Acta Dermatovenerol Croat 2008;16(1):19-24 CLINICAL ARTICLE

Oral Allergy Syndrome in Patients with Airborne Pollen Allergy Treated with Specific Immunotherapy

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Received: October 16, 2007
Accepted: January 3, 2008

SUMMARY According to literature, approximately 20%-70% of patients sensitized to pollen allergens experience oral allergy syndrome (OAS) symptoms after eating raw fruits and vegetables. There is no standard treatment established for OAS except avoiding implicated food. However, in patients with airborne pollen allergy treated with specific immunotherapy (SIT), an improvement of OAS symptoms has been reported in 30% to even 84% of individuals examined. The aim of the present study was to evaluate the prevalence of OAS symptoms in patients with various manifestations of pollen airborne allergy (atopic dermatitis (AD), asthma, allergic rhinitis) treated with subcutaneous type of SIT. In addition, the most common patterns of cross-reactivity in OAS were analyzed and correlations between OAS symptoms and patient age, type of sensitizing pollen allergens and atopy manifestations investigated. Also, the relationship between SIT duration and clinical improvement of both OAS symptoms and pollen allergy symptoms was analyzed. The study included 57 patients with airborne allergy treated with allergen vaccination (60% male and 40% female). Allergic rhinitis was diagnosed in 71%, AD in 19%, AD and asthma in 4%, allergic rhinitis and asthma in 4%, and both AD and allergic rhinitis in 2% of study patients. Twenty-eight percent of study patients complained of overt symptoms of OAS (22% of allergic rhinitis patients and 27% of AD patients); 69% of the subjects presenting with OAS showed polyvalent airborne allergy to pollens and 31% were sensitized to only one group of pollen allergens (mostly grass pollens, tree pollens and mugwort pollens). There was no statistically significant correlation between the presence of OAS symptoms and patient diagnosis, patient age and type of allergen vaccination used. According to patients' opinion, SIT significantly improved oral symptoms in 50% of study patients, 44% reported no impact of SIT on OAS symptoms and 6% of patients observed worsening of OAS symptoms after unintentional ingestion of implicated food during the course of SIT. The study revealed OAS as a significant problem in patients sensitized to various pollen allergens. The results on OAS prevalence in atopic subjects (28%) were consistent with some literature data. There was clear association between OAS and polyvalent airborne allergy (69%). Cross-reactivity patterns were typical (for example, tree pollen allergy – intolerance of apples, carrots and potatoes; grass pollen allergy – intolerance of kiwi fruit and tomatoes). Questionnaire analysis indicated that subcutaneous SIT significantly alleviated OAS symptoms associated with ingestion of the responsible fruit and vegetables in half of study subjects. Further evaluation of the duration/persistence and stability of the phenomenon is planned for the future.

KEY WORDS: atopic dermatitis, oral allergy syndrome, immunotherapy

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INTRODUCTION

According to early reports from 1948, "patients sensitive to catkin-bearing trees had inconveniences after eating hazelnuts, such as itching and burning in mouth and throat, and similar symptoms after eating raw apples and other kinds of fruits" (1). Indeed, it is currently well established that patients suffering from pollinosis often present various adverse reactions after ingestion of certain plant-derived foods (2). Unpleasant symptoms (oral pruritus, edema of the lips and tongue, hoarseness) are usually restricted to oral mucosa and most frequently the term oral allergy syndrome (OAS) is used, although according to some authors it may be misleading (2), for in many cases ingestion of some fruits, vegetables and spices may also cause laryngeal edema, bronchial asthma and severe gastrointestinal symptoms. Thus, the term pollen-food syndrome (PFS) has also been proposed and is by many considered more appropriate (3). The most common and well described PFSs or OASs include birch-fruit syndrome, celery-mugwort-spice syndrome and ragweed-melon-banana syndrome (2,4).

There is no standard treatment established for OAS except avoiding implicated food. However, it has been observed that approximately 50% of patients with airborne pollen allergy treated with specific immunotherapy (SIT) experience improvement of OAS symptoms (5-8). Therefore, it seems that SIT with pollen allergens may have a beneficial effect on OAS (4).

The aim of the present study was to evaluate the prevalence of OAS symptoms in patients with various manifestations of pollen airborne allergy (atopic dermatitis (AD), asthma, allergic rhinitis) treated with subcutaneous type of SIT. We also analyzed the most common patterns of cross-reactivity in OAS and investigated the association between OAS and patient age, type of sensitizing pollen allergens and atopy manifestations. Furthermore, relations between SIT duration and clinical improvement of both OAS symptoms and pollen allergy symptoms were analyzed.

