

Distinct patterns of cow's milk allergy in infancy defined by prolonged, two-stage double-blind, placebo-controlled food challenges

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Summary

Background The clinical manifestations of cow's milk allergy (CMA) are highly variable, and challenges usually identify only immediate, IgE mediated reactions.

Objective To clearly identify CMA of immediate and delayed types using a two-stage, double-blind, placebo-controlled food challenge (DBPCFC), and to prospectively compare the clinical history and analyses of specific IgE antibodies to milk in predicting outcome of DBPCFC.

Methods A total of 69 patients (33 girls, 36 boys) were recruited for study based on a history highly suggestive of CMA and resolution of symptoms on a bovine protein-free diet. After skin-prick tests (SPTs) and search for allergen-specific serum IgE antibodies by enzyme allergosorbent test (EAST), a two-stage DBPCFC was performed over several days.

Results Of 16 patients (mean age 36.9 months) classified as probable immediate reactors based on the history, 10 (62.5%) had a positive DBPCFC with similar patterns to historical adverse reactions (≤ 2 h after milk exposure). The other 53 (77%) patients (17.3 months) had a history of probable delayed type CMA presenting with predominantly gastrointestinal symptoms from 2 h and up to 6 days after milk exposure. Of these, 15 (28.8%) had a positive DBPCFC, again with a symptom pattern similar to the history. Sensitivity/specificity of SPT was similar to that of EAST for both immediate (70/83% and 62/83% respectively, NS) or delayed (0/97% and 0/97%) CMA confirmed by DBPCFC.

Conclusions Using our two-stage, prolonged DBPCFC, we clearly identified two groups of children with CMA, reflecting different pathogenesis of either immediate-type IgE-dependent, or delayed-type IgE-independent allergy. Although useful in immediate reactors, IgE antibody determination cannot predict the outcome of DBPCFC in delayed reactors. A thorough clinical history was the most helpful tool to predict the type of response in challenge positive patients.

Keywords: food hypersensitivity, food allergy, diagnosis, milk, food challenge

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Introduction

Cow's milk allergy (CMA) may be defined as an immune mediated, adverse reaction following the ingestion of one

or more milk proteins [1]. Estimates of prevalence vary, depending upon patient selection and diagnostic criteria. Prospective studies using oral challenges suggest that CMA affects approximately 2.5% of infants below age 3 years [2]. Establishing an accurate diagnosis of CMA remains a difficult task for paediatricians, due to the presence of often non-specific symptoms, and the lack of a specific diagnostic laboratory test [2–6]. The double-blind placebo-controlled food challenge (DBPCFC) is considered the gold standard to confirm a food allergy [2,5]. However, a number of practical problems of oral challenge exist in clinical practice. They are laborious, time-consuming, potentially dangerous, and may even be erroneous [5]. Their use has been generally restricted to the diagnosis of early, IgE-mediated reactions. Furthermore, no consensus exists concerning the choice and technical guidelines for challenge procedures in infants [5,7]. These considerations have been translated into the common clinical practice to opt for altering the infant's formula, associated with clinical improvement, as being diagnostic of CMA. However, studies using DBPCFC have found that the history will not be confirmed in 40–60% of cases [2].

The clinical manifestations of CMA are highly varied and usually non-specific [4,8]. Clinical investigators have identified three clusters of infants with CMA, on the basis of challenge outcomes [3]. The first group manifest immediate and potentially severe reactions, within minutes to 2 h. The second present symptoms in a more insidious nature, occurring within hours, while the third group's manifestations run a rather chronic nature, occurring over a period of one to several days. Among various proposed diagnostic methods, skin-prick tests (SPTs) and assays of circulating food allergen-specific IgE antibodies are commonly employed in patients suspected of CMA [2]. However, whereas these tests readily demonstrate an IgE-mediated immunological reaction, those caused by cellular, delayed type responses, are not generally positive. Therefore, the diagnostic value of both tests is reported to be similar, but their utility is confined to patients with immediate onset (Type I) reactions [2,3,9,10]. Moreover, the specificity of these tests is not always clear, as studies investigating IgE tests (SPT or serological assays) often did not confirm CMA according to the outcome of double-blind, placebo-controlled food challenges (DBPCFC). Furthermore, false negative tests are often unreliable in children with atopic dermatitis. False negative results have been reported in infants less than 1 year of age [2], while false positive SPT are common in older children with atopic dermatitis [6]. The purpose of the present study was therefore first, to clearly identify infants and children with CMA using a DBPCFC carried out in two stages over several days, in

