
Correlation of oral allergy syndrome due to plant-derived foods with pollen sensitization in Japan

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Background: The clinical features of patients with oral allergy syndrome (OAS) due to plant-derived foods related to pollen allergy have been rarely reported in Japan.

Objectives: To evaluate the characteristics of OAS and to investigate whether pollen sensitizations are correlated with the prevalence of OAS in Japan.

Methods: We measured specific IgE antibodies against 5 pollens in 622 outpatients (277 males and 345 females; mean age, 37 years) with atopic dermatitis, urticaria, angioedema, and food allergy during a 2-year period. Furthermore, OAS is diagnosed based on anamnesis and positive skin prick test reactions to suspected foods.

Results: Eighteen of the 436 patients (4.1%) sensitized to pollens were diagnosed as having OAS. Rates of specific IgE antibody-positive responses against Japanese cedar, ragweed, orchard grass, mugwort, and alder pollen were 69.8%, 35.3%, 29.1%, 24.1%, and 19.6%, respectively. The prevalence of OAS showed a significant positive correlation with sensitization to alder ($P < .001$). In addition, the most frequent causative foods were found to be apple, peach, and melon. The prevalence of OAS due to apple showed a significant positive correlation with sensitization to alder ($P < .001$) pollen, due to peach showed a significant positive correlation with sensitization to alder ($P < .001$) and orchard grass ($P < .05$) pollen, and due to melon showed a significant positive correlation with sensitization to alder ($P < .005$), orchard grass ($P < .05$), and ragweed ($P < .05$) pollen.

Conclusion: Sensitization to pollens from species in the Betulaceae family is most strongly implicated in causing OAS in Japan.

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INTRODUCTION

In 1987, Amlot et al¹ proposed the term *oral allergy syndrome* (OAS) to describe the phenomenon of the appearance of oral symptoms as the first major clinical sign after food intake in IgE-mediated food allergy. OAS is itself an IgE-mediated allergy, usually limited to the oropharynx, which often occurs after the ingestion of certain fresh fruits, nuts, or vegetables in pollen-sensitized individuals. In this case, OAS is considered to be caused by homologous proteins and cross-reacting antigenic determinants in pollens and different fruits, vegetables, and nuts.^{2,3} Systemic reactions are uncommon because the cross-reacting proteins tend to be heat-labile and presumably undergo rapid degradation during digestion.

OAS to fresh fruits and vegetables can occur in association with allergy to a variety of pollens, including birch pollen, grasses, ragweed, and mugwort. In particular, birch pollen-sensitized patients in central and northern Europe have been

reported to frequently react to plant-derived foods, particularly fruits belonging to the Rosaceae family, such as cherry, peach, apricot, pear, and apple.^{4–7} In contrast, in the United States, where ragweed pollen abounds, an association between ragweed allergy and sensitivity to melon and banana has been reported. In the United States, median estimates of the prevalence of OAS in patients with pollen allergy are 5% in children and 8% in adults. Birch and ragweed were more commonly identified as the cross-reacting pollens than were grasses.⁸ Therefore, the geographic prevalence of the local flora seems to be the most influential environmental factor in inducing sensitivity to fruits and vegetables. However, the clinical features of patients with OAS due to plant-derived foods have so far been reported only rarely in Asian countries, including Japan. In Japan, pollens of Japanese cedar and cypress, which belong to the Gymnospermae class, and alder, which belongs to the Betulaceae family, are released mainly in spring. In contrast, pollen of orchard grass, which belongs to the Poaceae family, peaks in summer, and ragweed and mugwort, which belong to the Asteraceae family, are most prevalent in the autumn. We need to recognize the possibility that patients with OAS might increase in number in the near future because of increases in pollen allergies. Geographic and dietary influences complicate epidemiologic studies of pollinosis-associated food allergy. It is, therefore, important

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to assemble accurate data on the frequency of plant-derived food allergies in different areas. Herein, we evaluate the characteristics of OAS due to plant-derived foods and identify the relevant pollens associated with this syndrome in Japan.