PATIENTS AND METHODS

The study included a group of 57 patients (23 female and 34 male), mean age 26.6±9.9, range 8-53 years. All subjects presented various manifestations of airborne allergy; the diagnosis of allergic rhinitis was made in 71%, AD in 19%, AD and asthma in 4%, allergic rhinitis and asthma in 4%, and AD and allergic rhinitis in 2% of study patients. All patients were treated with perennial SIT using depot aluminum hydroxide-adsorbed airborne allergen extracts (Novo Helisen Depot-NHD, Nexter Allergopharma) (Table 1). The mean duration of SIT was 2.7±1.7, range 1-6 years. A short questionnaire was used to get information on a wide variety of OAS symptoms in each atopic individual, together with a list of culprit fruits and vegetables. Moreover, patients complaining of OAS were asked about their opinion about the possible SIT effect on their oral symptoms (no effect, alleviation of OAS symptoms, complete resolution of OAS, or exacerbation of OAS symptoms), and to evaluate SIT general efficacy (improvement, complete remission, no effect or exacerbation of atopic dermatitis, allergic rhinitis or asthma).

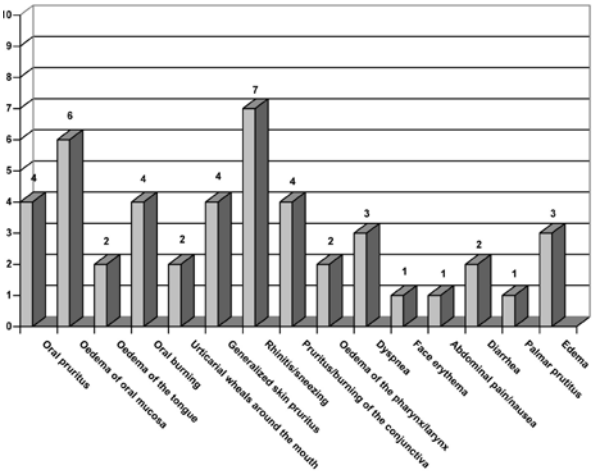

Figure 1. Symptoms present after ingestion of certain foods in patients suffering from PFS.

Table 1. An overview of allergen vaccines used in atopic patients

Allergen vaccine type	Number of patients
Novo Helisen Depot – grasses 100%	28
Novo Helisen Depot – grasses 80%, mugwort 20%	13
Novo Helisen Depot – grasses 80%, birch 20%	1
Novo Helisen Depot – mugwort 100%	3
Novo Helisen Depot – birch 35%, alder 30%, hazel 35%	8
Allergovit – grasses 100%	3
Allergovit – grasses 80%, mugwort 20%	1

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RESULTS

Sixteen (28%) atopic patients complained of clear OAS, or rather PFS symptoms (Fig. 1). Among OAS-positive patients, three suffered from AD, one patient had both AD and asthma, another one suffered from AD and allergic rhinitis, nine had isolated symptoms of allergic rhinitis, and two patients had allergic rhinitis and asthma. Furthermore, among individuals presenting with OAS, 11 (69%) had polyvalent airborne allergy to pollens and five (31%) were sensitized to only one group of pollen allergens (predominantly grass, tree and mugwort pollen allergens). Most of the patients presenting OAS symptoms were treated with Novo Helisen Depot allergy vaccines composed of tree and grass pollen allergens (Fig. 2). In the same group of patients, the cross-reactivity patterns between pollen and food allergens were typical (Table 2).

There was no statistically significant correlation between the presence of OAS symptoms and patient age, diagnosis and type of allergen vaccination used. According to the patients' opinion, SIT significantly improved OAS symptoms in eight (50%) of 16 subjects; seven of 16 (44%) subjects reported no clear impact of SIT on OAS symptoms, and one (6%) patient observed worsening of OAS symptoms after unintentional ingestion of implicated food during the course of SIT (Fig. 3).

