



Oral allergy syndrome

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Purpose of review

Oral allergy syndrome (OAS) is common in patients with allergic rhinoconjunctivitis. OAS may be less recognized in clinical practice leading to unclear diagnosis and treatment plans. Many aspects of OAS remain poorly understood, including a lack of a standard definition, limits in diagnostic tests, and complicated pathophysiology with a multitude of cross-reactivities. Understanding the range of mild-to-severe reactions will assist providers in developing the best approaches for diagnosis and management of patients with OAS.

Recent findings

A standardized definition of OAS does not exist in the current literature, which can make diagnosis and treatment of OAS difficult. Multiple studies have attempted to better define parameters for diagnosis and treatment; however, the complexity of the cross-reactivity between allergens makes this task difficult. Studies have investigated members in each of the protein families implicated in OAS, but largely without identification of broad candidate markers. Those candidate markers that have been established are typically too specific, which limits generalization.

Summary

This review will address current OAS definitions, pathophysiology, diagnosis, and available treatments. Current literature largely focuses on attempts to identify cross-reactivities and markers that may be useful in diagnosis and treatment of patients with OAS.

Keywords

allergic rhinitis, allergy, cross-reactivity, oral allergy syndrome

INTRODUCTION

The first description of an association between allergic rhinitis and oral allergy symptoms was published by Tuft and Blumstein in 1942 [1] that identified patients with a history of environmental allergies (hay fever) who also presented with oral symptoms including itching and swelling of oral mucosa after eating raw fruits. In 1987, Amlot *et al.* [2] coined the terminology 'oral allergy syndrome' (OAS) in a study comparing patients with atopy, who experienced oropharyngeal allergy symptoms alone, to those with oral symptoms and progression to systemic symptoms including vomiting, diarrhea, angioedema, and, rarely, anaphylaxis. Since that time, definitions have been confusing. OAS has been used to describe both subsets of patients – mild and severe – that can cause confusion for physicians when developing treatment plans. Pollen-food allergy syndrome is another term that has been broadly used to include cross-reactivity that leads to both oral and generalized symptoms. If using the pollen-food allergy syndrome definition, OAS is one subset and is defined as being limited to the oral cavity. For the purposes of this review, OAS will be defined as symptoms in the

upper aerodigestive tract, with or without progression to systemic symptoms.

PATHOPHYSIOLOGY OF ORAL ALLERGY SYNDROME

OAS is an immunoglobulin E-mediated cross-reactivity between an aeroallergen and a plant-derived antigen. The antigen present in the raw, ingested plant is active in the oral cavity but is rapidly degraded in the stomach. This leads to a local reaction in the mucosa of the oral cavity, typically without systemic symptoms. This is classified as a 'Class 2' reaction in contrast to 'Class 1' food allergy in which ingestion of an antigen that is sensitized in

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KEY POINTS

- OAS can be difficult to diagnose and complicated to manage given the extent of cross-reactivity, variable clinical presentation, and lack of a standardized treatment protocol.
- Avoidance remains the mainstay of treatment for OAS. Although rarely seen in OAS, severe systemic reaction including anaphylaxis should be recognized and managed appropriately.
- A variety of studies have been performed attempting to better define allergens, epitopes, and cross-reactivities that are important to develop new techniques for diagnosis and treatment.

the intestines leads to systemic symptoms and possible anaphylaxis [3,4].

Patients with OAS develop oral symptoms within minutes after ingestion of raw, cross-reactive foods. Typical symptoms include oral swelling, itching, and paresthesias, with rare progression to a more serious reaction. This reaction can be decreased or prevented by cooking raw vegetables and fruits to denature the cross-reactive proteins. A variety of proteins have been implicated in OAS. The most classic of these are the pathogen response proteins, including well known pathogen response-10. The pathogen response group and another family, the profilins, are typically heat labile and limited to oral symptoms. The lipid transfer protein (LTP) or pathogen response-14 protein family is more heat resistant because of increased structural stability, and is therefore more likely to present with both oral and systemic symptoms, similar to a class I reaction [3,4].

One aspect of OAS that is not well understood relates to cross-reactivity between unrelated aeroallergens and foods. Platt *et al.* [5^{*}] recently published a study attempting to identify clinical cross-reactivity in allergy and food protein epitopes. This was accomplished by comparing protein sequence of five common species from five inhalant allergen subclasses to each other, and to intact protein sequences from known cross-reactive foods. They identified cross-reactive epitopes that may be clinically significant. Further studies are needed to determine significance and investigate whether these cross-reactive epitopes may be candidates for immunotherapy or aid in allergy diagnosis [5^{*}].

