Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis

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Background: Atopic dermatitis is commonly associated with food allergy. In addition to skin prick tests (SPTs) and measurements of specific IgE levels, the atopy patch test (APT) has recently been introduced into the diagnostic procedure for food allergy.

Objective: Our aim was to evaluate whether a combination of allergologic tests could improve the prognostic value of the individual tests for positive food challenge results. We hypothesized that the combination of a positive APT result plus proof of specific IgE, a positive SPT result, or both would render double-blind, placebo-controlled, food challenges unnecessary.

Methods: One hundred seventy-three double-blind, placebo-controlled, food challenges were performed in 98 children (median age, 13 months) with atopic dermatitis. All children were subjected to SPTs, APTs, and determination of specific IgE. Sensitivity, specificity, and positive and negative predictive values were calculated.

Results: Ninety-five (55%) of 173 oral provocations were assessed as positive. For evaluating suspected cow's milk (CM) allergy, the APT was the best single predictive test (positive predictive value [PPV], 95%), and the combination of a positive APT result with evidence of specific IgE or an APT result together with a positive skin prick test response optimized the PPV to 100%. For hen's egg (HE) allergy, the APT was also the best single predictive test (PPV, 94%). The combination of 2 or more tests did not exceed the APT's predictive value. In both CM and HE challenges, the predictability of oral challenges depended on the level of specific IgE. For wheat allergy, the APT proved to be the most reliable test, and the PPV of 94% could not be improved by a combination with other allergologic tests.

Conclusion: The combination of positive APT results and measurement of levels of specific IgE (CM, ≥0.35 kU/L; HE, ≥17.5 kU/L) makes double-blind, placebo-controlled, food challenges superfluous for suspected CM and HE allergy. (J Allergy Clin Immunol 2001;107:548-53.)

Key words: *Allergy; atopy patch test; children; food challenge; double-blind, placebo-controlled, food challenge; skin prick test; specific IgE; positive predictive value; cow's milk; hen's egg*

Atopic dermatitis (AD) is an inflammatory skin disease of relapsing course presenting as an erythematous and xerotic skin disorder with severe pruritus. It is a common ailment in childhood, affecting 10% to 12% of infants.[1,2] AD is frequently associated with food allergy, which complicates the management in approximately 40% of these children.[3-5] The most commonly offending foods are cow's milk (CM), hen's egg (HE), wheat, and soy.[4] AD and food allergy are diseases with a predominance in early childhood, and food allergy is most prevalent in the first few years of life.[6,7]

The diagnostic work-up of suspected food allergy includes skin prick tests (SPTs)[8] and the measurement of food-specific IgE antibodies by means of serologic assays.[9,10] The results of SPTs were found to be indicative for early reactions to food challenges.[5-11] Although atopy patch tests (APTs) have shown efficacy in patients with AD in the diagnosis of pollen and house dust mite–associated allergy,[12-17] the effectiveness of APTs for diagnosing food hypersensitivity has only recently been studied.[11,18]

To date, double-blind, placebo-controlled, food challenges (DBPCFCs) remain the gold standard for diagnosing clinically relevant food allergy.[5,10,19] This procedure, with an elimination period before challenge, a 2:1 allergen/placebo ratio, and an observation period of 48 hours, is time consuming and costly. Food challenges also bear the risk of life-threatening anaphylactic reactions.[20-22] To minimize the frequency of DBPCFCs, attempts have been made to combine the above-described investigations to reliably predict the outcomes of oral food challenges.

The aim of our study was to evaluate whether the combination of allergologic tests could improve their diagnostic value. We hypothesized that the combination of a positive APT result with evidence of specific IgE in serum, a positive SPT result, or both would reliably predict food allergy to CM, HE, wheat, and soy with a positive predictive value (PPV) of greater than 90%, rendering the DBPCFC unnecessary.

