

Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome

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One hundred adult patients with a history of oral allergy syndrome (OAS) after ingestion of fruits and vegetables, 77 patients with hay fever and 13 with skin prick tests and RAST positive to pollens but without seasonal symptoms, and 32 normal nonallergic control subjects, had Phadebas RAST and skin prick tests with commercial extracts (CSPT) and with fresh foods (FFSPT) to assess the reliability of these three tests. Sensitivity was better with FFSPT for carrot, celery, cherry, apple, tomato, orange, and peach; better with CSPT for peanut, pea, and walnut; and better with RAST for hazelnut. Specificity, negative predictive value, and positive predictive value of the three tests were determined for apple, carrot, hazelnut, orange, pea, peanut, and tomato. Specificity in the patient groups ranged between 40% (pea) and 100% (apple) for CSPT, between 61% (peanut) and 87% (carrot) for RAST, and between 42% (carrot) and 93% (peanut) for FFSPT. However, all tests were negative in the control group. Thus, false positive results may result from cross-reactivity with pollen allergens. The diagnostic accuracy of these tests in the population with OAS proved comparable for peanut, carrot, hazelnut, and pea. FFSPT proved more sensitive than CSPT or RAST in confirming a history of OAS to certain alimentary allergens, such as apple, orange, tomato, carrot, cherry, celery, and peach. (J ALLERGY CLIN IMMUNOL 1989;83:683-90.)

Recent studies have highlighted the importance of the clinical aspects of allergy to fresh fruits and vegetables that provoke the OAS.¹ Patients with this allergy have oral itching and angioedema immediately after eating certain fruits and vegetables.²⁻⁵ This disease is often found in patients suffering from hay fever, especially provoked by birch pollen. Local symptoms quickly disappear and are not usually serious but can be accompanied by manifestations that are either local or systemic, for example, rhinoconjunctivitis, urticaria-angioedema, asthma, and anaphylactic shock.

The association of oral and systemic manifestations could be explained by structural similarities between

Abbreviations used

OAS:	Oral allergy syndrome
HS:	Hollister-Stier Laboratories
SPT:	Skin prick test
CSPT:	Commercial extracts skin prick test
FFSPT:	Fresh food skin prick test
SE:	Sensitivity
SP:	Specificity
PPV:	Positive predictive value
NPV:	Negative predictive value

pollen antigens (especially birch) and apple, carrot, potato, celery, and hazelnut.^{4, 6, 7} Minor allergens of birch and timothy pollen share epitopes with some fruit and vegetable foods, such as apple, carrot, and celery allergens.⁸ Moreover, celery OAS is associated with mugwort hay fever,⁹ just as melon and banana OAS appears to be associated with ragweed hay fever.¹⁰

The allergens of fruits and vegetables responsible for OAS are generally unstable^{3, 5, 6}; therefore, allergic patients can tolerate these foods when they are cooked or stored. The procedure of preparing a diagnostic

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TABLE I. Prevalence of adverse reactions to single fruits and vegetables in 100 patients

Fruit	
Apple	45
Hazelnut	32
Peanut	32
Walnut	31
Peach	30
Orange	17
Pear	15
Cherry	13
Melon	7
Banana	7
Almond	6
Plum	6
Watermelon	4
Vegetable	
Fennel	18
Tomato	16
Carrot	13
Pea	8
Potato	8
Bean	6
Celery	5

extract from these foods may also cause the loss of their allergenic activity. Therefore, SPT and RAST carried out with commercial extracts may yield unreliable results in many cases of allergy to fresh fruits and vegetables. In these cases, SPTs or RASTs with fresh foods elicit more reliable results.^{5, 9, 11}

We investigated the reliability of three procedures used for OAS diagnosis: CSPTs, FFSPTs, and RAST in 100 patients with a history of allergic reactions to vegetables and fruits.

