

Original article

Diagnostic accuracy of the atopy patch test in children with food allergy-related gastrointestinal symptoms

Background: Little is known about the diagnostic accuracy of atopy patch tests (APT) in the clinical practice of pediatric gastroenterology. Moreover, APTs containing purified food extracts have recently become available, but their diagnostic accuracy is largely undefined.

Patients and methods: We evaluated the diagnostic accuracy of food challenge, skin prick test (SPT), serum specific IgE determination, and APT using fresh food and commercial food extracts in parallel in children referred for suspected food allergy-related gastrointestinal symptoms.

Results: Eighty-nine food challenges were performed in 60 patients (38 boys, median age 23 months, range 3–48 months): 31 tested positive for cow's milk (CM), 19 for hen's egg (HE), and two for wheat. Specific immunoglobulin E (IgE) determination, and SPT, respectively, were positive in 7/31 and 14/31 of patients with cow's milk allergy (CMA), and in 7/19 and 7/19 with HE allergy. The results of APT with fresh food vs a commercial assay were (1) CM: sensitivity: 64.5% vs 6.4%, specificity 95.8% vs 95.6%, positive predictive value (PPV) 95.2% vs 66.6% and negative predictive value (NPV) 67.6% vs 43.1%; (2) HE: sensitivity 84.2% vs 5.2%, specificity 100% vs 100%, PPV 100% vs 100% and NPV 75.0% vs 33.3%.

Conclusions: Atopy patch test is a useful tool in the diagnostic work up of children with food-allergy-related gastrointestinal symptoms. The diagnostic accuracy of ATP was higher with fresh food than with commercial food extracts.

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A wide range of gastrointestinal diseases share a similar repertoire of symptoms: nausea, vomiting, abdominal pain, diarrhea, and hematochezia. The challenge for the pediatrician is to determine the origin of symptoms within a spectrum of illnesses spanning from infections, inflammation, metabolic and anatomic defects, and gastrointestinal manifestations of food allergy (FA) (1–4). While dermatologic, respiratory, and systemic manifestations of FA are well recognized, reactions manifesting primarily in the digestive tract can be difficult to recognize, diagnose, and treat (5–9). Food allergy is now being increasingly recognized in conditions previously not labeled as 'allergic', such as gastroesophageal reflux disease (8). Nonrecognition of FA may lead to inappropriate treatment and to confusion with primary gastroesophageal reflux with potentially hazardous decisions (e.g. surgery).

Abbreviations: APT, atopy patch test; FA, food allergy; CM, cow's milk; CMA, cow's milk allergy; HE, hen's egg; HEA, hen's egg allergy; SPT, skin prick test; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

The initial diagnostic work up of suspected FA includes patient's history, skin prick test (SPT), measurement of food specific immunoglobulin E (IgE) with serological assays, and more recently the atopy patch test (APT). A positive SPT seems to reflect early reactions to food challenges (10), whereas the APT has a high diagnostic efficacy for late phase clinical reactions (10). Although APTs are widely used, well designed studies on their clinical implications and applications in pediatric gastroenterology clinical practice are only just emerging (11–14). In addition, one of the difficulties in patch testing is the lack of standardization. Several commercial APTs containing freeze-dried food extracts are now available, but their diagnostic accuracy is still largely undefined. A recent pilot study demonstrated the safety and efficacy of one of these ready-to-use APTs (Diallertest) (15).

The aims of our study were to evaluate: (i) the diagnostic accuracy of APTs for FA-related gastrointestinal diseases, both alone and with more standardized tests, namely the SPT and serum specific IgE; and (ii) the diagnostic accuracy of APTs using fresh food vs commercially available freeze-dried purified food extracts.

Methods

Patients

From September 2005 to March 2006, all children aged 3–48 months referred to our tertiary Pediatric Gastroenterology and Allergology Center for suspected FA-related gastrointestinal symptoms were considered eligible for the study. Children with systemic diseases, active tuberculosis, autoimmune diseases, immune deficiency, chronic inflammatory bowel diseases, celiac disease, cystic fibrosis, metabolic diseases, malignancy, and malformation of the gastrointestinal tract were excluded. Approval for the study was obtained from our Institutional Ethics Committee and written informed consent was obtained from the parents of each child enrolled in the study.

