

The atopy patch test in the diagnostic workup of suspected food-related symptoms in children

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Background: There is an increasing need to develop test instruments that make oral food challenges superfluous. **Objective:** We sought to study the utility of atopy patch tests (APTs) in the diagnostic workup of food allergy. **Methods:** We investigated 437 children (median age, 13 months; 90% with atopic dermatitis) referred for evaluation of suspected food allergy. Specific serum IgE (sIgE) measurements, skin prick tests (SPTs), APTs, and controlled oral food challenges were performed. **Results:** We analyzed 873 oral challenges with cow's milk, hen's egg, wheat, and/or soy. One thousand seven hundred single APTs were performed. As a single parameter, the APTs showed the best specificity compared with sIgE measurements, SPTs, or both. Combining the APT with either the SPT or sIgE measurement resulted in improved sensitivity and specificity. Decision points for sIgE measurement and for the SPT showed lower values when combined with a positive APT result. Correctly bypassing an oral food challenge with combined testing, including APTs, only between 0.5% and 7% (99% predicted probability) and between 6% and 14% (using 95% predicted probability) of children would fulfill the criteria for avoiding an oral food challenge. **Conclusion:** Although the predictive capacity of the APT is improved when combined with sIgE measurement or the SPT, oral food challenges become superfluous in only 0.5% to 14% of study patients. In addition, the APT is time consuming and demands a highly experienced test evaluator. **Clinical implications:** For daily clinical practice, the APT adds only a small predictive value to the standard SPT and sIgE measurement in the diagnostic workup of suspected food-related symptoms in our study population. (*J Allergy Clin Immunol* 2006;118:923-9.)

Key words: Allergy, atopy patch test, atopic dermatitis, children, food, IgE, skin prick test

The prevalence of food allergy seems to be increasing,^{1,2} which might explain the increased demand for a

Abbreviations used

AD: Atopic dermatitis
APT: Atopy patch test
CM: Cow's milk
HE: Hen's egg
sIgE: Specific serum IgE
SPT: Skin prick test

reliable evaluation of patients with suspected food-related symptoms. This is especially true for infants and children, who might otherwise be unjustifiably subjected to even harmful dietary restrictions. Atopic dermatitis (AD) is commonly associated with food allergy.³ The proportion of children with AD who also have clinically relevant food allergy is reported to be up to 40%.⁴⁻⁶ The foods most commonly involved are cow's milk (CM), hen's egg (HE), peanut, tree nuts, soy, fish, and wheat.^{4,6} Clinical reactions to foods range from mild skin symptoms to life-threatening anaphylactic reactions, particularly with peanut and tree nut allergy.⁷⁻¹⁰

It is generally accepted that controlled food challenges still represent the gold standard for diagnosing food allergy.^{6,11-15} However, they are time consuming, troublesome for the patients, and not without risk of even severe allergic symptoms. Therefore there is a need to develop instruments that might make controlled oral food challenges superfluous, at least in part.

The determination of specific serum IgE (sIgE) has become popular in recent years. Several authors have established so-called decision points for specific IgE in serum that predict clinically relevant food allergy.¹⁶⁻²² However, they vary considerably between authors and seem to be dependent on the allergen and the population studied.^{23,24}

Skin prick tests (SPTs) have been used for decades to prove or exclude sensitization to allergens. For foods, the use of native allergens seems to be superior to commercially available extracts.²⁵ Several studies proposed cut-off values of wheal sizes, mostly using specificity, positive predictive values, or both.^{5,20,26-30} One study calculated decision points similar to those of specific IgE and found some advantages.³¹ However, taken together, the results of the SPT also vary considerably in the literature and are only provided for some foods.

Recently, the atopy patch test (APT) has been studied in patients with AD and food-related symptoms.^{29,32-41} The APT seems to have a better specificity than the IgE

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Disclosure of potential conflict of interest: K. Beyer has received grant support from the Danonc Institute FAAN, and the European Union. The rest of the authors have declared that they have no conflict of interest.

Received for publication March 13, 2006; revised July 4, 2006; accepted for publication July 5, 2006.

Available online August 25, 2006.

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0091-6749/\$32.00

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doi:10.1016/j.jaci.2006.07.003

methods and seems to reflect late-phase clinical reactions.³⁸ Especially when combining the APT with the SPT or sIgE measurement, high predictive values could be obtained, rendering oral food challenges superfluous in some cases.⁴²

This article draws on new data for a large number of children to examine the predictive capacity of the APT in the diagnostic workup of food allergy with respect to the 4 foodstuffs studied: CM, HE, wheat, and soy. A special focus was placed on whether oral food challenges can be made superfluous and how many children this would affect.

