

Role of atopy patch test for diagnosis of food allergy-related gastrointestinal symptoms in children

Onsuree Boonyaviwat, Punchama Pacharn, Orathai Jirapongsananuruk, Pakit Vichyanond & Nualanong Visitsunthorn

Division of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

To cite this article: Boonyaviwat O, Pacharn P, Jirapongsananuruk O, Vichyanond P, Visitsunthorn N. Role of atopy patch test for diagnosis of food allergy-related gastrointestinal symptoms in children. *Pediatr Allergy Immunol* 2015; **26**: 737–741.

Keywords

atopy patch test; commercial allergen extract; food allergy; food challenge test; gastrointestinal symptoms; lyophilized allergen extract; skin prick test

Correspondence

NualanongVisitsunthorn, Division of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Prannok Rd, Bangkoknoi, Bangkok 10700, Thailand
Tel.: 662-419-7000 X 5670
Fax: 662-418-4223
E-mail: nualanongv@yahoo.com

Accepted for publication 24 March 2015

DOI:10.1111/pai.12382

Abstract

Background: Double-blind, placebo-controlled food challenge is the gold standard for diagnosing food allergy. However, it is a time-consuming procedure and requires onsite medical supervision and resuscitating medicines and devices on hand. The objective of this study was to compare the atopy patch test (APT) with the oral food challenge test (OFC) in children with suspected food allergy-related gastrointestinal (GI) symptoms.

Methods: A prospective self-controlled study enrolled children with a history of suspected food allergy-related GI symptoms. Skin prick test (SPT) and APT using lyophilized and commercial allergen extracts for cow's milk, egg, wheat, soy, and shrimp were evaluated, and OFC was performed.

Results: Thirty-nine patients (25 boys, median age 2.4 yrs) with 76 events of suspected food allergy-related GI symptoms were enrolled. SPT was positive in 11/76 events (14.5%). Sensitivity, specificity, predictive values, and likelihood ratio were calculated related to the food challenge outcome. Of 41 OFC, 30 (73.2%) were positive. APT using lyophilized allergen extracts yielded high sensitivity (80%) and high positive predictive value (85.7%). APT using commercial allergen extracts yielded low sensitivity (30%) but high specificity (90%). The negative predictive value of APT using lyophilized and commercial allergen extracts was 53.8% and 32.2%, respectively. All cases with positive APT using lyophilized allergen extracts together with positive SPT also had positive OFC.

Conclusion: In contrast to commercial extracts, APT with lyophilized allergen extracts is reliable, safe, and maybe useful for the diagnosis of suspected food allergy-related GI symptoms in children. OFC is still needed in most of the cases.

The prevalence of food allergy is increasing. The dermatologic and systemic manifestations of food allergy are well recognized while reactions manifesting primarily in the digestive tract can be difficult to recognize, diagnose, and treat (1–5). Therefore, the reliable evaluation of patients with suspected food-related gastrointestinal (GI) symptoms is required. Most GI symptoms are non-IgE mediated (1). The skin prick test (SPT) or specific IgE alone are not helpful and may even not been indicated for the diagnosis of non-IgE-mediated food allergy-related GI symptoms (4).

Abbreviations

APT, Atopy patch test; SPT, Skin prick test; OFC, Oral food challenge test; GI, Gastrointestinal; DBPCFC, Double-blind, placebo-controlled, food challenge.

Previous studies suggested that evaluation of food protein sensitization by delayed skin atopy patch testing increases the identification of food allergy compared with skin prick testing alone (6–11). However, atopy patch test (APT) has a number of major disadvantages including variable reproducibility, optimum concentration, and the need to standardize allergens. Fresh foods rather than commercial extracts are preferred for testing (8), but there are problems in preparing allergens from fresh food. Furthermore, fresh foods may have irritative effects. Food allergens extracted under lyophilization might be a better alternative extract for APT.

To date, double-blind, placebo-controlled, food challenges (DBPCFCs) remain the gold standard for diagnosing clinically relevant food allergy. However, it is uncomfortable for

patients, time consuming, and requires a highly experienced test evaluator.

The purpose of this study was to evaluate the role of APT using lyophilized and commercial allergen extracts in combination with SPT in children with suspected food allergy-related GI symptoms and to compare it with the oral food challenge test (OFC).

