

Short communication

Relevance of pollen-specific IgE levels to the development of Apiaceae hypersensitivity in patients with birch pollen allergy

Asero R. Relevance of pollen-specific IgE levels to the development of Apiaceae hypersensitivity in patients with birch pollen allergy. Allergy 1997; 52: 560–564. © Munksgaard 1997.

R. Asero

Ambulatorio di Allergologia, Ospedale Caduti
Bollatesi, Milan, Italy

A large clinical/serologic study was carried out to determine the prevalence of Apiaceae (carrot, celery, and fennel) hypersensitivity in patients with birch pollen allergy, and to investigate its relationship with apple and hazelnut allergy and with birch pollen-specific IgE levels. A total of 196 birch pollen-hypersensitive patients with oral allergy syndrome (OAS) caused by different vegetable foods were examined in the cross-sectional part of the study. Of this total, 195 patients had apple and/or hazelnut allergy, and 103 had Apiaceae sensitivity; only one patient had Apiaceae allergy alone. Apiaceae-positive patients showed significantly higher birch pollen-specific IgE levels than negative ones (median 13 vs 7 AU/ml; $P < 0.0001$). The prospective part of the study was performed on 103 birch pollen-hypersensitive patients who were OAS-free at the time of the first visit and were periodically followed-up for OAS. Patients who developed Apiaceae sensitivity showed much higher birch-specific IgE levels than patients who developed apple/hazelnut allergy only (median 15.5 vs 8.5 AU/ml; $P < 0.05$), whereas those who remained OAS-free showed the lowest specific IgE levels (median 5 AU/ml). This study suggests that most Apiaceae determinants cross-react with apple or hazelnut determinants, whereas only some apple or hazelnut determinants cross-react with Apiaceae-allergenic determinants; moreover, it shows that birch-specific IgE levels heavily influence the onset of OAS as a whole, and probably play a critical role in the development of allergies to distinct vegetable foods as well.

Key words: Apiaceae; birch pollen allergy; food allergy; oral allergy syndrome.

Dr Riccardo Asero
Ambulatorio di Allergologia
Ospedale Caduti Bollatesi
Via Piave 20
20021 Bollate
Milan
Italy

Accepted for publication 2 December 1996

Patients with birch pollen allergy (BPA) often develop hypersensitivity to several fresh fruits, nuts, and vegetables due to cross-reactivity between pollen and food allergens (1–3). Apple and hazelnut are the most frequently involved foods; in effect, recent studies showed a significant homology between these food allergens and the major birch and hazel allergens, Bet v 1 (4) and Cor a 1 (5). Vegetables belonging to the Apiaceae family (including carrot, celery, and fennel) are also a frequent cause of oral allergy syndrome (OAS) in patients with BPA (2) and represent a well-known cluster of allergies (6); a recent study found a 40% identity between the celery major allergen

Api g 1, and Bet v 1 (7). By contrast, the cross-reactivity of Apiaceae-relevant allergens with allergens present in other vegetable foods is less defined. One study found that apple, celery, and carrot RAST results have a strong tendency to occur together, and showed a strong inhibition of both carrot and celery RAST by apple extract in patients with BPA (3); moreover, a recent paper showed common epitopes on a 17-kDa band shared by carrot, celery, and birch pollen (8). However, another study found only a 15-kDa protein band common to celery, carrot, and the unrelated Cucurbitaceae family members, cucumber and watermelon (9). The complexity of this matter is

further increased by the observation that a member of the Apiaceae family, celery, contains at least one distinct allergen which cross-reacts with mugwort pollen (10–12), and it has been claimed that this allergen (profilin) is responsible for most of the cross-reactivity between birch pollen and carrot, celery, or potato (13).