METHODS

Study population

We studied 437 children consecutively referred to our department for evaluation of suspected food allergy. Suspicion was defined as either the feeling of the parents that food could contribute to clinical symptoms of the child or that an IgE test result was positive in a child with moderate or severe eczema. Patients with a clear history of a severe allergic reaction to an isolated food were not included. Patients' ages ranged from 3 months to 14 years (median, 13 months), and the majority were boys (60%). Three hundred ninety-one (90%) patients had a history of AD, as defined by the criteria of Sampson⁴³ and Seymour et al⁴⁴ modified from those of Hanifin and Rajka⁴⁵: 43% of these patients had mild AD (SCORAD score, 1-24 points), 25% had moderate AD (SCORAD score, 25-49 points), 12% had severe AD (SCORAD score \geq 50 points), and 20% had no AD at the time of oral food challenge. The diagnosis of food allergy was based on the outcome of controlled oral food challenges.

Scoring of AD

Severity of AD was assessed according to the SCORAD score⁴⁶⁻⁴⁸ with topographic items (affected skin area), intensity criteria (extent of erythema, edema, crusts, excoriations, lichenification, and xerosis), and subjective parameters (itchiness and loss of sleep).

APT

One drop (50 μ L) each of fresh CM containing 3.5% fat, whisked HE (white of egg and yolk), wheat powder (Kröner, Ibbenbüren, Germany) dissolved in water (1 g/10 mL), and soy milk was put on filter paper and applied to the uninvolved skin of the child's back with 12-mm aluminum cups on adhesive tape (Finn Chambers on Scanpor, Hermal, Reinbek, Germany). Application sites were checked after 20 minutes for immediate reactions (contact urticaria). The results after 48 hours' occlusion time were read 20 minutes after removal of the cups to avoid false-positive results caused by an irritant effect of the plaster. The final evaluation of the test was done 24 hours later (after 72 hours). Reactions were classified as positive if there was erythema together with infiltration or papules.³⁸ Irritant reactions (sharply defined brownish erythema, decrescendo phenomenon, blistering, and lack of clear infiltration) were not regarded as positive.

SPT

One drop of each fresh food was applied to the patient's forearm: fresh CM containing 3.5% fat, native HE (whisked white of egg and yolk), wheat powder (Kröner, Ibbenbüren, Germany) dissolved in water (1 g/10 mL), and soy milk. SPTs were performed with 1-mm single-peak lancets (ALK, Copenhagen, Denmark). We used 10 mg/mL histamine dihydrochloride (ALK) as a positive control and saline solution as a negative control. SPTs were read after 15 minutes. All tests with a wheal diameter of less than 3 mm elicited by histamine or with a wheal of 2 mm or larger elicited by the negative control were excluded.⁴⁹

sIgE measurement

Blood was drawn before the oral challenge. Patient sera were analyzed for concentrations of specific IgE antibody titers to CM, HE, wheat, and soy, as determined by using FEIA with the ImmunoCAP (Phadia, Uppsala, Sweden).⁵⁰ The detection limit of the CAP system was 0.35 kU/L IgE, and children were regarded as sensitized if specific IgE levels were higher.

Food challenges

Oral challenges were performed as a result of a suggestive medical history and/or a positive SPT response and/or specific IgE levels of greater than 0.35 kU/L. We analyzed the 4 most common food allergens in European children: CM, HE, wheat, and soy. The majority of challenges (671/873 [77%]) were performed as double-blind, placebo-controlled food challenges. Open challenges were allowed in children younger than 1 year of age who had a clear history of immediate-type reactions ($n = 202$, 23%). The clinical dietician randomized and prepared the challenges. Briefly, successive doses (0.1, 0.3, 1.0, 3.0, 10.0, 30.0, and 100.0 mL) of fresh pasteurized CM containing 3.5% fat, soy milk, or placebo (Neocate, SHS, Liverpool, United Kingdom) were administered.^{14,51,52} Wheat powder (Kröner, Ibbenbüren, Germany) and raw HE (white and yolk) were given in successive doses, reaching a total amount of 5 g for wheat protein and 1 complete egg, respectively.

Doses were increased every 30 minutes. The time interval between different sets of challenges was 48 hours to evaluate late reactions as well. Children receiving an antihistamine were advised to avoid using it for at least 72 hours before provocation. Topical steroids were allowed twice daily at a concentration of 1% hydrocortisone or 0.01% betamethasone. For children with AD, challenges were only started when a stable clinical condition was reached. Before provocation, the patients had to have been on an elimination diet for the tested allergen for at least 1 week.

