

THE ATOPY PATCH TEST FOR DETECTION OF COW'S MILK ALLERGY WITH DIGESTIVE SYMPTOMS

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Infants (n = 35) with digestive symptom were investigated for diagnosis of cow's milk allergy (CMA). Milk atopy patch tests (APTs) were positive in 19 of 24 CMA versus 1 of 11 in non-CMA patients ($P < .001$). This sensitivity (79%) and specificity (91%) suggest that the APT could improve the detection of conditions related to CMA. (*J Pediatr* 2003;142:203-5)

During the first year of life, cow's milk is responsible for allergy in 2% to 7% of children, a large part of whom have predominantly gastrointestinal symptoms.¹ Reaginic antibodies cause only a part of the latter, so the diagnostic accuracy of the standard allergist's procedure—skin prick testing followed by measurement of specific immunoglobulin (Ig)E—is poor.² The atopy patch test (APT) has been shown to be useful in suspected delayed reactions to allergens in infants with atopic dermatitis.³ Majamaa et al⁴ demonstrated that many infants with a negative prick test had a positive cow's milk APT. The aim of our study was to provide an approach to the accuracy of the APT in the diagnosis of cow's milk allergy (CMA) in patients with digestive symptoms.

PATIENTS AND METHODS

This retrospective study includes 35 patients (15 girls, 20 boys) aged 2 to 57 months, referred for diagnosis of nonspecific persistent digestive symptoms. One was breast-fed at the time of referral, whereas all others had a normal diet for age, containing cow's milk proteins. Symptoms consisted of protracted gastroesophageal reflux despite treatment (n = 19), colics (n = 15), diarrhea (n = 19), constipation (n = 4), and failure to thrive (n = 5). No patient had atopic dermatitis. For diagnosis of CMA, patients were first given a cow's milk-free diet based on an extensively hydrolyzed whey protein formula (n = 28) or an amino acid-based formula (n = 7) during 4 weeks. A 1-week open challenge was then made with cow's milk, starting under medical survey with increasing doses of the infant formula (up to 100 mL), then continuing in the patient's home with increasing doses of cow's milk, monitored by a parental record of the child's symptoms. CMA was defined as the disappearance of symptoms under the cow's milk elimination and unequivocal adverse reaction to challenge. In 4 children, dubious symptoms prompted a double-blind placebo-controlled food challenge as already described.⁵

Skin Testing

Skin tests were carried out at the beginning of the elimination diet, before the results of oral challenge and together with serum total and cow's milk-specific IgE determination (CAP-RAST, Pharmacia, Peapack, NJ).

Prick testing was performed with a drop of cow's milk on the backs of children <12 months old and on the volar part of the forearm in children >12 months old. Histamine dihydrochloride was used as a positive controls and glycerosaline solution as a negative con-

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APT	Atopy Patch Test
CMA	Cow's milk allergy
Ig	Immunoglobulin

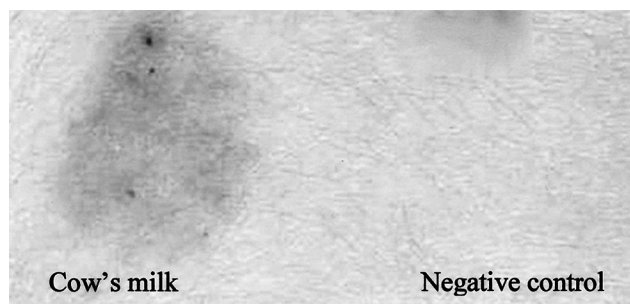


Figure. A positive APT for cow's milk in a patient from the CMA group.

trol. Reaction, assessed after 15 minutes, was labelled positive if the wheal diameter was at least 3 mm with a 0-mm negative control at the same time. The limited number of skin prick tests carried out in this study is related to a temporary interdiction of cow's milk skin testing in France in the period where the bovine spongiform encephalopathy epidemics began to spread.

