

Celery allergy confirmed by double-blind, placebo-controlled food challenge: A clinical study in 32 subjects with a history of adverse reactions to celery root

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Background: Celery root is a frequent cause of food allergy in pollen-sensitized patients. Because of problems in blinding challenges with fresh vegetables and the risk of anaphylactic reactions, no double-blind, placebo-controlled, food challenges (DBPCFCs) with celery have been published so far.

Objective: The aim of the study was to confirm the clinical relevance of celery as a food allergen by DBPCFCs and to evaluate current diagnostic procedures in patients with true allergy. **Methods:** DBPCFCs were performed in 32 patients with a history of an allergic reaction to celery. The patients underwent skin prick tests (SPTs) with celery extracts, crude celery, and different pollen extracts. Specific IgE for celery was determined by using the CAP method.

Results: Twenty-two of 32 patients had a positive DBPCFC result. Two patients reacted to placebo, and 8 patients did not respond to the challenge. Of the nonresponders, 4 reacted to an open provocation with celery. The sensitivity of CAP determination for specific IgE (≥ 0.7 kU/L) to celery in patients with a positive DBPCFC result was 73%, 48% to 86% for SPTs (≥ 3 mm) with commercial extracts, and 96% for prick-to-prick tests with crude celery. The positive predictive value of the SPT and CAP tests was between 87% and 96%, whereas the specificity and negative predictive values were poor.

Conclusion: This study confirms the importance of celery as a food allergen for use in DBPCFCs. The SPT and CAP methods proved to be reliable for the diagnosis of a relevant allergy to celery in regard to sensitivity and positive predictive value but not to specificity and negative predictive value. (*J Allergy Clin Immunol* 2000;106:373-8.)

Key words: Food allergy; double-blind, placebo-controlled, food challenge; celery allergy; oral allergy syndrome; systemic reaction

Sensitivity to food allergens, such as vegetables, fruits, and nuts, in patients with pollinosis is a well-recognized phenomenon. Allergy to celery root (or tuber or celeriac) is highly associated with birch and mugwort pollen sensitization.¹⁻⁵ In Switzerland about 40% of patients with food allergy are sensitized to celery root, some with severe anaphylactic reactions.^{6,7} In France André et al⁸ reported that 30% of 580 patients with food allergy were sensitized (positive RAST result) to celery and that 30% of severe anaphylactic reactions to food were thought to be due to celery according to each patient's history.⁸ In Germany 70% of patients with a pollen-related food allergy proved to have a positive skin prick test (SPT) or enzyme allergosorbent test response for celery.⁹

In 1995, an Expert Consultation of the Food and Agriculture Organization of the United Nations suggested a list of the most common allergenic foods. This list was proposed as a draft amendment to the General Standard for the Labelling of Prepackaged Food.¹⁰ On the basis of the Food and Agriculture Organization list, the food allergy task force of the International Life Science Institute Europe recently defined criteria for the selection of food that should be included on a major allergen list. Even though celery is a frequent cause of allergic reactions in Europe, it was decided that celery does not fulfill the criteria for inclusion on the list of food allergens for labeling. The main argument was that to date, no double-blind, placebo-controlled, food challenges (DBPCFCs) have been performed with this vegetable.¹¹

The purpose of this study was (1) to perform DBPCFCs in patients with the history of an allergic reaction to celery; (2) to validate current diagnostic methods, such as SPTs with commercial extracts and raw celery and in vitro determination of specific IgE (CAP) in patients, in whom allergy was confirmed by DBPCFCs; and (3) to assess the pollen sensitization in this group of patients.

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Abbreviations used

DBPCFC: Double-blind, placebo-controlled, food challenge

NPV: Negative predictive value

OAS: Oral allergy syndrome

PEI: Paul-Ehrlich-Institut

PPV: Positive predictive value

SPT: Skin prick test

METHODS**Patients**

Patients with the history of an allergic reaction to celery were recruited at the Allergy Unit of University Hospital Zürich from June 1998 to June 1999. Pregnancy, history of a severe life-threatening anaphylactic reaction after celery consumption, significant concurrent disease or intake of glucocorticosteroids, H₁-receptor antagonists, angiotensin-converting enzyme inhibitor, or β -blocking agents were exclusion criteria.

Ethical considerations

The study was reviewed and approved by the local ethical committee. All subjects provided written informed consent before enrollment in the study.

