

BRIEF COMMUNICATION

Atopy patch tests are useful to predict oral tolerance in children with gastrointestinal symptoms related to non-IgE-mediated cow's milk allergy

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Abstract

Atopy patch tests (APT) have been proposed for the diagnostic approach in children with non-IgE-mediated cow's milk allergy and gastrointestinal symptoms. We aimed to investigate the benefit of APTs in predicting oral tolerance in these patients. We prospectively evaluated 172 subjects with a sure diagnosis of non-IgE-mediated CMA and gastrointestinal symptoms (97 boys, 56.4%; age, 6.37 m; range, 2–12 m). At diagnosis, 113/172 (65.7%) children had positive APTs to cow's milk proteins (CMP). After 12 months of exclusion, diet APTs were repeated immediately before OFC. APTs significantly correlated ($P < 0.001$) with the OFC outcome ($r 0.579$). Diagnostic accuracy was sensitivity of 67.95%, specificity of 88.3%, PPV of 82.81%, NPV of 76.85%, and a +LR of 5.80. APTs are a valuable tool in the follow-up of children with non-IgE-mediated CMA-related gastrointestinal symptoms by contributing in determining whether an OFC can safely be undertaken.

Cow's milk allergy (CMA) is the most common food allergy in childhood (1). The prevalence and the risk of persistence of the disease are increasing (2). Clinical presentation of non-IgE-mediated CMA frequently involves the gastrointestinal tract, through a wide range of symptoms (3). Oral food challenge (OFC) is always required to confirm the diagnosis and to test the acquisition of oral tolerance to cow's milk proteins (CMP) (4). Atopy patch tests (APT) have been proposed for the initial diagnostic approach in children with suspected non-IgE-mediated CMA and atopic dermatitis (5) or gastrointestinal disorders (6–8). The use of APTs in the clinical practice of pediatric gastroenterology is still limited by the subjective interpretation and intra-observer variation. We have recently demonstrated that in these patients, the diagnostic accuracy of APTs is influenced by the severity of skin signs (9). The possible utility of APTs in predicting the occurrence of oral tolerance is still largely unknown. We

investigated the accuracy of APTs in predicting the occurrence of oral tolerance in children with non-IgE-mediated CMA and gastrointestinal symptoms.

From July 2010 to January 2012, we evaluated 210 consecutively subjects with suspected CMA at our tertiary center for pediatric gastroenterology and food allergy. Children with concurrent 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. Subjects with eosinophilic disorders of the gastrointestinal tract were also excluded. Approval for the study was obtained from our Institutional Ethics Committee, and written informed consent was obtained from the parents of each enrolled child. Three to five days before the diagnostic OFC, we performed in all subjects skin prick tests (SPTs) and APTs. Briefly, fresh cow's milk (CM) containing