All enrolled patients underwent a full diagnostic evaluation including clinical, laboratory, radiographic, endoscopic, and biopsy examinations. Two experienced pediatric gastroenterologists and one pediatric allergist assessed each case and made a final diagnosis of FA (16) or of other disorders (17). All patients underwent serum specific IgE determination, SPT, and APT. All tests were carried out by clinicians who were unaware of the final diagnoses. The results were coded to maintain blinding. All clinical data were collected by structured chart abstraction performed by investigators masked to all test results. If FA was strongly suspected from the anamnesis and clinical evaluation, an elimination diet was prescribed and, 4–6 weeks later, an open oral food challenge was performed. In case of cow's milk allergy (CMA), an extensively hydrolyzed protein milk diet (Nutramigen, Mead Johnson, Italy) was adopted. The flow of subjects throughout the study is shown in Fig. 1.

Tests to diagnose FA

Skin prick testing. Fresh foods were applied to the patients volar forearm: cow's milk (CM) containing 3.5% fat; native hen's egg (HE; whisked egg white and yolk); wheat powder dissolved in water (1 g/10 ml), and soy milk. Skin prick tests were performed using a 1-mm single peak lancet (ALK, Copenhagen, Denmark), with histamine dihydrochloride (10 mg/ml) and isotonic saline solution (NaCl

0.9%) as positive and negative control, respectively. Reactions were recorded on the basis of the largest diameter (mm) of the wheal and flare at 15 min. The SPT result was considered 'positive' if the wheal was 3 mm or larger, without reaction of the negative control (18, 19).

Determination of specific IgE antibodies. Serum samples from patients were analyzed for specific IgE antibody titers against the most common food allergens (CM, HE, wheat, soy, fish, peanut) using a commercially available kit (CAP-RAST, Pharmacia Diagnostics AB, Uppsala, Sweden). The detection limit of the system was 0.35 kU/l IgE. Subjects were deemed sensitized if their specific IgE levels exceeded the detection limit (20, 21).

Atopy patch testing. The APT was performed in all children using, in parallel, fresh foods and freeze-dried purified food extracts contained in a commercial kit (Atopy line 1, Euromedical, Lecco, Italy). The commercial APT was performed according to the manufacturer's instructions. The freeze-dried purified food protein extracts (Allergon AB, Angelholm, Sweden) were provided in a 20% protein concentration in a vaseline mixture. The APTs using fresh foods were performed using one drop (50 µl) each of fresh CM containing 3.5% fat, whisked HE (egg white and yolk), wheat powder dissolved in water (1 g/10 ml), or soybean milk. Fresh foods and freeze-dried purified extracts of the same foods were put on filter paper and applied with adhesive tape to the unaffected skin of the child's back, using 12-mm aluminium cups (Finn Chambers on Scan pore; Epitest Ltd Oy, Tuusula, Finland). Isotonic saline solution was the negative control. The occlusion time was 48 h and results were read 20 min and 24 h after removal of the cups. To exclude false positive reactions, we also tested allergens in a 1 : 10 solution (22). Seventy-two hours after the start of the test, reactions were classified as follows: –, negative; +/-, doubtful: erythema only; +, weak positive: erythema and slight infiltration; ++, strong positive: erythema, infiltration, papules; +++, very strong positive: erythema, infiltration, papules, vesicles. Children and their families were requested to report any delayed skin reaction that was noticed after this time. Irritant or doubtful reactions, including sharply demarcated confluent erythema, or reactions confined to margins without infiltration, were deemed negative (23).

Food challenge

Although double-blind placebo-controlled oral food challenges are ideal, we adopted open challenges because the gastrointestinal symptoms presented by the patients enrolled were not subjective. This diagnostic approach has been used by others who found that the bias in these patients is very infrequent (12, 24–28). We challenged children with CM, wheat and HE only because no one reacted to soy. The open food challenges were performed in a day ward and the results were assessed by two experienced pediatric gastroenterologists plus one pediatric allergist. The Clinical Dietician 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 were administered. Raw HE (egg white and yolk) and wheat powder (10 g of wheat powder dissolved in water) was given in the same doses (ml), except that the highest dose was not administered. Doses were given at 20-min intervals. Full emergency equipment and drugs (epinephrine, antihistamines, steroids) were at hand. The