Paul Ehrlich Institute celery extract

Celery extract was self-prepared from raw celery root (*Apium graveolens* variant Prinz). The plant material was frozen with liquid nitrogen and homogenized in a commercial blender (BioHomogenizer M133/2280-Zauberstab, ESGE) and extracted with 0.01 mol/L PBS, pH 7.4 (2 mmol/L KH₂PO₄, 8 mmol/L Na₂HPO₄, 3 mmol/L KCl, and 0.14 mol/L NaCl), by shaking at 4°C for 4 hours. Coarse components were removed by using a paper filter (Schleicher-Schuell). After centrifugation at 20,000g (4°C) for 30 minutes, the supernatant was passed through a cellulose acetate filter with a pore diameter of 0.45 μ m (Sartorius). The filtrate was dialyzed against distilled water overnight at 4°C and freeze-dried. The amount of extracted protein was estimated by using a commercial dye-binding assay according to the method described by Bradford.¹² Freeze-dried and redissolved extracts were kept at -20°C until used.

Skin tests

SPTs were performed on the flexor aspect of the forearm with a standardized prick needle (Stallerpoint, Stallergenes). Histamine dihydrochloride (10 mg/mL) was used as a positive control, and the glycerol diluent of the prick solution (Soluprick, ALK) was used as a negative control. Patients were tested with pollen extracts from alder, birch, hazel, ash, grass, rye, and mugwort (Soluprick, ALK), with two different celery root extracts (Stallergenes and Allergopharma) and the celery extract provided by Paul Ehrlich Institute (PEI extract). Raw native celery root and raw native celery stalk were tested by using the prick-to-prick-technique.^{2,13} The protein content of the celery extract from Stallergenes was 44 μ g/mL and of the celery extract from Allergopharma was 1.5 mg/mL, and that of the PEI extract was 1 mg/mL. Reactions were recorded after 15 minutes. An SPT result was considered positive if it produced a wheal with a diameter of at least 3 mm.¹⁴

In vitro diagnosis

Total IgE and specific IgE to celery, carrots, birch pollen, rBet v 1, rBet v 2, and mugwort pollen were measured by using the CAP FEIA system (Pharmacia & Upjohn). Specific IgE of at least 0.7 kU/L (class 2) was considered positive.

DBPCFC with celery root

Two different drinks (Table I) were prepared for the test meal, (ie, an active drink [with celery] and a placebo drink [without celery]). They were of identical color, consistency, and taste. Apart from celery, all ingredients were known to be tolerated by each patient.

Patients were first challenged in a single-blind way with a placebo drink. Patients were required to retain 5 mL of the placebo drink in their mouths for 1 minute and spit it out thereafter. If the patients reported a reaction, they were considered to be placebo responders and excluded from the study. If they did not report a reaction, DBPCFCs with celery were performed in a two-step procedure. Initially, the patients had to keep drink 1 in increasing amounts in their mouths and spit it out after 1 minute. The amount was doubled each 15 minutes (5, 10, 20, and 40 mL). After an interval of 1 hour, the same procedure was done with drink 2. If the patients consistently reported symptoms of an oral allergy syndrome (OAS) 3 times to the active drink but not to the placebo drink, they were regarded as responders. The OAS was defined as clinical symptoms localized to the mouth or lips appearing within a few minutes after the contact with the drink and consisting of an irritation or swelling of the lips or oral mucosa. If the patients did not complain about symptoms during this spit phase, they continued with step 2 of the DBPCFC; that is, the patients now had to swallow the drinks in increasing amounts (13, 26, 52, and 104 mL) at intervals of 15 minutes. Between the challenges with drink 1 and drink 2, there was an interval of at least 24 hours. Again, if the patients consistently reported symptoms to the active drink 3 times but never to the placebo drink or if they had objective signs of an allergic reaction (eg, urticaria, angioedema, rhinoconjunctivitis, wheezing, or decrease in blood pressure), they were considered to be responders. One milliliter of active drink contained 0.144 g of celery.

Open provocation with celery

In patients with a negative DBPCFC result, an open challenge was performed. These patients had to chew 5 g of raw celery root and spit it out. If they did not experience a reaction, they chewed 5 g and swallowed it and thereafter used 10 and 20 g, respectively.