In a recent retrospective/prospective study, we examined several clinical and serologic prognostic factors for OAS in patients with BPA (14). The present study focused on celery, carrot, and fennel allergy in order to determine the prevalence of hypersensitivity to the Apiaceae family in patients with BPA, to investigate its relationship with apple and hazelnut hypersensitivity, and to detect possible clinical and/or serologic risk factors for Apiaceae allergy in patients with BPA.

Material and methods

Patients

A total of 196 consecutive patients (83 males and 113 females; mean age [SD] 36.9 ± 11.7 years, range 13–70) with BPA and OAS were included in the present study.

Birch pollen hypersensitivity was diagnosed only in the presence of typical respiratory symptoms (from the end of February to the end of April) (15) and in the presence of positive SPT responses to one widely used commercial birch pollen extract (Bayer-DHS, Lofarma, or Bracco-Allergopharma).

The presence of OAS was assessed by specifically asking patients whether they 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 according to the prick plus prick technique (16), 1-mm disposable prick lancetters being used (Bayer). Fresh foods tested included apple (196 patients), hazelnut (196), celery (145), carrot (123), and fennel (108). A total of 168 patients also underwent SPT with commercial food extracts (Dome-Hollister Stier); their sensitivity is extremely poor in the diagnosis of Rosaceae allergy (i.e., apple, pear, peach, cherry, and plum), but it is acceptable in the case of Apiaceae allergy (16). Commercial food extracts included carrot and celery, but not fennel, which is not present in this commercial panel.

In all cases, wheals $\geq ++$ by comparison with histamine 10 mg/ml were considered positive (17).

Prospective study

A total of 103 patients with BPA who were OAS-free (i.e., regularly and currently ate any sort of

raw fruits and vegetables without any consequence) at the time of the first visit to our allergy center underwent SPT with fresh Golden Delicious apple and hazelnut and were periodically (every other month usually) followed-up for OAS. We previously showed that SPTs with these two fruits are reliable markers of OAS (14). 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 our allergy center as soon as possible. SPTs with fresh carrot, celery, and/or fennel were then performed. In these cases, the follow-up was stopped at the onset of OAS, and adequate advice was given; patients who remained OAS-free were followed-up until 31 March 1995 (range, 4–90 months).

Specific and total IgE measurements

At the first visit, blood samples were taken for the detection of specific antibirch IgE by immunoenzymatic RAST (Kallestad, Austin, TX, USA). Levels were expressed both in Allercoat arbitrary units per milliliter (AU/ml) and in five classes, 0–4. Only classes ≥ 2 (i.e., >0.7 AU/ml) were considered positive.

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

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 with the Mann-Whitney U-test. Proportions were compared by two-tailed chi-square test with Yates' correction. *P* values < 0.05 were considered significant.

Results

General population

Among the patients, 195/196 (99.5%) reported typical OAS symptoms caused by apple (191) and/or hazelnut (188).

Among the patients, 51/196 (26%) reported typical symptoms after eating one or more vegetables belonging to the Apiaceae family. Fourteen (7%) patients had OAS caused by celery, 33 (17%) by carrot, and 33 (17%) by fennel. In these patients, the sensitivity of SPT with fresh material was 58% (7/12), 95% (21/22), and 90% (18/20) for celery, carrot, and fennel, respectively; the sensitivity of

SPT with commercial extracts was 86% (12/14), and 75% (24/32) for celery and carrot, respectively.

Furthermore, 52/196 (27%) patients had positive SPTs with fresh material and/or with commercial extracts for at least one member of the Apiaceae family, despite the absence of clinical symptoms after eating these vegetables. Since SPT-positive patients with or without clinical sensitivity show the same clinical and serologic features (14), these two groups were considered a single population of 103 Apiaceae-positive subjects in the analysis.

Some 93/196 patients did not report any clinical symptom after eating celery, carrot, or fennel, and gave negative SPT responses with both fresh foods and commercial extracts. All had OAS caused by apple and/or hazelnut.