The provocation was stopped if clinical symptoms were observed or the highest dose was reached. The food challenges were scored as positive by a pediatric allergy specialist (blinded for the APT results) if one or more of the following objective clinical reactions were noted: urticaria, angioedema, wheezing, vomiting, diarrhea, shock, or exacerbation of eczema (at least a 10-point increase of the SCORAD score).⁵³ Symptoms within 120 minutes after administration of the last dose were defined as an early reaction, and symptoms occurring after more than 2 hours were defined as a late reaction.

Statistics

For the statistical analysis, we used SPSS for Windows (version 11.5; SPSS, Chicago, Ill). Predicted probabilities for the outcome of oral food challenges were calculated by using logistic regression, resulting in decision points.^{17,21,22,31} Comparisons were considered significant for a *P* value of less than .05.

RESULTS

Clinical outcome

We analyzed a total of 873 controlled oral challenges with CM, HE, wheat, soy, and placebo in 437 children. Three hundred ninety (73%) of 532 verum challenge results and 10 (3%) of 341 placebo challenge results were assessed as positive. One hundred twenty-eight (66%) of 193 egg challenge results, 168 (49%) 341 of those with CM, 57 (36%) 159 of those with wheat, and 37 (26%) 180 of those with soy were assessed as positive. Of the 390 positive food challenge results, 262 (67%) were assessed

TABLE I. Performance of single tests: sIgE measurement, the SPT, and the APT

	CM (n = 428)			HE (n = 424)			Wheat (n = 423)			Soy (n = 425)		
	sIgE	SPT	APT	sIgE	SPT	APT	sIgE	SPT	APT	sIgE	SPT	APT
Sensitivity (%)	87	85	31	96	93	41	82	75	27	65	29	23
Specificity (%)	49	70	95	48	54	87	34	64	89	50	85	86
PPV (%)	62	73	86	79	79	86	41	49	58	22	33	30
NPV (%)	79	83	60	85	81	43	77	85	69	86	82	82
Efficiency (%)	68	78	63	80	79	56	51	68	67	52	73	74

PPV, Positive predictive value; NPV, negative predictive value.

TABLE II. Performance of combination of sIgE measurement, the SPT, and the APT

	CM			HE			Wheat			Soy		
	A	B	C	A	B	C	A	B	C	A	B	C
	(n = 148)	(n = 138)	(n = 103)	(n = 68)	(n = 82)	(n = 53)	(n = 71)	(n = 57)	(n = 37)	(n = 111)	(n = 86)	(n = 67)
Sensitivity (%)	69	74	82	85	91	92	43	62	60	14	31	20
Specificity (%)	97	94	95	89	83	82	90	81	85	96	85	93
PPV (%)	92	90	91	92	91	92	50	65	60	43	27	33
NPV (%)	86	83	90	80	83	82	86	78	85	82	87	87
Efficiency (%)	87	86	90	87	88	89	80	74	78	79	77	82

A, APT + SPT; B, APT + sIgE; C, APT + SPT + sIgE; PPV, positive predictive value; NPV, negative predictive value.

as early, 58 (15%) were assessed as isolated late, and 70 (18%) were assessed as combined early plus late clinical reactions.

APT outcome

One thousand seven hundred separate APTs were performed in 437 children: 428 with CM, 424 with HE, 423 with wheat, and 425 with soy. Three hundred three (18%) of 1700 APT results were positive. One hundred fifty-five (37%) of 424 (37%) APT results were assessed as positive for HE, 70 (16%) of 428 for CM, 39 (9%) of 423 for wheat, and 39 (9%) of 425 for soy.

Single test parameter

The APT as a single parameter showed the best values for specificity for all 4 allergens (Table I). The sensitivity of the sIgE measurement and SPT was superior to that of the APT. Within the 2 IgE tests, the SPT showed a better specificity compared with sIgE measurement. Best specificity for the APT was found for CM (95%).

Combined test parameter

Combining the APT with either the SPT or sIgE measurement resulted in improved sensitivity and specificity for all 4 allergens when compared with the APT as a single test (Table II). Considering specificity, the combination of the APT and SPT was slightly superior to the APT together with sIgE measurement. Combining all 3 parameters could not markedly improve the predictive capacity; 100% values were not found in any constellation.