Data analysis

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated according to the method of Goldman as follows¹⁵: a true-positive (TP) result is defined as a patient with a positive DBPCFC result and a positive SPT, CAP, or both types of results; a false-positive (FP) result is defined as a patient with a negative DBPCFC result and a positive SPT, CAP, or both types of result; a true-negative (TN) result is defined as a patient with a negative DBPCFC result and a negative SPT, CAP, or both types of result; a false-negative (FN) result is defined as a patient with a positive DBPCFC result and a negative SPT, CAP, or both types of result; and prevalence (P) is defined as a patient with a positive DBPCFC result per total tested patients.

$$\text{Sensitivity} = \text{TP}/(\text{TP} + \text{FN}).$$

$$\text{Specificity} = \text{TN}/(\text{TN} + \text{FP}).$$

$$\text{PPV} = (\text{TP} \times \text{P})/[(\text{TP} \times \text{P}) + \text{FP} [1 - \text{P}]].$$

$$\text{NPV} = \text{TN} (1 - \text{P})/[(\text{TN} (1 - \text{P}) + (\text{FN} \times \text{P}))].$$

RESULTS**Patients**

Thirty-two patients (23 female and 9 male patients) aged 13 to 55 years (32 ± 11 years) entered the study. Case history in respect to celery allergy revealed that 16 patients complained of OAS after former consumption of celery root, 9 reported urticaria or flush, 6 reported

angioedema, and 2 reported a palmoplantar itch. Nausea was mentioned once, heartburn was mentioned twice, and flatulence and abdominal cramps were mentioned in 3 patients. One patient had cough, and another had slight dyspnea. None reported wheezing. Conjunctivitis or rhinitis was reported 4 times. One patient experienced rhinoconjunctivitis only when preparing, but not after eating, raw celery. A decrease in blood pressure after ingestion of celery was not reported by any of the patients. The symptoms appeared in all patients after ingestion of celery and were not associated with exercise.

Skin tests

SPTs with commercial celery extract and PEI extract and prick-to-prick tests with raw celery root are summarized in Table II; in one patient SPTs with commercial extracts were not performed. Sixteen patients with positive DBPCFC results had positive SPT results to raw celery stalk too. The PEI extract and the prick-to-prick test with raw celery root produced a positive SPT result in all but one patient. Thus their sensitivity (0.96) was higher than that of the commercially available extracts (celery extract from Allergopharma: 0.86; celery extract from Stallergènes: 0.48). The positive predictive value was between 0.87 and 0.96 for SPTs with commercially available celery extracts and PEI extract and prick-to-prick tests with raw celery root. The celery extracts from PEI and Allergopharma showed a low specificity (celery extract from PEI: 0.25; celery extract from Allergopharma: 0.13). The celery extract from Stallergènes, however, showed a specificity of 0.88. The negative predictive value was 0.43 for the PEI extract but below 0.2 for the other extracts and the prick-to-prick test with raw celery root. Table III summarizes the sensitivity, specificity, PPV, and NPV for SPTs with commercial extracts and PEI extract and prick-to-prick tests with raw celery.

Patients with positive DBPCFC results showed a positive SPT result to birch pollen in 91% (n = 20) and to mugwort pollen in 36% (n = 8). Six (27%) patients were sensitized to birch but not to mugwort pollen, and 2 (9%) patients were sensitized to mugwort but not to birch pollen. Patients with systemic reactions during DBPCFCs more often had positive SPT results to mugwort pollen than patients with pure OAS (60% vs 16%). Furthermore, a positive SPT result was found in 86% (n = 19) of patients with positive DBPCFC results for alder pollen, in 82% (n = 18) for hazel pollen, in 36% (n = 8) for ash pollen, and in 55% (n = 12) for grass and rye pollen.

In vitro diagnosis

CAP test results with celery were positive (>0.7 kU/L) in 16 of 22 patients with positive DBPCFC results and in 5 of 8 patients with negative DBPCFC results. Sensitivity, specificity, PPV, and NPV for celery CAP tests are summarized in Table III. A positive CAP test result was found in 91% of patients with positive DBPCFC results (n = 20) for birch pollen, in 91% (n = 20) for rBet v 1, in 27% (n = 6) for rBet v 2, in 64% (n = 14) for mugwort pollen, and in 77% (n = 17) for carrot.

TABLE I. Recipe for DBPCFCs with celery

Drink with celery (active drink)*	
30 g	Broccoli, cooked
20 g	Celery root, raw
12.5 g	Broccoli fond
5 g	Cream
50 g	Yogurt without flavor
25 g	Water
1 g	Salt
Drink without celery (placebo drink)*	
50 g	Broccoli, cooked
12.5 g	Broccoli fond
5 g	Cream
50 g	Yogurt without flavor
25 g	Water
1 g	Salt

*All ingredients were mixed in a blender.