MATERIAL AND METHODS

Human subjects

Patient group. The study group consisted of 100 patients (70 female and 30 male subjects; average age, 30.5 years; range, 10 to 61 years) who were observed with symptoms after eating fresh fruits and vegetables; 86 of these patients had a recent history of immediate hypersensitivity to fruits or vegetables (distinct symptoms appeared within 1 hour after eating the offending food and occurred repeatedly with the same food). In 14 patients in which the OAS had occurred more than 1 year earlier, we made an open oral food challenge with 15 gm of the following fresh fruits and vegetables: apple, apricot, banana, carrot, celery, fennel, melon, peach, and tomato. Vegetable or fruit pulps were chewed, kept in the mouth 1 minute, and then swallowed.

Control group. The control group consisted of 32 normal nonallergic subjects (23 female and nine male subjects; average age, 31.25 years; range, 15 to 50 years).

Commercial SPTs

CSPTs for foods were done with the following HS (Spokane, Wash.) extracts (1:20 wt/vol): apricot, apple, banana, bean, carrot, cherry, orange, pea, peach, pear, peanut, potato, plum, tomato, and walnut. For hazelnut we used an extract from Allergopharma (Reinbeck, West Germany) (1:20 wt/vol). All patients and control subjects also had CSPTs (HS) with 12 airborne allergens: grass, *Parietaria*, birch, mugwort, olive, *Dermatophagoides pteronyssinus* and *D. farinae*, cat and dog epithelia, *Alternaria tenuis*, *Cladosporium herbarum*, and *Aspergillus fumigatus*.

CSPTs were done on the volar side of the forearm with a lancet from Dome/Hollister-Stier, Slough, U.K. (1 mm tip), pricking through a drop of the extract, which was then immediately absorbed. The CSPT results were assessed relating every wheal area to that induced by histamine, 10 mg/ml, according to the Scandinavian Society of Allergy methods.^{12, 13} The average diameter of each wheal was established by measuring the longest diameter and the diameter perpendicular to it. Positivity was rated 3+ in the presence of a wheal with the same average diameter as the wheal induced by histamine, and 2+ if the average diameter was half that of the wheal induced by histamine. Only wheals half the average of the histamine wheal (2+) or more were considered positive.

Control-group subjects had CSPT with apple, carrot, hazelnut, orange, pea, peanut, and tomato.

FFSPTs

FFSPTs in all patients and control subjects were done by a prick + prick technique, according to the method of Dreborg and Foucard,³ with the following foods: almond, apple, apricot, banana, peach, bean, carrot, celery, cherry, fennel, hazelnut, melon, orange, pea, pear, peanut, potato, plum, tomato, walnut, and watermelon. Fruits and vegetables were cut, and the lancet was pricked into the pulp and then immediately afterward into the skin. We used the Golden Delicious apple and Kaiser pear, which are common varieties in Italy.

The results of FFSPTs were calculated by the same method as the CSPTs. Control group had FFSPTs with apple, carrot, hazelnut, orange, pea, peanut, and tomato.

RAST

All patients and control subjects were tested by Phadebas RAST (Pharmacia Diagnostics AB, Uppsala, Sweden) for the following food allergens: almond, apple, bean, carrot, celery, hazelnut, melon, orange, pea, peanut, potato, and tomato. RAST was also done for several airborne allergens: grass, *Parietaria*, birch, mugwort, olive, *Dermatophagoides pteronyssinus* and *D. farinae*, cat and dog epithelia, *Alternaria tenuis*, *Cladosporium herbarum*, and *Aspergillus fumigatus*. RAST scoring was adapted from the Phadebas RAST scoring system, as described in the Pharmacia RAST test kit instructions. Only results rated 2 or more were taken as positive.

Data analysis

We evaluated the agreement between the tests according to the method of Fleiss¹⁴ by calculating the k statistic. Significance was established by a two-tailed z test. As measures of accuracy and usefulness, we calculated SE, SP, PPV, and NPV according to the method of Goldman.¹⁵

We defined the above statistics as

$$P \text{ (prevalence)} = \frac{\text{Positive history patients tested}}{\text{Total patients tested}}$$

TP (true positive): patients with positive history of food hypersensitivity and CSPT or FFSPT or RAST positive

FP (false positive): patients with negative history of food hypersensitivity and CSPT or FFSPT or RAST positive

TN (true negative): patients with negative history of food hypersensitivity and CSPT or FFSPT or RAST negative