order to recognize both immediate and delayed responders. Second, to prospectively compare the clinical history of CMA and analyses of specific IgE antibodies to milk in predicting outcome of DBPCFC.

Patients and methods

Patient selection and inclusion criteria

Between March 1993 and June 1994, 123 consecutive infants and children, referred with the diagnosis of possible CMA to the Divisions of Allergy or Gastroenterology of the Department of Pediatrics at Hôpital Sainte-Justine, a tertiary referral centre, were evaluated for this study. The following inclusion/exclusion criteria were used for study entry: the clinical history, assessed by at least two experienced paediatricians, was considered as highly suggestive of CMA; other gastrointestinal disorders, such as celiac disease or disaccharidase intolerance, had been previously excluded; no acute or chronic concomitant disease was present at time of study entry. It was furthermore required that a strict bovine protein-free diet, maintained at least for 6 weeks and supervised by an experienced dietitian (L.B.), was associated with complete resolution of the patient's original symptoms. Infants and children with a history suggestive of CMA but in whom co-existing chronic atopic dermatitis was present were excluded, as they represent a subgroup of patients in whom the time-relationship between food ingestion and appearance of symptoms, either by history or challenge outcome, is very difficult to define [3]. It is well recognized that there is enormous variation in spontaneous relapses of cutaneous symptoms in this group, possibly because of multiple allergies. Rarely does atopic dermatitis remit completely when a single food is eliminated from an infant's diet [2]. Systemic treatment with antihistamines, steroids or immunosuppressants within the past 3 months also excluded patients from the study.

These criteria were initially met by 102 of the 123 evaluated patients. Of these, 33 were subsequently excluded for the following reasons: a blinded challenge was refused by the parents ($n = 13$); intercurrent concomitant disease (acute infectious gastroenteritis ($n = 5$), other infections ($n = 2$)) during the DBPCFC; the patient's diet was not strictly bovine protein-free ($n = 6$), assured follow-up was not feasible ($n = 4$), non-compliance during challenge procedure and follow-up ($n = 3$). Thus, a total of 69 infants and children (33 girls, 36 boys) were finally included for study. The mean age at the time of study entry was 22.1 months (range 3–105 months). The study protocol and challenge procedures were approved by the Ethics Committee of Hôpital Sainte-Justine. Written informed consent was obtained from each patient's parent.

Prechallenge work-up

Based on the detailed clinical history, particularly emphasizing the temporal relationship between milk ingestion and the appearance of adverse symptoms, patients were assigned to groups of either probable immediate reactors, with onset of symptoms within minutes up to 2 h, or probable delayed reactors, presenting a history of symptoms after a delay of more than 2 h. Subsequently, skin-prick tests (SPTs) were performed in all patients by a single investigator (Z.C.) according to standard technique [6]. The allergens tested were: cow's milk, casein, and α -lactalbumin (Hollister-Stier, Spokane, WA, USA). The SPT was considered positive if: at least one of tested antigen preparations elicited a weal diameter of at least 3 mm greater than the negative saline control, or the weal diameter was equal or greater than the positive histamine control in cases of a weal diameter smaller than 3 mm. SPT were carried out within 2.08 ± 0.28 months of DBPCFC.