Only one patient (0.5%) reported symptoms after eating celery, carrot, and fennel in the absence of clinical, SPT, and serologic evidence of apple or hazelnut hypersensitivity.

Patients with and without Apiaceae sensitivity are compared in Table 1. No difference in sex distribution, mean age at the first visit (36.7 ± 12.1 years vs 37.1 ± 11.4 years), mean duration of BPA (5.5 vs 6.3 years), or prevalence of asthma (63% vs 57%) was found between the two groups. By contrast, patients hypersensitive to Apiaceae showed much higher RAST levels (median 13 AU/ml vs 7 AU/ml; $P < 0.0001$) and higher total IgE levels (median 231 IU/ml vs 125 IU/ml; $P < 0.05$). The relationship between Apiaceae hypersensitivity and birch-specific IgE levels in patients with OAS is further analyzed in Fig. 1. The proportion of patients with Apiaceae allergy progressively increased from 26% in subjects with low (1–5 AU/ml) specific IgE levels up to 42%, 69%, and 74% in patients with higher IgE levels (6–10 AU/ml, 11–15 AU/ml, and >15 AU/ml, respectively).

Birch-pollen-monosensitive patients

To exclude possible bias caused by the association between OAS and seasonal respiratory allergies

Table 1. Comparison between patients with OAS with or without Apiaceae hypersensitivity

	Sensitive (n = 103)	Not sensitive (n = 93)	P
Sex (M/F)	38/65	45/48	NS
Age at first visit (years)	36.7 ± 12.1	37.1 ± 11.4	NS
Median BPAD (years)	4	3	NS*
Asthma (%)	65 (63%)	53 (56%)	NS
Median RAST (AU/ml)	13	7	$< 0.0001^*$
Median total IgE (IU/ml)	231	125	$< 0.05^*$

BPAD: birch pollen allergy duration; NS: not significant.

* Mann-Whitney U-test.

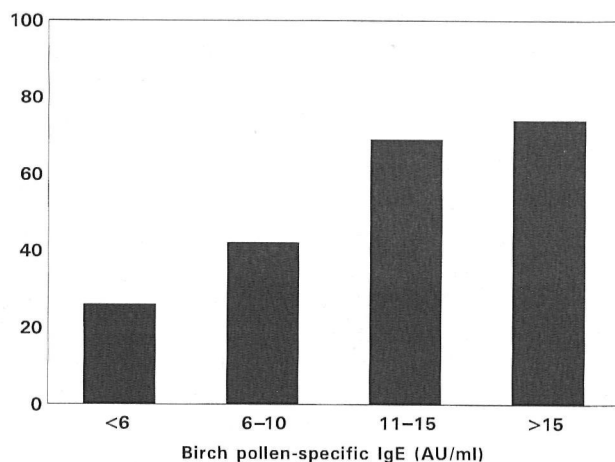


Fig. 1. Relationship between birch pollen-specific IgE levels and Apiaceae hypersensitivity in patients with oral allergy syndrome.

other than BPA (2, 12, 18, 19), 78 patients (43 with Apiaceae sensitivity) who had no positive SPT results for seasonal or perennial respiratory allergens other than birch and hazel tree pollen were analyzed separately (Table 2). Again, Apiaceae-positive subjects showed significantly higher birch-specific IgE levels (median 12 AU/ml vs 7 AU/ml; $P < 0.001$) in the absence of other significant differences between the two groups.

Apiaceae-positive patients with or without clinical sensitivity

In view of the observed differences in birch pollen-specific IgE levels (see above), Apiaceae-SPT-positive patients with and without Apiaceae OAS were also compared. No clinical or serologic difference was found between the two groups (data not shown); the median birch-specific IgE levels were 11 AU/ml and 13 AU/ml in patients with clinical and latent sensitivity, respectively.