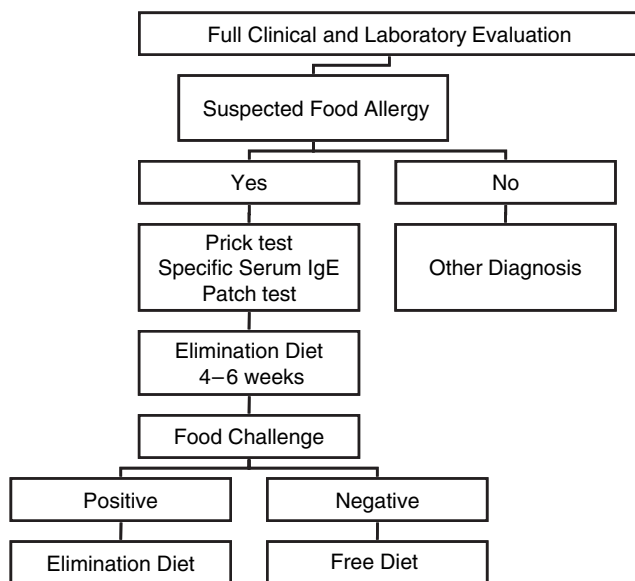


Figure 1. The flow of subjects throughout the study.

challenge was stopped upon the appearance of clinical symptoms or when the highest dose was reached. The child was observed for 4 h, and then discharged. The tested foodstuff was given by the parents at home for 7 days. If any symptoms occurred during this period the parents were told to contact the Center. On the seventh day after challenge the children were examined and the parents were interviewed at the Center. The food challenge results were scored 'positive' if at least one of the following clinical reactions was noted: vomiting, diarrhea, or hematochezia. Clinical symptoms occurring within 2 h of administering the highest dose were defined 'immediate reactions', and those occurring after 2 h were defined 'delayed reactions' (29). For patients with multiple FA, challenges were spaced 1 month apart to allow for a washout. Parents of children taking an antihistamine were advised to withhold the treatment for 72 h before and during the challenge.

Statistical analysis

The descriptive values of continuous variables were expressed as median (interquartile range). Two-by-two tables were used to calculate sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and likelihood ratio (LR). Comparison between two groups were performed using the chi-squared test. A *P* value of 0.05 or less was considered significant. The statistical analysis was performed using the SPSS software package for Windows (release 14.0.2, 21 April 2006; SPSS Inc., Chicago, IL, USA) and the diagnostic test analysis was performed with STATSDIRECT statistical software (release 2.5.6 15 April 2006).

Results

Patients

Sixty children (38 male) were considered for suspected FA-related gastrointestinal symptoms and completed the study. Their age ranged from 3 to 48 months (median age 23 months, interquartile range 35 months). Gastrointestinal symptoms were vomiting, chronic diarrhea, and hematochezia. There was a positive family history (at least one parent or sibling) of atopic disorders in 32 of the 60 subjects (53%). Table 1 shows the main clinical and demographic characteristics of the enrolled patients.

Food challenge

A total of 89 challenges were performed in 60 patients: 55 for CM, 28 for HE, and 6 for wheat. The challenge results are summarized in Table 2. All patients with a positive oral food challenge became symptom-free after re-eliminating the offending food from the diet. There were no differences in symptoms, age or sex between children who had an immediate reaction vs a delayed reaction or no reaction to oral food challenge. There were

Table 1. Main demographic and clinical characteristics of the study population

Patients, <i>n</i>	60
Age in months, median (interquartile range)	23 (35)
Sex, male, <i>n</i> (%)	38 (63.3)
Weight (g), median (interquartile range)	11.340 (12.350)
Positive family history for atopic disorders, <i>n</i> (%)	32 (53.0)
Age in months of food allergy-related symptoms onset, median (interquartile range)	10 (16)
Gastrointestinal symptoms, <i>n</i> (%)	60 (100)
Vomiting	37 (61.6)
Chronic diarrhea	17 (28.3)
Hematochezia	9 (15.0)
Suspected allergy to, <i>n</i> (%)	
Cow's milk	29 (48.3)
Cow's milk + hen's egg	22 (36.6)
Hen's egg	6 (10.0)
Cow's milk + wheat	4 (6.7)
Wheat	2 (3.3)

more positive reactions in the group that had a family history of atopy (61.5% vs 38.5%, *P* = 0.07). Food allergy was diagnosed in 35 patients (58.3%): 14 (40.0%) were allergic to CM, four (11.4%) to HE, 15 (42.8%) to CM and HE, and two (5.7%) to CM and wheat (Table 2).