Blood for determination of serum allergen-specific IgE antibodies was drawn on day 1, immediately prior to the onset of the challenge procedure (Fig. 1). IgE antibody titres to whole cow's milk proteins, β -lactoglobulin, casein and α -lactalbumin were quantitated using Allergo-coat Microplate EAST System[®] (Sanofi-Pasteur, Paris, France). Briefly, the test sera were incubated with an allergenic protein bound to a solid support. After washing to remove excess test serum, equine alkaline phosphatase-labelled antiserum to human IgE was added. The bound enzyme was revealed by incubation in presence of paranitrophenylphosphate. The chromogen was read at 405 nm using the LP-400 microplate reader. The activity was directly proportional to the amount of allergen-specific IgE antibodies bound to the solid sup-

port. As quality controls, standard positive (score 2 and 4) and a negative sera were added to each run. The test was considered positive if at least one of the tested allergens revealed a score ≥ 2 out of 4 (score range: 0–4).

Challenge procedure and blinding

The challenge protocol is summarized in Fig. 1. Most of the challenges were carried out in an outpatient setting. However, if potentially severe reactions were anticipated, the child was admitted. On day 1, after a clinical examination to exclude acute concomitant disease, blood was drawn for milk allergen-specific IgE antibodies, and an iv line was installed. The short-term DBPCFC was first performed in order to detect immediate responders who react within the initial 2 h. One hundred millilitres of the patient's usual formula, mixed with either 10 g of glucose polymers (Caloreen[®], Clintec Canada, or corn starch) as placebo, or with 10 g of skim milk powder (Carnation Canada), were prepared by the Dietetics Department, and labelled as milk 'A' or 'B', in a random and blinded fashion. Increasing quantities were then administered orally every 15 min, according to the following schedule: 1 drop, 0.5 mL, 1 mL, 2.5 mL, 5 mL, 10 mL, 20 mL, 30 mL, 60 mL. Randomization was performed by a dietitian (L.B.), and neither patient, parent, nor investigators were aware of the formula assignment order.

Challenge with either milk 'A' or 'B' was carried out separately, one in the morning, and the second in the afternoon. If no reaction ensued, the patient returned home 4 h after the beginning of the second part of the short-term DBPCFC. On day 2, the prolonged DBPCFC was started, in order to detect delayed responders. A special formula powder, based on the patient's usual formula was prepared by the Dietetics Department, as above, adding either skim milk powder or glucose polymers as placebo, and randomly labelled as milk 'A' or 'B', in order to blind the family and the medical team. The amount of this formula administered was based on the child's usual daily intake, assuring that the consumed amount was the equivalent of at least 210 mL of cow's milk per day. If the patient's prechallenge diet contained no formula at all, the challenge was performed using orange juice, with either skim milk powder or placebo added, as above. The appearance of the active and placebo material was similar, satisfactorily maintaining the blinded nature of the challenge.

On days 8 and 15, clinical follow-up was arranged, and a patient's diary of the past 7 days (Fig. 1) was verified and discussed with the parent(s) for any adverse or new symptoms. Ingestion of an adequate quantity of

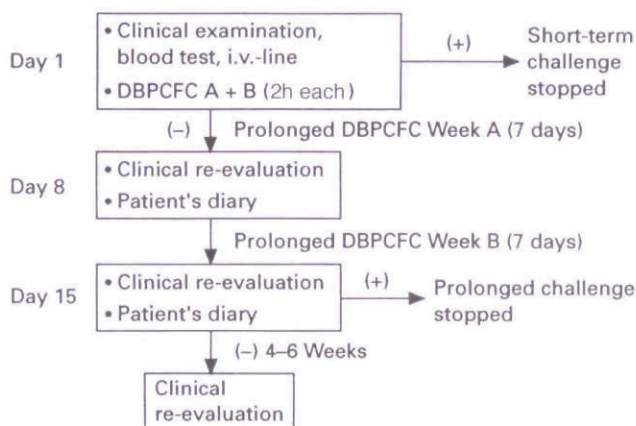


Fig. 1. Protocol for the two-stage double-blind, placebo-controlled food challenge (DBPCFC) to milk.

