ORAL ALLERGY SYNDROME – THE NEED OF A MULTIDISCIPLINARY APPROACH

Nikolina Kelava, Liborija Lugović-Mihić, Tomislav Duvančić, Renata Romić and Mirna Šitum

Clinical Department of Dermatovenereology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia

SUMMARY – Oral allergy syndrome (OAS) is one of the most common types of food allergy. The syndrome includes itching and swelling of the lips, palate and tongue, usually after consuming fresh fruits and vegetables. The underlying pathogenic mechanism is cross-reactivity between IgE antibodies specific to pollen, and antigens in food, such as fresh fruits, vegetables and nuts that are structurally similar to pollen. Both pollen and food antigens can bind to IgE and trigger type I immune reaction. Diagnosis is primarily based on the patient's history, and confirmed by skin tests, *in vitro* tests, and oral provocation tests. Differential diagnoses include many diseases (such as burning mouth syndrome, angioedema, hay fever, various other oral diseases, etc.), and for this reason a multidisciplinary approach is necessary, as different specialists need to be involved in the diagnostic procedure. Therapy includes avoiding, or thermal processing of, fruit and vegetables known to trigger a reaction, and antihistamine medications. If a more severe anaphylactic reaction develops, more aggressive therapy is required. The goal of this article is to present OAS, its etiopathogenesis, clinical picture, and symptoms, diagnostic approach and therapy for OAS.

Key words: *Food hypersensitivity; Mouth diseases – immunology; Oral allergy syndrome; Pollen*

Introduction

Oral allergy syndrome (OAS) is an allergic reaction in the oral cavity caused by the consumption of food (mostly fresh) such as fruits, nuts and vegetables, which occurs in adults who suffer from allergic rhinitis1. Another term used for this syndrome is the "pollen-food allergy". The first description of oral allergic syndrome comes from 1942, when Tuft and Blumstein described hypersensitivity to fruits and vegetables associated with sensitivity to birch pollen1-3. However, it was only in 1987 that Almont et al. described the clinical changes in the oral cavity as OAS1-3. It can be said that OAS in adults probably represents the most common allergic reaction caused by food; and also, that more than 60% of all food allergies are actually cross-reactions between food and inhaled allergens3. OAS is not an isolated food allergy, but cross-reaction caused by the components of pollen (from trees or weeds) that are also found in certain fruits and vegetables (Table 1). Allergic proteins that cause OAS are generally destroyed by cooking, so the reaction mainly occurs after eating raw food. The main exceptions are celery and nuts that can both cause a reaction, even when cooked. Unlike other food allergies, OAS is a reaction limited to the oral mucosa, lips, tongue and throat4. It can occur at any time of the year, but usually occurs during the pollen season. OAS patients usually develop symptoms within minutes of eating the food1.

Given the pathogenic mechanism, OAS belongs to the allergy type I group, i.e. allergic reactions mediated by immunoglobulin E (IgE). Thus, in patients with OAS, the immune system produces IgE antibodies against pollen (which causes hay allergy), which also act against similar proteins found in food. Pollen allergies (allergic rhinitis, pollinosis/hay fever

Correspondence to: *Prof. Liborija Lugović-Mihić, MD, PhD*, Clinical Department of Dermatovenereology, Sestre milosrdnice University Hospital Center, Vinogradska c. 29, HR-10000 Zagreb, Croatia

E-mail: liborija@gmail.com

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Table 1. Types of pollen and food associated with oral allergy syndrome

