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Evaluation of Food Allergy in Children by Skin Prick Tests with Commercial Extracts and Fresh Foods, Specific IgE and, Open Oral Food Challenge: Our Five Years Experience in Food Allergy Work-up

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ABSTRACT

IgE- mediated food allergy affects 6-8% of children. Our study aimed to define the correlations between the results obtained with skin prick tests (SPTs) using commercial extracts and fresh foods, and the correlations between these result and those obtained with specific IgE (sIgE) and/ or challenge.

Children aged from 2 months to 6 years were recruited prospectively. Overall 571 children were positive to one food. In all children we performed SPT using commercial extracts of suspected food and fresh foods and sIgE. If SPT and sIgE test results did not correspond to the history, we performed open oral food challenge.

Sensitivity of SPT with commercial extracts for all tested food was poor (3-35%), while sensitivity of fresh food skin prick tests (FFSPT) was excellent (50-100%), and showed correlation with open oral food challenge ($p<0.001$).

Our results suggest that fresh food extracts are more effective in detecting sensitization and with levels of sIgE greater than class 3 could predict clinical reactivity, without the need for potentially hazardous food challenges.

Keywords: Children; Food hypersensitivity; Open oral food challenge; Skin test; Skin prick testing

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INTRODUCTION

Food allergy has been defined as adverse reactions to food mediated by an immunologic mechanism

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involving specific IgE (IgE-mediated) or cell–mediated mechanisms (non IgE- mediated) or both IgE and cell-mediated mechanisms (mixed IgE and non IgE-mediated).[1] IgE- mediated food allergy affects 6-8% of children, and the prevalence is believed to be increasing.[2] These reactions are characterized by an acute onset of symptoms generally within 2 hours after ingestion of or exposure to the trigger food. They involve the skin, gastrointestinal and respiratory tract. Diagnosis includes skin prick testing (SPT), serum specific IgE testing (sIgE) and oral food challenge.[3]

An accurate diagnosis is particularly important because a misdiagnosis could lead to life-threatening reactions or to unnecessary restrictive diets. However, allergy tests currently used in clinical practice have limited accuracy, and a open oral food challenge, considered as the gold standard, is often required to confirm or exclude a food allergy.[2] However, food challenges are time-consuming and not without risk.[4]

SPT is able to detect sensitization, but it has low specificity for clinically significant food allergy. To reduce the need for food challenge, it has been suggested that food challenge can be perform if SPT wheal size exceeds a cut off that has a high predictability for food allergy. The 95% positive predictive values (PPVs) vary substantially between studies, because of variability in participant's age, test allergens, and food challenge protocol.[5]

We were seeking a simple diagnostic tool to use in clinical practice that could reliably identify children with food allergy without the need for potentially hazardous food challenges.

The aim of our study was to define the correlations between the results obtained with SPT using commercial extracts and fresh foods, with sIgE and open oral food challenge.

METHODS AND PATIENTS

Subjects

Children ranging in age from 2 months to 6 years were recruited prospectively from a large outpatient population with histories of IgE-mediated reactions to food. This population was evaluated between January 2004 and December 2009 in the University Children's Hospital of Belgrade and Special Hospital "Sokobanja". Overall 571 children were positive to one food. The inclusion criterion required a history of IgE-mediated reaction to foods such as cow's milk, egg white, soybean, wheat flour, peanut and kiwi fruit. The exclusion criteria was non IgE-mediated reactions to food. Prior to the study, the parents of all the children received information about the possible risks of skin and challenge tests, and written informed consent was obtained from them.

Ethics

This study was reviewed and approved through the local ethics (No. 29/I-16 , 017-2571/1) and research committees of the University Children's Hospital in Belgrade.