Follow-up arm of the study

Of 103 patients with BPA included in the follow-up arm of the study, 49 were negative on SPT with fresh apple and hazelnut, and all remained OAS-free; on the basis of our previous study, these subjects were considered "not prone to OAS" (14). Of 54 patients who showed strongly positive SPTs with fresh apple and hazelnut, 27 remained OAS-free and were excluded from the analysis, whereas the remaining 27 developed OAS during the follow-up period (average 12.4 months; range, 1–60 months). On the basis of SPT results, 17/27 were considered apple- and/or hazelnut-hypersensitive only, whereas 10 developed Apiaceae allergy too. The clinical and serologic features of followed-up

Table 2. Comparison between birch pollen-monosensitive patients with OAS, with and without Apiaceae hypersensitivity

	Sensitive (n=43)	Not sensitive (n=35)	P
Sex (M/F)	18/25	19/16	NS
Age at first visit (years)	42.2 ± 10.9	42.4 ± 9.6	NS
Median BPAD (years)	4	4	NS*
Asthma (%)	27 (62%)	22 (63%)	NS
Median RAST (AU/ml)	12	7	<0.001*
Median total IgE (IU/ml)	149	96	NS*

BPAD: birch pollen allergy duration; NS: not significant.

* Mann-Whitney U-test.

patients with and without OAS are shown in Table 3. Again, patients with Apiaceae hypersensitivity showed significantly higher birch-specific IgE levels (median 15.5 AU/ml) than patients with apple/hazelnut hypersensitivity only (8.5 AU/ml, $P < 0.05$). Patients who did not develop OAS and were SPT-negative showed the lowest birch-specific IgE levels (5 AU/ml). No other differences were found between these groups.

Clustering of allergies

The concordance between celery and carrot hypersensitivity was 83% (85/103), between celery and fennel 73% (46/63), and between carrot and fennel 77% (49/63).

Of 60 patients undergoing SPT with all three fresh vegetables, only four (7%) were monosensitive (one carrot, three fennel); 15 (25%) were sensitive to two vegetables, and 41 (68%) were sensitive to all three vegetables.

Discussion

One of the aims of this study was to investigate some clinical features of patients with Apiaceae hypersensitivity and to clarify the relationship between this and other kinds of food allergy in patients with BPA.

Carrot, celery, and fennel sensitivity showed a strong tendency to occur together, and their concordance was nearly identical to that found in other works (3), a further confirmation that allergenic determinants of these botanically related vegetables are largely cross-reacting.

As in previous works (2), patients with BPA much more frequently had apple and hazelnut allergy than Apiaceae allergy. Moreover, apple and/or hazelnut allergy was quite common in the absence of Apiaceae hypersensitivity, whereas the opposite situation was extremely rare (1/196 patients). This fact, together with the observation of a strong

Table 3. Comparison between followed-up patients who developed OAS, with (A) and without (B) Apiaceae hypersensitivity, and who did not develop OAS (C)

	A (n=10)	B (n=17)	C (n=49)	P	
				A vs B	B vs C
Sex (M/F)	3/7	10/6	27/22	NS	NS
Age (years)	34.1 ± 10.6	33.8 ± 8.5	36.5 ± 11.5	NS	NS
Median BPAD (years)	3.5	2	2	NS*	NS*
Asthma (%)	5 (50%)	10 (59%)	20 (41%)	NS	NS
RAST (AU/ml)	[15.5]	[8.5]	[5]	<0.05*	<0.05*
Total IgE (IU/ml)	[208]	[159]	[87.5]	NS*	NS*

Figures in brackets are medians.

BPAD: birch pollen allergy duration; NS: not significant.

* Mann-Whitney U-test.

inhibition of both carrot and celery RAST by apple extracts (3), suggests that most Apiaceae allergenic determinants cross-react with apple determinants, whereas only some apple determinants cross-react with Apiaceae allergenic determinants. Such a situation is very similar to the one previously shown for birch pollen and vegetable foods, including apple and hazelnut (5, 20, 21).