METHODS

Patients

Outpatients with atopic dermatitis, urticaria, angioedema, and food allergy attending the Department of Dermatology of Yokohama City University Hospital between January 1, 2006, and December 31, 2007, were recruited into this study. After providing written informed consent, participating patients underwent skin and blood tests to diagnose pollen allergy and OAS. This research study was approved by the institutional review board of Yokohama City University Hospital.

Skin Testing

All the patients were subjected to diagnostic skin prick tests using commercial extracts of Japanese cedar, orchard grass, ragweed, and mugwort (Torii, Tokyo, Japan) and alder (Hollister Stier Laboratories, Spokane, Washington) according to standard procedures.⁹ Plant-derived foods were tested according to the prick-prick technique.¹⁰ Prick-prick tests with fresh materials were performed for all foods suspected of causing OAS in the clinical history of the patients by physicians. Histamine dihydrochloride, 10 mg/mL, and phosphate-buffered saline served as positive and negative controls, respectively. Responses to the prick test were classified as negative when the average wheal diameter was the same as that of the negative control or as equivocal, positive (2+), strongly positive (3+), and very strongly positive (4+) when the average wheal diameter was greater than 25%, 50%, 100%, and 200%, respectively, of the positive control response induced by histamine, 10 mg/mL. The elicited response was considered positive when the average wheal diameter induced by the allergen extract was 50% or more of the positive control.⁹ Prick-prick tests with all the foods were also performed on 5 control subjects who were not allergic to any food; all had negative prick-prick test results with all the materials.

Serum Specific IgE Measurements

Specific IgE levels (ImmunoCAP; Phadia, Uppsala, Sweden) of pollens of Japanese cedar, alder, orchard grass, ragweed, mugwort, and foods were measured. The cutoff value for the assay was 0.35 kUA/L.

Diagnosis of OAS

Patients experiencing oropharyngeal symptoms, such as itching, tingling, and swelling in the oral cavity, immediately after ingesting plant-derived foods and who also had positive skin prick test results with the suspected foods were diagnosed as having OAS.

Statistical Analysis

Correlations between the prevalence of OAS and sensitization to the pollens were analyzed using the Fisher exact test.

RESULTS

Prevalence of Pollen Sensitization

A total of 622 patients (277 men and 345 women) with a mean age of 37 years (range, 1-83 years) were enrolled in this study. Four hundred thirty-six patients were found to be sensitized to at least 1 of the 5 pollens examined. Among pollens investigated, the highest rates of positive responses assessed using ImmunoCAP were against Japanese cedar (69.8%), followed by ragweed (35.3%), orchard grass (29.1%), mugwort (24.1%), and alder (19.6%) (Table 1).

Clinical Characteristics of Patients With OAS

Eighteen of the 622 outpatients (2.9%) with atopic dermatitis, urticaria, angioedema, and food allergy were diagnosed as having OAS (Table 2). Eighteen of the 436 patients (4.1%) sensitized to pollens were diagnosed as having OAS. Thirty-seven patients had oropharyngeal symptoms after food ingestion but did not have positive skin test results and were, therefore, not diagnosed as having OAS. The mean age of these 18 patients (3 males and 15 females) was 30.9 years (range, 10-56 years). Regarding allergic history, 14 patients (77.8%) had pollinosis, 9 (50.0%) had atopic dermatitis, 6 (33.3%) had bronchial asthma, and 4 (22.2%) had food allergy.

In the 18 patients with OAS, oropharyngeal symptoms were accompanied by skin symptoms, such as generalized

Table 1. Prevalence of Oral Allergy Syndrome (OAS) in Patients With Pollen Sensitization

	Specific IgE									
	Japanese cedar (n = 613)		Alder (n = 622)		Orchard grass (n = 560)		Ragweed (n = 346)		Mugwort (n = 453)	
	Positive group (n = 428) ^a	Negative group (n = 185) ^b	Positive group (n = 122) ^a	Negative group (n = 500) ^b	Positive group (n = 163) ^a	Negative group (n = 397) ^b	Positive group (n = 122) ^a	Negative group (n = 224) ^b	Positive group (n = 109) ^a	Negative group (n = 344) ^b
Frequency in all patients, %	69.8	30.2	19.6	80.4	29.1	70.9	35.3	64.7	24.1	75.9
Patients with OAS, No.	17	1	14	4	9	8	9	7	7	9
Prevalence of OAS, %	4.0	0.5	11.5	0.8	5.5	2.0	7.4	3.1	6.4	2.6

^a The positive group includes patients with class 2 or greater in specific IgE measurement against each pollen.

