

Detection of prognostic factors for oral allergy syndrome in patients with birch pollen hypersensitivity

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To determine why a significant proportion of birch pollen-sensitive patients do not have the oral allergy syndrome (OAS), possible predictive in vivo or in vitro tests for OAS were sought in a large retrospective and prospective follow-up study performed in 283 patients with clinical evidence of birch pollen hypersensitivity. OAS was associated with more severe respiratory symptoms and with higher birch-specific and total IgE levels; moreover, its onset was clearly related to duration of birch pollinosis. The prospective part of this study, performed in 63 patients without OAS, confirmed these findings and highlighted the very high negative predictive value of both skin prick tests with fresh foods and RAST with food allergens. This work suggests that about 15% of patients with birch pollen hypersensitivity are not prone to OAS and that their anti-birch IgE might be directed against determinants that do not cross-react with food allergens. (J ALLERGY CLIN IMMUNOL 1996;97:611-6.)

Key words: oral allergy syndrome, food allergy, birch pollen allergy, skin prick tests

Up to 70% of patients with birch pollen allergy (BPA) have the so-called "oral allergy syndrome" (OAS), an IgE-mediated food allergy characterized by immediate oral itching and angioedema after eating several fruits and/or vegetables.¹⁻⁵ The association between respiratory allergy and food allergy is due to structural similarities (and hence cross-reactivity) between birch pollen and vegetable foods; the presence of common epitopes has been demonstrated both by RAST-inhibition studies and by Western and Northern blot analysis.^{1, 2, 6-8}

Specific IgE against apple allergens is detectable in sera from virtually all birch pollen-sensitive patients^{2, 9}; however, a significant proportion of them do not show any food intolerance. This has been related to the existence of an individual threshold for anti-birch pollen IgE titers to cause apple intolerance²; actually, several studies demonstrated higher birch pollen-specific IgE titers, larger birch skin prick test (SPT) wheals, or more severe nasal symptoms in patients with OAS.^{3-5, 10}

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Abbreviations used

AU:	Arbitrary units
BPA:	Birch pollen allergy
NPV:	Negative predictive value
OAS:	Oral allergy syndrome
PPV:	Positive predictive value
SPT:	Skin prick test

Moreover, some patients have OAS symptoms only during the pollen season, when anti-birch-specific IgE titers rise.¹¹ However, other studies demonstrated no difference in serum or secretory apple-specific IgE between birch-sensitive patients with or without apple-triggered OAS⁹ or demonstrated an inverse relationship between the risk of having OAS and total IgE levels.⁵ All these studies were performed in a relatively small number of patients, and none of the studies were carried out in a prospective fashion. To better define the relative importance of several risk factors for OAS in patients with BPA, we carried out this retrospective, prospective follow-up study.

METHODS

Identification of patients with BPA

Over 2000 patients (age >12 years) living in the Milan area, who were referred to our allergy center from

TABLE I. Comparison between patients with and without OAS

	OAS-negative (n = 117)	OAS-positive (n = 166)	p Value
Sex (M/F)	54/63	59/107	NS
Age at first visit	36.9 ± 12.3	37.6 ± 12.3	NS
Age at onset (yr)	33.4 ± 12.0	31.3 ± 11.9	NS
Mean BPAD (yr)	3.6 [2]	6.2 [4]	<0.0001*
Asthma (%)	48 (41%)	102 (61%)	<0.001
Other allergy (%)	48 (41%)	91 (55%)	<0.05
Mean RAST (AU/ml)	8.3 [7]	10.7 [10]	<0.0005*
Median total IgE (IU/ml)	118	158	<0.05*

Figures in brackets are medians.

BPAD, Birch pollen allergy duration; NS, not significant.

*Mann-Whitney U test.

September 15, 1987 to September 15, 1994 for treatment of rhinoconjunctivitis and/or asthma possibly caused by respiratory allergy, were considered eligible for the study. A careful clinical history was recorded at the first visit, and all the individuals underwent diagnostic SPTs with extracts of the main seasonal or perennial allergens present in this geographic area (grasses, birch, hazel, mugwort, ragweed, *Parietaria* species, mites, molds, and dog and cat dander). Wheals equal to or greater than 2⁺⁺ by comparison with histamine 10 mg/ml were considered positive.¹² A patient was diagnosed as having clinical birch pollen hypersensitivity only in the presence of typical seasonal respiratory symptoms (from the end of February to the end of April¹³) and in the presence of positive SPT responses to one widely used commercial birch pollen extract (Lofarma Allergeni, Milan, Italy). When we were in doubt or when results of SPTs were positive for several seasonal or perennial respiratory allergens, patients were asked to record and score their daily symptoms on a standard form; only patients showing a significant worsening of their symptoms during the birch pollen season were included. Patients with positive SPT results who lacked typical seasonal symptoms were excluded. Two hundred eighty-three subjects with clinical evidence of birch pollen hypersensitivity were finally enrolled in the study.