SPT with Commercial Extracts

SPT were performed on the volar side of the forearm with Torlak (Serbia) extracts (1:10 w/v) of cow's milk, egg white, wheat flour, soybean, peanut and kiwi fruit, which was in accordance with general EAACI, WAO, NICE, NIAID guidelines for evaluating and diagnosing subjects on a suspicion of IgE-mediated reaction to food.[6-9]

SPT were interpreted as positive if a wheal larger than 3 mm[10,11] in diameter accompanied by erythema was present 20 min later. Histamine hydrochloride was used as the positive control and 0.9% sodium chloride as the negative one.

SPT with Fresh Foods (FFSPT)

SPT with fresh foods (FFSPT) were done by the prick to prick metode.[11-13] The results of FFSPT were calculated by the same method as the SPT.

We compared the diameter of the wheal obtained with commercial extracts and with fresh foods for the above mentioned foods.

sIgE

Commercially available assays for sIgE (UniCAP System; Pharmacia, Uppsala, Sweden) were used for cow's milk, egg white, wheat flour, soybean, peanut and kiwi fruit. Levels of sIgE greater than 0.10 kU/L were considered positive.

Open Oral Food Challenges

We carried out open oral food challenge according to EAACI position paper[14] in children if SPT and sIgE test results did not correspond to the history. In children

with positive sIgE and positive SPT with commercial extracts and FFSPT, we did not perform open oral food challenges.

The diagnostic accuracy of SPT and sIgE was based on the results of food challenges. Food allergy was diagnosed on the basis of positive skin tests, associated with positive sIgE and/or positive open oral food challenges.

Statistical Analysis

For the statistical analysis we used SPSS (version 15, SPSS, Inc., Chicago, IL, USA). Two by two tables were used to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV). Test sensitivity was defined as the proportion of true positives detected, specificity as the proportion of true negatives detected. The PPV describes the proportion of the true positive among the apparent positives and the NPV the proportion of true negatives among the appparent negatives.

RESULTS

Out of the total of 571 tested children, 297 (52%) were boys and 274 (48%) were girls. The ages ranged from 2 months to 6 years (mean age 3.33±1.42 years).

Various clinical reactions were described as being induced by food such as urticaria or angioedema or both in 322 children, respiratory symptoms such as wheezing and urticaria in 127, immediate gastrointestinal symptoms such as: vomiting, cramps and urticaria in 122 children.

No systemic allergic reactions occurred during the SPT and FFSPT.

44 children had postive history of IgE-mediated reaction to kiwifruit, 142 to cow's milk, 137 to egg white, 74 to wheat flour, 76 to soybean, and 98 to peanut (reported reactions and suspected food are shown in Table 1).

Out of 44 tested children to kiwifriut 29 (65.91%) were diagnosed to have positive results. Nine children had positive SPT, FFSPT and sIgE results and 20 (57.14%) children had positive challenges. SPT with commercial extracts were positive in 12 (27.27%) children, and in 7 were false positive, as challenges were negative. FFSPT were positive in 29 (65.91%) children, and false positive in 5. sIgE was positive in 22 (50%) children, and in 2 false positive.

Out of 76 tested children with soybean 44 (57.89%) were diagnosed positive results. 12 children were positive to SPT, FFSPT and sIgE and 32 (50%) children showed positive challenges. SPT with commercial extracts were positive in 18 (23.68%) children, and in 6 were false positive. FFSPT were positive in 34 (44.74%) children, and in 19 false positive. sIgE was positive in 44 (57.89%) children, and false positive in one child.

Out of 98 tested children to peanut 55 (56.12%) were diagnosed positive results. 20 children had positive SPT, FFSPT and sIgE and 35 (35.71%) children showed positive challenges. SPT with commercial extracts were positive in 26 (26.53%) children, and in 13 were false positive. FFSPT were positive in 48 (48.98%) children, and in 28 false positive. sIgE was positive in 39 (39.79%) children, and false positive in 6.

Out of 74 tested children to wheat flour 52 (70.27%) were diagnosed positive results. 15 children were positive to SPT, FFSPT and sIgE and 37 (62.71%) children showed positive challenges. SPT with commercial extracts were positive in 16 (21.62%) children, and in 7 false positive. FFSPT were positive in 47 (63.51%) children, and in 13 false positive. sIgE was positive in 39 (52.70%) children, and false positive in 8.

