

Toward a standardized reading of the atopy patch test in children with suspected cow's milk allergy-related gastrointestinal symptoms

R. Berni Canani*, A. Buongiovanni,
R. Nocerino, L. Cosenza & R. Troncone

Keywords: diagnostic accuracy of atopy patch test; eosinophilic esophagitis; food allergy.

Patients with non-IgE-mediated cow's milk allergy (CMA) often present with gastrointestinal symptoms (1). Atopy patch tests (APT) have been proposed for the diagnosis of non-IgE-mediated food allergy (2) and are recommended for the diagnosis of eosinophilic esophagitis in adults and children (2). We previously found them to be a useful diagnostic tool in children with gastrointestinal symptoms and suspected CMA (1). These tests have also been proposed for the early diagnosis of CMA-related gastrointestinal symptoms in preterm infants (3). However, the use of APTs in the clinical practice of pediatric gastroenterology is still limited by the subjective interpretation and intra-observer variation. Moreover, the diagnostic accuracy of the test varies

between studies, and data about the effect of the severity of skin signs on APTs are scarce.

A standardized interpretation of APTs in children with atopic dermatitis has been proposed (4), whereas the issue of APT reading in children with suspected CMA-related gastrointestinal symptoms has yet to be addressed. Consequently, we evaluated whether the diagnostic accuracy of APTs in children with suspected CMA-related gastrointestinal symptoms could be influenced by the severity of skin signs. From October 2008 to September 2010, 119 consecutive children (77 boys, median age 26.7 months, range 3–48 months) with suspected CMA-related gastrointestinal symptoms were evaluated in our tertiary Pediatric Gastroenterology and Allergy Center. Gastrointestinal symptoms at presentation were vomiting (73/119, 61.3%), chronic diarrhea (34/119, 28.5%), and hematochezia (17/119, 14.2%). The APTs were performed in all enrolled subjects using previously reported method in which a drop (20 µl) of fresh cow's milk containing 3.5% fat is placed on filter paper and applied with adhesive tape to the unaffected skin of the child's back using a 12-mm aluminum cup (1). Isotonic saline solution was used as negative control to exclude false positive reactions. The occlusion time was 48 h, and the results were read 20 min and 24 h after removal of the cups. Antihistamines and anti-inflammatory agents were discontinued at least 7 days before the test. All tests were performed by the same nursing staff, and the results were read by two expert pediatric allergists blind to the outcome of the double-blind, placebo-controlled food challenges (DBPCFC). Skin findings were recorded on a standardized form. Reactions were judged to be either negative or positive.

Positive skin reactions on the APT site were classified mild (erythema and slight infiltration, +), moderate (erythema plus papules, ++), or severe (erythema plus vesicles, +++), as previously suggested (1, 5). All children enrolled in the study also underwent skin prick tests (SPT) with fresh cow's milk containing 3.5% fat and evaluation of specific serum IgE with a commercial kit (CAP-RAST; Pharmacia Diagnostic AB, Uppsala, Sweden), as reported previously (1). The children subsequently underwent DBPCFC as previously described (5, 6). Briefly, successive doses (0.1, 0.3, 1.0, 3.0, 10.0, 30.0, and 100.0 ml) of fresh cow's milk containing 3.5% fat or placebo (Neocate®, Nutricia, Italy) were administered at 20-min intervals.

Data were analyzed with the Stats Direct statistical software (Altrincham, Cheshire, UK, release 2.5.6, 15 April 2006). Regarding DBPCFC outcomes, we calculated sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and likelihood ratio (LR) for single and several combinations of skin signs at 72 h. The Ethics Committee of our Institution approved the study, and written informed consent was obtained from the parents of each child.

The diagnosis of CMA was confirmed in 66/119 subjects (78.5%) by a positive reaction at DBPCFC. In all cases, a delayed reaction was observed > 2 h after challenge with fresh pasteurized cow's milk containing 3.5% fat (vomiting = 39, vomiting and diarrhea = 22, diarrhea and severe abdominal pain = 5). No positive reaction to placebo was observed. The SPT and specific serum IgE evaluation were positive in 40/119 (47.6%) and in 24/119 children (28.5%), respectively. The diagnostic accuracy of APTs is reported in Table 1. The presence of erythema plus

Erythema plus papules at APT has high diagnostic accuracy in children with CMA-related gastrointestinal symptoms.

Table 1 Diagnostic accuracy of the atopy patch tests (APT) in children with suspected cow's milk allergy-related gastrointestinal symptoms

APT skin signs	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR + (95% CI)
Erythema and slight infiltration $\pm$ papules $\pm$ vesicles ($\geq +$)	66.7 (49.8–80.9)	84.1 (69.9–93.4)	78.8 (61.1–91.0)	74.0 (59.7–85.4)	4.19 (2.1–8.6)
Erythema plus papules and/or vesicles ($\geq ++$)	53.8 (37.2–69.9)	97.8 (88.2–99.9)	95.4 (77.1–99.9)	71.0 (58.0–81.8)	24.2 (4.5–138.29)

PPV, positive predictive values; NPV, negative predictive values; LR, likelihood ratio.

papules had the best specificity and PPV in children with suspected CMA-related gastrointestinal symptoms.

A standardized procedure and standardized reading plus documentation of the severity of the skin signs may improve the reproducibility of APT interpretation and reduce intra- and inter-observer errors, thereby increasing the accuracy of this noninvasive diagnostic procedure in children with suspected CMA-related gastrointestinal symptoms.

*Department of Pediatrics
European Laboratory for the Investigation of Food-Induced Diseases
University of Naples "Federico II"
Via S. Pansini 5 80131 Naples
Italy
Tel.: +390817462680/3266
Fax: +390815451278
E-mail: berni@unina.it

Accepted for publication 22 June 2011
Allergy 2011

© 2011 John Wiley & Sons A/S
DOI: 10.1111/j.1398-9995.2011.02674.x

Conflict of interest

None.

References

- Berni Canani R, Ruotolo S, Auricchio L, Caldore M, Porcaro F, Manguso F et al. Diagnostic accuracy of the atopy patch test in children with food allergy-related gastrointestinal symptoms. *Allergy* 2007;**62**:738–743.
- Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE et al. First International Gastrointestinal Eosinophilic Research Symposium (FIGERS) Subcommittees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;**133**:1342–1363.
- Dupont C, Soulaines P, Lapillonne A, Donne N, Kalach N, Benhamou PH. Atopy patch test for the early diagnosis of cow's milk allergy in preterm infants. *J Pediatr Gastroenterol Nutr* 2010;**50**:463–464.
- Heine RG, Verstege A, Mehl A, Staden U, Rolinck-Werninghaus C, Niggemann B. Proposal for a standardized interpretation of the atopy patch test in children with atopic dermatitis and suspected food allergy. *Pediatr Allergy Immunol* 2006;**17**:213–217.
- 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**:281–285.
- Bindslev-Jensen C. Standardization of double-blind, placebo-controlled food challenges. *Allergy* 2001;**56**(Suppl 67):75–77.