Identification of patients with OAS

The presence of OAS was assessed by specifically asking each patient whether he or she sometimes experienced oral itching and/or angioedema immediately after eating any type of fresh fruits or vegetables. The diagnosis of OAS was confirmed by SPTs with fresh material performed according to the prick + prick technique, as previously described.¹⁴ All of the patients

with OAS had positive SPT responses to the offending fresh foods (most commonly apple and nuts). Not surprisingly, on the basis of well known cross-reactions,^{1, 4, 15, 16} all patients with OAS had positive SPT responses to fresh Golden Delicious apples and/or fresh hazelnuts. Positive SPT responses to these two fruits were considered reliable markers of the syndrome and were used to test OAS-negative patients in the prospective part of this study.

Prospective study

Sixty-three randomly selected patients from the OAS-negative group, 59 of whom had SPTs with fresh Golden Delicious apples and hazelnuts at the time of diagnosis of BPA, were periodically followed up (every other month in most cases) for OAS. Patients were given complete information about OAS, were asked to maintain their dietary habits, and were told to record the date of onset of OAS and the offending food (or foods), and to contact us as soon as possible. In these cases the follow-up was stopped at the onset of OAS, and adequate advice was given; patients who did not have OAS were followed up until September 15, 1994 (range, 4 to 84 months).

Specific and total IgE measurements

At the time of the first visit, blood samples were taken for the detection of specific anti-birch IgE by immunoenzymatic RAST (Kallestad, Austin, Texas). Levels were expressed both in Allergen arbitrary units per milliliter (AU/ml) and in 5 classes, 0 to 4, the upper limits of which were: class 0, 0.35 AU/ml; class 1, 0.7 AU/ml; class 2, 3.5 AU/ml; class 3, 17.5 AU/ml; and class 4, greater than 17.5 AU/ml. Only classes equal to or greater than 2 were considered positive.

Thirty-one OAS-negative patients included in the prospective arm of the study were tested for anti-apple (*n* = 31) and anti-hazelnut (*n* = 24) specific IgE levels by an immunoenzymatic method (Phadezym; Pharmacia, Uppsala, Sweden) at the time of the first visit. Results were expressed as previously described.

Total IgE levels were measured immunoenzymatically (Kallestad), and results were expressed in international units per milliliter.

Statistical methods

Differences between means were assessed by a two-tailed *t* test. Because of the skewed distribution of duration of BPA, specific IgE, and total IgE, these data were compared by nonparametric means by using the Mann-Whitney U test. Proportions were compared by two-tailed chi square test with Yates' correction. Probability (*p*) values of less than 0.05 were considered significant.

The usefulness of SPTs with fresh foods and of anti-apple and anti-hazelnut IgE as predictive tests for OAS was assessed by calculating positive predictive

value (PPV) and negative predictive value (NPV) with Goldman's method.¹⁷

RESULTS

General population

Two hundred eighty-three patients with BPA (113 male and 170 female patients) were included in the study. One hundred sixty-six (59%) had OAS at the time of the first visit; in 12 cases, OAS preceded respiratory symptoms. Patients with and without OAS are compared in Table I. There was a slightly higher prevalence of OAS in female patients (male, 59/113 [52%] female, 107/170 [63%]). No difference in mean age at the first visit (37.6 ± 12.3 years vs 36.9 ± 12.3 years) or at the onset of BPA (31.3 ± 11.9 years vs 33.4 ± 12.0 years) was observed between the OAS-positive and the OAS-negative groups; by contrast, OAS-positive patients showed a much longer duration of BPA (mean, 6.2 [median, 4] vs mean, 3.6 [median, 2] years; $p < 0.0001$). The relationship between OAS and duration of BPA is further analyzed in Fig. 1. The proportion of patients with OAS progressively increased from 41% in subjects with BPA duration of 1 year up to 86% in subjects with BPA duration of more than 15 years.

Asthma was significantly more common in OAS-positive patients (102/166 [61%] vs 48/117 [41%]; $p < 0.001$), and a higher proportion of patients with respiratory allergies other than BPA was observed in OAS-positive group (91/166 [55%] vs 48/117 [41%]; $p < 0.05$; Table I). Serum samples from 270 patients were submitted to the detection of specific anti-birch pollen IgE; all of the samples were RAST-positive. Significantly higher RAST values (mean, 10.7 [median, 10] vs mean, 8.3 [median, 7] AU/ml, $p < 0.0005$) were found in OAS-positive patients, who also showed higher total IgE levels (Table I).