Pollen	Fruit	Vegetable	Nuts	Grains
Birch	Kiwi, peach, apple, nectarine, apricot, banana, pear, plum, avocado, cherry, fig, strawberry, dried plum	Potato, carrot, celery, chicory, cilantro, fennel, pepper (green), parsley, parsnip, dill, cumin, tomato	Hazelnut, almond, walnut	Soybeans, wheat, lentils, peas, beans, peanuts
Ragweed	Banana, melon, honey, dew, watermelon	Pepper, squash, cucumber, artichoke, hibiscus, chamomile tea		Sunflower seeds
Weeds	Melon, watermelon, orange, kiwi	Tomato		
Grasses	Fig, melon, orange	Tomato		
Alder	Apple, cherry, peach, pear, strawberry, raspberry	Celery, parsley	Hazelnut almond walnut	
Wormwood	Apple, melon, watermelon	Carrot, celery, parsley, pepper, cilantro, fennel		Sunflower
Parietaria	Cherry, melon			

or respiratory problems) are caused by repeated exposure to the pollen of some plants, usually of those that pollinate by air (wind) and have such pollen quantities that inhalation of the pollen easily reaches the surface of the pulmonary alveoli. These allergens are usually birch pollen, lime, meadow kittens (*Phleum pratense)*, ragweed, mugwort, etc.[5]. The disease is characterized by a distinct seasonal pattern, as it coincides with the flowering of some plants. Among allergens in our country, there have been increasingly frequent and important allergies to ragweed in recent years. Ragweed (*Ambrosia artemisifolia*) is a weed that arrived in Europe, specifically in the Ukraine, in the 19th century, in shipments of grain from North America, and since then has gradually spread southward. The ragweed came to Croatia in 1941, and so far it has spread everywhere in the inland part of the country, and in several places along the coast (Istria, Zadar, Makarska)[5]. Ragweed is one of the commonest inhaled allergens to cause allergic disorders in patients, and therefore OAS often occurs in these individuals due to cross-reactions to food (an allergy to ragweed pollen is often associated with allergy to bananas, watermelons, melons, squash and cucumbers).

Etiological Factors of Oral Allergy Syndrome

Oral allergy syndrome manifestations occur after the patient who is allergic to pollen consumes certain fruits, vegetables or nuts. Some of these patients show reaction to a particular food, while others may respond to a whole range of foods[1]. The OAS patient is first sensitized by inhaling pollen that contains the antigens, and then after consuming food that contains cross-antigens (to the inhaled antigens) the symptoms characteristic of OAS appear. Sensitization actually originates from abnormally stable food proteins that are consumed orally. After abatement of the symptoms, OAS may later appear after each episode of consumption of food containing the protein. The key factor is that the same antigen plays an important role in the sensitization process and in the process of appearance of symptoms[6].

Certain allergens include several allergenic proteins that stimulate the production of specific IgE antibodies in humans. Thus, allergenic proteins for birch pollen (*Betula verrucosa*) are represented by proteins Bet v 1, Bet v 2, Bet v 3, etc., while apple pollen (*Malus domestica*) is represented by the proteins Mal d 1, Mal d 2, Mal d 3, etc. Food allergens may be complete (class

I) or incomplete (class II)[7]. Some nutritional allergens are resistant to heat and digestive enzymes, and may enter the body unchanged through the digestive system (even after heat treatment) and lead to allergic sensitization. Because of their excellent resistance, these allergens may cause systemic allergic reactions in sensitized individuals. These allergens are called complete nutritional allergens, from which group the same allergen leads to sensitization of the body and appearance of the symptoms (food allergy type I). An example of a complete nutritional allergen is the Mal d 3 protein from apple[7]. On the other hand, there are also incomplete nutritional allergens, i.e. nutritional allergens that are sensitive to heat and digestive enzymes, and rapidly denature during thermal treatment or on contact with gastric contents. They accordingly lack the ability to raise sensitization of the body, but the body that has previously been sensitized (by inhalation or contact) to a cross-reactive allergen can trigger the symptoms. In this case, the symptoms appear only after eating raw foods and mainly on the oral mucosa (as with further passage through the digestive tract they lose their allergenic properties). A nutritional allergy type II is one in which one allergen leads to sensitization of the body, and another to the onset of symptoms. An example of an incomplete nutritional allergen is Mal d 1 from apple, which induces OAS symptoms in individuals sensitized to Bet v 1 from birch.

