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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

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Aim: To evaluate the diagnostic value of the skin-prick test and the atopy patch test in diagnosing basic food allergy in young children suffering from atopic eczema/dermatitis syndrome. *Methods:* 141 children, the majority under 2 y of age (mean 16 mo) with atopic eczema/dermatitis syndrome were investigated using skin-prick and atopy patch tests for milk, egg, wheat and rye. Open diagnostic elimination challenge was done since this has been reported to be a reliable method in young children. *Results:* A positive challenge response was found to milk in 63 (45%), egg in 78 (55%), wheat in 61 (43%) and rye in 61 (43%). Sensitivity/specificity of the atopy patch test was 60%/97% for milk, 71%/97% for egg, 90%/94% for wheat and 93%/90% for rye. For the skin-prick test the corresponding figures were 41%/99%, 60%/97%, 13%/98% and 15%/99%.

Conclusion: Patch testing was found to be a more sensitive method than the skin-prick test in diagnosing food allergy in children with atopic eczema/dermatitis syndrome, especially in those under 2 y of age. Many children with a negative skin-prick test result have a positive patch test result, especially in the case of cereals. A diagnosis of food allergy should be confirmed by elimination and in the research setting also by challenge.

Key words: *Early childhood, food allergy, patch test, prick test*

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Since the late 1970s the prevalence of atopic eczema/dermatitis syndrome (AEDS) has doubled in Sweden (1), as in the rest of the Western world (2). Food allergy affects about 8% of children and AEDS is the most common clinical presentation (3, 4). The more severe AEDS is in young children, the more likely they are to have food allergy (5). There seem to be two forms of AEDS: one in which the disease is triggered by allergens with potential immunoglobulin E (IgE) dependency and one in which the disease appears to be IgE independent (6). Infants who are exclusively breastfed may become sensitized to dietary antigens from the mother's diet since theses are present in her breast milk (7–9).

Since the mid-1990s the author's department has received an increasing number of referrals regarding infants and small children with AEDS. Many have been exclusively breastfed and have presented with severe eczema with a high SCORAD index (10).

The cornerstone of food allergy diagnosis is relief of symptoms on elimination of the suspected foodstuff and the return of symptoms on reintroduction (11). This, however, is often a laborious process. The results can be difficult to interpret, especially if the allergic reaction is of delayed-onset type. It is even more difficult if several food allergens are involved and the child is exclusively breastfed. This may be the case in infants suffering from AEDS.

Skin tests and *in vitro* tests can be of help in finding the offending foodstuff. A positive skin-prick test (SPT) result to a foodstuff, however, does not prove that the allergen has a pathogenic role (12). No relationship has been demonstrated between SPT results and delayed-onset clinical reactions (13). It has been demonstrated, however, that some patients with AEDS have rapid-onset reactions such as urticaria, pruritus and erythema during food challenge, whereas others have delayed-onset eczema reactions (14, 15). Skin-prick testing can be considered a good test for diagnosing immediate food hypersensitivity (16, 17). It is of less help in identifying responsible allergens in delayed-onset reactions (11, 18–20). Patch testing for foodstuffs has been described by some authors as a method with high sensitivity and specificity to identify delayed hypersensitivity in small children (17–21), while others have concluded that the patch test does not separate subjects

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with immediate- or delayed-onset reactions from those with negative reactions (22).

In patch testing, the allergen is applied to the skin under occlusion. The allergen penetrates the epidermis, where it is thought to be captured by IgE molecules which then bind to IgE receptors on Langerhans' cells (23). Allergen-specific T cells are thereby activated and initiate an eczematous reaction, which immunocytochemically is the same as that found in atopic dermatitis lesions (24). Atopy patch test (APT) reactions are associated with the T lymphocyte-mediated allergen-specific immune response (25).

The aim of this study was to evaluate the ability of the APT and the SPT to demonstrate atopic sensitization to basic foodstuffs in infants and young children suffering from AEDS. A further aim was to see whether the two tests are clinically useful in the identification of food allergens causing AEDS in small children.