FN (false negative): subjects with positive history of food hypersensitivity and CSPT or FFSPT or RAST negative

$$SE = TP/TP + FN$$

$$SP = TN/TN + FP$$

$$PPV = \frac{TP \cdot P}{TP \cdot P + FP(1 - P)}$$

$$NPV = \frac{TN(1 - P)}{TN(1 - P) + FN \cdot P}$$

RESULTS

Most patients were sensitive to more than one food. When all symptoms in all patients to every nontolerated food were totaled, 70% had oral itching and/or oral angioedema, 27.6% had skin itching, 6.7% had gastrointestinal symptoms, 8.2% had oculonasal symptoms, and 2.4% of the patients had asthmatic symptoms. Eleven patients had laryngeal edema associated with anaphylactic shock in one case of hypersensitivity to peach. The foods responsible for this syndrome are presented in Table I. Seventy-seven patients had hay fever (seasonal symptoms and positive SPT and RAST); another 13 patients had positive SPT and RAST to pollens but without seasonal symptoms. Birch and grass were most often responsible, the prevalence varying in relation to the type of food.

The clinical characteristics of 14 patients with OAS, together with their symptomatology after oral food challenge, are presented in Table II. The CSPT, FFSPT, and RAST results are presented in Table III for the food allergens studied. This analysis was only done for patients who had had at least two of the three tests. The SE of the skin tests performed with CSPT varied widely, depending on the food tested, from 87.5% for potato to 0% for pear. After the potato, the test demonstrated greatest SE for carrot, pea, and peanut. The SE of the FFSPT varied widely, from 100%

for carrot, cherry, and celery, to 12.5% for peanut. The test was especially sensitive with tomato, potato, and apple, but poorly sensitive with nuts. The SE of RAST also varied widely, from 75% for celery and 71% for apple, to 0% for melon. RAST was particularly insensitive for almond, orange, and tomato. The SE, SP, PPV, and NPV were established for the seven foods tested by all three methods on a large enough number of patients (Table IV). Only data referring to patients who had completed all three tests were analyzed. Tests in the control group all elicited negative results, indicating SP of 100% for all three methods with the seven foods tested in normal, nonallergic subjects. Combining results of FFSPT, CSPT, and RAST did not improve significantly the SE over results of the most sensitive test used individually.

The degree of correlation between CSPT, FFSPT, and RAST was analyzed separately. The SE of the tests in symptomatic patients were in significant agreement for CSPT and RAST in the case of tomato and hazelnut, and for FFSPT and RAST for apple (Table V).

DISCUSSION

Our study analyzed the reliability of three diagnostic tests (CSPT, FFSPT, and RAST) for OAS in a group of patients allergic to fruit and vegetables, selected on the basis of their clinical histories. It is now generally accepted that an oral provocation test, preferably double-blinded, should be done for the diagnosis of food allergy,¹⁶⁻¹⁸ but in this syndrome the blindness of a provocation test raises many problems. The blind procedure may not guarantee oral contact with a high concentration of the offending food, since just the squeezing and handling needed to mask the food may be enough to cause the loss of its allergenic properties.⁵ In addition, there is no certainty that the syndrome will be reproduced when capsules are used, since they bypass the oropharynx that is the main target of this syndrome. Additionally, considering the severity of the symptoms that may appear in some patients, this method may involve the administration of a potentially dangerous dose. Apart from this possible problem, no blind provocation testing is reported in the literature.

Today OAS diagnosis is essentially based on the clinical history, which is usually very characteristic. Allergic subjects rapidly develop the typical symptoms of mediated IgE allergy on oral contact with the food, the symptoms recurring on subsequent contact. The diagnosis can be confirmed by SPTs with fresh foods and/or commercial extracts and RAST. The reliability of tests with commercial preparations has been debated by several authors who have