When considering food allergies, different pathogenic factors should be taken into account. Food allergies occur when there is a disturbed immune response in the mucosal part of the gastrointestinal tract (GIT). The mucosal barrier of the GIT is a large surface barrier that makes a physical and chemical (epithelial cells, mucus, enzymes, pH), as well as cellular barrier (NK cells, polymorphonuclear cells, macrophages, epithelial cells, toll-like receptors), and suppresses the immune response to the enormous amount of foreign antigens entering the GIT lumen. It is probably the immaturity of the mucosal barrier of the GIT (e.g., suboptimal enzymatic activity, immaturity of the sIgA) that causes an increased prevalence of allergic reactions and infections in the first years of life. Food allergies occur in genetically predisposed people who have not developed oral tolerance, or in whom this tolerance has been violated. When antigens from food bind to IgE on mast cells, this leads to the release of mediators and symptoms, and also to some of the so-called non-IgE reactions in which eosinophils play a key role. The intestinal flora also has an important role in the development of oral tolerance, which is supported by the beneficial effect of probiotics in preventing the development of atopic disease. In recent years, it has been revealed that the occurrence of OAS with tropical foods is often caused by the underlying reaction to latex[8,9]. It is estimated that 50%-70% of people allergic to latex have a cross-reactive IgE to antigens from plant foods[9]. Fruit is particularly known for its frequent cross-reactivity with latex, which is called "latex-fruit syndrome". People allergic to latex often show an allergy to food derived from plants and pollen, and therefore caution is needed[9].

Clinical Features of Oral Allergy Syndrome

Patients who show symptoms of OAS may have a number of other allergic reactions that start very quickly, even minutes after consuming trigger food. Changes often occur in the season of pollination of the plants to which the person is allergic. Usually, it is manifested by itching and a burning sensation of the lips, mouth, ear and throat, or by the appearance of perioral erythema, sometimes generalized urticaria, and even anaphylaxis. Sometimes, reactions can manifest themselves in the eyes, nose and skin. The patient may develop swelling of the lips, tongue and uvula, occasionally a sense of suffocation, and rarely anaphylaxis[10]. Symptoms usually last for a few minutes to half an hour. Indigestion is also possible. If the patient consumes food containing an allergen that has not been destroyed by stomach acid, reactions caused by the subsequent release of histamine in the digestive system can be experienced. Digestive problems can also occur, including diarrhea, vomiting, bloating and cramps[11]. In rare situations, OAS may be manifested as difficulty in breathing, appearance of a rash, or hypotension[1].

Epidemiology

There are no precise data on the actual prevalence of OAS, since such reactions are often unrecognized and vary depending on the geographical area. Significantly, cross-reactions show geographical and climatic

differences, depending on exposure to inhaled and consumed allergens. Thus, in central and northern Europe, there is no confirmed association between allergies to fruits of the family Rosaceae (peach, apricot, cherry, plum, apple, and pear) and allergy to birch pollen. On the other hand, in North America, allergy to fruits is associated with that of grass or ragweed pollen, while in Europe it is associated with wormwood and in Japan with cedar[12].

The majority of patients start experiencing OAS as hay fever, and it occurs in children and adults. Some studies show that it is more frequent in women[13]. According to the research conducted, adults who are allergic to pollen develop OAS in 26%-40% of cases[13]. Research carried out in Spain on patients allergic to peach has shown that more than 80% of these patients also suffer from some kind of allergy to pollen. However, some studies have shown that up to 9% of OAS patients may develop severe symptoms of food allergies, including anaphylaxis (up to 2% of cases)[13]. The symptoms are often severe during the season in which the responsible pollen dominates. Therefore, to help patients avoid pollen reactions, calendars can be useful, based on which such persons may plan preventive measures and use of appropriate therapy.