Diagnostic tests for FA

The results of the APTs, specific IgE tests and SPTs are shown in Table 2. Among the 31 patients with CMA, 20 had a positive APT with fresh food: three in the group with an immediate reaction, and 17 in the group with a delayed reaction. Only one child had a positive APT carried out with a commercial assay. This subject also had a positive APT with fresh food. Only one patient with a positive challenge (delayed reaction) had negative SPTs and APTs. In the group with no reaction to oral CM challenge, one child had a positive APT-fresh food result. Among the 19 patients with HEA, 16 had a positive APT-fresh food result: two in the group with an immediate reaction and 14 in the group with a delayed-type reaction. Only one patient had both a positive commercial APT and a positive ATP with fresh food. In the group with no reaction to oral HE challenge, none had a positive APT-fresh food result. There were no adverse reactions to the adhesive used to fix the aluminium cups on the backs of the children. No patient developed a reaction to the control cup (negative control) or to 1 : 10 allergen dilutions.

Diagnostic accuracy of the FA tests

The diagnostic accuracy of specific IgE, SPT, and APT (using fresh food or freeze-dried commercially available allergens) for CM- and HE-induced FA is reported in Tables 3 and 4, respectively. The APT results, particularly as regards sensitivity and NPV, differed remarkably depending on whether fresh food or freeze-dried allergens were used. In the case of CMA, the data for fresh food vs freeze dried allergens are: sensitivity 64.5%

Table 2. Food challenge and diagnostic test results in the study population

	Patients with early reaction (n = 10)	Patients with late reaction (n = 21)	Patient with no reaction (n = 24)
Cow's milk			
Specific IgE, n (%)			
Positive	4 (40.0)	3 (14.2)	6 (25.0)
Negative	6 (60.0)	18 (85.8)	18 (75.0)
SPT, n (%)			
Positive	6 (60.0)	8 (38.0)	7 (29.0)
Negative	4 (40.0)	13 (61.9)	17 (71.0)
APT-fresh food, n (%)			
Positive	3 (30.0)	17 (80.9)	1 (4.1)
Negative	7 (70.0)	4 (19.1)	23 (95.8)
APT-commercial assay, n (%)			
Positive	0 (0.0)	1 (4.7)	1 (4.1)
Negative	10 (100)	20 (95.2)	23 (95.8)
Hen's egg	Patients with early reaction (n = 5)	Patients with late reaction (n = 14)	Patient with no reaction (n = 9)
Specific IgE, n (%)			
Positive	3 (60.0)	4 (28.6)	3 (33.3)
Negative	2 (40.0)	10 (71.4)	6 (66.7)
SPT, n (%)			
Positive	4 (80.0)	3 (21.4)	3 (33.3)
Negative	1 (20.0)	11 (78.6)	6 (66.7)
APT-fresh food, n (%)			
Positive	2 (40.0)	14 (100)	0 (0.0)
Negative	3 (60.0)	0 (0.0)	9 (100)
APT-commercial assay, n (%)			
Positive	0 (0.0)	1 (7.1)	0 (0.0)
Negative	5 (100)	13 (92.8)	9 (100)
Wheat	Patients with early reaction (n = 1)	Patients with late reaction (n = 1)	Patient with no reaction (n = 4)
Specific IgE, n (%)			
Positive	0 (0.0)	0 (0.0)	1 (25.0)
Negative	1 (100)	1 (100)	3 (75.0)
SPT, n (%)			
Positive	1 (100)	0 (0.0)	0 (0.0)
Negative	0 (0.0)	1 (100)	4 (100)
APT-fresh food, n (%)			
Positive	0 (0.0)	1 (100)	0 (0.0)
Negative	1 (100)	0 (0.0)	4 (100)
APT-commercial assay, n (%)			
Positive	0 (0.0)	0 (0.0)	0 (0.0)
Negative	1 (100)	1 (100)	4 (100)

APT, atopy patch test; SPT, skin prick test.

vs 6.45% and NPV 67.4% vs 43.1%. In the case of HEA, the data are: sensitivity 84.2% vs 5.26%, and NPV 75.0% vs 33.3%. We did not evaluate the accuracy of diagnostic tests for wheat allergy because of the very small number of patients presenting with this condition.

Discussion

Studies on the use of APT have been mainly performed in patients affected by atopic dermatitis (10, 22) and it has been suggested that APT works only in patients with this condition. Here, we report one of the largest groups of children with FA-related gastrointestinal symptoms prospectively investigated by APT. Previous studies involved a small number of pediatric gastroenterology patients (12), they were retrospective (30), and did not include all the tests (SPT, APT, specific IgE) in all patients (29, 30), or were carried out in eosinophilic esophagitis-affected subjects (13). Our results support the use of APT in combination with SPT in the diagnostic approach to a child with suspected FA-related gastrointestinal symptoms. In fact, if FA is suspected from the anamnesis and clinical evaluation, our findings suggest that the results of APT and SPT can indicate the diagnosis before oral food challenge. The combined use of APT and SPT has a high sensitivity and NPV, which indicates that false-negative results are very uncommon, and that FA is highly unlikely when both tests are negative. However, the definitive diagnosis of FA should rest upon the outcome of elimination diet and food challenge.