Table 1. Clinical patient data: Relationship between type of positive DBPCFC, volume of milk consumed, timing, and antigen-specific IgE antibody assays

Patient group	Patient	Volume ingested* (mL)	Onset of adverse reaction† (h)	Primary symptoms	SPT	EAST
<i>Immediate reactors (n = 10)</i>	L.B.	19	1.7	urticaria	+	—
	J.C.	1.5	0.6	urticaria, erythematous rash	+	ND
	S.L.	0.5	0.3	urticaria, angioedema	—	—
	S.J.	9	1.0	wheezing, cough	+	+
	J.B.	39	1.5	urticaria, angioedema, erythematous rash	—	—
	G.C.	19	1.2	urticaria, erythematous rash	+	+
	J.L.	9	1.1	urticaria, sneezing, rhinorrhoea, cough, oro-pharyngeal oedema, erythematous rash	+	+
	J.F.V.	5	1.2	vomiting, rhinorrhoea, wheezing, urticaria, angioedema	+	+
	A.S.J.	0.5	0.2	oro-pharyngeal oedema	+	+
	J.D.	10	1.2	urticaria, erythematous rash	—	ND
<i>Delayed reactors (n = 15)</i>	K.G.	99	4.5	vomiting, diarrhoea	—	—
	M.L.	99	3.5	vomiting, diarrhoea	—	—
	J.D.	99	2.5	vomiting, diarrhoea	—	—
	P.L.B.	99	5.0	vomiting, diarrhoea	—	—
	E.B.	99	3.0	vomiting, diarrhoea	—	—
	A.D.	280	23.0	diarrhoea	—	ND
	L.M.	99	5.2	vomiting, diarrhoea	—	—
	A.B.	69	2.1	vomiting	ND	—
	O.S.	99	12.5	colic	—	—
	J.C.R.	99	4.5	diarrhoea	—	—
	J.K.	2700	71.7	vomiting, diarrhoea, eczema, rhinorrhoea	—	—
	A.P.	280	48.0	colic, eczema	—	—
	M.C.C.	810	45.0	colic	—	—
	J.E.	99	3.0	vomiting, diarrhoea	—	—
	S.R.	280	10.0	vomiting, diarrhoea	—	—

*Test formula, containing skin milk powder (as described in 'Material and methods').

†Time lapse between onset of feeding of the test formula and appearance of first symptoms.

challenge formula was also verified. If the challenge remained negative at day 15, the child was then put on an open trial of a milk containing diet, and a final follow-up evaluation 4–6 weeks later was done in order to confirm normal weight gain and definitive milk tolerance. In cases of unequivocal adverse reactions, the challenge was stopped, the patient re-examined and the code was broken. In equivocal responses, the code was not opened, and the challenge procedure was repeated after a suitable delay. In all, eight equivocal challenges were encountered, with diarrhoea, anorexia and mild fever. In four such cases, a Rotavirus gastroenteritis was confirmed.

Statistics

Student's *t*-test was used to analyse differences between patient groups, and chi-square test was used to compare frequencies between groups.

Results

Challenge outcomes and characteristics

According to the detailed clinical history of the most recent adverse reaction(s) prior to study entry, 16 of the 69 patients were classified as probable immediate reactors, with predominantly cutaneous symptoms, within

2 h following ingestion of milk. This group was comprised of eight females and eight males, with a mean age of 36.9 months at study entry (range: 8–105 months). The remaining 53 patients were classified as probable delayed responders, with predominantly gastrointestinal symptoms, occurring usually later than 2 h, and up to 6 days after milk exposure, as defined above (see prechallenge work-up). This group was comprised of 25 females and 28 males, with a mean age of 17.3 months (range: 3–72 months). These patients generally had a history of chronic recurrent gastrointestinal symptoms, including diarrhoea, colic, vomiting, irritability and failure to thrive. Although some reported adverse reactions within 2 h after initiation of feeding (e.g. colic), they were classified as probable delayed reactors due to the chronic nature of their milk ingestion and related symptoms.