TABLE II. Celery sensitization determined by using an SPT with two commercial extracts and PEI extract and by using a prick-to-prick test with raw celery root in patients with positive and negative DBPCFC results with celery

Testing agent	Positive DBPCFC results	Negative DBPCFC results
Celery extract (Stallergènes), positive	10	1
Celery extract (Stallergènes), negative	11	7
Celery extract (Allergopharma), positive	18	7
Celery extract (Allergopharma), negative	3	1
Celery PEI extract, positive	21	6
Celery PEI extract, negative	1	2
Raw celery root (prick-to-prick test), positive	21	8
Raw celery root (prick-to-prick test), negative	1	0

DBPCFCs with celery root

Two patients reported symptoms of OAS after the single-blind challenge with the placebo drink. They were regarded to be placebo responders and excluded from the study.

Twenty-two patients produced symptoms to the active drink but not to the placebo drink. They were regarded to be responders. Eleven of 22 patients complained about symptoms strictly localized to the oral cavity (OAS). The mean provocation dose to elicit OAS was 1.3 ± 1.4 g of celery. In all but one patient OAS appeared during the spit phase; in one patient OAS appeared after swallowing 13 mL of the active drink.

Eleven patients showed systemic reactions. Three patients complained about gastrointestinal symptoms. Three patients experienced dyspnea or cough; 5 patients experienced pruritus, flush, or urticaria; 3 patients experienced angioedema; and 3 patients experienced rhinitis or conjunctivitis. One patient had rhinoconjunctivitis not after ingestion of the active drink but after handling and inhaling it. The mean provocation dose to elicit a systemic reaction was 19.3 ± 11.8 g, excluding the patient with the inhalative celery allergy. Systemic reactions appeared in 8 patients when ingesting active drink, in 2 patients during the spit phase, and in one patient not after

TABLE III. Sensitivity, specificity, PPV, and NPV for CAP and SPT with two commercial extracts and PEI extract and by prick-to-prick test with raw celery root in patients with positive DBPCFCs with celery

Testing agent	Sensitivity	Specificity	PPV	NPV
Celery extract (Stallergènes)	0.48	0.88	0.96	0.19
Celery extract (Allergopharma)	0.86	0.13	0.87	0.11
Celery PEI extract	0.96	0.25	0.9	0.43
Raw celery root (prick-to-prick test)	0.96	0	0.88	0
CAP (>0.7 kU/L)	0.73	0.38	0.9	0.17

TABLE IV. Symptoms and dose of celery-produced symptoms in patients with positive DBPCFC results with celery

Patient No.	Symptoms	Dose of celery (g)
1	Itch of palate and lips (OAS)	0.7
2	Itch of palate and tongue (OAS)	0.7
3	Itch of lips (OAS)	0.7
4	Itch of lips and throat (OAS)	0.7
5	Rhinoconjunctivitis, cough, flush, generalized pruritus	28.5
6	Itch of lips (OAS)	0.7
7	Burning sensation of lips and tongue (OAS)	0.7
8	Flatulence, abdominal cramps	28.5
9	Conjunctivitis, flush, urticaria, cough, dyspnea	28.5
10	Itch of lips and tongue (OAS)	5.6
11	Itch of lips (OAS)	0.7
12	Itch of throat and ears (OAS)	1.9
13	Itch of lips, palate, and tongue (OAS)	0.7
14	Nausea and dyspnea	1.9
15	Flush, angioedema of lips and eyelids	28.5
16	Itch of scalp and angioedema of lips	13.3
17	Itch of throat (OAS)	0.7
18	Urticaria	5.6
19	Angioedema of lips	28.5
20	Itch of palate (OAS), rhinoconjunctivitis, cough, dyspnea	0.7
21	Nausea and emesis	28.5

ingesting but after inhaling the vapor above the active drink. The symptoms provoked by DBPCFCs and the dose of celery that produced symptoms in each patient are summarized in Table IV.

Eight patients reported no symptoms to the active drink or to the placebo drink. They were regarded as non-responders.

Open provocation with celery

The 8 nonresponders subsequently underwent an open challenge with raw celery root. Four patients now complained about symptoms of OAS. In all patients symptoms started when chewing 5 g of celery. The other 4 patients did not have any symptoms during the open challenge.