Methods

Study population

From April 2010 to March 2013, all children aged 1 month to 18 yrs old who were referred to the Department of Pediatric Allergy, Siriraj Hospital, Mahidol University because of suspected food allergy-related GI symptoms were considered eligible for the study. Subjects with chronic diseases (such as autoimmune diseases, immune deficiency, and cancer) or pregnancy were excluded. Antihistamines, systemic corticosteroids (≥ 20 mg/day), and topical corticosteroids were discontinued for at least 7 days before testing. Approval of the study was obtained from our Institutional Ethics Committee. Written informed consent and informed assent were obtained from the parents and patients before enrolling into the study. The study is registered with ClinicalTrials.gov (NCT01164293).

Intervention

Atopy patch test

APT was performed in all subjects using lyophilized (1:10 W/V) and commercial (1:10 W/V) food allergen extracts in parallel (ALK-Abello, Port Washington, NY, USA). Lyophilized foods were prepared under lamina flow as follows: 1 mg of lyophilized cow milk, egg white, egg yolk, soy bean, and shrimp in 10 ml of Coca's solution (0.9% NaCl [5 g], 0.4% phenol [4 g], and NaHCO_3 [2.5 g] in sterile water [1 l], pH 7.0). One drop (50 μl) of dissolved lyophilized foods and commercially food allergen extracts of the same food were placed into 12-mm aluminum test cups (Finn Chambers on Scan pore; Epitest Ltd. Oy, Tuusula, Finland) with filter paper and adhesive tape was applied to the unaffected skin of the subject's back. Isotonic saline solution was the negative control. The occlusion time was 48 h and results were evaluated at 20 min and 24 h after removal of the cups (48–72 h after the test started). The reactions were classified according to the European Task Force on Atopic Dermatitis (ETFAD) guidelines (12) as follows: negative (no reaction), + doubtful reaction (only erythema, questionable), + weak reaction (erythema, infiltration), ++ moderate reaction (erythema, few papules), +++ strong reaction (erythema, many papules) and ++++ extreme reaction (erythema, vesicles). Erythema alone without infiltration was regarded as negative, as it can be caused by local irritation. Irritant or doubtful reactions, including sharply demarcated confluent erythema, or reactions confined to margins without infiltration, were deemed negative. Subjects were asked to report any delayed skin reactions that were noticed after testing.

Skin prick test

A simple blood lancet (Vitrex Medical A/S, Herlev, Denmark) was used for SPT in the study. Each child was tested with commercial allergen extracts of cow's milk, egg white, egg yolk, soy bean, wheat, and shrimp. Histamine dihydrochloride (10 mg/ml) and 0.9% normal saline were used as positive and negative controls, respectively. Wheals and flares induced by allergens were recorded 15 min after testing, whereas those induced by histamine solution (10 mg/ml) were recorded at 10 min after testing. The mean wheal diameter (longest diameter plus rectangular diameter divided by 2) was calculated. A reaction of at least 3 mm larger than the negative control reaction was considered positive.

Food challenge test

An open OFC was performed after 2 wks of an elimination diet, where one foodstuff at a time was tested, starting with the food to which the patients had negative SPT and APT results. The OFC was performed in hospital when increased doses of food to 8 g of dry food were administered, to allow the immediate treatment of serious or acute adverse reactions. If there were no reactions, then OFC of one serving amount of that food continued for at least 2 wks at home with the symptoms being observed and recorded by the parents. The OFC was discontinued when a clinical reaction was noted. If any adverse reactions occurred, the patients were told to call and visit the investigator as soon as possible. All patients were evaluated on days 7, 14, and 21 of the challenge by telephone.

Results

Thirty-nine patients (25 boys) completed the study. The mean age was 2.42 yrs (range, 2 months to 10 yrs). Seventy-six events (event means number of reactions) of suspected food allergy-related GI symptoms were reported. Cow's milk was the most common causative food. The GI symptoms found in this study were chronic diarrhea, hematochezia, vomiting, and abdominal pain (Table 1).

Food challenge results

Forty-one OFCs in 39 children were analyzed. Positive challenge results were found in 30 challenges (73.2%). Positive challenge tests were found in 64.7% of those challenged with cow's milk, 83.3% with egg white and egg yolk, 62.5% with soy and 100% with wheat (Table 2). No patients with suspected shrimp allergy were permitted to be challenged because the parents were afraid of severe reactions. All patients with positive oral food challenges became symptom-free after re-eliminating the offending foods from the diet.