The clinical details regarding individual patients with a positive DBPCFC are summarized in Table 1. In the probable immediate reactor group, 10 out of 16 (62.5%) children had their history confirmed by a positive DBPCFC. In all 10 cases, their reactions were also of the immediate type. Amongst the group of probable delayed reactors, in only 15 out of 53 (28.3%) was the history confirmed by a positive DBPCFC. Once again, the reactions were uniformly concordant to the history, all of delayed type onset. Thus, on the basis of their classification by history, no patient turned out to be assigned to the wrong group. As anticipated, the average time at onset of symptoms was much less in the immediate, compared with delayed reactor group (1.0 vs 16.2 h, respectively), as was the average amount of test formula ingested (11 vs 354 mL, respectively).

Characteristics of patients with CMA

Age The relationship between age at study entry and the interval between the last reported adverse reaction according to the clinical history is shown for both patient groups in Fig. 2. The mean age (17.3 months) for the probable delayed reactor group was significantly less than that (36.9 months) of immediate reactors ($P < 0.001$). Similarly, the interval between last reaction and study entry followed the same pattern, with a significantly shorter interval ($P < 0.001$) for delayed (6.1 months) compared with that for immediate reactors (21.5 months).

Among the group of confirmed delayed reactors, 87% of subjects manifested their first symptoms very early in infancy, within the first month of life, whereas in immediate reactors, the age of onset was far more spread out over the first year of life. Indeed, 50% of confirmed immediate CMA infants, exposed to cow milk proteins

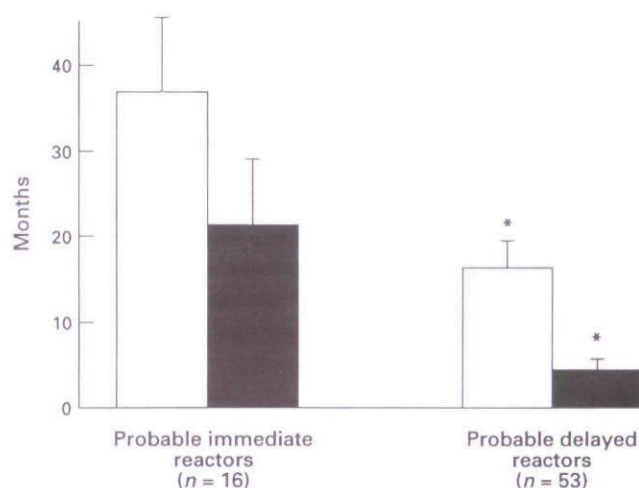


Fig. 2. Relationship between age at study entry (□) and the interval between last observed adverse reaction according to history and study entry (■), for the two patient groups. Results are expressed as mean $\pm$ SEM; * $P < 0.001$ vs probable immediate reactors.

within the first month of life, nevertheless presented their first symptoms after the age of 3 months. This may, in part, be explained by age at first exposure to cow's milk. In the group of probable delayed responders with histories unconfirmed by food challenges, 92% were given cow milk protein containing formulas in the first 2 months of life, compared with 75% of probable immediate reactors (not significant by chi-square test). In both groups, a small number of patients (<10%) were uniquely breastfed during the first 2 months. Their symptoms resolved upon elimination of bovine proteins from the material diet.

Correlation between historical and challenge symptoms

Comparing historical symptoms (most recent adverse clinical reactions) and those observed at the positive DBPCFC in the group of probable immediate reactors, predominantly cutaneous symptoms (acute urticaria, angioedema) were most often reported, followed by gastrointestinal (immediate projectile vomiting, diarrhoea), respiratory (coughing, wheezing) and systemic reactions (anaphylaxis). The overall correlation of symptoms between history and DBPCFC was 62.5% in this group. The probable delayed reactor group was characterized by infants presenting primarily with gastrointestinal-related symptoms. Typically, a mixture of vomiting, regurgitation, diarrhoea, colic and failure to thrive was most often seen. Several of the patients in this group had previously had bowel biopsies consistent with cow's milk enteropathy or with an allergic (eosinophilic) colitis [4,8]. Unlike the group of immediate

reactors, the history correlated to a much lesser extent (28.8% overall) with outcome of DBPCFC in the delayed reactors. In particular, among the sub-group of infants with a history of severe and prolonged colic ($> 3\text{h/d}$) as the sole symptom, CMA was confirmed by DPBFCF in only two out of 14 cases (14%). The majority of challenge positive patients (67%) reacted within 2–12 h after the onset of the challenge. Others were even more delayed, requiring up to 6 days before symptoms became clearly evident, as shown in Table 1.

