

Clinical manifestations of cows' milk allergy in childhood. II. The diagnostic value of skin tests and RAST

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Summary

In a study of cows' milk allergy (CMA) in infancy, 135 consecutive challenges were performed on children with a good clinical history of the disorder. Of these, only half of the patients were shown to have the disease. Highly atopic patients responded rapidly to small volumes of milk with acute urticaria, wheezing, stridor and eczema, whereas patients who were relatively non-atopic developed symptoms of eczema, bronchitis and wheezing over several hours or days. In a statistical evaluation of the diagnostic value of skin tests and RAST it was shown for the extracts used in this investigation, and for the population studied, all patients with $\text{SPT} \geq 4$ had CMA. The results highlight the potential diagnostic value of SPT in the identification of children with some forms of CMA if standardized cows' milk allergen extracts can be prepared.

Introduction

Several investigators have examined the value of skin-prick tests (SPT) and circulating IgE antibodies to foods in the diagnosis of food allergy in children. In placebo-controlled studies Bock *et al.* [1] showed that children with skin reactions > 3 mm to 1/20 (w/v) extracts of cows' milk, egg, peanuts and soy developed adverse reactions within 2 hr of challenge, whereas children who took longer to respond were skin-test negative. Danneus *et al.* [2] demonstrated elevated circulating IgE antibodies to foods, measured by RAST, in children with rapid reactions to food challenges, in contrast to Fallstrom *et al.* [3] who described similar findings in patients with slow-onset clinical reactions. In food-related eczema, Sampson and Albergo [4] reported that children with SPTs > 3 mm to various foods developed rapid exacerbations of eczema on challenge, in contrast to Atherton *et al.* [5] who did not find SPTs of value in identifying foods that exacerbated childhood eczema. In all these studies, children with a history of an anaphylactic reaction to foods were excluded from investigations that required formal food challenges. Although Hoffman *et al.* [6] suggested measurement of

circulating IgE antibodies to foods by RAST might be a useful indicator of food allergy in childhood eczema, Sampson and Albergo [4] found these measurements were not superior to SPTs.

We recently completed a study of 100 infants and young children, less than 3 years of age, with unequivocal evidence of cows' milk allergy (CMA) demonstrated by a standardized milk challenge procedure. Statistical methods, based on clinical and challenge data, identified three groups of children with CMA [7, 8]. The first, some of whom had a history of an anaphylactic reaction to milk ingestion, were IgE sensitized and demonstrated urticarial, angioedematous and eczematous eruptions within 40 min of challenge. The second, a non-IgE sensitized group, developed vomiting and diarrhoea more than 1 hr, but less than 20 hr, after commencing milk challenge; some have described these as cows' milk enteropathy. The third group of patients developed symptoms affecting the skin, gastrointestinal and/or respiratory systems, more than 20 hr after commencing milk challenge; only those with eczema had positive skin tests and elevated IgE antibodies to milk.

In an attempt to resolve some of the apparently conflicting data regarding the value of SPTs and RAST in the diagnosis of paediatric food allergy, we used these two procedures to investigate children of different ages with suspected CMA. In addition to the patients with a history suggestive of either rapid cutaneous reactions or slow-onset gastrointestinal responses, children with a history suggestive of anaphylaxis following milk ingestion, as well as those with clinical features suggestive of multi-system disease, were included.

Subjects and methods

Patients

Over a 2-year period, 135 consecutive milk challenge procedures were conducted on 75 boys and 45 girls referred by medical practitioners for investigation of possible CMA. They had a history of urticaria, eczematous and other skin eruptions, vomiting and/or diarrhoea, bronchitic, wheezing or anaphylactic responses, which had been attributed to milk ingestion by their referring medical practitioner. New data regarding the effect of milk challenge, SPT and RAST were collected on two separate occasions on three girls and 10 boys, and on three occasions on one boy, at 12-month intervals over the study period. The age of the patients ranged from 5 months to 13 years (median 24 months); only 18 patients were older than 5 years.

In order to reproduce safely the conditions of natural milk exposure, patients attended a specialized paediatric allergy unit in a university hospital for the first 2 days of the challenge procedure, until they were tolerating normal volumes of fresh whole cows' milk for age. Patients who developed adverse reactions after this period were reviewed in the Unit at the time of the reaction, as well as 1 week and 1 month after commencing milk ingestion.

Children were defined as having CMA if they demonstrated an unequivocal adverse reaction following ingestion of cows' milk. Cows' milk intolerance caused by disaccharidase deficiency and other gastrointestinal tract diseases was excluded by duodenal biopsy. Milk aspiration as a cause of recurrent bronchitis was excluded by demonstrating a reproducible relapse of symptoms following milk ingestion, but not following the ingestion of other non-cows' milk infant formulas.

