. Those who argue against its prescription argue that the cost of the device and the burden of having to carry one [17,18] are not warranted for a clinical entity with such a low risk of a systemic reaction. However, as has been discussed above, there is a risk of systemic reaction for some and at this time, there is no way of predicting this with certainty in all individuals.

Given the Northern European experience, those with Birch pollen allergy and PFS with apple appear to have a very low risk of progression to systemic symptoms and as up to 70% of such patients have been found to have PFS, it is not warranted that epinephrine autoinjectors be prescribed to this group. However, a patient from Southern Europe presenting with a history of symptoms following apple ingestion needs careful evaluation for the risk of a systemic reaction because of the possibility of LTP sensitization [19]. Furthermore, in countries

where there are many migrants, country of origin needs to be considered when evaluating the risk because the means of acquiring sensitization varies with geographic location.

For individuals who have current asthma or who have experienced any urticaria or angioedema beyond the lips, or who have a history of progression to a systemic reaction, provision of an epinephrine autoinjector is an advisable precautionary step. At this time, little is known or written about the possibility of cofactors, such as vigorous exercise, presence of a viral illness, ingestion of medication such as aspirin and non-steroidal anti-inflammatory drugs having potentiating effects on reactions if the particular food is ingested.

Finally, risk stratification and need for an epinephrine autoinjector may be considered on the basis of the particular sensitization pattern. Evidence suggests that those reacting because of sensitization to LTP are more at risk of systemic progression [20[¶]]. Similarly, certain foods (e.g. tomato, peach [21], and food/pollen combinations such as those with celery/mugwort/spice reactivity [20[¶]]) appear to carry a greater risk as well. Clearly, primary sensitization to a particular fruit or vegetable in the absence of pollen reactivity falls into a different category as these individuals should not be classified as having PFS.

CONCLUSION

The decision to prescribe an epinephrine autoinjector for any allergic disorder remains a clinical one, determined by the physician after careful consideration of the risks posed by the particular allergy, relevant patient factors such as comorbidities and ease of access to emergency treatment, and the likelihood that an exposure may result in a systemic reaction. For patients presenting with PFS, sensitization to LTP, implication of certain foods, for example, tomato and peach, or food/pollen combinations such as those with celery/mugwort/spice reactivity appear to carry a greater risk of progression to a systemic reaction.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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