Table 1. Clinical manifestations induced by suspected foods

Clinical manifestation	Cow's milk	Egg white	Peanut	Wheat flour	Soybean	Kiwi friut	Total
Urticaria	37	34	24	22	24	10	151
Angioedema	17	22	22	11	15	6	93
Urticatia + angiedema	16	20	20	10	8	4	78
Urticaria + Respiratory symptoms	32	28	18	20	14	15	127
Urticaria + Gastrointestinal symptoms	40	33	14	13	13	9	122
Total	142	137	98	76	74	44	571

Out of 142 tested children to cow's milk, 99 (69.71%) were diagnosed as positive. 21 children had positive SPT, FFSPT and sIgE and 78 (64.46%) children showed positive challenges. SPT with commercial extracts were positive in 33 (23.24%) children, and in 10 were false positive. FFSPT were positive in 88 (61.97%) children, and in 32 false positive. sIgE was positive in 72 (50.70%) children, and false positive in 16.

137 tested children to egg white, 78 (56.93%) were diagnosed to have positive results. 23 children had positive SPT, FFSPT and sIgE and 55 (48.24%) children showed positive challenges. SPT with commercial extracts were positive in 35 (25.55%) children, and in 22 were false positive. FFSPT positive in 62 (45.25%) children, and false positive in 27 were. sIgE was positive in 48 (35.04%) children, and in one child false positive.

sIgE was done in 571 children (100%) and it was positive in 287 (50.26 %) of cases, but 34 (5,95%) of them were false positive, with levels of sIgE below 3.50 kU/l (<class 3).

Open oral food challanges were done in 471 (82.49%) children and positivively noted in 257 (54.56%) of cases. The reactions observed after open oral food challenges were identical to those reported in the history.

The correlations among sIgE, SPT, FFSPT and open oral food challenges are presented in Table 2.

Wheal diameter was larger with fresh food than commercial extracts, but the difference was not significant.

Sensitivity, specificity, NPV and PPV are presented in Table 3.

Table 2. Comparison of sIgE, SPT with commercial extracts and fresh food and oral food challenges

Foods	Positive oral challenges						Negative oral challenges					
	SPT +	SPT -	FFSPT +	FFSPT -	sIgE +	sIgE -	SPT +	SPT -	FFSPT +	FFSPT -	sIgE +	sIgE -
Kiwifruit	3	17	20	0	13	7	7	3	5	5	2	8
Egg white	12	43	39	16	25	30	22	37	27	32	1	58
Cow's milk	12	66	67	11	51	27	10	33	32	11	16	27
Wheat flour	1	36	32	5	24	13	7	15	13	9	8	14
Soybean	6	26	29	3	21	11	6	26	19	13	1	31
Peanut	6	29	28	7	19	16	13	30	28	15	6	37

SPT: skin prick test with commercial extract, FFSPT: skin prick test with fresh food, sIgE: specific IgE

Table 3. Sensitivity, specificity, positive and negative predictive values of SPT, FFSPT, sIgE according to results of oral food challenges

Foods	SPT				FFSPT				sIgE			
	Sens %	Spec %	PPV %	NPV %	Sens %	Spec %	PPV %	NPV %	Sens %	Spec %	PPV %	NPV %
Kiwi fruit	15	30	30	15	100	50	80	100	65	80	87	53
Egg white	35	46	22	63	59	67	71	54	96	66	45	98
Cow's milk	15	77	55	33	86	26	68	50	65	63	76	50
Wheat flour	3	68	13	29	86	41	71	64	65	64	75	52
Soybean	19	81	50	50	91	41	60	81	66	97	95	74
Peanut	32	51	17	70	50	68	80	35	76	70	54	86