The Pathogenesis of Oral Allergy Syndrome and Allergic Reactions

Commonly, hypersensitivity reactions are divided into four types. The first three types are related to antibody-mediated reactions (early hypersensitivity), and the fourth type is related to the cell-mediated response (delayed hypersensitivity). Individual types of hypersensitivity often have no clear boundary, as they may overlap. When it comes to allergies, it is usually referred to as type I (where OAS belongs) when the mediators are released after reaction of IgE with target cells[14-16]. The first type of immune hypersensitivity includes the creation of specific IgE antibodies and the activation of mast cells and basophils. Significantly, IgE has a unique structure of Fc-fragment that binds to the fragment on mast cells and basophils (FcεRI). Allergic reactions to allergens begin with the antibody binding to the receptor, leading to a signal sequence of intracellular events that result in the activation and release of inflammatory mediators (histamine, leukotrienes, chemotactic substances, platelet activating factors, proteases, etc.). Released mediators first act locally, causing increased permeability of blood capillaries, vasodilatation, smooth muscle contraction, secretion by mucus glands, etc. This is the first, acute phase, which occurs after contact with an allergen within the first 15-30 minutes. During the next 6-12 hours, there is increased tissue infiltration by inflammatory cells (eosinophils, neutrophils, and mononuclears). It is the late phase of the reaction that is characterized by clinical signs of inflammation (e.g., rhinitis, asthma, or angioedema). Allergic reactions are usually stimulated by antigens that have entered the body through the respiratory system (e.g., allergens from pollen, house dust, animal hair and feathers) and the digestive system (e.g., allergens in milk, eggs and fruit). An allergic reaction that occurs in the upper airways can be manifested as conjunctivitis and pollen sneeze, and one in the lower airways as bronchial asthma[16]. Allergens that enter through the digestive system can cause vomiting and diarrhea, and if they reach the skin they can cause redness, itching and swelling (urticaria or angioedema). Some people are genetically prone to having elevated levels of IgE. They display local anaphylactic reactions (atopy) and are referred to as atopic patients. There are many different allergens that can cause atopic reactions (flower pollen, house dust, animal hair and feathers, and sometimes milk and eggs, etc.)[14-16].

The mechanism of the release of mediators is complex. To release mediators from target cells, an allergen molecule must react with two molecules of the antibody and overcome them. After the allergen binds to an IgE receptor, aggregation occurs and activation of the intracellular part of tyrosine kinase protein complexes begins. Thus a complex sequence of events begins that ultimately leads to target-cell degranulation and the release of mediators. The target cells release different mediators, most important of which is histamine (the primary mediator), which is produced in mast cells and basophil leukocytes through decarboxylation of histidine. Histamine stimulates various pharmacological effects by binding to histamine receptors: the contraction of intestinal and bronchial smooth muscle, increased capillary permeability, secretion of exocrine glands, etc. The cells of peripheral organs have three types of receptors for histamine.

The effect of histamine and its chemotactic activity in eosinophilic leukocytes is also important. Antihistamines are important in the treatment of these reactions because they can prevent most allergic hypersensitivity reactions, but not all, given that these events involve other mediators. The secondary mediators include leukotrienes (also called slow-acting substances or SRS-As (slow-reacting substances of anaphylaxis), whose main effect is prolonged contraction of smooth muscle. The pathogenesis of OAS also corresponds to the first type of allergic sensitization, with the participation of IgE. In OAS, the immune system produces antibodies that are directed against the proteins of pollen and structurally similar proteins in food. Such cross-reactivity occurs when two or more allergens have the same or very similar epitopes, and the result is the binding of IgE antibodies. Thus, patients sensitized to an allergen can also react to another allergen, without prior contact and sensitization. Thereby, plants that are more similar in their botanical relationship have more immunogenic similarities of allergens in their pollen particles[17]. The basis of cross-reactivity in terms of molecular similarity lies in the three-dimensional structure of the conformational epitopes. Created antibodies specific to the allergen epitopes recognize them on allergens. If the allergens are homologous to more than 70% of amino acid sequences, it usually leads to their binding; while for homology below 35% the binding is unlikely[17].