Patients and methods

Patients

In total, 141 children, aged 2 mo to 4 y (mean 16 mo), all with AEDS fulfilling the Hanifin–Rajka criteria (26), were included in the study. They had been referred to the Pediatric Allergy Unit for evaluation of eczema by child health centres, general practitioners and paediatricians. All had been followed at child health centres and their status and diet recorded. The mean age at onset of symptoms was 3.4 mo. The mean duration of exclusive breastfeeding was 4.7 (0–6) mo and partial breastfeeding 7.3 (0–12) mo. The mean time from onset of symptoms to skin testing and clinical challenge was 6.3 (1–20) mo. Gastrointestinal symptoms such as loose stools, colic and vomiting were seen in 42 (30%) patients. Children with suspected food allergy but without AEDS were not included. Those being treated with antihistamine drugs had a washout period of at least 72 h before testing. Skin tests were performed at the patient's first visit to the hospital and before any elimination of foodstuff from the child's or lactating mother's diet. To assess objectively the severity of atopic dermatitis, all children were scored at each visit using the SCORAD method (10).

Skin-prick test

The SPT were performed by the same nurse on the volar side of the forearm in accordance with the instructions of the European Academy of Allergy and Clinical Immunology (27). A lancet with 1 mm tip was used. Each child was tested with low-fat cow's milk, egg white, wheat and rye (1 g of flour diluted with 0.3 ml physiological saline). Histamine dihydrochloride, 10 mg ml^{-1} ALK (Allergologisk Laboratorium A/S, Horsholm, Denmark) was used as s positive control. Reactions were read after 15 min. The mean weal diameter was calculated. A reaction of at least 3 mm was considered positive. All test results were read by the author.

Atopy patch test

All APT were applied by the same nurse according to the method described by Isolauri and Turjanmaa (17). A "porridge" was made fresh every day with 0.2 ml isotonic saline and cow's milk powder (300 mg), egg white (40 mg), wheat (200 mg) or rye (200 mg). Approximately 20 mg of each porridge was put into aluminium test cups without filter paper (Finn Chamber; Epitest, Hyrylä, Finland) and attached to eczema-free skin on the back of the child with Scanpore tape (Norgesplaster, Norway). A porridge of microcrystalline cellulose was used as a negative control. The occlusion time of the patch test was 48 h. The result was read for the first time 15 min after removal of the cups at 48 h and again at 72 h. Reactions were classified as: negative (no reaction, either visible or palpable), + (redness), ++ (redness and palpable infiltration) or +++ (redness, palpable infiltration and eczema). In this investigation ++ and +++ reactions at the second reading at 72 h were considered positive reactions. + reactions were not regarded positive, as redness alone can be the result of local irritation. All test reactions were classified by the author. The test material used was not standardized as such materials are not available.

Elimination diet

The parents of all children who were prescribed an elimination diet met a dietician at every visit to the clinic. Dietary instructions were given both verbally and in writing. Telephone contact between visits was encouraged.

Oral challenge

An open challenge was done in all children after 2 wk on an elimination diet with one foodstuff at a time, starting with those foodstuffs to which the child had the weakest or negative skin test results. For the lactating mothers one foodstuff at a time was reintroduced into the diet after an interval of at least 7 d. Children who were not breastfed were given increasing amounts (1, 5, 10, 50 and 100 g) of the foodstuff in the hospital at 30 min intervals until intake appropriate for their age was reached, and then continued at home for 1 wk unless obvious symptoms were noted earlier. A reaction within 2 h of challenge was regarded to be of immediate-onset type. Telephone contact with the parents was maintained twice a week and if reactions such as skin eruptions, pruritus, vomiting, diarrhoea and irritability were suspected the child was seen by the author within 2 d. SCORAD index and other clinical symptoms were evaluated by the author at visits to the clinic before and after each challenge period. The appearance of clear and distinct symptoms during the challenge period which subsided or disappeared when

Table 1. Percentage of positive reactions in skin-prick tests (SPT) and atopy patch tests (APT) with cow's milk, egg, wheat and rye in 141 young children with atopic eczema/dermatitis syndrome.

	SPT ($n = 141$)	APT ($n = 141$)
Milk	19	28
Egg	35	40
Wheat	7	43
Rye	7	46

Table 2. Percentage of positive atopy patch tests with a negative skin-prick test result in different age groups of children with atopic eczema/dermatitis syndrome and suspected food allergy.

	Age (mo)				
	<6 ($n = 47$)	6–12 ($n = 31$)	12–24 ($n = 39$)	>24 ($n = 24$)	All ages ($n = 141$)
Milk	36	42	23	8	29
Egg	47	26	26	4	29
Wheat	68	58	46	13	50
Rye	72	55	44	26	53

the foodstuff was eliminated again was defined as a positive challenge test result and used to calculate sensitivity and specificity. The results of SPT and APT were kept by the nurse and not revealed to the author until after evaluation of the challenge. The decision to stop a challenge was made by the investigator.