For patch testing, a blotting paper soaked with 50% skimmed cow's milk was applied on uninvolved skin of the children's backs, using aluminium cups (Finn Chambers, Allerderm Laboratories, Sonoma, Calif) and Scanpore tape (Alpharma Norgespilster AS, Vennessla, Norway). Isotonic saline solution was used as a negative control. The occlusion time was 48 hours and the results were assessed 15 minutes after removal of the cups, with a second evaluation at 72 hours. Reactions were considered positive (Figure) with the presence of clear redness and palpable infiltration or eczema, as described by Majamaa et al.⁴

Statistics were performed with the Statview program (SAS Institute, Cary, NC). The descriptive values of variables were expressed as means and SDs with analysis of variance for statistical evaluations.

RESULTS

Of the 35 children tested, 24 were allergic to cow's milk (CMA group) and 11 were not (non-CMA). Groups were comparable for sex, age, symptoms, and total and specific IgE (Table). APTs were positive in 19 of 24 (79%) children in the CMA group versus 1 of 11 (9%) children in the non-CMA group ($P < .001$). In the CMA group, cow's milk-specific IgE were positive in 3 of 24 children (0.6 KUI/L, 0.36 KUI/L, and 0.49 KUI/L), one of them with a negative APT, whereas skin prick tests were negative in all 12 patients tested.

DISCUSSION

We report 79% positivity of patch testing in children with CMA and gastrointestinal symptoms, contrasting with 9% positivity in the control group. Several authors underline the usefulness of the APT for the diagnosis of food allergy in children with atopic dermatitis.^{3,6} Isolauri et al³ reported that combining skin prick and patch testing significantly enhances the diagnosis accuracy of specific dietary allergies in patients with atopic dermatitis. Niggemann et

Table. Clinical data, IgE, and skin tests in CMA and non-CMA groups

	CMA group (n = 24)	Non-CMA group (n = 11)	P value
Male/female	14/10	6/5	ns
Age (mo)	15.5 ± 13.2	20.8 ± 16	ns
Symptoms (n)			
Gastroesophageal reflux	15	4	ns
Colics	11	4	ns
Diarrhea	13	6	ns
Constipation	3	1	ns
Failure to thrive	3	1	ns
Blood in stools	1	0	ns
Total IgE (KUI/L)	29 ± 58	15 ± 5	ns
Positive milk-specific IgE (n)	3	0	ns
Positive skin prick test	0/6	0/6	ns
Positive APT	19/24	1/11	< .001

al⁶ found an association between immediate-type reactions with the positive skin prick test and specific IgE, whereas late-phase reactions were associated with a positive APT (sensitivity 76%, specificity 95%) in 75 children with atopic dermatitis. Roehr et al⁷ reported that for evaluating CMA in children with atopic dermatitis, the APT was the best single predictive test.

To our knowledge, Majamaa et al⁴ were the first to report children suspected to have CMA with isolated gastrointestinal symptoms (n = 21) in a cohort of 143 children suspected of CMA, mainly composed of children who had skin symptoms. Many patients with a negative prick test had a positive cow's milk APT, which revealed a more sensitive method than prick tests or radioallergosorbent test. The combination of skin prick testing and patch testing was recently proposed to identify potential causative foods that contribute to the pathogenesis of eosinophilic esophagitis.⁸

The current study provides an approach to the sensitivity (79%) and specificity (91%) of the APT in CMA without skin involvement. The considerably higher sensitivity of the APT over skin prick tests in this category of patients is in agreement with the dominant delayed type of allergic reactions usually reported.^{5,9}

CMA is now increasingly recognized in conditions previously not labelled as allergic, such as gastroesophageal reflux.¹⁰ Its underrecognition may lead to inappropriate therapeutic handling and to confusion with primary gastroesophageal reflux, with potentially hazardous decisions (eg, surgery). A good marker of CMA in this group of patients could lead to better and earlier diagnosis.

In summary, we report a good sensitivity and specificity for the milk APT in patients with CMA and digestive symptoms. A large use of the APT in the presence of isolated digestive symptoms could improve detection of conditions

related to CMA. A standardization of the technique, therefore, seems to be mandatory.