^b The negative group includes patients with less than class 2 in specific IgE measurement against each pollen.

Table 2. Characteristics of the 18 Patients With OAS

Patient No./ Sex/Age, y	Causative foods of OAS	Symptoms other than oropharyngeal symptoms	History				Serum specific IgE class ^a				
			PO	BA	AD	FA	Japanese cedar	Alder	Orchard grass	Ragweed	Mugwort
1/F/52	Cherry, loquat, strawberry, soybean, potato	None	+	–	–	–	2	4	2	0	0
2/M/11	Rice, iyokan	None	+	+	+	+	5	2	1	2	1
3/F/50	Peach, melon, papaya, watermelon, tomato, radish	AE, EA	+	+	–	–	3	3	3	2	1
4/F/30	Peach, lychee, melon, lettuce	UR, DY, EA	+	–	–	–	3	3	3	2	0
5/F/43	Soybean, loquat, alfalfa	AE	+	–	+	+	4	4	3	0	0
6/F/10	Peach, apple, cherry, lychee, melon	None	+	–	–	–	4	5	2	2	2
7/M/16	Peach, apple, pear	AB	+	+	+	–	6	6	2	1	2
8/F/36	Melon	AE	+	–	+	–	2	0	0	1	2
9/F/43	Soybean	None	–	–	–	+	1	0	1	2	2
10/F/17	Almond	None	+	+	+	–	4	1	3	3	4
11/F/25	Pineapple, yam	None	–	–	+	–	2	0	0	0	0
12/F/56	Apple, peach, pear, strawberry, kiwi, grape, tomato, lettuce	EA	+	+	–	–	2	3	0	0	0
13/F/26	Cashew nut, pistachio, hazelnut	UR, AE, DY, AB	+	–	–	–	4	4	1	2	0
14/F/24	Kiwi, melon, banana, grapefruit, tomato, cucumber, soy milk	None	+	–	+	–	5	3	4	3	2
15/M/21	Apple, kiwi	None	–	–	–	–	2	3	0	ND	ND
16/F/19	Peanuts, cashew nut, walnut	UR, AE	–	+	+	+	5	2	ND	ND	ND
17/F/39	Apple, peach, pear, strawberry, melon, banana, loquat	AE, DY, AB	+	–	–	–	4	3	ND	ND	ND
18/F/38	Apple	AB, EA	+	–	+	–	4	4	0	ND	ND

Abbreviations: AB, abdominal symptoms; AD, atopic dermatitis; AE, angioedema; BA, bronchial asthma; DY, dyspnea; EA, itching of the ear; FA, food allergy; ND, not done; PO, pollinosis; UR, urticaria; +, positive; –, negative.

^a Results range from class 0 (<0.35 kIU/L) to class 6 (≥100 kIU/L).

urticaria, in 3 (16.7%) and by facial angioedema in 6 (33.3%). In addition, dyspnea developed in 3 patients (16.7%), abdominal symptoms in 4 (22.2%), and itching of the ear in 4 (22.2%). The foods most frequently causing these symptoms were found to be apple, peach, and melon in 6 patients each (33.3%) (Table 3). Of the 18 patients with OAS, 17 (94.4%)

were sensitized to Japanese cedar pollen, 14 (77.8%) to alder pollen, 9 (56.3%) to orchard grass pollen, 9 (56.3%) to ragweed pollen, and 7 (43.8%) to mugwort.

Correlation Between Pollen Sensitization and OAS Due to Plant-Derived Foods

Of the 428 patients sensitized to Japanese cedar pollen, 17 (4.0%) had OAS, which was the lowest rate among all pollens. On the other hand, of 122 patients sensitized to alder pollen, 14 (11.5%) had OAS, which was the highest rate. Patients with OAS accounted for 5.5% (9 of 163), 7.4% (9 of 122), and 6.4% (7 of 109) of orchard grass, ragweed, and mugwort pollen-sensitized patients, respectively. The prevalence of OAS showed a significant positive correlation with sensitization to alder pollen ($P < .001$) but no correlation with sensitization to Japanese cedar, orchard grass, ragweed, or mugwort pollen (Table 4).