Decision points

Decision points were calculated for sIgE measurement and the SPT in the case of a positive APT result. Choosing

a 95% predicted probability as proposed in the literature resulted in a decision point for sIgE measurement of 27.5 kU/L for CM and 11.5 kU/L for HE. The 99% predicted probability for HE was 54.0 kU/L; no 99% predicted probability could be found for CM. The criterion for a 95% predicted probability was met by 22 (5.0%) of 437 for CM and 56 (12.8%) 437 for HE. For 99% predicted probability, the criterion was met by 16 (3.7%) of 437 for HE.

For the SPT, the 95% predicted probability was 9.2 mm for CM and 9.0 mm for HE. The 99% predicted probability was 14.5 mm for CM and 11.9 mm for HE. The criterion of a 95% predicted probability was met by 19 (4.3%) of 437 for CM and 68 (15.6%) of 437 for HE; the corresponding figures for 99% predicted probability were 2 (0.5%) of 437 for CM and 31 (7.1%) of 437 for HE. For children with a negative APT result and for all children, 95% and 99% decision points for sIgE measurement and for the SPT, respectively, were also calculated (Table III). No decision points could be calculated for wheat and soy (neither for sIgE measurement nor SPT).

Early, late, and combined clinical reactions

Looking separately at the test performances for the APT depending on the pattern of clinical reaction, specificity did not show any differences. The APT for CM was more sensitive in children with late reactions (sensitivity of 45%) compared with in those with early (sensitivity of 27%) or combined (sensitivity of 36%) reactions. However, APTs for HE were less sensitive for late reactions (sensitivity of 17%) than for early (sensitivity of 45%) and combined (sensitivity of 32%) reactions. For wheat, sensitivity was higher in late reactions (29%) than in early reactions (22%) and highest in combined reactions (50%). No differences in sensitivity were seen for the APT for soy.

TABLE III. Decision points for sIgE measurement and SPT for patients with positive APT results and patients with negative APT results

	All		APT ⁺		APT ⁻	
	CM	HE	CM	HE	CM	HE
sIgE measurement						
95%	*	15.9 kU/L	27.5 kU/L	11.5 kU/L	*	23.5 kU/L
99%	*	75.5 kU/L	*	54.0 kU/L	*	*
SPT						
95%	13.8 mm	14.0 mm	9.2 mm	9.9 mm	15.5 mm	16.8 mm
99%	20.0 mm	20.0 mm	14.5 mm	11.9 mm	*	*

*95% and/or 99% predictive values could not be calculated.

Presence of AD

The specificity of the APT for CM was lower in children with a history of AD (93%) than in children without AD (100%), and no significant difference was found for sensitivity (32% and 30%, respectively). Looking at the APT for HE, specificity was higher in children with AD than in those without (91% and 85%, respectively), whereas sensitivity was lower: 40% in children with AD and 60% in those without. For wheat, no children without AD had positive APT results, and therefore no test performances could be calculated. For soy, sensitivity of the APT in children with AD was 25% against 0% in children without AD, and specificity showed no significant difference (88% and 86%).

Influence of age

For CM, wheat, and soy, the sensitivity of the APT increased with age, but for HE, there was no significant difference in sensitivity between the children younger than 1 year, 1 to 2 years of age, 3 to 6 years of age, and older than 6 years. For CM, a specificity of 100% was found in children 3 to 6 years of age; for wheat and soy, a specificity of 100% was found in children older than 6 years. In HE the highest specificity was found in children 1 to 3 years old (91%).

Nonsensitized patients

Ten (6%) of 168 children with challenge-proved CM allergy had negative results on both the SPT and sIgE measurement (IgE double negative or nonsensitized). Three of these 10 children had a positive reaction on the APT. For HE, 3 (2%) of 128 children were nonsensitized, of which 0 of 3 had positive APT results. Four (7%) of 57 for wheat and 9 (24%) of 37 for soy were nonsensitized. The numbers of nonsensitized children with both a positive APT result and a positive oral food challenge result were 0 of 4 for wheat and 1 of 9 for soy. Specificity for the APT was significantly higher in double-negative children than in double-positive children for CM (97% vs 91%), wheat (96% vs 84%), and soy (89% vs 73%), but no significant difference was found for HE (87% vs 83%).