Birch pollen-monosensitive patients

To exclude a possible bias caused by the association between OAS and seasonal respiratory allergies other than BPA,^{4, 8, 10, 18-22} 144 patients (75 with OAS) who had positive SPT results for only birch or hazel tree pollen were analyzed separately (Table II). Again, there was a slightly higher prevalence of OAS in female patients. No difference in age at the onset of BPA was found between patients with and without OAS, whereas the former were older at the first outpatient clinic visit (42.5 ± 11.2 years vs 38.4 ± 11.7 years; $p < 0.05$). As in the general population, there was a marked difference in BPA duration (mean, 5.76 [median, 4] vs mean, 3.03

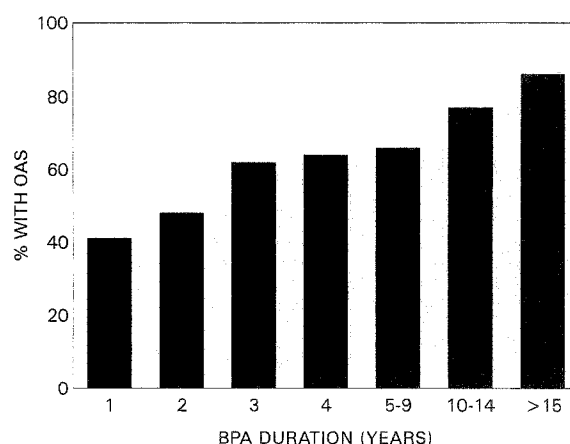


FIG. 1. Prevalence of OAS in 283 patients with different durations of BPA.

[median, 2] years; $p < 0.0005$) and anti-birch IgE levels (mean, 10.1 [median, 9] vs mean, 7.36 [median, 6] AU/ml; $p < 0.01$), whereas no difference was observed in total IgE levels.

Comparisons between male and female patients

In view of the higher prevalence of OAS in female patients, we looked for differences in clinical and laboratory data between male ($n = 113$) and female ($n = 170$) patients. Female patients showed a longer duration of the disease (mean, 5.8 [median, 4] years vs mean, 4.1 [median, 3] years; $p = 0.01$); no other relevant difference was found (data not shown).

Monosensitive versus multisensitive patients

OAS was more common in patients with multiple respiratory allergies (91/139, 65%) than in patients with BPA only (75/144, 52%) ($p < 0.05$). The influence of respiratory allergies other than birch pollinosis on clinical and serologic data was investigated by comparing findings in OAS-positive or OAS-negative patients with or without multiple respiratory allergies (Table II).

Within both the OAS-negative and the OAS-positive subgroups, patients with multiple respiratory allergies showed significantly higher total IgE levels. OAS-positive patients with multiple allergies were much younger than patients with BPA only (33.6 ± 11.7 years vs 42.5 ± 11.1 years; $p < 0.0001$).

Follow-up arm of the study

Four of 63 patients were lost to follow-up, leaving 59 patients for the analysis. Fifty-seven had

TABLE II. Comparison between birch-monosensitive patients and subjects with multiple respiratory allergies with and without OAS

	OAS-negative			OAS-positive		
	BPO	MS	<i>p</i> Value	BPO	MS	<i>p</i> Value
No.	69	48		75	91	
M/F	32/37	22/26	NS	27/48	32/59	NS
Asthma (%)	30 (43)	18 (38)	NS	48 (64)	54 (59)	NS
Age (yr)	38.4 ± 11.7	34.9 ± 12.9	NS	42.5 ± 11.2	33.6 ± 11.7	<0.0001
BPAD (yr)	3.0 [2]	4.4 [2.5]	NS	5.8 [4]	6.6 [4]	NS*
RAST (AU)	7.5 [6]	9.4 [7]	NS	10.1 [9]	11.1 [11]	NS*
Total IgE	91.5	165	<0.005*	101	398	<0.0001*

Figures in brackets are medians.

BPO, Birch pollinosis only; MS, multisensitive patients; BPAD, birch pollen allergy duration; NS, not significant.

*Mann-Whitney U test.

TABLE III. Comparison between followed-up patients who experienced OAS or remained free of OAS

	OAS-negative (<i>n</i> = 34)	OAS-positive (<i>n</i> = 25)	<i>p</i> Value
M/F	15/19	8/17	NS
Age at first visit (yr)	36.0 ± 11.8	37.2 ± 13.8	NS
Mean BPAD (yr)	3.4 [3]	3.5 [2]	NS
SPT+ (%)	13/32 (41)	23/25 (92)	<0.001*
Asthma (%)	11 (32)	15 (60)	NS
Other allergies	12 (35)	14 (56)	NS
Mean RAST (AU/ml)	6.7 [5.5]	11.9 [11.5]	<0.0005*
Median total IgE (IU/ml)	95	260	<0.01*

Figures in brackets are medians.