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Abbreviations used
AD: Atopic dermatitis
APT: Atopy patch test
CM: Cow's milk
DBPCFC: Double-blind, placebo-controlled, food challenge
HE: Hen's egg
NPV: Negative predictive value
PPV: Positive predictive value
SPT: Skin prick test

METHODS

Patients

We studied 173 oral provocations in 98 children (51 boys and 47 girls) with suspected food allergy admitted consecutively to our ward. Ages ranged from 2 months to 11.2 years (median, 13 months). All children had AD, as defined by the criteria of Sampson[23] and Seymour et al[24] modified from Hanifin and Rajka.[25] Of these, 61 children had mild AD (SCORAD ≤25 points), 27 had moderate AD (25-50 points), and 10 had severe AD (≥50 points).

Scoring of AD

Severity of eczema was scored according to the SCORAD score,[26] with assessment of topography items (affected skin area), intensity criteria (extent of erythema, edema, crusts, excoriations, lichenification, and xerosis), and subjective parameters (extent of itch and loss of sleep). The maximum possible score was 103 points.

Skin prick test

Fresh foods were applied to the patients volar 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 by using a 1-mm single-peak lancet (ALK, Copenhagen, Denmark). Reactions were read at 15 minutes, and the SPT result was assessed as positive if the wheal was 3 mm or larger without reaction of the negative control (NaCl 0.9%). We used 10 mg/mL histamine dihydrochloride (ALK) as a positive control.[8,9]

Atopy patch test

One drop (50 μL) each of fresh CM containing 3.5% fat, of whisked HE (white of egg and yolk), of wheat powder (Kröner) dissolved in water (1 g/10 mL), and of soy milk was put on filter paper and applied to the uninvolved skin of the child's back by using 12-mm aluminum cups on adhesive tape (Finn Chambers on Scanpor; Hermal, Reinbek, Germany). Application sites were checked after 20 minutes for immediate reactions. The occlusion time was 48 hours, and results were read 20 minutes after removal of the cups and again 24 hours later for the final evaluation of the test. After 72 hours, reactions were classified as positive if erythema with infiltration occurred.[18] Irritant reactions (sharply defined brownish erythema, decrescendo phenomenon, blistering, and lack of clear infiltration) were not regarded as positive.

Determination of specific IgE antibodies

Blood was drawn before food challenge. Patient sera were analyzed for concentrations of total IgE and specific IgE antibody titers to CM, HE, wheat, and soy, as determined by using an FEIA with the Pharmacia CAP system (Kabi-Pharmacia, Uppsala, Sweden).[27] The detection limit of the CAP system is 0.35 kU/L IgE; children were regarded as sensitized if their specific IgE levels were above the detection limit.

Food challenges

The most commonly tested food allergens in children were CM, HE, wheat, and soy. Those children taking an antihistamine (solely cetirizine) were advised to avoid it for 72 hours before provocation. Topical glucocorticosteroids were allowed twice daily at a concentration of 1% hydrocortisone or 0.1% betamethasone. All food challenges were performed in a double-blind, placebo-controlled manner.[19] Randomization and preparation of the challenges were performed by the clinical dietician. 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, and wheat powder (Kröner; total amount of 10 g of wheat protein) or placebo (Neocate; SHS, Liverpool, United Kingdom) were administered. Raw HE (white of egg and yolk) was given in a similar way, except that the highest dose was omitted. The time interval between doses was 20 minutes. Full emergency equipment, including drugs (antihistamines, glucocorticosteroids, and β-agonists), was at hand. The provocation was stopped if clinical symptoms were observed or the highest dose was reached. The children were observed for 48 hours after each challenge on an inpatient basis. The food challenge results were scored as positive by a pediatric allergy specialist if one or more of the following objective clinical reactions were noted: urticaria, angioedema, wheezing, vomiting, diarrhea, abdominal pain, shock, or exacerbation of eczema. Early reactions were defined as clinical symptoms within 120 minutes after administering the highest dose and late symptoms if occurring after more than 2 hours. For presentation and calculation of data, combined reactions were added to late-phase reactions.