Milk challenge procedure

Challenge procedures were undertaken once other causes of milk intolerance had been excluded, according to a previously published protocol [7, 8]. Patients were on a milk-free diet in symptomatic remission for 6–12 weeks prior to milk challenge. In the week prior to the challenge, patients were skin tested, had blood taken for RAST and other investigations, and were issued with a diary to record symptoms up to and during the first week of the milk challenge. The following volumes of milk were administered:

day 1: 0.5 ml, 2.5 ml and 5 ml at 10-min intervals, then 10, 20 and 30 ml at 30-min intervals;

day 2: 30, 60 and 120 ml at 30-min intervals;

day 3: normal volumes of milk, i.e. >450 ml per day.

Every effort was made to follow this schedule, but where severe hypersensitivity was suspected, one drop was used as the first dose. Where parents were reluctant to increase milk intake rapidly, a slower incremental dose was used. In a few instances, where slow-onset reactions were suspected, milk intake was increased more rapidly than indicated by the protocol.

Patients attended a specialized unit on day 1 and day 2 of the challenge procedure but subsequent volume increases were undertaken at home after discharge. All patients were reviewed in the Unit at the time of an adverse response, as well as at 1 week and 1 month after commencing cows' milk.

The time of onset of any reaction was taken as the time from the beginning of milk challenge procedure on day 1. The volume of milk administered up to the time of any reaction, as well as the symptomatic effect of milk ingestion, was recorded on daily diary score-cards.

Criteria for positive milk challenge

Patients were regarded as having CMA if: (i) adverse reactions were observed on day 1 or day 2 in the Unit; (ii) adverse reactions occurred after day 2 were confirmed by diary recording and clinical assessment, and were reproduced on two further occasions.

The patient was classified as 'milk tolerant' if the reaction was not able to be reproduced. This procedure was followed in an attempt to minimize the possibility that these non-immediate reactions were the result of intercurrent infection or accidental exposure to other dietary or environmental allergens.

The follow-up challenges were conducted within 2 weeks of the initial challenge procedure but the skin test and laboratory data generated in the week prior to the first challenge procedure were used in the final analysis.

Skin tests

The size of the skin test weal to whole cows' milk allergen extract was compared with histamine and a control [9].

A single batch of whole cows' milk allergen extract (WCM) 1/20 (w/v) was purchased from Dome-Hollister-Stier (Spokane, WA, U.S.A.; no. 3380) and the control solution, provided by the manufacturers, was used throughout the study.

Skin-prick tests were performed by a single investigator as follows. One drop of the extract, control solution, and antihistamine were placed on the patient's back, and the point of a blood lancet was passed through the drop to indent the skin but not cause bleeding. The size of the skin weal elicited by the milk extract was compared with that

of histamine acid phosphate, 1 mg/ml and the control solution. The area of weal and pseudopodia elicited by the histamine was designated as 3, and the reactions to milk graded by reference as follows:

- > 4 area of milk reaction = > twice the area of histamine standard;
- 4 area of milk reaction = twice area of histamine standard;
- 3 area of milk reaction = area of the histamine standard;
- 2 area of milk reaction = half of the area of histamine standard;
- 1 area of reaction = one-quarter the area of histamine standard, or any reaction greater than control solution.

The weal of the control solution provided by Dome-Hollister-Stier on skin-prick test was deducted from that of the milk antigen before the score test was given.

Skin-prick tests were performed 1 week before the milk challenge and were scored before the result of the milk challenge was known.

RAST studies

Milk-specific IgE antibodies were measured with commercially purchased Phadebas RAST kits (Pharmacia, Uppsala, Sweden). The RAST scoring scale used was as advised by the manufacturers and graded from 0 to 4. These tests were done as part of the routine hospital immunology laboratory service and results were not available until after the milk challenge procedure was completed.

Statistics

Skin test levels and RAST scores were dichotomized and a discriminant analysis for categorical data [10] was performed to determine which of the tests, skin and/or RAST, significantly discriminated the milk-allergic and non-allergic children. Two age groups were considered, those under 5 years, and those 5 years and over. Children were classified as either milk-allergic or non-allergic according to a logit rule [10, 11]. The discriminant analysis allowed calculation of the predictive accuracy of both a positive test result and negative test result, and of measures of sensitivity, specificity and overall efficiency of the test [12]. Statistical significance was achieved at $P < 0.05$ and all discriminant analyses were carried out on the BMDP [13] computer package of the Melbourne University VAX system.