Correlation Between Pollen Sensitization and OAS Due to the Most Frequent Causative Foods

Correlations between pollen sensitization and the most frequent causative foods (apple, peach, and melon) were then analyzed (Table 4). Patients with OAS due to apple accounted for 1.4% (6 of 428), 4.9% (6 of 122), 1.8% (6 of

Table 3. Foods That Caused Oral Allergy Syndrome in 18 Patients

Causative food	Patients, No.
Apple	6
Peach	6
Melon	6
Kiwi	3
Strawberry	3
Soybean	3
Pear	3
Cherry	2
Loquat	2
Lychee	2
Banana	2
Tomato	2
Lettuce	2
Cashew nut	2

Table 4. Correlations Between Pollen Sensitization and Oral Allergy Syndrome

Pollen	Causative foods of oral allergy syndrome			
	All plant-derived foods	Apple	Peach	Melon
Japanese cedar	$P = .03$	$P = .23$	$P = .23$	$P = .23$
Alder	$P < .001^a$	$P < .001^a$	$P < .001^a$	$P < .005^a$
Orchard grass	$P = .06$	$P = .48$	$P < .05^a$	$P < .05^a$
Ragweed	$P = .13$	$P = .84$	$P = .24$	$P < .05^a$
Mugwort	$P = .13$	$P = .19$	$P = .31$	$P = .06$

^a Statistically significant.

163), 0.8% (1 of 122), and 2.8% (3 of 109) of patients sensitized to Japanese cedar, alder, orchard grass, ragweed, and mugwort pollen, respectively. The prevalence of OAS due to apple showed a significant positive correlation with sensitization to alder pollen ($P < .001$).

Patients with OAS due to peach accounted for 1.4% (6 of 428), 4.9% (6 of 122), 3.1% (5 of 163), 3.3% (4 of 122), and 2.8% (3 of 109) of patients sensitized to Japanese cedar, alder, orchard grass, ragweed, and mugwort pollen, respectively. The prevalence of OAS due to peach also showed a significant positive correlation with sensitization to alder pollen ($P < .001$) and orchard grass pollen ($P = .009$).

Furthermore, patients with OAS due to melon accounted for 1.4% (6 of 428), 4.1% (5 of 122), 3.1% (5 of 163), 4.1% (5 of 122), and 3.7% (4 of 109) of patients sensitized to Japanese cedar, alder, orchard grass, ragweed, and mugwort pollen, respectively. The prevalence of OAS due to melon showed a significant positive correlation with sensitization to 3 pollens: alder ($P < .005$), orchard grass ($P = .009$), and ragweed ($P = .022$).

DISCUSSION

In this study, the profile of OAS due to plant-derived foods was reported for Japanese patients, complementing several previous studies of OAS in Western countries. In 436 patients sensitized to at least 1 of the 5 pollens (Japanese cedar, alder, orchard grass, ragweed, and mugwort) and having atopic dermatitis, urticaria, angioedema, and food allergy, it was found that the prevalence of OAS due to plant-derived foods was 4.1% and that the foods most frequently causing this were apple, peach, and melon, in that order. Symptoms other than oropharyngeal symptoms included facial angioedema in 33.3% of patients, abdominal symptoms in 22.2%, itching of the ear in 22.2%, generalized urticaria in 16.7%, and dyspnea in 16.7%. However, the prevalence of OAS in pollen-sensitized patients in the allergy clinic under the aegis of dermatology may be underrepresented compared with the prevalence in patients with allergic rhinitis, bronchial asthma, or both because much of the OAS is due to primary sensitization with inhalant allergens having cross-reactive epitopes with foods.