SPT+, SPT performed with fresh foods that produced a wheal ≥2+; NS, not significant.

*Mann-Whitney U test.

SPTs with fresh apple and hazelnut at the time of the first visit. Twenty-five subjects (42%) experienced OAS during the follow-up period (average, 11.8 months; range, 1 to 60 months). The most frequently reported offending foods were apple (17 patients), peach (7), hazelnut (5), and apricot (4); OAS was less frequently triggered by cherry, carrot, kiwi, fennel, pear, orange, or walnut. Thirty-four subjects were OAS-negative after 18.3 months of follow-up (range, 4 to 84 months). Comparisons between the two groups are shown in Table III. As expected, no differences in age, sex, duration of BPA, and prevalence of allergies other than BPA were found; in contrast, patients who experienced

OAS more commonly had asthma (60% vs 32%, *p* = NS), positive SPT responses to fresh apple and hazelnut (23 of 25 vs 13 of 32, *p* < 0.001), and by far higher birch-specific IgE levels (mean, 11.9 [median, 11.5] vs mean, 6.7 [median, 5.5] AU/ml, *p* < 0.0005) and total IgE levels (*p* < 0.01).

OAS-negative patients who had OAS during the follow-up period showed strikingly higher anti-birch-specific IgE levels than the remaining 93 OAS-negative patients (mean, 11.9 [median, 11.5] vs mean, 7.3 [median, 6] AU/ml; *p* < 0.0005). Moreover, notably, in this subgroup specific anti-birch IgE levels, as well as the proportions of patients with asthma and respiratory allergies other than BPA, were nearly identical to those found in patients with OAS at the first visit (Tables I and II).

Among patients with positive SPT responses to fresh fruits, those who had OAS (*n* = 23) showed higher specific anti-birch-pollen-specific IgE levels than patients who did not (*n* = 13) (mean, 12.1 [median, 12] vs mean, 8.6 [median, 8]; *p* = 0.06). In turn, the latter group showed higher anti-birch-pollen-specific IgE levels than patients with negative results who did not have OAS (*n* = 19) (mean, 8.6 [median, 8] vs mean, 4.8 [median, 3.5] AU/ml; *p* < 0.005). PPV and NPV of SPT responses to fresh fruits were 58% and 92%, respectively.

Anti-apple and/or anti-hazelnut IgE were detectable in sera from 9 of 19 (47%) OAS-negative patients and in 11 of 12 (92%) patients who had OAS (*p* < 0.05). PPV and NPV of serologic tests were 41% and 93%, respectively.

DISCUSSION

The aim of this study was to identify possible predictive tests for OAS in a large group of

patients with clinical evidence of BPA. The retrospective part of this study confirmed that OAS is more common in female patients^{4, 14, 23}; that OAS is associated with a more severe allergic disease, as shown by the higher proportion of patients with asthma and with respiratory allergies other than BPA³; and that sera from OAS-positive patients contain higher levels of both specific anti-birch IgE and total IgE.^{3, 5, 10} This study, like others,⁹ did not confirm the reported inverse relationship between total IgE levels and OAS.⁵

The role of BPA duration was seldom investigated previously; one study⁹ demonstrated a much longer BPA duration in OAS-positive patients, but differences lacked statistical significance because of the small number of patients. This study clearly highlights the association between BPA duration and OAS, showing the increasing incidence of the syndrome over time from 1 to more than 20 years of BPA.

In the prospective part of this study, SPTs with fresh fruits and anti-apple or anti-hazelnut IgE measurements showed an extremely high NPV; thus, they seem most useful for identifying patients who are not prone to have OAS. In contrast, and not surprisingly, PPVs of these tests were rather low because of many false-positive results: better PPVs would have been likely found with a longer follow-up period.

About 15% of patients were still free of OAS even after 15 or more years of BPA (Fig. 1). This is the same proportion of patients who had negative SPT responses to fresh fruits at the first outpatient visit (37% of OAS-negative population, which represented 41% of patients with BPA). Because all OAS-positive patients had positive SPT responses to fresh fruits and only a negligible proportion of patients with negative SPT results had OAS during the follow-up period, one can infer the existence of a subgroup of subjects (about 15% of all patients with BPA) who are not prone to OAS.

Previous studies demonstrated a complete inhibition of reactivity against apple by minimum amounts of birch pollen extract, while even high amounts of apple extracts were unable to inhibit birch pollen reactivity, suggesting that all the immunologic determinants in fruits were present in birch pollen but not all birch pollen determinants were present in fruits and vegetables.^{2, 7, 16, 24} Our results raise the possibility that anti-birch IgE antibodies found in patients who do not experience OAS even after many years of BPA may be

directed against pollen antigens that do not cross-react with food allergens.

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