Our results are relevant for pediatric gastroenterology clinical practice and indicate that a number of procedures could be eliminated by including APT in the routine clinical evaluation of patients with suspected FA-related gastrointestinal symptoms. Finally, the combination of all three tests (specific IgE, SPT, and APT) only negligibly improved the diagnostic efficacy. Whereas SPT had a high sensitivity, but low specificity for predicting the outcome of oral food challenge, APT had a high specificity but low sensitivity. Combining these two tests improves the overall predictive power. Similar results have recently been obtained in children affected by atopic dermatitis in whom the APT was the best single predictive test, and the

Table 3. Diagnostic accuracy of the test used in CMA affected patient

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR +/-
CM specific IgE	22.5 (0.09–0.41)	73.9 (0.51–0.89)	53.8 (0.25–0.70)	41.6 (0.26–0.57)	0.86/1.04
SPT	45.1 (0.27–0.63)	69.5 (0.47–0.86)	66.6 (0.43–0.85)	51.2 (0.30–0.66)	1.48/0.78
APT using fresh food	64.5 (0.45–0.80)	95.8 (0.78–0.99)	95.2 (0.76–0.99)	67.4 (0.49–0.82)	15.4/0.37
APT using commercial assay	6.45 (0.00–0.21)	95.6 (0.78–0.99)	66.6 (0.09–0.99)	43.1 (0.29–0.57)	1.48/0.97
APT using fresh food or SPT	87.1 (0.70–0.96)	65.2 (0.42–0.83)	77.1 (0.59–0.89)	78.9 (0.54–0.93)	2.5/0.19
APT using fresh food or SPT or CM specific IgE	90.3 (0.74–0.97)	52.1 (0.30–0.73)	71.7 (0.55–0.84)	80.0 (0.51–0.95)	1.8/0.18

APT, atopy patch test; CMA, cow's milk allergy; IgE, immunoglobulin E; LR+/-, likelihood ratio positive/negative test; NPV, negative predictive value; PPV, positive predictive value; SPT, skin prick test.

Table 4. Diagnostic accuracy of the tests used in HEA affected patient

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR +/–
HE specific IgE	31.5 (0.12–0.56)	66.6 (0.29–0.92)	66.7 (0.66–0.92)	31.5 (0.42–0.94)	0.94/1.02
SPT	57.8 (0.33–0.79)	66.6 (0.29–0.92)	78.5 (0.49–0.95)	42.8 (0.17–0.71)	1.73/0.63
APT using fresh food	84.2 (0.60–0.96)	100 (0.66–1)	100 (0.79–1)	75.0 (0.42–0.94)	–/0.15
APT using commercial assay	5.26 (0.00–0.26)	100 (0.66–1)	100 (0.02–1)	33.3 (0.16–0.53)	–/0.94
APT using fresh food or SPT	94.7 (0.73–0.99)	66.7 (0.29–0.92)	85.7 (0.63–0.96)	85.7 (0.42–0.99)	2.84/0.07
APT using fresh food or SPT or HE specific IgE	94.7 (0.73–0.99)	44.4 (0.13–0.78)	78.2 (0.56–0.92)	80.0 (0.28–0.99)	1.70/0.11

APT, atopy patch test; HEA, hen's egg allergy; LR+/, likelihood ratio positive/negative test; NPV, negative predictive value; PPV, positive predictive value; SPT, skin prick test.

combination of a positive APT with a positive SPT optimized the PPV to 100% for some foods (10).

Our results also show that the diagnostic accuracy of an APT with fresh food is much better than that of a commercial APT assay with freeze-dried purified food extracts. This difference may be caused by various factors, including protein purification procedure, antigen concentration, and capability of penetrating the skin. Further studies are necessary to investigate these variables. In particular, APTs should be standardized not only for the amount of antigen deposited in the Finn Chamber but also for the amount of antigen able to reach the reactive cells. This is an important point in clinical

practice because many commercial APTs have not been accurately standardized.

To conclude, our data demonstrate that the APT is a reliable, safe, and useful diagnostic tool with which to evaluate suspected FA-related gastrointestinal symptoms in childhood and infancy, and that APT with fresh foods has a higher diagnostic accuracy than ATP with freeze-dried food extracts.

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