The same immune system can trigger allergic symptoms in two different ways: in the presence of pollen, when rhinitis emerges, as well as in the presence of a particular food leading to symptoms of food allergy. Different allergens vary in their stability, with differences in digestion survival, storage, high temperature, cold, and cooking or pasteurization survival. As important drivers of anaphylaxis, the lipid transporting proteins (LTP) play an important role, since they cannot be easily denatured by digestion or cooking. Antibodies can react to linear (amino acid) sequences of the protein, or a conformational epitope. Persons who respond to the linear sequence of the protein can tolerate neither raw nor cooked food (so cooking the food does not help prevent an allergic reaction); while those that respond to a conformational epitope can consume cooked food, but not raw food.

Due to the structural similarity of individual protein molecules, a large number of allergens that exist in nature can be classified into a few groups (*Fagales* pollen – group 1, prophylin, polycalcinates, etc.). Among the allergens in each group there is a possibility of cross-reactivity of IgE antibodies: that is, antibodies binding to one of two or more allergens. So, allergenic tree pollen, *Fagales,* shows a high degree of allergic cross-reactivity due to high propinquity between members of different families[18]. Allergic reactions to certain pollens are associated with the emergence of OAS with certain foods (e.g., allergy to ragweed pollen is associated with allergy to bananas, watermelons, melons, squash and cucumbers). This does not mean that all patients allergic to ragweed develop symptoms to all, or even to any of these foods. The reaction may start with one type of food, and subsequently allergies to other types can develop. Therefore, the response to one food from a particular category does not necessarily mean that the person is allergic to all foods from that group.

Diagnosis

Lots of people are not aware of the fact that they have OAS, and they are not aware of the disease before diagnostic procedures and recommendations of specialists. Therefore, if a person notes tingling or pain during consumption of certain foods, it is recommended that they visit a specialist in allergic diseases.

However, differential diagnoses include many diseases, such as burning mouth syndrome, angioedema, hay fever, various other oral diseases, etc. A multidisciplinary approach in patients with OAS is therefore necessary, which involves different professions (ear-nose-throat specialists, oral pathologists, allergologists, immunologists, dermatologists, pediatricians, gastroenterologists, and various other specialties), given that this is the only way to take into consideration all the history and clinical elements of the disease, without which the disease would be left unrecognized.

For a correct diagnosis, it is necessary to obtain thorough patient history. Patients usually already have an atopy and allergy listed in their own or in their family history[19,20]. The most common changes are expressed as hay fever, asthma, otorhinolaryngological symptoms, eczema, etc., but food allergy often remains undiscovered. Patients should

also pay attention to the preservatives in foods that may trigger the manifestation of the disease. Often, well-cooked, pasteurized, canned and frozen food causes minimal reaction, or no protein denaturation, due to cross-reactions causing a delay in response, and acts as a confusing factor in the diagnosis[10]. It is usually difficult to determine the allergen that has caused an allergic reaction. OAS patients may be allergic to multiple allergens, not just to pollen. Often the patients report vague symptoms, which are usually suspected of having a different etiology (which is often incorrect). There are other reactions to foods (e.g., lactose intolerance), which should be distinguished from systemic symptoms of OAS. To identify the relevant allergens, a strict diet can be followed, by including foods that could cause a reaction one at a time, and thus eliminating specific foods one at a time. Skin tests (usually prick tests) and blood tests (usually the RAST test) are used as an aid in the diagnosis, but they are not sufficient for definitive diagnosis. The "prick-to-prick" test using fresh food can be also conducted, and is more reliable for some very labile allergens (e.g., apple) than tests prepared commercially that may give false-negative results. If the history is positive and the prick test is negative, a provocation test with fresh food should be conducted. When OAS is suspected, an oral provocation test is usually conducted, which represents the safest confirmation of the presence of the disease. In doing so, the person first consumes a suspected food, and subsequently the onset of symptoms is recorded. To set up an accurate diagnosis, it would be necessary to keep a diary of food consumption as the basis for determination of which food tests to undertake. Good history can focus the testing on a specific type of food, and thus the specialist can act more rationally.