Diagnostic tests for food allergy

A positive SPT to commercial food extracts was observed in 11 of 76 events (14.5%) of suspected food allergy-related GI symptoms. APT to lyophilized food allergen extracts showed more positive results than to commercial allergen extracts.

Table 1 Demographic characteristics of the study population (n = 39)

Characteristics	
Age (years): mean (interquartile range)	2.42 (0.16–10.3)
Sex: n (%)	
Male	25 (64.1)
Female	14 (35.9)
Weight (kg): median (interquartile range)	11.67 (3.0–37.2)
Gastrointestinal symptoms: n (%)*	
Chronic diarrhea	24 (61.5)
Blood in stool	19 (48.7)
Vomiting	14 (35.9)
Abdominal pain	4 (10.2)
Suspected causative foods, n (%)†	
Cow's milk	32 (82.0)
Egg white	12 (30.8)
Egg yolk	11 (28.2)
Soy	12 (30.8)
Wheat	5 (12.8)
Shrimp	4 (10.3)

*One case may have more than one gastrointestinal symptom.

†One case may have more than one suspected causative food.

Table 2 Outcomes of oral food challenge test in children with food allergy-related gastrointestinal symptoms

Foods	GI food allergy events, n	Food challenges, n	Positive challenges, n (%)
Cow's milk	32	17	11 (64.7)
Egg white	12	6	5 (83.3)
Egg yolk	11	6	5 (83.3)
Soy	12	8	5 (62.5)
Wheat	5	4	4 (100.0)
Shrimp	4	0	0 (0.0)

The results of APT to each food were shown in Table 3.

There were no adverse reactions to the adhesive tape used for fixing the aluminum cups to the backs of the children. No patients developed reactions to the negative control.

Table 4 Skin prick test/atopy patch test (with lyophilized and commercial food allergen extracts) and oral food challenge test in children with food allergy-related gastrointestinal symptoms

APT					Challenge result	
Lyophilized allergen	Commercial allergen	SPT	Events, n	Oral food challenges, n	Positive	Negative
+	+	+	1	—	—	—
+	+	—	15	8	7 (87.5%)	1
+	—	+	6	4	4 (100.0%)	—
+	—	—	28	16	13 (81.25%)	3
—	+	—	4	2	2 (100.0%)	—
—	—	+	4	3	1 (33.33%)	2
—	—	—	18	8	3 (37.5%)	5

Events mean number of reactions.

Table 3 Positive skin prick test (SPT) and atopy patch test (APT) in children with food allergy-related gastrointestinal symptoms

	Number of tests	Positive SPT, n (%)	Positive APT lyophilized allergens, n (%)	Positive APT commercial allergens, n (%)
Cow's milk	32	3 (0.09)	16 (50.0)	10 (31.3)
Egg white	12	2 (0.16)	11 (91.7)	4 (33.3)
Egg yolk	11	3 (0.27)	10 (90.9)	3 (27.3)
Wheat	5	1 (0.20)	3 (60.0)	1 (20.0)
Soy	12	2 (0.16)	7 (58.3)	1 (8.3)
Shrimp	4	0 (0.00)	4 (100.0)	1 (25.0)
Total	76	11 (14.50)	51 (67.1)	20 (26.3)

The results of the skin prick test/atopy patch test (with lyophilized and commercial food allergen extracts) and the result of oral OFC were shown in Table 4. In 16 events with positive APT to both lyophilized and commercial allergens, 7 of 8 events (87.5%) had positive oral OFC. In 28 events with positive APT to lyophilized allergens with negative APT to commercial allergens and negative SPT, 13 of 16 events (81.25%) had positive oral OFC.

All of four OFCs that were performed with positive APT events to lyophilized allergens and positive SPT showed positive results (100%). Three of 8 events (37.5%) with challenge-proven food allergy had negative results by all tests (SPT, APT using both lyophilized and commercial food allergens).

There were no serious adverse reactions by oral OFC and positive reactions observed were mild.