TABLE II. Open oral food challenge results in 14 patients with OAS

Patients	Sex	Age (yr)	Food	Time of onset (min)	Symptoms
P. A.	F	25	Peach	5	Oral itching and tingling
			Apple	2	Oral itching and tingling
G. I.	F	40	Apple	3	Oral itching and tingling
			Pear	6	Oral itching and tingling
			Carrot	5	Oral itching and tingling
G. B.	F	47	Apple	4	Asthma
			Carrot	6	Oral itching and lip angioedema
			Pear	5	Oral itching and lip angioedema
			Orange	10	Oral itching and lip angioedema
			Peach	5	Oral itching and lip angioedema
P. C.	M	37	Orange	5	Generalized urticaria
			(two segment)		
D. M.	F	51	Apple	5	Oral itching
			Pear	10	Oral itching
P. R.	F	34	Cherry	5	Oral itching
D. M. S.	F	17	Carrot	6	Oral itching
			Peach	2	Oral itching
S. R.	F	33	Apple	5	Oral itching
B. G.	F	54	Apple	2	Oral itching
			Peach	3	Oral itching
			Orange	7	Oral itching
P. D.	F	33	Carrot	4	Oral itching
			Fennel	6	Oral itching
			Apple	3	Asthma
			Potato	5	Asthma
			Pear	4	Oral itching
			Walnut	3	Oral itching
			Peanut	5	Oral itching
			Hazelnut	5	Oral itching
B. L.	F	40	Apple	2	Oral itching, eyelid angioedema
			Fennel	4	Oral itching, eyelid angioedema
			Celery	4	Oral itching, eyelid angioedema
			Walnut	5	Oral itching, eyelid angioedema
			Hazelnut	6	Oral itching, eyelid angioedema
			Peanut	5	Oral itching, eyelid angioedema
V. B.	F	33	Carrot	5	Oral itching
			Fennel	4	Oral itching
			Apple	3	Asthma
			Potato	5	Asthma
			Peach	4	Oral itching
			Tomato	6	Oral itching
			Melon	5	Oral itching
D. E.	F	37	Hazelnut	9	Oral itching
S. M. G.	F	41	Carrot	8	Oral itching plus eyelid angioedema
			Fennel	6	Oral itching plus eyelid angioedema
			Apple	3	Oral itching plus eyelid angioedema
			Pear	5	Oral itching plus eyelid angioedema
			Peach	3	Oral itching plus eyelid angioedema
			Celery	6	Oral itching plus eyelid angioedema

suggested the use of fresh foods both for RAST⁶ and SPT.^{3-7, 9}

Diagnostic tests reported with allergens of vegetables and fruits are limited. Several authors have

made cutaneous tests with commercial and/or fresh foods, and in some cases have done RAST, also prepared with fresh foods. In each case SE toward the foods was established exclusively on the basis of the

TABLE III. Sensitivity of tests

Food	Patients with positive history	% Tests positive		
		FFSPT	CSPT	RAST
Almond	6	16.7	ND	16.7
Apple	44	81.1	2.3	70.5
Banana	4	25	25	ND
Carrot	10	100	80	50
Celery	4	100	ND	75
Cherry	5	100	40	ND
Hazelnut	27	40.7	22.2	48.2
Melon	7	42.8	ND	0
Orange	15	66.7	26.7	20
Pea	8	62.5	75	50
Peach	22	59.1	13.7	ND
Peanut	24	12.5	66.7	41.7
Pear	14	42.9	0	ND
Potato	8	87.5	87.5	37.5
Tomato	16	75	25	31.2
Walnut	23	34.8	47.8	ND

ND, Not done.
Only patients who had had at least two of the three tests are reported.

TABLE IV. Sensitivity, specificity, and predictive indices for seven food antigens associated with OAS

Food	N	P		FFSPT	CSPT	RAST
Apple	73	60	SE	82	2	70
			SP	65	100	72
			PPV	78	100	79
			NPV	71	40	62
Peanut	52	46	SE	12	67	42
			SP	93	46	61
			PPV	59	51	48
			NPV	55	62	55
Orange	52	29	SE	67	27	20
			SP	73	97	81
			PPV	50	79	30
			NPV	84	76	71
Carrot	50	20	SE	100	80	50
			SP	42	65	87
			PPV	30	36	49
			NPV	100	93	87
Tomato	44	36	SE	75	25	31
			SP	61	79	86
			PPV	52	40	55
			NPV	81	65	69
Hazelnut	47	57	SE	41	22	48
			SP	80	85	75
			PPV	73	66	72
			NPV	51	45	52
Pea	18	44	SE	62	75	50
			SP	50	40	80
			PPV	49	50	66
			NPV	63	67	67

N, Number of patients studied; P, prevalence.