Open challenge was chosen since it has been shown to be a reliable method in young children when performed in the hospital setting under experienced professional observation (17, 28).

Statistics

The χ^2-test was used for group comparison. Descriptive values of variables are expressed as means and percentages. The presence of food hypersensitivity was based on a positive elimination–reintroduction test. Sensitivity, specificity, and positive and negative predictive value for SPT and APT are presented.

Ethics

Informed consent was obtained from the parents. The study was approved by the Ethics Committee of Linköping University.

Results

In this material comprising 141 children, a positive APT was found more often than a positive SPT, especially for wheat and rye (Table 1). The frequency of positive patch test results was lower in children older than 2 y than in those younger than 2 y (Table 2). Wheat and rye were often positive simultaneously.

A positive open challenge provocation was found with cow's milk in 63 (45%), egg in 78 (55%), wheat in 61 (43%) and rye in 61 (43%). In children with a positive open challenge an immediate-onset reaction was seen with milk in 6 (13%), egg in 11 (14%), wheat in 2 (3%) and rye in 2 (3%). The number of children with a delayed-onset reaction was 57 (87%), 67 (86%), 59 (97%) and 59 (97%) for milk, egg, wheat and rye, respectively.

Of the children who developed an immediate-onset reaction within 2 h of challenge, a positive SPT result was found with milk in 5/6, egg in 11/11, wheat in 2/2 and rye in 2/2. In those with positive SPT results 80% were positive to two or more foodstuffs. In patients positive to challenge 41% had a positive SPT result to milk, 60% to egg, 13% to wheat and 15% to rye. A negative challenge was associated with positive SPT results in 2–3% for the foodstuffs tested. The APT result was positive in patients with positive challenge result to milk in 60%, egg in 71%, wheat in 90% and rye in 93%. False-negative APT results were found to milk in 3%, egg in 3%, wheat in 8% and rye in 13% (Table 3). Figures of sensitivity, specificity, positive and negative predictive values for APT and SPT are presented in Table 4. A false-positive SPT result together with a false-positive APT result was uncommon. A positive challenge result coupled with negative patch and SPT results were seen in 20% for milk, 5% for egg, 3% for wheat and 2% for rye. All of these children had

Table 3. Atopy patch and skin-prick tests for cow's milk, egg, wheat and rye allergy in relation to open challenge in children with atopic eczema/dermatitis syndrome.

	Milk		Egg		Wheat		Rye	
$n =$	Positive 63 (45%)	Negative 78 (55%)	Positive 78 (55%)	Negative 63 (45%)	Positive 61 (43%)	Negative 80 (57%)	Positive 61 (43%)	Negative 80 (57%)
Atopy patch test								
Positive	38	25	55	23	55	6	57	4
Negative	2	76	2	61	5	75	8	72
Skin-prick test								
Positive	26	37	47	31	8	53	9	52
Negative	1	77	2	61	2	78	1	79

Table 4. Sensitivity, specificity, positive and negative predictive value for atopy patch and skin-prick tests in diagnosing cow's milk, egg, wheat and rye allergy in children with atopic eczema/dermatitis syndrome.

	Milk	Egg	Wheat	Rye
Atopy patch test				
Sensitivity	0.60	0.71	0.90	0.93
Specificity	0.97	0.97	0.94	0.90
Positive predictive value	0.95	0.96	0.92	0.88
Negative predictive value	0.75	0.73	0.93	0.95
Skin-prick test				
Sensitivity	0.41	0.60	0.13	0.15
Specificity	0.99	0.97	0.98	0.99
Positive predictive value	0.96	0.96	0.80	0.90
Negative predictive value	0.68	0.67	0.60	0.60

gastrointestinal symptoms in addition to atopic dermatitis.

Patch testing was found to be a much more sensitive method than the SPT ($p < 0.0001$) in diagnosing food allergy in the study population, especially regarding wheat ($p < 0.00001$) and rye ($p < 0.00001$). For milk the statistical significance was lower ($p < 0.05$) and for egg the difference was not significant.

A challenge-verified allergy to wheat but not to rye was found in 5 (8%) and to rye but not to wheat also in 5 (8%) patients. Several patients, who had a negative SPT result and a positive APT result, when tested for the first time before the age of 6 mo, had strongly positive SPT results when retested 6–9 mo later. This was true for milk, egg, wheat and rye. In some children infiltration and redness of the patch test area remained up to 2 mo after allergen application. This was most often seen with cereals.