Statistical analyses

Statistical analyses were performed by using SPSS for Windows software (version 8.0; SPSS, Chicago, Ill). Two-by-two tables were used to calculate sensitivity, specificity, PPV, and negative predictive value (NPV). The outcomes of tests were analyzed both individually and combined, focusing on the combination of tests with equal outcomes and those with divergent outcomes (late-phase reactions were defined as late reactions, combined reactions, or both). Test sensitivity was defined as the proportion of true-positive results detected, and specificity was defined as the proportion of true-negative results detected. The PPV describes the proportion of symptomatic individuals among those with positive test results, and the NPV describes the proportion of nonsymptomatic individuals among those with negative test results.

RESULTS

Clinical outcomes of challenges

We analyzed a total of 173 DBPCFCs: 71 (41%) children were challenged with CM, 42 (24%) with HE, 35 (20%) with wheat, and 25 (15%) with soy. Of this total, 95 (55%) challenge results were positive: 45 (63%) with CM, 28 (67%) with HE, 18 (51%) with wheat, and 4 (16%) with soy. The distribution of early-phase (0-120 minutes after provocation) and late-phase (3-48 hours after provocation) reactions are shown in Fig 1.

Outcomes of allergologic tests

All 98 patients were subjected to DBPCFCs, SPTs, APTs, and determinations of allergen-specific IgE antibodies. Of these, 86 (87%) expressed specific IgE to one or more of the 4 allergens: CM, 54 (55%); HE, 36 (37%); wheat, 21 (21%); and soy, 12 (12%). Positive SPT reactions were found to CM in 43 (44%) children, to HE in

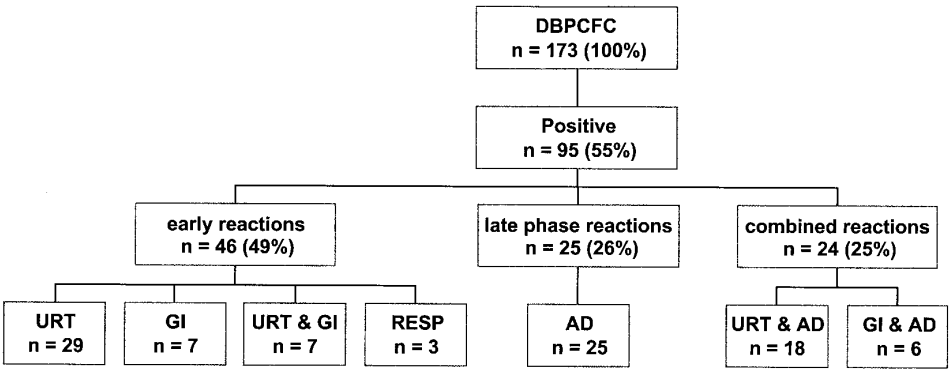

FIG 1. Outcomes of food challenges. *URT,* Urticaria; *GI,* gastrointestinal; *RESP,* respiratory.

TABLE I. Performance of single tests: APT, SPT, and specific IgE (≥0.35 kU/L)

	CM (n = 71)			HE (n = 42)			Wheat (n = 35)			Soy (n = 25)		
	IgE	SPT	APT	IgE	SPT	APT	IgE	SPT	APT	IgE	SPT	APT
Sensitivity (%)	84	78	47	96	89	57	67	67	89	75	50	75
Specificity (%)	38	69	96	36	57	93	47	53	94	52	90	86
PPV (%)	70	81	95	75	81	94	57	60	94	23	50	50
NPV (%)	59	64	51	83	73	52	57	60	89	92	90	95

31 (32%), to wheat in 20 (20%), and to soy in 4 (4%), respectively. Sixty-two (63%) children had positive APT results: 22 (22%) to CM, 17 (17%) to HE, 17 (17%) to wheat, and 6 (6%) to soy.