Value of the APT in the diagnostic workup of food allergy

Reviewing all our data, we established a hypothetical flow chart for the diagnostic workup of children with

suspected food-related clinical symptoms. Fig 1 shows how many children fulfill the criteria of 95% decision points of the different diagnostic branches for CM and HE (sIgE measurement and SPT). Corresponding numbers in Fig 1 for 99% predicted probability are as follows: CM sIgE measurement, 24%, 5%, 3%, 26%, 43%, 0%, and 0%; CM SPT, 34%, 6%, 3%, 15%, 42%, 0.5%, and 0%; HE sIgE measurement, 14%, 3%, 2%, 17%, 62%, 0.5%, and 2%; HE SPT, 16%, 4%, 3%, 17%, 53%, 6%, and 1% (from left to right).

Attention was paid to those children who would theoretically bypass an oral food challenge because of the APT (children with a positive APT result but a negative sIgE measurement/SPT result or a positive APT result and a positive sIgE measurement/SPT result above the decision point), irrespective of the outcome of the oral food challenge. In general, between 2.5% and 9% (99% predicted probability) and between 7% and 16% (using 95% predicted probability) of children would fulfill these criteria for avoiding an oral food challenge. However, taking box 3 (Fig 1, A, last row from the left) as an example, only one third of the 3% had a positive oral food challenge result. Considering children correctly bypassing an oral food challenge (in terms of a positive oral food challenge result) by using combined testing, including APT, only between 0.5% and 7% (99% predicted probability) and between 6% and 14% (using 95% predicted probability) of children would fulfill the criteria of avoiding an oral food challenge.

DISCUSSION

Single test parameters

Considering the APT as a single test, our data show that specificity of the APT was higher than that for sIgE measurement or the SPT for all 4 allergens (Table I). In contrast, sensitivity was lower. This confirms previous investigations of the APT.^{38,42} Between the 2 IgE-testing parameters, the SPT was superior to the determination of specific IgE regarding specificity, whereas sensitivity was lower for all 4 foodstuffs. Regarding the predictive parameters of specificity, sensitivity, positive predictive value, and negative predictive value, our values for the APT are comparable with those in the literature in almost all cases and for all 4 allergens.^{36,40-42}

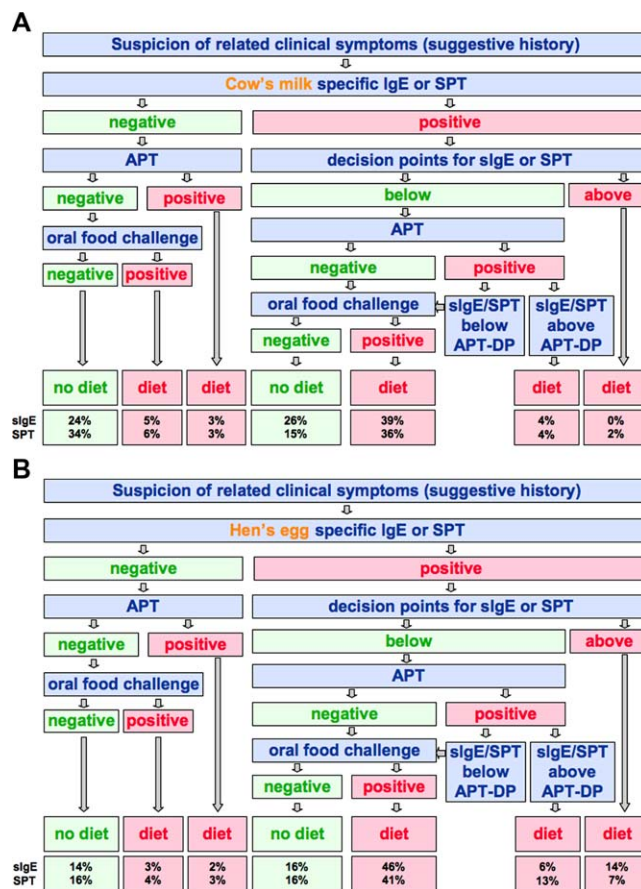


FIG 1. Working hypothesis for the diagnostic workup of children with suspected food allergy. The *last row* shows 7 boxes as the results of the different diagnostic pathways. **A** shows data for CM (n = 317 for sIgE, n = 275 for SPT), and **B** shows data for HE (n = 178 for sIgE, n = 149 for SPT). *APT-DP*, Decision point for sIgE measurement and the SPT for a positive APT result (95% predicted probability).

Combining test parameters

Combining the APT with one of the IgE-testing parameters (sIgE measurement and the SPT) resulted in significantly improved test performance parameters for all 4 allergens (Table II). Using the combination of all 3 diagnostic tests does not seem necessary because it does not further improve the predictive capacity, except in the case of sensitivity for CM and HE. However, in our view sensitivity is a less relevant parameter in food allergy testing because the key aim is to avoid unnecessary diets.