Of 436 pollen-sensitized patients with atopic dermatitis, urticaria, angioedema, and food allergy, OAS was diagnosed in 18 (4.1%). OAS due to plant-derived foods related to

pollen allergy, which is also called *pollen-food allergy syndrome*, represents possibly the most common food allergy in adults, with up to 70% of patients allergic to pollen being affected.^{1,11–15} Among those patients, upward of 70% react to 2 or more foods. Only a few studies have addressed the prevalence of OAS, all of which have concentrated on OAS caused by fruits and vegetables. A study⁷ from Switzerland reported that approximately 35% of patients with pollen allergy were also sensitive to fresh fruits and vegetables. A similar prevalence was found in Italy in 283 patients allergic to pollen.¹⁶ Allergy to fruits and vegetables occurs most frequently in individuals with hay fever from birch pollen; a Scandinavian study⁴ found that 63% of birch pollen-allergic patients were sensitive to 1 or more fruits or vegetables; similar findings have been reported in Austria by Ebner et al,¹¹ who found that more than 75% of birch pollen-allergic patients developed symptoms of OAS after eating apples. OAS seems to be more common in adults than in children. The rate of OAS in pollen-allergic patients in Japan was less than that reported in other areas.

In the present study, it was suggested that sensitization to pollens from species of the Betulaceae family, ie, alder and birch, would be the most strongly implicated in causing OAS in Japan, as is the case in northern and central Europe. Previous studies^{4–7} also documented that birch pollen is associated with allergy to foods of the Rosaceae family, such as peach and apple. The cross-reactivity of the major allergens of sweet cherry (Pru av 1), apple (Mal d 1), pear (Pyr c 1), celery tuber (Api g 1), and carrot (Dau c 1) is due to structural similarities reflecting high amino acid sequence identities with Bet v 1, the major birch allergen, which belongs to pathogenesis-related protein type 10.^{17–25} In the present study, of the 5 pollens investigated, alder was correlated most frequently with the presence of OAS. Thus, OAS was present in 11.5% of all patients with alder pollen sensitization in Japan. This percentage seems to be lower than that reported in patients sensitized to pollens from species belonging to the Betulaceae family in European countries. It is not clear whether this difference between Japan and Western countries depends on different species of the Betulaceae family, the involved allergens, foods consumed generally, race, or other factors.

In the present study, the most frequent causative foods were found to be apple, peach, and melon. The prevalence of

OAS due to apple correlated with sensitization to alder pollen, peach with alder and orchard grass pollen, and melon with alder, orchard grass, and ragweed pollen. These results indicate that sensitization to pollens other than alder could also partly affect the prevalence of OAS due to some fruits in Japan. In Spain, peach was the most OAS-provoking fruit in a birch- and ragweed-free area, and most patients allergic to peach with pollinosis were mainly sensitized to grass pollens.²⁶ In 1970, Anderson et al¹⁴ documented an association between melon allergy and ragweed pollen. Furthermore, they also suspected the existence of an association between melon allergy and grass pollen and surmised that that association would be confirmed in ragweed-free areas. In the present study, allergy to mugwort, a type of weed, was associated with sensitivity to 3 frequent causative foods. However, it has been reported²⁷ that allergies to celery tuber, carrot, and spices can occur in patients sensitized to pollens of mugwort. Profilins, ubiquitous plant proteins that regulate components of the actin cytoskeleton of plants, are homologous proteins found in grass and associated foods.²⁸

In Japan, Japanese cedar pollinosis is the most prevalent allergy and is considered a significant sociomedical issue. Approximately 80% and 60% of adults with rhinitis and asthma, respectively, were reported to be sensitized to Japanese cedar pollen in Japan.²⁹ Herein, a high percentage of patients (69.8%) sensitized to Japanese cedar pollen was also found. Cross-reactivity between Japanese cedar pollen and tomato fruit has been reported,^{30,31} whereas in Western countries, tomato was reported to be cross-reactive with grass and ragweed pollen.³² However, we found no correlation between OAS and sensitization to Japanese cedar, and we also found that tomato was not a frequent causative food for OAS. This suggests that Japanese cedar is not a major inducer of OAS due to plant-derived foods in Japan.

In conclusion, these data show that the Betulaceae family of pollens, such as alder, are important sources of pollen allergy related to OAS in Japan and that different pollens affect the prevalence of OAS caused by defined fresh food sensitizations. Further identification and characterization of the involved cross-reacting allergens is necessary for a better understanding of OAS to plant-derived foods and for establishing effective therapies.

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