Allergy testing is usually carried out through the skin, with a very small amount of standard solution of purified allergens being applied to the skin and then observed and measured by local allergic reactions. Skin testing for the detection of type I reactions can be carried out using different methods: the prick method (prick test); by application of allergens *via* scratching the skin (scratch test); and rarely an intradermal test (application of allergens into the skin by a needle). For the diagnosis of OAS, skin prick tests, blood tests, patch tests or oral provocation tests (the most reliable in OAS) can be used.

The prick test is the method that most commonly determines sensitivity to inhalant and nutritive allergens. A prick test is performed on the skin of the forearm by placing a small amount of the extract of the potential allergen on the skin, which is then pierced by a lancet, and after 15-20 minutes the size of urticaria at the injection site is measured. The size of the urticaria can be correlated with the intensity of allergic reaction. The prick test, because of its simplicity, security, and low number of false-positives, is the most commonly performed test. The downside of the prick test is the lower sensitivity of results; accordingly, after a negative prick test, more sensitive tests may be conducted, if the doctor strongly suspects the allergy. Testing by prick test is considered to be one of the safer methods, and only very exceptionally, systemic anaphylactic reaction can develop as a result; so, whenever performing the test, the physician must have emergency anti-shock therapy present and readily available.

The scratch test is performed on the volar side of the forearm with a lancet. The skin surface is scratched with a linear groove, and buffer solution (negative control) and individual allergens in the test concentrations are applied. The test demonstrates sensitivity to preservatives, additives, medicines and fresh nutritive allergens. The reaction is read after 20 minutes. Positive allergic reactions are considered when urticaria is observed with a transverse diameter greater than 3 mm.

The intradermal test is performed by injecting a small amount of allergen into the skin using an intradermal needle. The method is more sensitive than the skin-prick test, since there is a large amount of skin exposed to allergens. An intradermal test may be carried out when a skin-prick test has shown negative reaction, but it is still suspected that the allergen does cause a reaction. Significantly, the intradermal test is more sensitive than the skin-prick test, but sometimes false-positive reactions are possible.

Blood tests are mostly performed as RIST (Radio-Immuno-Sorbent-Test) for the determination of total IgE and RAST (Radio-Allergy-Sorbent-Test) for the determination of specific IgE antibodies to a particular allergen. A blood test is usually used when there is no possibility of skin tests: if the patient has skin changes in the area of testing; if the patient uses drugs that are long-acting and whose use cannot be

stopped; in dermographism; distended skin changes; small children, or if there is a history of anaphylaxis, etc. However, there are some disadvantages of blood tests, such as the high cost, the inability to simultaneously test a large number of allergens (as is possible in the skin test), the longer time required to obtain results, etc.

In order to examine the possible allergies in people who do not have clear evidence after skin or blood testing, a provocation test (challenge test) can be performed. There are two types of provocation test, open and blind. In an open provocation test, a suspected allergen is given to the patient by gradually increasing the amount of allergen consumed until allergic symptoms are observed. In the blind provocation test, the patient consumes a small amount of suspected allergens (such as milk or antibiotic), usually in a capsule, but he/she does not know what the purpose is. It turns out that the best test of provocation by food is a "double-blind, placebo-controlled test". Due to the risk of severe allergic reactions such as anaphylaxis, provocation tests are performed in a hospital environment, and implemented only when absolutely necessary.