Results

Clinical

There were 68 positive and 67 negative milk challenges. Cows' milk allergy was demonstrated in 43 boys and 25 girls. Of the 68 positive challenges adverse reactions developed within 48 hr of starting milk ingestion, but in 13 instances they took longer than this period; in these 13 patients the challenge procedure was repeated on two further occasions to confirm slow-onset reactions. In 43 boys and 24 girls there was no adverse reaction to milk ingestion.

Details regarding adverse effects of milk ingestion in the CMA patients are shown in Tables 1 to 3. From Table 1, 29 out of 32 children with SPTs ≥ 4 responded within 40 min of ingestion of small amounts of milk; ten developed a reaction to less than 10 ml milk. Thirty of these patients with SPT ≥ 4 developed acute urticaria or eczema, and in 12 cough and/or wheeze was associated. All patients with SPTs ≥ 4 showed skin weal

Table 1. Skin test ≥ 4

Skin test	RAST	Case no.	Volume	Reaction*	Time (min)	
> 4	4	1	5 ml	U	10	
				E,R	90	
		2	1 drop	S,C	1	
		3	30 ml	U,Rh,E,C	35	
		4	1 drop	U	1	
		5	2 ml	U,D	5	
		3	6	5 ml	V,C,U,E,R,W	5
			7	1 drop	U,C,R	1
		8	1 drop	U	1	
	> 4	9	1 drop	U	5	
		10	0.5 ml	U,R,C	10	
		11	10 ml	E,R,C	5	
		12	105 ml	E,D,W	24 hr	
		13	3 ml	U,C,E	15	
		14	1 drop	S	5	
		15	2 ml	E,C,A	1	
> 4		2	16	10 ml	U,C	20
	17		10 ml	U	20	
	18		1500 ml	U,V,D	Day 5	
	19		1 ml	E,R,C,U	4	
4	3	20	10 ml	U	5	
		21	5 ml	U	7	
		22	0.5 ml	S,E,R	1	
		23	10 ml	U	1	
		24	1 drop	U	10	
		25	2 ml	C,U	5	
		26	15 ml	U,S	10	
		4	2	27	10 ml	U,V,E,R
28	10 ml			U	15	
29	8 ml			U,S	5	
30	30 ml			U,M	30	
31	0.5 ml			S,R,D	1	
4	1	32	2 ml	U	5	

Abbreviations: U, urticaria; E, eczema; R, rhinorrhoea; V, vomiting; S, stridor; C, cough; D, diarrhoea; M, morbilliform rash; A, angioedema; W, wheeze.

diameters > 3 mm diameter (data not shown) but there were two patients with skin weals of > 3 mm who had SPT scores of only 3, and were milk tolerant. From Tables 2 and 3, children with small or negative SPTs ingested larger volumes of milk than those with high SPTs, before a clinical adverse response was observed.

Eczema developed in 28 patients; of these, eight patients with SPTs ≥ 4 developed acute erythema and intense pruritus without urticaria, leading to an immediate flare of eczematous lesions within 1 hr of milk ingestion. Conversely, 12 patients who took more than 24 hr to develop eczema were SPT negative. One patient (no. 46) developed

Table 2. Skin test ≤ 3

Skin test	RAST	Case no.	Volume	Reaction*	Time
3	2	33	60 ml	C,R	45 min
	0	34	1000 ml	I,C,R	Day 3
2	3	35	80 ml	E,R	20 min
	0	36	1000 ml	I,D,E, Rectal bleeding	Day 3
	0	37	180 ml	E	24 hr
	0	37	180 ml	E	24 hr
1	3	38	900 ml	E,W	24 hr
	3	39	10 ml	U,A	5 min
	2	40	130 ml	R,I,W	20 min
	2	41	500 ml	E,I,D	Day 3
	0	42	37 ml	W	2 hr
	0	43	90 ml	I,C,R	Day 2
	0	44	900 ml	D	Day 4
	0	45	600 ml	D	Day 2

* For abbreviations see Table 1.

eczema gradually from day 3 as the sole manifestation of CMA, but all other patients with eczematous eruptions that developed slowly showed associated gastrointestinal and/or respiratory manifestations of their disease. Stridor, cough or wheeze developed rapidly in 13 patients with SPTs ≥ 4 , in contrast to 5 patients whose respiratory symptoms developed more than 12 hr after milk ingestion and were SPT negative. Rhinitis developed in 25 patients; 10 children with SPTs ≥ 4 developed rhinorrhoea within minutes of milk ingestion, whereas eight patients who took more than 24 hr to develop these symptoms were SPT negative. With regard to gastrointestinal symptoms, there were three patients with SPTs ≥ 4 in whom vomiting developed as part of a rapid reaction in association with cutaneous eruptions, while diarrhoea without preceding vomiting occurred in 12 SPT negative patients.