Subgroup analysis

To find whether any subgroup would especially profit from an APT, we analyzed test performance parameters depending on (1) the pattern of clinical reaction, (2) the presence of AD, (3) the age of the children, and (4) the IgE sensitization to any other allergen.

First, concerning the pattern of clinical reaction, we hypothesized that the APT, because of its mechanism of T lymphocyte-mediated cutaneous late-phase reaction,^{54,55} might be more sensitive in children with late-phase reactions after oral provocation, with the 2 IgE-dependent

diagnostic tests (determination of sIgE and the SPT) being more sensitive in early-phase reactions. For the APT, this can be confirmed for CM and wheat, but sensitivity for the APT with HE was surprisingly lower in children with late-phase reactions than in those with early-phase reactions. As expected for sIgE measurement and the SPT, sensitivity was highest in children with early-phase reactions, except for soy, where no difference was found. Because of the conflicting results, the APT does not seem to add diagnostic information, not even in children with late-phase clinical reactions.

Second, theoretically, the skin of children with AD might be more prone to irritation and might therefore show more false-positive APT results. Indeed, in our study specificity for CM and soy was lower in children with AD compared with that in children without AD. However, there is no explanation why this was reversed for HE. Overall, because of the lack of a uniform pattern, the APT does not add information for the diagnostic workup of suspected food-related symptoms in children without AD.

Third, investigating the influence of age on the APT, we found differing results again: for HE, the highest specificity was found in children 1 to 3 years of age. For CM,

wheat, and soy, specificity increased with age, reaching 100% for CM in children more than 2 years of age and for wheat and soy in children more than 6 years of age. A reason for this might be more sensitive skin in younger children and therefore more false-positive APT results.

Fourth, children with a negative sIgE measurement and a negative SPT result (nonsensitized children) showed higher specificity values for the APT than those children with 1 or 2 positive IgE test results. This is an interesting finding, confirming the hypothetical indication for the APT in IgE-negative children. However, the number of nonsensitized children was low in our study population, and therefore data should be considered with caution. Moreover, specificity was still not high enough to meet the requirements of a replacement diagnostic test.

Decision points

As proposed in the literature,^{16-18,21,22,31} we calculated predicted probability curves and decision points for sIgE measurement and the SPT. In children with a positive APT result, decision points were lower than in those with a negative APT result. Therefore in children with the combination of a positive APT result and an sIgE or SPT value exceeding the corresponding decision points, oral challenges become superfluous. Using the combination of the 2 tests allows more children to avoid an oral food challenge. In the literature decision points for a 95% predicted probability are commonly used. However, we propose using a 99% predicted probability, which might lead to a false-positive diet in only 1 of 100 children instead of 1 (5%) of 20. In our view unnecessary and restrictive diets might be more harmful to the child than performing a food challenge.

Differences in decision points between our results and those in the literature might have many explanations, such as (1) study population referral bias, (2) age of patient population, (3) criteria for defining an oral food challenge as positive, and (4) inclusion of late-phase clinical reactions in the observation time.

Value of the APT in the diagnostic workup of food allergy

Using the established flow chart for the diagnostic workup of children with suspected food-related clinical symptoms, we found that if the APT is integrated, an oral provocation becomes superfluous for only a small number of children. An IgE test is considered to be helpful, not least because it is easy to perform. However, comparing sIgE measurement and the SPT, the SPT should be given preference because (1) it is cheaper than determination of sIgE, (2) the result is obtained promptly, (3) specificity is generally higher, and (4) in contrast to sIgE measurement, decision points could be calculated for CM, making the performance of an oral food challenge superfluous. On the other hand, it should be mentioned that an SPT is unpleasant, and a 20-minute test procedure could be stressful for young children and their parents. Additionally, in children with AD, eczematous involvement in the test area might make an SPT impossible.

Conclusion

Although the APT showed the best specificity and its predictive capacity can be improved when combining with sIgE measurement or the SPT, an oral food challenge becomes superfluous in only 0.5% to 14% of study patients. In addition, the APT is time consuming and demands a highly experienced evaluator. Thus for daily clinical practice, the APT adds only a small predictive value to the standard SPT and sIgE measurement in the diagnostic workup of suspected food-related symptoms in our study population.

We thank our dieticians, Christiane Binder and Mandy Ziegert, for diligently performing the oral food challenges and Gabriele Schulz for perfect technical assistance.

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