DISCUSSION

The first case of an allergic reaction to celery root was observed by Jadassohn and Zaruski¹⁶ in 1926 in Zürich. Since this time, many reports of celery allergy have been published, indicating the high prevalence of this food allergy in European countries.^{1,7,9,17,18} In all of these publications, diagnosis was based on case history, SPT results, or determination of specific IgE in vitro. Accord-

ing to the recommendation of the American and European Academies of Allergy and Clinical Immunology, however, the diagnosis of food hypersensitivity must rely entirely on the outcome of DBPCFC.^{11,19-23} Because DBPCFCs are the only scientifically accepted test for the confirmation of food allergy, other diagnostic methods can be validated only in patients in whom allergy was confirmed by using DBPCFCs.²⁴ We therefore evaluated 32 patients with a history of an allergic reaction to celery determined by using DBPCFCs. Whereas pollen-related allergies to fruits and nuts often induce symptoms localized to the oral cavity (OAS), allergic reactions to celery are often more severe and can even be life-threatening.^{1-2,17} Therefore we established a new protocol for DBPCFCs that consisted of a 2-step procedure of DBPCFCs with a spit and a swallow phase. Twenty-two (69%) of 32 patients showed a positive DBPCFC result. Twelve patients had OAS, and 10 patients had systemic reactions. In 12 patients symptoms occurred during the spit phase of the DBPCFC; that is, the diagnosis in this subset of patients was made without their obligation to swallow the ingredient to which they were supposed to be allergic. Thus our 2-step procedure of DBPCFC allowed us to identify over 50% of allergic patients when they just produced local oral symptoms, eventually omitting more

severe systemic reactions in these patients. Four patients with a negative DBPCFC result complained of OAS in the open provocation. False-negative DBPCFC results are common and thus far have been described for fish and hazelnut.^{25,26} This finding raises the issue of the reliability of DBPCFCs as the gold standard for the diagnosis of food allergy because a subset of patients may only produce OAS if there is direct contact between the incriminated food and the oral mucosa.

The sensitivity for CAP determination of specific IgE to celery in patients with positive DBPCFC results was 73%. SPT results with commercially available extracts showed a sensitivity of 48% and 86%, respectively, depending on the brand used, whereas prick-to-prick tests with crude celery and the PEI extract had a sensitivity of 96%. The self-prepared PEI extract had the highest allergenic activity among the extracts applied in SPTs, simulating fresh celery. This superior quality is somewhat surprising because a simple extraction procedure was used. Apart from keeping the extract at -20°C for most of the time, we hypothesize that phenol, which serves as a standard preservative of commercial prick test solutions, might have caused degradation processes in the commercial extracts by interaction with polyphenoloxidases.

The specificity and NPV of these diagnostic procedures were poor. These results, however, must be interpreted carefully because all participants of the study were sensitized to pollen. The discordance of positive CAP or SPT results and negative DBPCFC results may just result from the correct in vivo or in vitro detection of antibodies to epitopes existing in pollen and in celery and not from a lack of specificity of these methods. Thus in a previous study all patients ($n = 12$) with a negative history of celery allergy and without allergy to birch and mugwort pollen had negative SPT results with commercial celery extracts and with native celery root.²

In the present study 77% of patients with positive DBPCFC results were also sensitized to carrots (CAP >0.7 kU/L), confirming once more the association of carrot and celery sensitization referred to as *celery-carrot-mugwort-birch-spice syndrome*.^{1,5,27}

Recently, a study was published, reporting the use of recombinant Api g 1, the major allergen from celery, for in vivo and in vitro diagnosis of celery allergy in a Central European and Mediterranean (French) population.²⁸ The study population was selected on the basis of a positive history for celery allergy, and no DBPCFCs were performed to prove the diagnosis of celery allergy in these patients. Reactivity to Api g 1 was high in individuals living in Central Europe, where sensitization to Bet v 1 (which shares sequence homology with Api g 1) is frequent, whereas in the French subjects living in Mediterranean areas where birch is rare, reactivity to Api g 1 was low. These results suggest that primary sensitization takes place predominantly through birch pollen in Central Europe and through other pollen (eg, mugwort) in Southern Europe.

In the present study population all patients with positive DBPCFC results were sensitized either to birch (91%) or to mugwort (64%) pollen. Because two patients

with positive DBPCFC results were not sensitized to birch pollen and Bet v 1, respectively, we could not confirm the overall observation of Hoffmann-Sommergruber et al²⁸ that patients with the history of celery allergy in Central Europe in general are allergic to birch pollen. Also in a previous study performed in Swiss patients, 8% of patients allergic to celery allergic were not sensitized to rBet v 1 or rBet v 2.²⁷

In conclusion, we were able to confirm celery allergy in 22 of 32 patients by using a DBPCFC protocol to celery root for the first time. Because of the high incidence of celery allergy in different European countries, we urgently recommend the addition of celery to the list of food allergens for labeling. Our further work will focus on the identification of the allergens recognized by IgE from patients with confirmed allergy to celery.

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