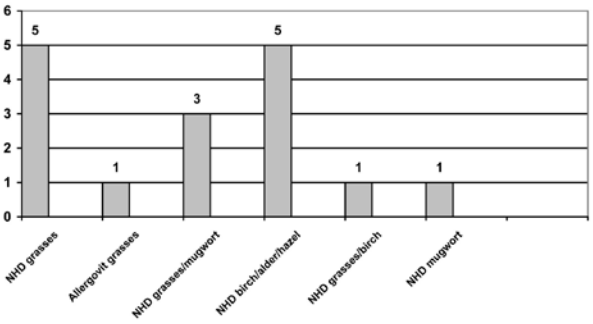

Figure 2. Composition of allergy vaccines in patients presenting OAS symptoms

Table 2. Most common cross-reactivity patterns between pollen and food allergens observed in study patients presenting oral allergy syndrome symptoms

Type of sensitizing airborne allergens	Cross-reacting foods/spices	Number of patients
Patients allergic to: grasses, trees and weeds	Stone fruits	10
	Kiwi	3
	Carrot	2
	Celery	2
	Pepper	2
	Nuts	3
	Tomato	1
Patients allergic to: grasses	Melon	1
	Tomato	1
	Kiwi	1
Patients allergic to: grasses, mugwort	Stone fruits	2
	Kiwi	2
	Curry	1
	Celery	1
	Tomato	2
	Peas	1
Patients allergic to: grasses, trees	Stone fruits	1
	Kiwi	2
	Carrot	1
	Nuts	1
Patients allergic to: trees	Stone fruits	2
	Carrot	1
	Potato	1
Patients allergic to: mugwort	Nuts	1
	Carrot	1
	Peas	1

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Consecutive analysis concerned overall impact of SIT on disease severity in allergic rhinitis, AD and asthma (presented in Table 3). Among patients suffering from allergic rhinitis, three patients achieved asymptomatic status, four patients observed improvement, whereas in two patients there was no impact of SIT on disease severity. Complete remission was observed in one AD patient, whereas in two patients SIT led to improvement. According to the opinion of two patients presenting the symptoms of allergic rhinitis and asthma, the symptoms of asthma improved in both patients and those of allergic rhinitis in one patient, whereas the other

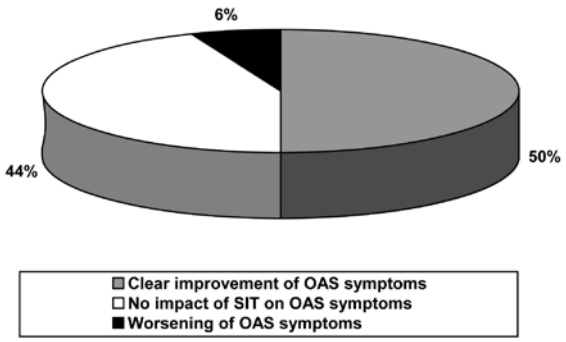

Figure 3. Effect of SIT on OAS symptoms according to patients' opinion.

Table 3. Impact of specific immunotherapy (SIT) on both oral allergy syndrome (OAS) symptoms and disease severity in 16 study patients

Patient No.	Age/Sex	Allergen vaccine used	SIT duration (months)	Status of OAS symptoms*	Status of disease symptoms**
1	19/F	Novo Helisen Depot grasses 80%, birch 20%	12	A	AR – B
2	32/M	Novo Helisen Depot grasses 80%, mugwort 20%	12	B	AD – A
3	27/F	Novo Helisen Depot grasses 80%, mugwort 20%	12	C	AD – D AR – B
4	30/M	Novo Helisen Depot birch 35%, alder 30%, hazel 35%	24	B	AR – C
5	26/F	Novo Helisen Depot mugwort 100%	36	A	AR – A
6	30/M	Allergovit grasses 100%	36	A	AR – A
7	23/M	Novo Helisen Depot grasses 80%, mugwort 20%	12	A	AR – C As – B
8	13/M	Novo Helisen Depot grasses 100%	48	B	AR – B As – B
9	32/M	Novo Helisen Depot birch 35%, alder 30%, hazel 35%	12	B	AD – B
10	22/F	Novo Helisen Depot grasses 100%	12	B	AD – B As – B
11	25/M	Novo Helisen Depot grasses 100%	60	A	AR – B
12	11/F	Novo Helisen Depot birch 35%, alder 30%, hazel 35%	36	A	AD – B
13	53/M	Novo Helisen Depot birch 35%, alder 30%, hazel 35%	48	A	AR – A
14	16/M	Novo Helisen Depot birch 35%, alder 30%, hazel 35%	6	B	AR – C
15	31/F	Novo Helisen Depot grasses 100%	36	B	AR – B
16	29/M	Novo Helisen Depot grasses 100%	36	A	AR – B