Statistical

With skin test levels dichotomized as (0,1,2) *vs* (3,4 > 4) and RAST scores partitioned as (0,1,2) *vs* (3,4), discriminant analysis [10] showed that both the skin test and RAST scores were significant ($P < 0.05$) discriminators of the milk-allergic from the non-allergic children. The effect of age grouping was not significant (data not shown). From Table 4, 54% (37/68) of the allergic children were correctly classified by high scores (≥ 3) on both skin test and RAST, and 91% (61/67) of children without CMAs were correctly classified by low levels (≤ 2) of both skin test and RAST. Thus, the overall efficiency of the skin test and RAST based on this dichotomy was 73%. Using a prevalence of 50% for milk-allergic children (68/133) the predictive value of a positive test result (score ≥ 3 on both skin and RAST test) was 86%, i.e. in this study 14% of children with RAST and SPT > 3 were negative to milk challenge. The predictive value of a negative result of the combined RAST and SPT, i.e. ≤ 2 , was 66%, or 34% of the

Table 3. Skin test = 0

RAST	Case no.	Volume	Reaction*	Time
2	46	1200 ml	E	Day 3
1	47	1 drop	U	10 min
	48	100 ml	I,R	60 min
0	49	700 ml	D	Day 3
	50	120 ml	V	26 hr
	51	3700 ml	I,D	Day 5
	52	700 ml	I,D,R	Day 3
	53	100 ml	R,D,E	26 hr
	54	50 ml	R,E,D	26 hr
	55	100 ml	R,E,D	24 hr
	56	135 ml	E,C,I	Day 3
	57	200 ml	I,E,C	Day 3
	58	60 ml	E,D,I	24 hr
	59	700 ml	D,I	36 hr
	60	260 ml	I,R,E,D	36 hr
	61	240 ml	V,I,M	Day 3
	62	400 ml	D,I	24 hr
	63	420 ml	I,C,R,D,E	36 hr
	64	1200 ml	R,C,E	48 hr
	65	600 ml	D,I,E	36 hr
	66	600 ml	W	12 hr
	67	700 ml	E,R	Day 3
	68	90 ml	R,E,I	30 min

* For abbreviations see Table 1.

Table 4. Comparison of results of milk challenge and predicted results based on SPT, RAST dichotomized as ≥ 3 and ≤ 2

	Predicted response to milk ingestion	
	Positive (SPT, RAST ≥ 3)	Negative (SPT, RAST, ≤ 2)
Clinical response CMA +	37	31
to milk ingestion CMA -	6	61

children in this study with this level of RAST and SPT developed symptoms following milk ingestion.

In order to explore the value of SPT and RAST in the diagnosis of CMA, the skin-test result dichotomy was changed to (0,1,2,3) *vs* (4, > 4), and RAST scores partitioned either as before, i.e. (0,1,2) *vs* (3,4) or as (0,1,2,3) *vs* (4). The discriminant analysis [10] showed that only the skin-test result significantly ($P < 0.005$) discriminated between the milk-allergic and the non-allergic children. This means that the RAST results did

Table 5. Comparison of results of milk challenge and predicted results based on SPT alone dichotomized as ≥ 4 and ≤ 3

	Predicted response to milk ingestion	
	Positive SPT ≥ 4	Negative SPT ≤ 3
Clinical response CMA +	32	36
to milk ingestion CMA -	0	67

not improve the discriminatory power of the skin-test results with the skin-test dichotomized as ≥ 4 vs ≤ 3 . These results were independent of the age grouping of the child (data not shown). From Table 5 the specificity of the skin test (i.e. the incidence of true negative results on skin-test results ≤ 3 obtained when the test is applied to children in whom milk allergy was not demonstrated) was calculated to be 100%. The sensitivity of the skin test (i.e. the incidence of true positive skin test results ≥ 4 , when the test is applied to patients known to be milk positive) was 47%.

The overall efficiency of the test is 73%. If we assume an incidence of 50% of milk-allergic children for this population then the predictive value of a positive (≥ 4) skin-test result is 100%, and the predictive value of a negative (≤ 3) skin test is 65%, indicating that 4 in 10 children with a negative skin test according to this criteria are, in fact, allergic to cows' milk.