Pathogen response-10 family

A well known member of the pathogen response-10 family is the Bet v 1 protein, a birch-tree allergen. Bet

v 1 is cross-reactive with the Rosaceae fruits including apple, cherry, apricot, kiwi, pear, carrots, celery, soybean, and hazelnut. It is easily degraded and typically causes oral cavity without systemic symptoms. Almost all birch-pollen allergic patients are sensitized to Bet v 1 putting them at risk of developing OAS to all plants with cross-reactivity; however, most patients develop allergies to a limited number of fruits or vegetables. Similarly, the presence of allergen-specific immunoglobulin E does not predict a clinically symptomatic allergy. Because the factors contributing to clinically significant food allergen in birch-sensitized patients are largely unknown, a study was performed by Guhl *et al.* [6] that specifically investigated whether allergen-specific immunoglobulin G and immunoglobulin A antibodies clinically affect the activity of allergen-specific immunoglobulin E. There was no significant correlation between Bet v 1-related food allergy and change in immunoglobulin levels. They did note, however, a significant elevation of immunoglobulin E specific to Api g 1, a protein found in celery, in celery-allergic patients. The protein is not denatured by heat and, unlike most members of the pathogen response-10 family, is responsible for more generalized symptoms including anaphylaxis, than Bet v 1 [6].

Gly m 4 is an antigen typically found in soybean products and may lead to OAS as well as angioedema, dyspnea, and urticaria [7]. In 2002, Kleine-Tebbe *et al.* [8] demonstrated Gly m 4 in patients with birch pollinosis who developed soybean allergies, and the presence of birch pollen actually inhibited the binding of immunoglobulin E to soybean protein. Multiple studies have demonstrated that this cross-reactivity can be of a severe nature with generalized reaction. A recent study by Berneder *et al.* [9] demonstrated that Gly m 4 may be a marker identifiable by ImmunoCAP (Phadia AB, Uppsala, Sweden) for severe allergy to soy in allergic patients with birch pollinosis.

Profilins

Within the profilin family, there is a very broad range of cross-reactivity between multiple pollens with multiple fruits and vegetables. Profilins are panallergens or ubiquitous proteins that are involved in pollen, latex, and plant-food allergy syndromes that are not specifically related to birch pollinosis [10]. Generally, profilins are thought to lead to mild or incomplete food allergies, given the easily denatured structure by thermal and enzymatic means. However, a recent study published by Alvarado *et al.* [11] suggests that profilins may be associated with severe, complete food allergies in

patients sensitized to grasses. This study was performed in patients classified as either mild or severe reactors to grasses who were provoked with purified profilin administered orally in a double-blind placebo-controlled trial and found to elicit reactions consistent with food allergy at low levels.

Lipid-transfer proteins

LTPs are panallergens that belong to the pathogen response-14 family. Allergens are typically to the Rosaceae family including peach, apricot, plum, cherry, apple, tomato, carrot, barley, corn, wheat, rice, broccoli, and onion. They have also been found in nuts, seeds, pollen, and latex [12]. In contrast to other protein families discussed, LTPs can cause OAS through food allergens, even without pollinosis [4]. LTPs have a stable three-dimensional structure that resists enzymatic and thermal degradation. This allows the antigenic structure to act not only as an allergen both in the oral cavity and the lower gastrointestinal tract, but also as a traditional Class 1 food allergen through intestinal sensitization. As stated by Morales *et al.* [12], the cross-reactivity and allergenic relationship between allergenic sources is unknown. As such, this group performed a study to evaluate cross-reactivity between varying sources including pollen versus foods. They also investigated if Pru p 3 (peach) may serve as a universal LTP for diagnosis of LTP-sensitized patients. As such, LTPs were extracted, purified, and cross-reactivity was determined by various methods between Pru p 3 (peach) and Par j 1/Par j 2 (pellitory) that are common allergens in the region where the study was performed. The results of this study ultimately showed some cross-reactivity between Pru p 3 and hazelnut, onion, corn, peanut, and apple, but no cross-reactivity was present in pollens. In addition, Pru p 3 was noted to share a large number of epitopes with most fruits; however, use of this alone for detection of LTP would not be a sensitive method of diagnosis or screening. In summary, cross-reactivity between LTPs is difficult to predict, may be patient specific, with a multitude of epitopes [12].

DIAGNOSIS

There are no new methods of diagnosis of OAS published in the literature over the past year. The following are the currently accepted methods of diagnosis of OAS. Although not directly tied to diagnosis, a study recently published by Platt *et al.* [5[¶]] demonstrates the potential usefulness of newly established cross-reactivity between aeroallergen and food allergen epitopes.

Clinical diagnosis

Many authors support that OAS can be diagnosed based on clinical history given the unique set of symptoms. Other authors argue that objective evidence is needed to accurately diagnose allergic cross-reactivity between pollens and foods [3,4].