Virtually all patients with BPA react to the birch pollen major allergen Bet v 1 (4, 22), and it has been found that Bet v 1 is the main allergen responsible for cross-reactivity with apple (4), hazelnut (5), and, possibly, celery and carrot (7, 8). By contrast, other studies claim that profilin (Bet v 2) could be the main cross-reacting antigen in Apiaceae and birch pollen (13). However, the prevalence of antiprofilin IgE in patients with BPA seems too low (23) to account for the high prevalence of Apiaceae hypersensitivity observed in this study. Moreover, 41% of our patients with Apiaceae allergy were birch pollen-monosensitive, a fact which seems to re-emphasize the role of profilin in cross-reactivity (11, 23, 24). Finally, sera from five patients with Apiaceae hypersensitivity included in this study were recently subjected to the detection of IgE specific for recombinant Bet v 1 and Bet v 2 (by the CAP-System, kindly supplied by Pharmacia, Milan, Italy) (25): all showed strong Bet v 1-reactivity (classes IV–V); by contrast, 3/5 were Bet v 2-negative, and only 2/5 showed a weak Bet v 2-reactivity (class II). Altogether, data from this and other studies suggest that Bet v 1 is the main allergen causing cross-reactivity among birch pollen, apple, hazelnut, and vegetables from the Apiaceae family. Profilin probably contributes to cross-reactivity in a few cases.

Patients with Apiaceae hypersensitivity showed significantly higher birch pollen-specific IgE levels than patients without this kind of skin test positivity in all comparisons performed. Differences

found in the prospective part of the study suggest a strong relationship between birch-specific IgE levels and the likelihood of developing allergies to distinct fruits and vegetables. All patients with BPA react against Bet v 1, an allergen that seems to contain several determinants scattered over its amino acid sequence, only some of which cross-react with fruits and vegetables (13, 21, 25, 26). Birch pollen-specific IgE levels heavily influence the onset of OAS as a whole (14); the present study suggests that they are critical for the development of allergies to specific fruits and vegetables as well. Dietary habits and individual thresholds could also play a role in the onset of a clinical food allergy. Western blot studies with Apiaceae vegetable extracts are in progress to clarify these clinical findings.

Acknowledgments

I thank Ms Simona Gorla, Ms Anna Mavelli, Ms Sonia Minisini, and Mr Enos Venturini for their skillful technical assistance.