Clearly, a high skin-test reading (≥ 4) has an excellent positive predictive accuracy index. Based on these results, the likelihood that a child with an SPT ≥ 4 will develop symptoms on a milk challenge is 100%.

Discussion

In this investigation CMA was confirmed in only half the patients tested, emphasizing the limitation of relying on history alone to make the diagnosis of milk allergy [1,4,8]. However, the value of high SPT and RAST scores in identifying CMA patients with urticarial, eczematous, respiratory or anaphylactic responses to milk ingestion was confirmed [1,2,4], although these tests did not identify patients who developed gastrointestinal, eczematous, and/or respiratory symptoms over several hours or days. The aetiology of the symptoms of this slow reacting group is controversial [14].

The relative 'slowness' of reactions in some of our patients was in part an effect of our protocol of milk challenge, which commenced at small volumes and built up to normal volumes of cows' milk over 48 hr. This was done in order to avoid serious reactions in patients with a history of anaphylaxis to cows' milk, and inevitably extended the period between commencement of milk challenge on day 1 and the identification of an adverse clinical response. Previous studies have drawn attention to these slow reacting patients who have separate clinical and immunological features from the rapidly reacting highly atopic individuals [8,15].

High positive SPTs were seen in patients who developed eczema rapidly, whereas the negative SPTs were seen in those who developed eczema more than 24 hr after commencing milk ingestion. Sampson and Jolie [16] showed that children with positive SPTs to foods, including cows' milk, developed high levels of plasma histamine during acute eczematous reactions following placebo-control food challenges; they probably correspond with our rapid reacting CMA eczematous patients with high SPTs. By contrast, our patients who developed eczema over several days appear similar to those of Atherton *et al.* [5]; he demonstrated gradual onset of eczema following ingestion of milk and egg in placebo-controlled studies. Based on our data, Sampson [4] and Atherton *et al.* [5] were probably studying different ends of the spectrum of eczema, i.e. high SPTs being associated with immediate eczematous eruptions, and negative SPTs associated with slower onset reactions.

Similarly, Dannaus *et al.* [2] and Fallstrom *et al.* [3] would appear to have been studying different groups of children, all suffering from IgE food hypersensitivity. Dannaus *et al.* [2] documented patients who responded rapidly to ingestion of various foods, whereas Fallstrom *et al.*'s patients responded slowly. Based on our findings for children with CMA, patients with very high levels of SPT or RAST positively responded very rapidly to small volumes of milk, whereas those with low SPT and low RAST scores responded slowly.

Practising clinical allergists frequently ask what is the diagnostic value of SPT and RAST in the diagnosis of CMA? Our results show that if SPTs and RASTs are moderately elevated, i.e. ≥ 3 , only half the children with CMA are correctly identified, and nearly 10% of the patients who were challenge negative have these findings. However, if a patient presents to this unit with a history suggestive of CMA and SPT ≥ 4 , the probability that the patient has CMA is 1 (i.e. all children with these findings will react positively to milk challenge). Although our patients with a RAST of 4 had CMA, this represented less than 10% of our milk-allergic children, suggesting it is not as useful as skin testing. Possibly regrading the RAST score system for infants and young children with suspected CMA may improve the diagnostic value of this test. However, if the low RAST scores in our patients, despite high SPTs, reflects incomplete saturation of peripheral tissue binding reagenic sites [3], it is unlikely that such regrading will improve the diagnostic value of RAST.

Based on the results of our previous investigations [8], which examined the separate clinical manifestation and immunological features of CMA, approximately 25% of all children with CMA have an immediate type hypersensitivity reaction that may be identified by the use of simple SPTs as described in the current investigation. In most children with this pattern of CMA the diagnosis will be clear from the clinical history but there are two clinical situations in which SPT may be of assistance. Firstly, in the occasional infant who presents with anaphylactic or severe hypersensitivity reactions where the causative allergen is unknown, a strongly positive SPT to milk may identify a causative agent. Secondly, in infants with a history of an anaphylactic reaction to cows' milk, where there is a reluctance to re-challenge the child for several years, SPT may be used to follow the natural history of the disease. Based on the results of this study it would seem unwise to milk challenge a child who has a previous history of anaphylaxis if the SPT remains $\geq +4$.

The findings of this study are only valid for the population of patients investigated and the reagents used. However, the results highlight the potential diagnostic value of simple SPTs if standardized allergen extracts of cows' milk can be prepared. Although

it is not possible to extrapolate from these results to other food allergies, there is some evidence that the diagnostic value of SPT in patients with suspected allergy to foods may be improved using a similar statistical analysis [4].

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