Performance of allergologic laboratory tests and outcome of challenges

The sensitivity, specificity, PPVs, and NPVs for positive provocations of the tests were calculated in 3 blocks. The performance of the single tests for any reaction to food challenges is shown in Table I. Positive APT results were correlated with very high PPVs for CM (95%), HE (94%), and wheat (94%) but with only a 50% PPV for soy. Positive SPT reactions resulted in PPVs of 81% for CM and HE, 60% for wheat, and 50% for soy, respectively.

The performance of the combination of tests is shown in Table II. The PPVs for a combination of 2 tests (APT plus specific IgE and APT plus SPT) for any reaction (early or late phase) to CM, HE, and wheat were high when tested for specific IgE (≥0.35 kU/L): 100% for CM, 94% for HE, and 92% for wheat. Forty percent of children had positive results on all 3 tests. The predictive capacity of the combination of both skin tests (APT plus SPT) together with specific IgE was highest in CM (100%) and soy (100%), followed by HE (94%) and wheat (91%).

The combination of tests used to discriminate between early- and late-phase reactions for CM and HE are shown in Table III. For CM, early- and late-phase reactions were best predicted by a combination of APT and specific IgE of any level (PPV, 100%). For HE, early- and late-phase reactions were equally well predicted by a combination of APT and specific IgE of 17.50 kU/L or greater (CAP class 4) or by specific IgE levels of 17.50 kU/L or greater as a single test, resulting in a PPV of 100%.

Positive outcomes of food challenges were related to the level of specific IgE in the case of CM and HE. Eighty-three percent of children with a level of specific IgE of 3.5 kU/L or greater (CAP class 3) had positive oral challenge results to CM, and 94% of children had positive results to HE (Fig 2). The likelihood of a positive challenge result was 100% for specific IgE of 50.0 kU/L or greater (CAP class 5) for CM and 17.50 kU/L or greater for HE, respectively. For wheat and soy, no such clear delineation could be observed. The PPV increased with increasing levels of specific IgE, but sensitivity dropped reciprocally (data not shown).

DISCUSSION

We recently published our first results on the value of the APT in the diagnosis of food allergy.[18] The present study (1) comprises a greater number of patients, (2) looks separately at several food allergens (CM, HE, wheat, and soy) in detail, (3) focuses on the combination of different diagnostic tests, and (4) defines cutoff levels of specific IgE levels in serum. Comparing both studies, we found similar results for each single test's (SPT, APT, and measurement of specific IgE) performance. However, additional information concerning PPVs was gained by combining APTs with determinations of levels of specific IgE.

Food allergy was confirmed by DBPCFCs in 95 (55%) of 173 of the oral provocations. Laboratory evaluations for allergen-specific IgE, SPTs, and APTs all proved to be helpful diagnostic tools, but their predictive capacity varied by allergen and for predicting early- or late-phase reactions.

TABLE II. Combinations of APT, SPT, and specific IgE determinations (≥0.35 kU/L)

	CM (n = 71)				HE (n = 42)				Wheat (n = 35)				Soy (n = 25)			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
Sensitivity (%)	85	79	74	81	96	94	84	94	71	92	86	91	100	100	67	100
Specificity (%)	56	100	100	100	43	83	89	75	50	89	90	86	91	83	100	100
PPV (%)	83	100	100	100	86	94	94	94	63	92	92	91	50	50	100	100
NPV (%)	60	64	74	67	75	83	73	75	60	89	82	86	100	100	94	100

A, Specific IgE plus SPT; *B*, APT plus specific IgE; *C*, APT plus SPT; *D*, APT plus specific IgE plus SPT.