TABLE V. Agreement between results of FFSPT, CSPT, and RAST with foods responsible for symptoms in patients with positive history of OAS

Food	FFSPT and CSPT		FFSPT and RAST		CSPT and RAST	
	OAS* pts	Tests in agreement	OAS* pts	Tests in agreement	OAS* pts	Tests in agreement
Tomato	16	8	16	9	16	13†
Hazelnut	29	16	27	17	30	23‡
Pea	8	3	8	5	8	2
Carrot	9	5	10	5	10	5
Orange	17	10	16	6	15	10
Apple	44	9	45	34†	44	14
Peanut	24	11	24	15	31	18

*Patients with positive history of OAS.

† $p < 0.05$.‡ $p < 0.01$ two-tailed.

clinical history. These studies cannot be compared, however, since the selection of cases and the methods were different. Nevertheless, there are some points in common with our study.

We found high SE with FFSPT that is $>80\%$, for celery, cherry, carrot, potato, and apple. It was lower for other foods, peanut, almond, and banana. CSPT demonstrated low SE for all the foods tested except pea, carrot, peanut, and potato. It was particularly low for pear and apple. The SE of RAST was good only for apple and celery. This difference in results could reflect differences between extracts more than between methods. In fact, the low SE of CSPT for many allergens of fruits and vegetables may be due to a loss of allergenicity during extract preparation. In their study, too, Lowenstein and Eriksson⁴ found a poor correlation between history of apple allergy and SPT by use of commercial and lyophilized storage extracts. Other investigations have assessed the reliability of diagnostic tests in food allergies other than OAS. Bernstein et al.¹⁸ studied 22 adults with a history of reactions to foods. The correlation with positive skin tests and double-blind food challenge was 30% (4/13) against only 7.7% (1/13) between RAST and double-blind food challenge. Atkins et al.¹⁹ found that in open conditions the suspected food caused an immediate oral reaction in 10 of 25 patients with a positive history of immediate reactions to foods. Skin tests were positive, in agreement with these results, in nine of the 10 patients.

Lessof et al.²⁰ investigated the agreement between the results of skin tests and RAST and clinical history of adverse reactions to foods in 100 patients. When at least one of two tests elicited a positive result, they took this finding as indicating positivity. Agreement with the history was found in 30% to 75% of patients,

depending on the food considered and the interval between ingestion of that food and the onset of symptoms.

Sampson and Albergo²¹ did double-blind, oral food challenges in 40 children with atopic dermatitis. In 24 of the children, 33 tests elicited positive results; thus, agreement between positive skin test and positive food test was 73% to 100%, depending on the food, with better results than with RAST. Clearly, there is a variety of published results indicating that diagnostic-test (SPT and RAST) reliability ranges from 7.7% to 100%. These differences may depend on different case-list selection methods (clinical history and double-blind or open food challenge), on different syndromes studied, on the different ages of the patients, on the variety of extracts used, and, finally, on the variety of foods causing the symptoms. It is hard to compare the present study with studies cited above because the present study concentrated on OAS, a rather particular syndrome. However, as regards CSPT SE to tomato, our result in 16 patients (25%) was comparable to that obtained with the same commercial extract (HS) by Bernstein et al.¹⁸ in three patients who had a positive response to tomato in a double-blind food challenge (33%).

In the control group of 32 normal, nonallergic subjects, the three tests for the seven foods tried elicited 100% SP. In the patient group, however, SP was lower for all the allergens and all tests except CSPT with apple.

RAST demonstrated good overall SP except with peanut. There are other examples that fresh fruit does not induce false positive skin reactions in normal subjects. Andersen and Lowenstein⁷ had no positive cutaneous test results for apple and potato with either the peel of the fresh food or a lyophilized commercial

extract in 30 healthy control subjects, whereas false positive results were numerous among patients with birch hay fever. Pauli et al.,⁹ with both commercial extracts and fresh food, found no positive cutaneous tests with celery in 25 control subjects, whereas all 20 patients with a history of hypersensitivity to celery had positive skin tests to both the commercial extract and the fresh food.