REFERENCES

1. Hill DJ, Hosking CS. The cow milk allergy complex: overlapping disease profiles in infancy. *Eur J Clin Nutr* 1995;49:S1-S12.
2. Zeiger RS. Atopy in infancy and early childhood: natural history and role of skin testing. *J Allergy Clin Immunol* 1985;75:633-9.
3. 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.
4. Majamaa H, Moisio P, Holm K, Kautiainen H, Turjanmaa K. Cow's milk allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 1999;54:346-51.
5. de Boissieu D, Matarazzo P, Dupont C. Allergy to extensively hydrolyzed cow milk proteins in infants: identification and treatment with an amino acid-based formula. *J Pediatr* 1997;131:744-7.
6. 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.
7. Roehr CC, Reibel S, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. Atopy patch test, together with determination of specific IgE levels, reduces the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;107:548-53.
8. 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.
9. Carroccio A, Montalto G, Custro N, Notarbartolo A, Cavataio F, D'Amico D, et al. Evidence of very delayed clinical reactions to cow's milk in cow's milk-intolerant patients. *Allergy* 2000;55:574-9.
10. Hill DJ, Heine RG, Cameron DJ, Catto-Smith AG, Chow CW, Francis DE, et al. Role of food protein intolerance in infants with persistent distress attributed to reflux esophagitis. *J Pediatr* 2000;136:641-7.

50 Years Ago in The Journal of Pediatrics

MEDICAL PROGRESS: PINK DISEASE (INFANTILE ACRODYNIA): A PHYSIOLOGICAL APPROACH (AN EVALUATION OF ADRENAL FUNCTION AND THE IMPORTANCE OF WATER AND ELECTROLYTE METABOLISM)

Cheek D. *J Pediatr* 1953;42:239-60

A mysterious ailment primarily affecting infants and young children was well known to physicians in 1953. Its common names, acrodynia and pink disease, described its characteristic early presentation of painful extremities exhibiting a slight pinkness. Other clinical features included irritability, anorexia, weight loss, constipation, photophobia, weakness, hypotonia, sweating, tachycardia, and hypertension. Later in its course the "slight pinkness" gave way to "raw beef hands and feet" as successive desquamation exposed increasingly tender underlying epithelium. Recovery was anticipated but convalescence prolonged. A feared complication, especially in hot weather, was shock, collapse, and death. Diverse etiologies of pink disease were proposed and included virus, vitamin deficiency, dysregulation of adrenal hormones, and autonomic nervous system, allergy, toxin, and psychosomatic. The finding of elevated mercury excretion in the urine of most of the afflicted patients had strongly implicated mercury, but did not satisfy all of the peculiarities of the observed clinical and epidemiologic picture. Observers correctly noted that the purported agent of most exposures, teething powders and medicines containing mercurous chloride, did not cause pink disease in the majority of child users. Bypassing the debate about etiology, Cheek explored alterations in physiology in acrodynia through the blossoming science of biochemical assay. Sympathetic overactivity, suggested clinically, was supported experimentally by mydriasis induced in an enucleated frog eye bathed in solution containing patient plasma. Sodium loss and volume contraction suggested an adrenal or renal tubule locus for electrolyte and water imbalance. Experimental manipulation of fluid and electrolytes given patients showed potassium to be a necessary adjunct to sodium chloride in correcting the volume depletion and alkalosis. Withdrawal from the market of mercury containing baby products virtually eliminated the disease and firmly settled the question of etiology. Incidence of pink disease plummeted, as did physician familiarity with its presentation and course. This once common ailment is now rare; physicians clearly have difficulty recognizing it. Once the disease waned, mechanistic research dwindled. Only lately has the sympathetic overactivity proposed by Cheek been confirmed by catecholamine excess found in patients' urine and originating in mercury inhibition of catecholamine N-methyltransferase. Other mysteries await elucidation. Does pink disease reflect an age-related, immunologically-controlled or idiosyncratic reaction to mercury? Is there truly some risk to the very small mercury exposures from thimerosal in childhood vaccines and from dental amalgam? Pink disease represents opportunities lost in gaining control but not mastery over a mysterious disease.

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