TABLE III. Values for early- and late-phase reactions: performance of individual tests and combination of 2 tests

	CM						HE					
	Specific IgE ≥0.35 kU/L (CAP 1)	Specific IgE ≥17.5 kU/L (CAP 4)	SPT	APT	Specific IgE ≥0.35 kU/L + APT	Specific IgE ≥17.5 kU/L + APT	Specific IgE ≥0.35 kU/L (CAP 1)	Specific IgE ≥17.5 kU/L (CAP 4)	SPT	APT	Specific IgE ≥0.35 kU/L + APT	Specific IgE ≥17.5 kU/L + APT
Early reactions												
Sensitivity (%)	85	22	78	26	64	6	94	28	89	44	94	35
Specificity (%)	38	96	69	96	100	100	36	100	57	93	83	100
PPV (%)	59	86	72	88	100	100	65	100	73	89	94	100
NPV (%)	71	54	75	56	69	62	83	52	80	57	83	54
Late reactions												
Sensitivity (%)	83	17	78	78	92	40	100	20	90	80	100	50
Specificity (%)	38	96	69	96	100	100	38	100	57	93	83	100
PPV (%)	48	75	64	93	100	100	53	100	60	89	89	100
NPV (%)	77	63	82	86	90	89	100	64	89	87	100	87

In the evaluation of CM allergy, the most reliable test to predict any type of reaction to CM challenge was the APT (PPV, 95%). The combination of 2 tests, APT plus specific IgE or APT plus SPT, further improved the PPV, with both showing equally convincing PPVs of 100%. When all 3 tests were taken together, no further improvement was gained. When distinguishing between early- and late-phase reactions, the APT as a single test also showed a convincing PPV of 93% and proved to be superior to evidence of specific IgE or positive SPT results in predicting early reactions. Late-phase reactions were best predicted by a combination of APT and any level of specific IgE (PPV, 100%; Table III).

In suspected HE allergy, a positive APT result showed the best results for any reaction to HE (PPV, 94%); the combination of APT plus either specific IgE or SPT produced equally good results (PPV, 94%). The performance of APT in predicting early- or late-phase reactions was identical, whereas a level of specific IgE of 17.50 kU/L or greater (CAP class 4) alone or in combination with a positive APT result produced the highest PPV (100%) for early- and late-phase reactions. Therefore no additional information was gained by combining the 2 tests.

Evaluating wheat allergy, a positive APT result was the best single predictor of reactivity (PPV, 94%). Combining either specific IgE and APT or SPT and APT provided slightly lower PPVs (92%). Only 4 children reacted to soy, and therefore no reliable conclusions can be obtained for the test's performance in soy challenges (details are found in Tables I-III).

The level of specific IgE has often been used as a quantitative measure for the reactivity to various allergens. Our results are in keeping with those of other authors, showing excellent PPVs and NPVs for CM- and HE-specific IgE.[28-31] Norgaard et al[28] investigated the predictive capacity of serum IgE to CM and HE in relation to DBPCFCs. The authors found high sensitivities and NPVs (100%) and PPVs of 69% and 67% for egg white– and CM-specific IgE, with a high correlation with DBPCFCs for egg white only. The PPVs found by Norgaard et al are similar to those in our own data, although their study comprised adults.

Sampson and Ho[32] studied the predictive capacities of allergen-specific IgE levels in children and adolescents (median age, 5.2 years). They retrospectively analyzed data from 300 patients with AD and described a positive relationship between the level of specific IgE for egg, milk, and peanut. In their patient collective, positive challenges could be predicted with 90% certainty in those individuals with levels of specific IgE of 23 kU/L for CM (CAP class 4) and 2 kU/L for HE (CAP class 2). Similar to Sampson and Ho, we show that reactivity to DBPCFCs correlates with the level of allergen-specific IgE (Fig 2 and Table III), finding only marginally different cutoff levels for the individual allergens; for CM, 83% of children with levels of specific IgE of 3.5 kU/L or greater (CAP class 3) reacted to the oral food challenges, and 94% reacted to HE. In accordance with Sampson and Ho, we could not define satisfactory cutoff levels for soy or wheat. The poor predictive values of