References

- Dreborg S, Foucard T. Allergy to apple, carrot and potato in children with birch pollen allergy. *Allergy* 1983;38:167-72.
- Eriksson NE, Formgren H, Svenonius E. Food hypersensitivity in patients with pollen allergy. *Allergy* 1982;37:437-43.
- Halmepuro L, Vuontela K, Kalimo K, Björkstén F. Cross-reactivity of IgE antibodies with allergens in birch pollen, fruits, and vegetables. *Int Arch Allergy Appl Immunol* 1984;74:235-40.
- Ebner C, Birkner T, Valenta R, et al. Common epitopes of birch pollen and apples – studies by Western and Northern blot. *J Allergy Clin Immunol* 1991;88:588-94.
- Hirschwehr R, Valenta R, Ebner C, et al. Identification of common allergenic structures in hazel pollen and hazelnuts: a possible explanation for sensitivity to hazelnuts in patients allergic to tree pollen. *J Allergy Clin Immunol* 1992;90:927-36.
- Ortolani C, Pastorello EA, Farioli L, et al. IgE-mediated allergy from vegetable allergens. *Ann Allergy* 1993;71:470-6.
- Breiteneder H, Hoffmann-Sommergruber K, O'Riordan G, et al. Molecular characterization of Api g 1, the major allergen of celery (*Apium graveolens*), and its immunological and structural relationships to a group of 17-kDa tree allergens. *Eur J Biochem* 1995;233:484-9.
- Helbling A, Lopez M, Schwartz HJ, Lehrer SB. Reactivity of carrot-specific IgE antibodies with celery, apiaceous spices, and birch pollen. *Ann Allergy* 1993;70:495-9.
- Jordan-Wagner DL, Whisman BA, Goetz DW. Cross-allergenicity among celery, cucumber, carrot, and watermelon. *Ann Allergy* 1993;71:70-9.
- Vallier P, Dechamp C, Vial O, Deviller P. A study of allergens in celery with cross-sensitivity to mugwort and birch pollens. *Clin Allergy* 1988;18:491-500.
- Vallier P, Dechamp C, Valenta R, Vial O, Deviller P. Purification and characterization of an allergen from celery immunochemically related to an allergen present in several other plant species. Identification as a profilin. *Clin Exp Allergy* 1992;22:774-82.
- Wüthrich B, Stäger J, Johansson SGO. Celery allergy associated with birch and mugwort pollinosis. *Allergy* 1990;45:566-71.
- Akkerdaas JH, van Ree R, Aalbers M, Stapel SO, Aalberse RC. Multiplicity of cross-reactive epitopes on Bet v I as detected with monoclonal antibodies and human IgE. *Allergy* 1995;50:215-20.
- Asero R, Massironi F, Velati C. Detection of prognostic factors for oral allergy syndrome in patients with birch pollen allergy. *J Allergy Clin Immunol* 1996;97:611-16.
- Ortolani C, Fontana A, Bosetti M, Ciccarelli M. Pollinosis in Lombardia. *G Ital Allergol Immunol Clin* 1991;1:515-19.
- Ortolani C, Ispano M, Pastorello EA, Ansaloni R, Magri GC. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989;83:683-90.
- Bousquet J. *In vivo* methods for the study of allergy: skin tests, techniques and interpretation. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, editors. *Allergy: principles and practice*. 3rd ed. St Louis, MO: CV Mosby, 1988:419-36.
- Calkhoven PG, Aalbers M, Koshte VL, Pos O, Oei HD, Aalberse RC. Cross-reactivity among birch pollen, vegetables, and fruits as detected by IgE antibodies is due to at least three distinct cross-reactive structures. *Allergy* 1987;42:382-90.
- Pauli G, Bessot JC, Dietmann-Molard A, Braun PA, Thierry R. Celery sensitivity: clinical and immunological correlations with pollen allergy. *Clin Allergy* 1985;15:273-9.
- Lahti A, Björkstén F, Hannuskela M. Allergy to birch pollen and apple and cross-reactivity of the allergens studied with the RAST. *Allergy* 1980;35:297-300.
- Vieths S, Janek K, Aulepp H, Petersen A. Isolation and characterization of the 18-kDa major apple allergen and comparison with the major birch pollen allergen (Bet v I). *Allergy* 1995;50:421-30.
- Valenta R, Duchene M, Vrtala S, et al. Recombinant allergens for immunoblot diagnosis of tree-pollen allergy. *J Allergy Clin Immunol* 1991;88:889-94.
- Valenta R, Duchene M, Ebner C, et al. Profilins constitute a novel family of functional pan-allergens. *J Exp Med* 1992;175:377-85.
- van Ree R, Fernandez-Rivas M, Cuevas M, van Wijngaarden M, Aalberse RC. Pollen-related allergy to peach and apple: an important role for profilin. *J Allergy Clin Immunol* 1995;95:726-34.
- Asero R, Mistrello G, Gentili M, Zelaschi D, Minisini S. Birch pollen-hypersensitive patients with and without oral allergy syndrome: a study of their serological reactivity [Abstract]. *Allergy* 1996;51 Suppl 31:50.
- Ebner C, Szepfalusi Z, Ferreira F, et al. Identification of multiple T cell epitopes on Bet v I, the major birch pollen allergen, using specific T cell clones and overlapping peptides. *J Immunol* 1993;150:1047-54.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.