Treatment

The treatment of OAS must be carried out in parallel with the treatment of other allergies, especially allergies to pollen. It should be taken into consideration that there are usually variations of the clinical picture and severity of symptoms that can reduce or amplify the level of pollen. Because of this, pollen calendars are often useful, but they are not valid during strong winds or unusual weather, when grass and tree pollen can travel to remote areas.

It has been shown that cooking food can sometimes eliminate the causes of allergies, but only in certain species (e.g., apples), while it is impossible to destroy allergens in celery and strawberries. For some types of food (e.g., nuts) that contain more than one allergen, heat treatment will destroy certain allergens, while some of them can cause a reaction even after that. The most important therapy includes antihistamines and sometimes corticosteroids, which can alleviate allergic symptoms by blocking specific immune pathways. Patients with a history of anaphylaxis should always carry a shot with a dose of epinephrine (such as EpiPen) with them. In the event of a reaction, the patient is advised to stay calm, rinse his/her mouth with plain water, and rest. The patient can help him/herself with hot (but not boiling) beverages that can inactivate residual allergens. This usually leads to withdrawal of the sensation of prickling, itching and swelling, which stops within 30 minutes to an hour (before the antihistamine makes an effect). Sometimes, there is difficulty in breathing, the voice becomes hoarse, the throat closes, or the person feels weak. In this situation, additional treatment and call for emergency medical assistance is needed, as it usually signifies an anaphylactic reaction. If the person has an auto-injector with epinephrine, he/she should apply it and call an ambulance. When the patient is able to swallow a dose of antihistamines, they definitely need to be taken. However, severe symptoms are rare in patients with OAS. In patients with suspected OAS, preemptive caution is necessary because the preparation of food can be connected to reactions. Different reactions may appear at different times, such as sneezing attacks during scraping of fruits and vegetables, when particles can get into the air; or conjunctivitis if the patient touches his/her eyes after touching the fruit or vegetables. Wearing gloves and masks can help prevent contact with allergens. It is also recommended to avoid latex (rubber gloves) that can cause cross-allergic reactions to foods of plant origin. If the patient avoids areas of certain types of pollen, the syndrome usually relieves after two to three years.

Discussion

It can be said that OAS is an IgE-mediated allergic response usually to fresh fruits, vegetables and nuts, due to cross-reactivity between pollen allergens and structurally similar proteins in foods[21]. Since the disease is often unrecognized, there are only a few studies on the occurrence, etiology, pathogenesis, and treatment of OAS. It is particularly important to take proper medical history. In one study in the UK, Skypala *et al.* examined the usefulness of good history that may lead to suspicion of OAS[22]. They surveyed 123 adult patients with rhinoconjunctivitis in the season of spring-flowering birch, who had independently completed a questionnaire and were tested by prick test and provocation food test; 42.2% of the patients were diagnosed with OAS, and the diagnostic questionnaire was particularly useful[22].

In another study, Caliskaner *et al*. determined risk factors for the development of OAS in 111 patients with seasonal allergic rhinitis. It was shown that OAS occurred more often in women than in men, and was more common in elderly patients and asthmatic patients. It was also found that OAS did not occur in all patients suffering from seasonal allergies, but only in some patients (probably those with atopic constitution)[13]. In patients with a history of OAS, a "prick-to-prick" test on (fresh) fruits and vegetables may be also performed.

Jagdis *et al*. analyzed OAS and the incidence of food allergies *via* a cross-sectional study. Given the spread of alder tree pollen in the area (on the coast of British Columbia, in the period from February to April), they investigated whether exposure to the allergen could cause an increased prevalence of allergies to pollen and the appearance of OAS. Sixty-three patients with OAS and allergic rhinitis were included in the study (average age 37 years; 83% of women and 17% of men; 36% with accompanying atopic dermatitis and 24% with concomitant asthma). Each patient completed a survey and 14 patients were tested by skin test. The proven prevalence of OAS reached 42%, and skin tests of all 14 patients were positive for alder and birch pollen. The most common allergens responsible for the appearance of OAS were apples (70%), cherries (59%), and peaches (60%)[21].