Sens: Sensitivity, Spec: Specificity, PPV: positive predictive value, NPV: negative predictive value, SPT: skin prick test with commercial extract, FFSPT: skin prick test with fresh food, sIgE: specific IgE

DISCUSSION

SPT is the most widely used test for detecting IgE-mediated food allergy. However, the quality of allergen extracts used in SPT influences the results. Some food allergens rapidly lose their antigenic properties and the corresponding extracts sometimes have no allergenic activity.[12] When evaluating allergy to fruits and vegetables, commercially prepared extracts are generally inadequate because of the lability of the responsible allergen; therefore, fresh food must be used for skin testing.[15] Rance et al[12] showed that fresh food extracts give a stronger, more sensitive response than commercial extracts. Results of their study showed better correlation with positive challenges (91.7%). Some other studies also have demonstrated the superiority of SPT with fresh foods,[13,16] which is in accordance with the results of our study that confirm superiority of FFSPT (p<0.001), and suggest that fresh food extracts are more effective in detecting sensitization.

Sampson and Ho showed that diagnostic levels of IgE, which could predict clinical reactivity in the studied population with greater than 95% certainty, were identified: egg: 6 kU/L; milk: 32 kU/L and peanut: 15 kU/L. However, the performance characteristics of the CAP System FEIA for soy and wheat were poor.[17]

Previous studies reported that levels of IgE antibody to egg white of greater than 7 kU/L in older children and 2 kU/L or greater in infants younger than 2 years, are highly predictive of clinical reactivity to egg, and lower levels often require evaluation with oral food challenge to establish definitive diagnosis.[18,19]

Kinght et al showed that for egg white sIgE levels of less than 2.5 kU/L, and SPT wheal of 3 mm or an egg/histamine index of 0.65 was associated with a 50% chance of passing oral food challenge.[20]

Our results showed that levels of sIgE greater than 3.50 kU/L (> class 3) could predict clinical reactivity for all tested food (cow's milk, egg white, wheat flour, soybean, peanut and kiwifruit).

Norgaard et al[21] showed that the sensitivity of SPT with commercial extracts was 75% and none of the tests showed correlation with oral food challenge. Sensitivity of SPT with fresh foods was 100% and showed correlation with oral food challenge (p<0.05). Rance et al[12] showed that the sensitivity of SPT with commercial extracts for egg white and peanut was 56% and 66%, respectively, while for cow's milk was 73%. Sensitivity of SPT with fresh foods for egg white and peanut was excellent (100%, 90% respectively), while specificity for cow's milk was 100%.

In the present study we showed that sensitivity of SPT with commercial extracts for all tested food (cow's milk, egg white, wheat flour, soybean, peanut and kiwifruit) was poor (3-35%), while sensitivity of FFSP was excellent (50-100%), and showed correlation with open oral food challenge (p<0.001).

sIgE for peanut and soybean showed the best concordance with open oral food challenge (p<0.001).

Rance et al[12] showed that PPV was higher with commercial extract, except for cow's milk. The NPV was higer with fresh foods for egg white, peanut and cow's milk. In the present study, we found that PPV was high with SPT with fresh food with egg white (71%) and peanut (80%), while PPV was high with sIgE for cow's milk (76%), for wheat flour (75%) for kiwifruit (87%) and for soybean (95%). The hightest NPV was seen in FFSP for kiwifruit (100%).

These results suggest that fresh food extracts are more effective in detecting sensitization. It has previously been suggested that fresh foods should be used for primary testing for egg, peanut, and cow's milk sensitivity.[12] According to our results, it can also be suggested for kiwifruit sensitivity, as fresh kiwifruit testing was far more superior than commercial fruit extract in predicting food allergy.

Levels of sIgE greater than class 3 could predict clinical reactivity for cow's milk, egg white, wheat flour, soybean, peanut and kiwifruit. Altogether SPTs with fresh food in combination with sIgE are simple diagnostic tools to use in clinical practice that could reliably identify children with food allergy, without the need for potentially hazardous food challenges. Our study will be continued with working on other foods.

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