*A = clear improvement of OAS symptoms; B = no impact of SIT on OAS symptoms; C = worsening of OAS symptoms

**AD (atopic dermatitis): A = asymptomatic status; B = improvement; C = no impact of SIT on disease symptoms; D = exacerbation of the disease

AR (allergic rhinitis): A = asymptomatic status; B = improvement; C = no impact of SIT on disease symptoms; D = exacerbation of the disease

As (asthma): A = asymptomatic status; B = improvement; C = no impact of SIT on disease symptoms; D = exacerbation of the disease

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one observed no significant effect of SIT on the severity of allergic rhinitis. In one patient presenting AD and asthma, improvement occurred in both diseases, whereas only one patient with AD and allergic rhinitis reported exacerbation of AD along with improvement of allergic rhinitis.

DISCUSSION

According to several authors, from 23% to even 70% of individuals diagnosed with pollen allergy experience symptoms referred to as OAS after ingestion of raw fruits and vegetables, as a consequence of cross-reactivity between pollen and food allergens (9-12). Reactions to certain foods are often confined to oral itching or burning sensation, but may also involve more severe systemic reactions (2). In the present study, the overall prevalence of OAS in atopic patients was 28% (which is consistent with literature data), and predominantly affected individuals suffering from allergic rhinitis (over 56%) and patients presenting polyvalent allergy to various airborne pollen allergens (69%). It is worth emphasizing that apart from complaints restricted to oral mucosa (oral pruritus, edema, burning), several patients presented symptoms originating from respiratory and alimentary system (dyspnea, abdominal pain, nausea, diarrhea, sneezing). Therefore, in accordance with some authors' opinion mentioned above (2,3), the term PFS, or pollen-food allergy syndrome may be more precise and appropriate.

In respect to the cross-reactivity pattern, apple is definitely considered as the most commonly involved food, probably due to the high homology between its major allergen (Mal d 1) and major birch pollen allergen (Bet v 1) (5). Specific IgE against apple is detectable in sera of almost all birch pollen-sensitive patients (13). In our study, stone fruits (apple, pear, plum and peach) predominated in the cross-reactivity pattern, especially in patients with polyvalent airborne allergy to grasses, trees and weeds but also to grasses and mugwort, and in individuals with monovalent allergy to tree pollen allergens. Less common but noteworthy would be the cross-reactivity pattern observed in two of our patients allergic to mugwort and to both mugwort and grass pollen allergens and presenting OAS symptoms after ingestion of peas. Recently, Figueroa *et al*. (14) have proposed a novel mustard-mugwort allergy syndrome to describe associations with mugwort pollinosis and several botanically unrelated plant-derived foods, especially nuts and legumes. The possible causative allergens include Art v 60 kDa, Art v 4 (profilin) and Art v 3, a mugwort nonspecific lipid transfer protein (LTP).

SIT is an established method of treatment in pollen allergy (presenting as allergic rhinitis, asthma or AD), influencing the natural course of allergic inflammatory process (4,15,16). Since OAS, or PFS is associated with cross-reactivity of certain allergens, SIT may lead to resolution not only of allergic rhinitis or AD but also of the associated food intolerance (2). According to early reports by Möller (7) in 72 children with severe rhinoconjunctivitis due to birch pollinosis, hay fever symptoms improved by SIT but neither subcutaneous (n=42) nor oral (n=14) immunotherapy with birch pollen allergen preparations made the food sensitivity decrease significantly more than the placebo oral immunotherapy (n=16). Kelso *et al*. (6) have described a patient with allergic rhinitis and oral allergy syndrome in which the disease symptoms resolved after one year of SIT, and he was able to eat fresh fruits and vegetables without any reaction. Skin testing and specific IgE immunoassay demonstrated marked reduction in sensitivity not only to pollen allergens but to foods as well. In the authors' opinion, these results support the concept that OAS is due to cross-reacting allergens in foods and pollens and may be amenable to treatment with SIT. Subsequent open apple challenge in a placebo-controlled prospective study performed by Asero (5) demonstrated significant reduction or complete disappearance of OAS symptoms in 84% of individuals monosensitized to birch pollen allergens, suggesting a beneficial effect of SIT on the food-pollen allergy syndrome. On the other hand, according to Bucher *et al*. (4), in spite of the favorable impact of OAS to apple or hazelnut in birch pollen-allergic individuals, the amount of fruit tolerated is still very small and thus the effect of SIT on the patients' management of OAS remains limited.