The diagnosis of IgE-mediated allergies (including OAS) is based on a skin-prick test, and is usually confirmed by standard specific IgE *in vitro* tests and provocation tests. However, skin tests use natural allergen extracts (mixture of allergenic and non-allergenic molecules) that are difficult to standardize, and mainly define the source, but this does not reveal which allergen molecules triggered the sensitization[22,23]. In recent years, along with the diagnosis by standard methods, microarray-based IgE detection can be used, with an assay based on soluble components and the use of microarray technology. It is particularly useful in multi-sensitized patients. The diagnostic soluble component is based on natural or recombinant allergens with structural and immunobiological characteristics of natural resources, resulting in a detailed reactive IgE profile for each patient[24]. It is expected that the diagnostic methods for allergies in people who are multi-sensitized will be further improved, leading to better knowledge of the nature and cause of allergic reactions, and thus achieving more effective treatment. In any case of the occurrence of OAS, nonspecific oral changes, urticaria, angioedema, or serious gastrointestinal/respiratory or cardiovascular symptoms, the physician should always consider the possibility that the reaction may be the result of food intake.

Conclusion

An increase in the prevalence of OAS has been observed, but it often goes unrecognized because of its nonspecific symptoms. The physician should therefore pay attention to the subjective symptoms in patients allergic to pollen, since OAS occurs as a cross-reaction between pollen and nutritional allergens. It is also important to know the etiology and diagnosis of OAS in order to properly approach the patient and apply appropriate therapy to avoid more serious consequences. It should be emphasized that a multidisciplinary approach is important in OAS involving different professions (ear-nose-throat specialists, oral pathologists, allergologists, immunologists, dermatologists, pediatricians, gastroenterologists, and various other specialties), as such a joint approach is the only way to take into consideration all the history and clinical elements of the disease, so that its true identity can be recognized.

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Sažetak

SINDROM ORALNE ALERGIJE – POJAVA KOJA ZAHTIJEVA MULTIDISCIPLINARNI PRISTUP

N. Kelava, L. Lugović-Mihić, T. Duvančić, R. Romić i *M. Šitum*

Sindrom oralne alergije je jedan od najčešćih oblika alergije na hranu. Ovaj sindrom uključuje simptome kao što su svrbež i oticanje usnica, nepca i jezika, koji nastaju obično nakon konzumacije svježeg voća i povrća. Patogenetski, dolazi do križne reakcije između antigena peludi i antigena iz hrane kao što je svježe voće, povrće i orašasti plodovi, koji su strukturalno slični peludi. Ovaj sindrom pripada alergijskim reakcijama tipa I (IgE posredovane reakcije) koje uključuju reakciju specifičnog IgE sa specifičnim alergenom odnosno proteinom peludi i s proteinom iz hrane. Dijagnozu postavljamo prvenstveno na temelju anamneze, te potvrđujemo kožnim testiranjem, testovima *in vitro* i provokacijskim testovima. Diferencijalna dijagnoza uključuje mnoge bolesti (npr. sindrom pečenja usta, angioedem, peludna groznica i još različite oralne bolesti) pa je upravo zbog toga potreban multidisciplinarni pristup te uključiti stručnjake različitih specijalnosti u postupak dijagnostike i liječenja. Terapija uključuje izbjegavanje odgovornog voća i povrća ili njihovu termičku obradu te primjenu antihistaminika, ponekad su potrebne i jače terapijske mjere, npr. u liječenju anafilaktične reakcije. U ovome radu prikazana je etiopatogeneza, klinička slika i simptomi, dijagnostički postupci i liječenje oralnog alergijskog sindroma.

Ključne riječi: *Alergija na hranu; Oralne bolesti – imunologija; Sindrom oralne alergije; Pelud d*