The absence of positive skin tests in a control population suggests that the false positives among patients may be indicative more of asymptomatic hypersensitivity caused by cross-reactivity than a true false reaction. Atkins et al.¹⁹ offered a similar conclusion to explain the high percentage of false positive SPT results in patients with food allergy compared to control subjects.

Dreborg and Foucard³ stressed the risk of false positive reactions, since they, too, found a large number of children with positive FFSPT for apple, potato, and carrot who had no history of SE to these foods. Most patients were allergic to birch, and the food positivities may thus have depended on a cross-reactivity of foods with pollens.⁸ Although these results are in line with those we report for OAS, they contrast with the widely known findings in other forms of food allergy, confirmed by blinded food challenges in which the PPV of each test varied widely with different allergens. Any calculation of predictive values is known to depend closely on the prevalence of the disorder in the population under study. In our case list, selected for contact symptoms to vegetables and fruits, the PPV was still not particularly high, ranging between 40% and 73% for all the foods except apple, which elicited a better PPV (78% to 100%), and CSPT, which elicited a PPV of 79% for orange. These low values may be due to the presence of false positive results in these patients arising from cross-reactivity between allergens of fruits and vegetables and pollens, as suggested above. Our NPV was low also. The NPV elicits information on how likely a patient is not to have hypersensitivity if the test is negative. NPV depends, overall, on how reliably the test diagnoses the disease in question. Thus, if the available allergenic material is not properly prepared, the test will have a low SE. Equally, if patients are not properly selected, the NPV will be lower than the true value. In our study, the low NPV of the CSPT for apple and pea might have been due to a scarcity of proper allergenic material in commercial extracts. Apple allergens are in fact very labile, and phenols may easily develop, thus reducing the allergenic property of this food.²² This should not be the case for peanuts, whose allergens are very stable in commercial preparations. However, selection

of patients on the basis of a history of intolerance might have presented an overestimate of peanut intolerants in our study population. Sampson and Albergo,²¹ in fact, describe a series of eight patients, five of them selected on the basis of unequivocal intolerance and three on the basis of double-blind challenge, in which SE was 100% and NPV obviously also 100%. Lessof et al.²⁰ selected their patients only on the basis of clinical history and found SE of 45.4% (10/22) for SPT for the nut/peanut group. The variety in results might depend on differences in the number, age, and selection criteria for patients, and on different symptoms. We therefore maintain that for some foods, such as peanuts, double-blind food challenge may be necessary, even for OAS. The NPV of FFSPT was quite reliable for some fruits, like apple, orange, carrot, and tomato (71% to 100%). This accounts for the reliability of this test with these allergens. Differences between this value and the higher values found by many other authors might again arise from the different approaches to selecting patients. In the study by Sampson and Albergo,²¹ the NPV was between 90% to 95%, but the patients were selected by double-blind food challenge. Thus, it appears that, although oral food challenge would improve the diagnosis of OAS for some fruits and vegetables, clinical history is often sufficient and reliable enough.

Clearly, the NPV and PPV reported here only refer to the OAS population; they cannot be extrapolated to the allergic population as a whole because of the different prevalence of the disease.^{15, 17} Any such calculation can only be made on a theoretical basis because of the lack of epidemiologic data on OAS. In any event, PPV and NPV of diagnostic tests applied to a wider population do not appear very useful for OAS because this syndrome is clearly identified, even by the patient himself. These values are, however, important among patients in view of their typical hypersensitivity to multiple foods and the need to confirm hypersensitivity to various allergens. In conclusion, the present study appears to confirm the use of SPTs with some fresh foods, apple, carrot, tomato, orange, cherry, celery, and peach, in the diagnosis of OAS. The false positive results appear to be due, not so much to a lack of SP of FFSPT, but more to the presence of cross-reactivity with pollen allergens. The study confirms the need for better standardization of food allergens. Finally, none of the tests available (skin or RAST) are exhaustive in themselves, their efficiency varying depending on the type of food. One goal for the future would be to standardize an oral double-blind provocation test for OAS, since this would permit much improvement in diagnostic methods.

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