Food challenges

The gold standard for classic food allergy diagnosis is food challenge that is performed by feeding increasing doses of suspected foods and observing for a reaction [13]. Optimal testing is the double-blind, placebo-controlled food challenge; however, open food challenge is often more practical. Food challenges have advantage over other testing methods [skin prick testing and specific immunoglobulin E testing] that have poor sensitivity and specificity and are unable to diagnose nonimmunoglobulin E-mediated reactions. However, food challenges are time consuming, results can vary depending on the foods being tested, and they are not without risk [13].

Skin prick testing

Fresh fruit or commercial skin prick test can be used to aid in diagnosis of food allergies and OAS by detection of sensitization. In both, the substance being tested is placed on ventral forearm, and skin is pricked and observed for formation of wheal and erythema that signifies positivity [3,13]. In commercial testing, labile proteins may degrade during processing, yielding false-negative results, and false-positive results may occur from use of ubiquitous proteins such as profilins or LTPs [3].

Specific immunoglobulin E testing

In-vitro testing for specific immunoglobulin E can identify sensitizations rather than a clinical allergy syndrome. A gap exists in the in-vitro diagnosis of OAS when the sensitization is to an inhalant allergen rather than the food itself. A recent study by Beyer *et al.* [14[¶]] compared open food challenge to component immunoglobulin E levels in peanut and hazelnut allergies to determine if this method may be useful for diagnosis of tolerant versus allergic children. This study determined that use of the peanut and hazelnut components is better at diagnosing clinical allergy than use of specific immunoglobulin E.

Basophil activation test

Basophils are the circulating effector cells involved in immunoglobulin E-mediated allergy that when

activated, exhibit CD63 surface marker and secrete various mediators. The expression of CD63 and CD203c allow detection of activated basophils by flow cytometry. The basophil activation test can detect sensitization to foods, but has not been endorsed in the most recent food allergy guidelines [3,15–17].

TREATMENT

OAS is a Class 2 food allergy, typically without severe systemic effects that are seen with Class 1 food allergy. Like other food allergies, the mainstay of treatment of OAS is education, avoidance, and emergency administration of epinephrine for severe, generalized reactions. Given the confusion that exists regarding the OAS definition, and possibility of progression to anaphylaxis, it is important for providers to counsel and prepare their patients for possible severe events.

Immunotherapy with birch pollen has been previously described to be efficacious when used for allergic rhinoconjunctivitis in this patient population [18–20]. Various studies have documented the subjective improvement in OAS symptoms in patients undergoing immunotherapy for birch; however, there are also reports suggesting that immunotherapy does not necessarily lead to reduction in related food allergies. This may be due to the fact that cross-reactivity of epitopes only has a certain degree of similarity [21]. Subbarayal *et al.* [22] recently investigated the usefulness of birch-pollen immunotherapy in reducing cross-reactivity with Bet v 1 homologous food proteins. In this study, 42 patients with birch-pollen allergy underwent birch-pollen immunotherapy. Immunoglobulin E and immunoglobulin G4 levels, specific for Bet v 1, Mal d 1, and Cor a 1, were determined in patients before, during, and after immunotherapy. Inhibition of immunoglobulin E binding and immunoglobulin E-activated T cell lines was also studied. The authors found a significant increase in Bet v 1 immunoglobulin G4 antibodies and a significant decrease in allergen-specific immunoglobulin E levels. They also described inhibition of immunoglobulin E binding, specific T-cell proliferation, and basophil activation in these patients. These data suggest that immunotherapy with birch pollen may be beneficial in stimulating an immune response against cross-reactive foods that may ultimately reduce OAS symptoms [22]. Spertini *et al.* [23[¶]] recently published a study regarding the immunologic response to immunotherapy after subcutaneous administration of continuous overlapping Bet v 1 peptides. They reported a strong immune response only after five injections of

continuous overlapping peptides over 2 months, which was similar to the immune response elicited after 50 injections over 3 years with other allergens [23[¶]]. This supports the importance of cross-reactivity between epitopes and will likely be an important aspect of immunotherapy in the future. This idea is further elucidated by Roulias *et al.* [21] who suggest that the high allergenicity of Bet v 1 is due to both epitope as well as unique structure that are not entirely shared between food homologs. This explains the discrepancy in improvement of rhinoconjunctivitis symptoms but persistent OAS symptoms with birch immunotherapy. Further elucidation of target cross-reactive epitopes is necessary to develop treatments for both pollen and food allergies.

CONCLUSION

OAS is a complicated syndrome of cross-reactive allergy between pollens and food proteins that typically manifests as mild oral symptoms, but can be associated with more generalized severe reactions such as anaphylaxis, especially when related to LTPs and particular members of pathogen response-10 and profilin families. Diagnosis and treatment has been classically described and there have been no significant advances over the past year; however, multiple studies have taken steps to make advances in that direction. The clinical application of this research will assist providers and patients in the diagnosis and management of cross-reactive pollen and food allergies.

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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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