Discussion

The results of the present study conflict with the findings of Vanto et al. (22), who concluded that the APT was of little value in diagnosing food allergy in small children. Conversely, the results of this study are in close accordance with the findings of both Isolauri and Turjanmaa (17) and Majamaa et al. (19, 20) and support their conclusion that the APT significantly increases the chances of early detection of food allergy in infants. The present study confirms that the APT tends to be positive in patients with delayed-onset reactions, while the SPT tends to be positive when the reaction is immediate onset, and vice versa (17, 18).

In this investigation the same person examined all of the children and read all of the test results. The same criteria for evaluating the severity of eczema and SCORAD grading as well as the grading of patch test results were thereby applied. The fact that the same investigator read the skin test results and interpreted the challenge results involves potential investigator bias. To reduce the influence of this risk on the outcome of the study the SPT and APT results were not available to the author when evaluating oral challenges. The application of skin tests was performed by the same nurse. Elimination diet prescriptions were given verbally and in writing by the same dietician. To ensure good adherence to the elimination diet the parents met the dietician at every visit to the clinic and there was regular telephone contact between visits. This was essential when evaluating the outcome of an elimination diet as even small amounts of the offending foodstuff can maintain symptoms. Previous studies of the diagnostic value of atopy patch testing (17–22) do not describe how careful supervision of the diet was performed.

The time elapsed between skin testing and elimination challenge was usually 4 wk and in no case longer than 8 wk. If this time interval were extended some patients could have developed clinical tolerance, since in early childhood a shift from allergy to tolerance can occur within months. This may partly explain the divergent results of sensitivity and specificity presented by Vanto et al. (22). An important fact concerning that study, which investigated 301 children with suspected cow's milk allergy, is that it provides figures for immediate-onset reactions but not for delayed-onset reactions. Another explanation for the divergence is that the clinical presentation of the patients was different. In the present study children with obvious immediate-onset reactions such as urticaria, vomiting or respiratory symptoms within a short time of contact with or intake of the foodstuff but without eczema were not included. This fact influences the specificity figures of SPT in this study. In this respect the current study relates to the cow's milk study of Majamaa et al. (19), as do the results. This is also the case for the 20% of patients in this study who manifested gastrointestinal symptoms after milk provocation and had negative prick and patch test results. All of these children also had negative radioallergosorbent test (RAST) results for milk. A non-IgE-mediated hypersensitivity reaction is thought to be responsible (5, 19).

The lower prevalence of positive APT results in children older than 24 mo of age may be due to some children having developed tolerance to foodstuffs, or to the skin perhaps becoming thicker so that the allergen applied did not penetrate as readily as in smaller children.

The quality of the allergen extracts used in skin-prick testing influences the result. Fresh foodstuffs were therefore used as they give results that correlate better with positive challenges (29). The allergenicity of the foodstuffs used in this and other investigations (11–14) was not established. Patch testing with standardized foodstuffs of known allergen content would greatly improve the quality of future studies of this kind. This would facilitate comparison between different studies and centres, and enable follow-up of reactivity in individual patients over time.

It has been speculated that a positive SPT result to cereal reflects grass pollen allergy. This is an unlikely explanation in infants and young children as allergic sensitization to such allergens is rarely proven in infancy, even in patients who have developed food sensitization (30).

This study also shows that children with food allergy and eczema are often sensitized to more than one food allergen, as has been described previously (18, 20).

Further investigation of the diagnostic capacity of the APT in patients of different age groups and clinical symptoms is necessary. Studies of the repeatability of tests in the same patient and trials with duplicate tests should also be performed. A standard technique for atopy patch testing should be established and criteria for positive results agreed upon. The solvent that best enhances allergen penetration should be found. Test material with standardized known composition and major allergen content should be available and its diagnostic capacity at different concentrations documented. Test materials, such as fresh food and freeze-dried extracts, should be investigated to see which material gives the best response, and this should be standardized.

The main finding of this study is that the APT is a method with high specificity and sensitivity when investigating the existence of delayed hypersensitivity to food. It can significantly enhance accuracy in the diagnosis of food allergy in young children with AEDS and is of great help in identifying elimination diets. The clinical relevance of a skin test result should be confirmed by at least elimination and in research also by challenge. The value of atopy patch testing seems to be greatest in children less than 2 y of age. It is clinically more reliable than the SPT, especially when testing with cereals. It was also found that AEDS is the dominating symptom in many young children suffering from food allergy, and that many of them are exclusively breastfed when the first signs of AEDS appear.

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