In the present study, 50% of patients observed clearly a beneficial effect of SIT on OAS. Almost all of these patients suffered from allergic rhinitis (7 of 8) and most of them also observed either improvement of the primary airborne allergy symptoms or even were in asymptomatic status in the course of SIT. However, 44% of study patients reported no impact of SIT on their food-related complaints, while most of them still noted improvement of their airborne allergy symptoms. Therefore, the advantage of SIT in OAS still remains controversial and needs to be further evaluated. Only one patient (a 27-year-old female) reported exacerbation of both OAS symptoms and AD symptoms during 12

months of SIT with grass and mugwort pollen extracts, but unfortunately in this case we observed both the lack of compliance and reluctance towards SIT.

Undoubtedly, an interesting issue for the future, also in case of the group of patients analyzed in the present study, would be evaluation of long-term efficacy of SIT with pollen extracts on the pollen-related food syndrome. According to a recent study by Asero (12), at least in some patients pollen SIT can exert a long-lasting effect on pollen-associated food allergies (patients sensitized to birch pollen were still able to eat apples without any complaints as long as 30 months after the end of SIT). However, the study was carried out in a selected population characterized by total remission of clinical symptoms and skin reactivity to apple at the end of SIT course, and these results might not be valid for the whole population. Moreover, in many cases apple intolerance showed a tendency to recur upon SIT discontinuation, probably due to prolonged and repeated exposure to the primary sensitizing allergen (birch pollen).

References

1. Juhlin-Dannfelt C. About the occurrence of various forms of pollen allergy in Sweden. Acta Med Scand 1948;130:563-77.
2. Kelso JM. Pollen-food allergy syndrome. Clin Exp Allergy 2000;30:905-7.
3. Egger M, Mutschlechner S, Wopfner N, Gadarmaier G, Briza P, Ferreira F. Pollen-food syndromes associated with weed pollinosis: an update from the molecular point of view. Allergy 2006;61:461-76.
4. Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. Allergy 2004;59:1272-76.
5. Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. Clin Exp Allergy 1998;28:1368-73.
6. Kelso JM, Jones RT, Tellez R, Yunginger JW. Oral allergy syndrome successfully treated with pollen immunotherapy. Ann Allergy Asthma Immunol 1995;74:391-6.
7. Möller C. Effect of pollen immunotherapy on food hypersensitivity in children with birch pollinosis. Ann Allergy 1998;62:343-5.
8. Herrmann D, Henzgen M, Frank E, Rudeschko O, Jager L. Effect of hyposensitization for tree pollinosis on associated apple allergy. J Invest Allergol Clin Immunol 1995;5:259-67.
9. Eriksson NE, Formgren H, Svenonius E. Food hypersensitivity in patients with pollen allergy. Allergy 1982;37:437-43.
10. Stich O, Pichler WJ. Nährungsmittel-Allergien bei Pollensensibilisierungen Teil I: Kreuzreaktionen bei Birkenpollen – Sensibisierung. Allergologie 1993;16:288-94.
11. Ebner C, Hirschwehr R, Bauer L, Breiteneder H, Valenta R, Ebner H *et al*. Identification of allergens in fruits and vegetables: IgE cross reactivities with the important birch pollen allergens Bet v 1 and Bet v 2 (birch profilin). J Allergy Clin Immunol 1995;95:962-9.
12. Asero R. How long does the effect of birch pollen injection SIT on apple allergy last? Allergy 2003;58:435-8.
13. Ebner C, Birkner T, Valenta R, Rumpold H, Breitenbach M, Scheiner O *et al*. Common epitopes of birch pollen and apple. Studies by Western and Northern blot. J Allergy Clin Immunol 1991;88:588-94.
14. Figueroa J, Blanco C, Dumpierrez AG, Almeida L, Ortega N, Castello R *et al*. Mustard allergy confirmed by double-blind placebo-controlled food challenges: clinical features and cross-reactivity with mugwort pollen and plant derived foods. Allergy 2005;60:48-55.
15. Czarnecka-Operacz M, Silny W. Specific immunotherapy in atopic dermatitis - Four-year treatment in different age and airborne allergy type subgroups. Acta Dermatovenerol Croat 2006;14:230-40.
16. Hansen KS, Khinchi MS, Skov PS, Bindslev-Jensen C, Pohlsen LK, Malling HJ. Food allergy to apple and specific immunotherapy with birch pollen. Mol Nutr Food Res 2004;48:441-8.