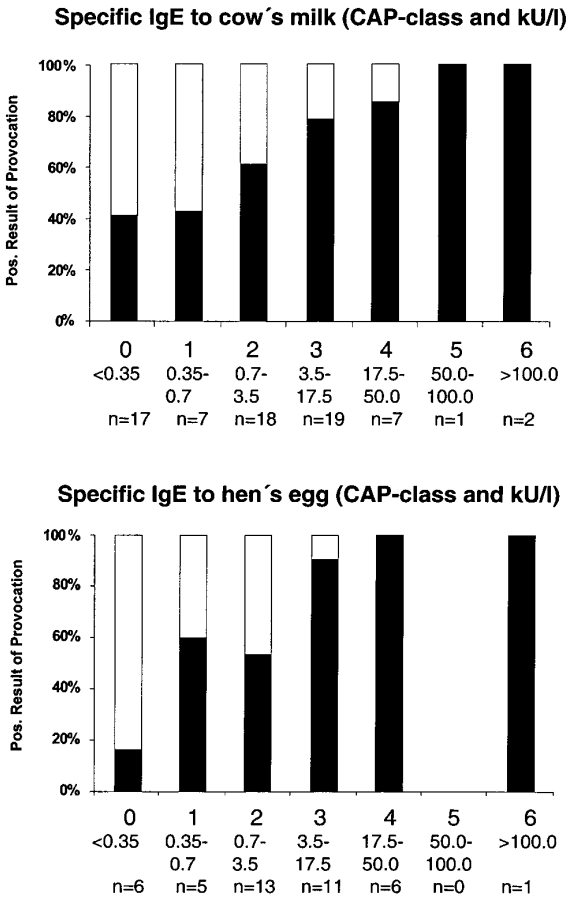

FIG 2. Specific IgE in relationship to outcome of food challenges. CAP class values are given in kilounits per liter.

specific IgE to these allergens could be due to cross-reacting proteins between these foods and grass pollen, as proposed by Yunginger et al.[33]

There are few studies of the reliability of APTs in the diagnosis of food allergy, and these show inconsistent results. Isolauri et al[11] first showed that positive APT results reflect late-phase reactions during oral food challenges in children allergic to CM with AD. The authors conclude that combined SPT and patch tests significantly enhance the accuracy in diagnosis of specific dietary allergies in children with AD.[11,34] Our results match those of Isolauri et al for CM; additionally, similar results were found for HE, wheat, and soy. Furthermore, besides SPTs, specific IgE measurements in serum were used, giving similar results. The measurement of specific IgE in serum offers the advantage of allowing determination of cutoff levels and is more practical in atopic children with eczematous skin lesions.

Majamaa et al[35] and Vanto et al[36] investigated the performance of tests in suspected CM allergy. In the study of Majmaa et al, the APT result was positive in 44% of cases of challenge-proven CM allergy; APTs were found to have a PPV of 63% in this study, which is comparable with our PPV of 70%. Similar to their findings, we found the APT to be the best predictor for positive challenge results to CM. Vanto et al, investigating 301 children with suspected CM allergy, found a PPV of 40% for the APT for immediate reactions, but no data could be provided for late-phase reactions. The authors conclude that APT results with CM were not related to acute or delayed challenge reactions. The data of our present study, however, prove the utility of the APT, particularly in suspected CM, HE, and wheat allergy.

Majamaa et al[37] also investigated the usefulness of SPTs, APTs, and measurements of specific IgE in 39 patients with wheat allergy, most of whom had AD. In their collective, 56% had positive challenge results, which is similar to that found in our patient group, in which 51% reacted to wheat. Regarding the APT, these authors found a PPV to wheat of 63% compared with the PPV of 94% found in our study. Similar to our results, the authors conclude that atopy patch testing is helpful in identifying food allergy.

Positive APT results showed very good predictive values. Combining the APT with proof of specific IgE slightly enhanced PPVs, giving values of 100% for CM and 94% for HE. Adding SPTs to the 2 other tests did not further improve results. For wheat, APT alone provided the best PPV values. In conclusion, the combination of positive APT results, together with defined levels of specific IgE (CM, ≥0.35 kU/L; HE, ≥17.5 kU/L), makes DBPCFCs superfluous for suspected CM and HE allergy.

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