Diagnostic accuracy of the tests for food allergy

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR) of SPT and APT, both to lyophilized or commercially food allergen extracts used for the diagnosis of children with food allergy-related GI symptoms were shown in Table 5. APT using lyophilized allergen had a high sensitivity (80%) and high PPV

Table 5 Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR) of atopy patch test (APT) and skin prick test (SPT) in children with food allergy-related gastrointestinal symptoms

Test	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR–
APT (lyophilized allergen)	80.0	63.4	85.7	53.8	2.2	0.3
APT (commercial allergen)	30.0	90.0	90.0	32.2	3.0	0.8
SPT	16.7	81.8	71.4	25.7	0.9	1.0
APT (lyophilized allergen) and SPT	16	100	100	34.38	∞	0.84

(85.7%). APT using commercial allergen had a low sensitivity (30%) but high specificity (90%). The NPVs of APT using lyophilized and commercial allergens were 53.8% and 32.2%, respectively. LR+ was 2.2 and 3.0 and LR– was 0.3 and 0.8 in APT using lyophilized and commercial allergens, respectively. When combined SPT and APT, the specificity and PPV increased to 100% and LR+ was infinity.

Discussion

Several studies have investigated the use of APT for the diagnosis of non-IgE-mediated food allergy, primarily in patients with atopic dermatitis, and digestive disorders. However, one of the difficulties of APT is the lack of standardization. Several commercial freeze-dried food extracts are now available, but their diagnostic accuracy is still largely undefined.

In this study, we described for the first time the use of APT using lyophilized food allergen extracts to determine potential food antigens as the cause of food allergy-related GI symptoms in children. The lyophilized food allergen extracts were tested for sterility, reproducibility and efficacy in SPT and APT up to 3 months after preparation (13). A study to exclude false-positive reactions in Thai non-atopic volunteers showed no irritant reaction to either lyophilized or commercial food allergen extracts (14).

Currently, the usefulness of APT is controversial. A previous study showed that the predictive capacity of APT was improved when combined with sIgE measurements while oral food challenges were superfluous in only 0.5% to 14% of study patients (15). Another study demonstrated that APT was a reliable, safe, and useful diagnostic tool for the evaluation of suspected food allergy-related GI symptoms in childhood and infancy (8). This study supports our study findings that APT with fresh foods has a higher diagnostic accuracy than APT with commercial extracts.

Our data in children with suspected food allergy-related GI symptoms showed that the skin prick test was positive in only 14.5%, while APT with lyophilized food allergen and commercial food allergen extracts were positive in 67.1% and 26.32%, respectively. Furthermore, the diagnostic accuracy of APT with lyophilized food allergen extracts was much greater than that of APT with commercial allergen extracts.

Although DBPCFC is an ideal gold standard for the diagnosis of food allergy, open oral OFCs were performed in

our study because the GI symptoms observed by challenge were not subjective. This diagnostic approach has been used by other studies where bias in patients was very infrequent (16–20).

Compared with oral challenge test, APT using lyophilized allergen yielded high sensitivity (80%) and high PPV (85.7%). The NPV of APT using lyophilized extracts (53.8%) was not as good as for PPV. Therefore, if APT was negative, food allergy could not be ruled out. APT using commercial allergens yielded a low sensitivity (30%) but high specificity (90%). LR+ was 2.186 and 3.000 and LR– was 0.315 and 0.778 in APT using lyophilized and commercial allergens, respectively, suggesting little difference in post-test and pretest probability for the presence or absence of food allergy. The probability of not having disease (LR–) was greater in APT when using lyophilized rather than commercial allergens.

The most common food that caused GI allergic reactions in this study was cow's milk (82%). However, only 50% of the suspected cases had positive APT using lyophilized cow's milk and 64.7% of the cow's milk challenge showed positive results. Previous studies showed that more than 50% of reported food allergies are negative by OFC (9, 10). Although DBPCFC is a gold standard, it is difficult to perform and time consuming. Here, we conclude that APT using lyophilized food allergen extracts and SPT should be performed to identify the possible causative food before OFC is used in children with GI allergy to avoid unnecessary diet restrictions. Individual cases with mucous bloody stool and have positive result for both SPT and APT, the OFC can be abstained.

In the current study, all GI allergy children with positive results to APT using lyophilized allergen extract and SPT had positive oral OFC. We found that combining the APT using lyophilized food allergens with SPT improved the chance of a positive challenge. This result confirmed previous studies (7–9).