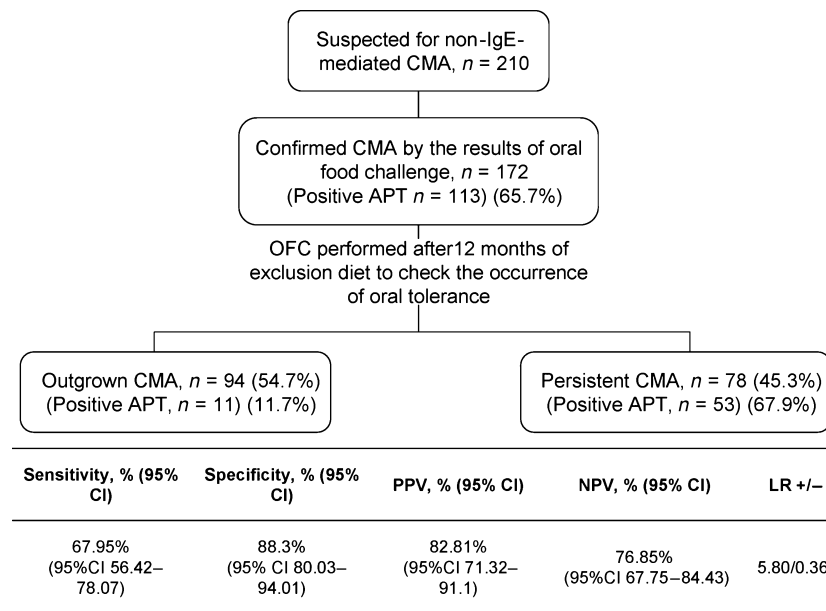


Figure 1 Flow of patients through the study and diagnostic accuracy of atopy patch tests performed immediately before oral food challenge after 12 months of exclusion diet.

3.5% fat was applied to the patient's volar forearm. SPTs 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 (in millimeters) of the wheal and flare at 15 min. The SPTs result was considered 'positive' if the wheal was 3 mm or larger, without reaction of the negative control.

APT were performed using a drop (20 µl) of fresh cow's milk containing 3.5% fat placed on filter paper and applied with adhesive tape to the unaffected skin of the child's back using a 12-mm aluminum cup. 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. Skin findings were recorded on a standardized form. Reactions were judged to be either negative or positive. Positive skin reactions on the APTs site were classified mild (erythema and slight infiltration, +), moderate (erythema plus papules, ++), or severe (erythema plus vesicles, +++). Irritant or doubtful reactions, including sharply demarcated confluent erythema, or reactions confined to margins without infiltration, were deemed negative (5).

A new OFC to evaluate the possible occurrence of oral tolerance was repeated after 12 months of exclusion diet. Immediately before OFC, we performed APTs. Accuracy of APTs and their correlation (Spearman's test) with OFC results was calculated. All food challenges were performed in a double-

blind, placebo-controlled food challenge (DBPCFC) manner and took place in the outpatient clinic of the Department of Pediatrics of our Center, as previously described (10). Briefly, randomization and preparation of the challenges were performed by a clinical dietician not directly involved in the procedures. Briefly, every 20 min, successive doses (0.1, 0.3, 1, 3, 10, 30, and 100 ml) of fresh pasteurized CM containing 3.5% fat or a standard extensive hydrolyzed casein formula were administered. Full emergency equipment and drugs were at hand. The food challenge results were scored positive if at least one of the following clinical reactions was noted: vomiting, diarrhea, abdominal pain, and/or hematochezia. The results were assessed simultaneously by three experienced pediatric allergists.

A sure diagnosis of CMA was obtained in 172 children (97 boys, 56.4%; age, 6.37 months; range, 2–12 months). The final diagnosis of CMA-induced disorders were as follows: enterocolitis (72, 41.9%), enteropathy (36, 20.9%), and gastro esophageal reflux disease (64, 37.2%). No eosinophilic disorders were included in the study. At diagnosis, all study subjects presented negative SPT. The flow of patients and the results of APTs and OFC are reported in the Fig. 1, together with the diagnostic accuracy of APTs in predicting the results of oral challenge after 12 months of exclusion diet. The APTs results significantly correlated with OFC outcomes (r 0.579, P < 0.001).

Our results demonstrate that APTs could be a valuable tool in the follow-up of pediatric patients with gastrointestinal symptoms related to non-IgE-mediated CMA by contributing in determining whether an OFC can safely be undertaken. Negative APTs would incite the clinician to plan a challenge, whereas a persistent positivity of APTs should

lead to greater caution. We therefore believe that the amount of unnecessary, costly, and potentially dangerous positive challenge could be avoided adding these simple and cheap test.

Author's contribution

Rita Nocerino, Roberto Berni Canani, and Riccardo Troncone designed the study, coordinated the research team, and wrote the first draft of the report.

Viviana Granata, Margherita di Costanzo, Cinzia Pezzella, Ludovica Leone, Annalisa Passariello, and Gianluca Terrin cared for the patients.

Conflict of interest

All authors had no personal, commercial, political, or academic conflict of interest.

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