About one-third (37.5%) of children with challenge-proven GI food allergy had negative results by SPT and APT using either lyophilized or commercial food allergens. We recommend that GI allergy children with negative SPT and APT should undergo OFC or have the foods introduced to their diet carefully with close observation to prevent possible reactions.

A limitation of this study was that some parents denied oral OFC for safety reasons. They preferred avoidance of the suspected foods until the next evaluation, 6–12 months later.

Conclusion

APT with lyophilized allergen extracts is reliable, safe, and useful for the diagnosis of suspected food allergy-related GI symptoms in children. APT is more sensitive and predictive than SPT. Combining APT using lyophilized food allergens with SPT improved the chance of positive OFC in children with food allergy-related GI symptoms.

Acknowledgments

This study was partially supported by Mahidol University and the National Research University grant from Commission on Higher Education (CHE) through the Center for Biopharmaceutical Development and Innovative Therapy, Mahidol University, Thailand.

References

1. Sicherer SH. Clinical aspects of gastrointestinal food allergy in childhood. *Pediatrics* 2003; **111**: 1609–16.
2. Kay AB. Allergy and allergic disease. First of two parts. *N Engl J Med* 2001; **344**: 30–7.
3. Kay AB. Allergy and allergic disease. Second of two parts. *N Engl J Med* 2001; **344**: 109–13.
4. Sampson HA, Sicherer SH, Birnbaum AH. AGA technical review on the evaluation of food allergy in gastrointestinal disorders. *Gastroenterology* 2001; **120**: 1026–40.
5. Bischoff S, Crowe SE. Gastrointestinal food allergy: new insights into pathophysiology and clinical perspectives. *Gastroenterology* 2005; **128**: 1089–113.
6. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002; **109**: 363–8.
7. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996; **97**: 9–15.
8. Canani RB, Ruotolo S, Auricchio L, et al. Diagnostic accuracy of the atopy patch test in children with food allergy-related gastrointestinal symptoms. *Allergy* 2007; **62**: 738–43.
9. Roehr C, Reibel S, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. Atopy patch test together with level of specific IgE reduces the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2001; **107**: 548–53.
10. Niggemann B, Reibel S, Wahn U. The atopy patch test (APT) a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy* 2000; **55**: 281–5.
11. Strömberg L. Diagnostic accuracy of the atopy patch test and the skin prick test for the diagnosis of food allergy in young children with atopic eczema/dermatitis syndrome. *Acta Paediatr* 2002; **91**: 1044–9.
12. EAACI/GALEN Position paper. Present status of the atopy patch test. *Allergy* 2006; **61**: 1377–84.
13. Chaidaroon D, Visitsunthorn N, Vichyanond P. Seafood allergy: clinical manifestation in Thai patient who was referred to referral allergy center, Siriraj Hospital. *J Allergy Clin Immunol* 2003; **111**: s106.
14. Boonyaviwat O, Pacharn P, Piboonpocanun O, Vichyanond P, Visitsunthorn N. Comparison of irritant reactions between using lyophilized and commercial food allergen extracts in atopy patch tests in a normal population. *Asian Pac J Allergy Immunol* 2012; **30**: 158–61.
15. Mehl A, Rolinck-Werninghaus C, Staden U, et al. The atopy patch test in diagnostic work up of suspected food-related symptoms in children. *J Allergy Clin Immunol* 2006; **118**: 923–9.
16. Fogg MI, Brown-Whitehorn TA, Pawlowski NA, Spergel JM. Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome. *Pediatr Allergy Immunol* 2006; **17**: 351–5.
17. Bindslev-Jensen C, Ballmer-Weber B, Bengtsson U, et al. Standardization of food challenges in patients with immediate reactions to foods—position paper from the European Academy of Allergy and Clinical Immunology. *Allergy* 2004; **59**: 690–7.
18. Sicherer SH. Food protein-induced enterocolitis syndrome: clinical perspectives. *J Pediatr Gastroenterol Nutr* 2000; **30**: S45–9.
19. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. *J Pediatr* 1978; **93**: 553–60.
20. Powell GK. Food protein-induced enterocolitis of infancy: differential diagnosis and management. *Compr Ther* 1986; **12**: 28–37.