Immunological data We compared the sensitivity and specificity of skin-prick tests and specific circulating IgE antibodies by EAST for the two patient groups, as shown in Table 2. Among the probable immediate reactor group, only one case out of six had positive results for both SPT and EAST, despite a negative DBPCFC. Similarly, one patient out of 34 in the DBPCFC negative probable delayed reactor group had both a positive EAST for α -lactalbumin (score 2+), and a positive SPT to milk. Despite the presence of IgE antibodies to milk, the latter infant's history was typical for delayed type symptoms, with colic and regurgitations starting approximately 24 h after milk intake. Nevertheless, both acute and prolonged DBPCFC to milk were negative. Among patients who had both SPT and EAST performed ($n = 62$), the correlation between the two tests was 100% for both patient groups. The three immediate reactors who were SPT negative were also negative by EAST.

Discussion

In this prospective study, using a two-stage, short-term and prolonged DBPCFC, we were able to clearly identify two groups of infants and children with cow milk allergy with distinct clinical and immunological features. The first group corresponds to the classic immediate IgE reactions, as described by other investigators [3,9–19]. The second group of patients presenting with primarily

gastrointestinal symptoms, manifested delayed reactions (2 or more hours up to 6 days) after milk ingestion. This group is similar to the 'intermediate reactors', as previously defined by Hill *et al.* [3]. The same authors also defined another subgroup of patients, not encountered in this study, termed 'late reactors' with CMA. This latter group manifested quite heterogeneous symptoms and immunological findings. However, several differences between this study and that of Hill's group must be noted. Hill's classification was based a K-means algorithm to identify their three clinical groups, rather than the details obtained from the clinical history, as herein. Furthermore, Hill's late reactor group were significantly older, and included an increased incidence of eczema, an exclusion criteria in the present study. Furthermore, the challenge in Hill's study was not carried out in a double-blind, placebo-controlled fashion. The discrepancies may be due to the differences in challenge techniques. Hill's challenge protocol precluded the administration of the larger amounts of milk proteins on day one as in our DPBFCF, and normal milk intake was only started on days 3 and 4 of the challenge procedure. In this regard, those patients that manifested acute angio-oedema and/or urticaria on day 2 (considered intermediate reactors) or day 3 (considered delayed reactors), might have been classified to the immediate reactor group if subjected to our protocol.

We believe that our two-stage DBPCFC, using a short-term challenge on day 1 with the administration of 10 g of skim milk powder (corresponding to approximately 250 mL of cow's milk) more clearly distinguishes IgE-dependent immediate responders from non-IgE-mediated food reactions, which we have designated as delayed responders. Moreover, our challenge technique, disguising cow milk powder or a carbohydrate placebo in the patients' usual formula or juice, proved to be practical and reliable, especially in infants and young children where capsules cannot be used. Other investigators have also used the same method in infants [2]. Except in two cases, where the patients categorically refused to drink,

Table 2. Sensitivity and specificity of skin-prick tests and circulating IgE antibodies to milk proteins (EAST) compared with the outcome of the DBPCFC

	Probable immediate reactors		Probable delayed reactors	
	Sensitivity	Specificity	Sensitivity	Specificity
SPT	70%	83%	0%	97%
EAST	63%	83%	0%	97%

Correlation SPT-EAST among 62 patients who had both tests performed was 100%.

acceptance of the test formula preparations was excellent, and the double-blind nature of the 2 week challenge procedure was easily maintained.

Overall, 36% of the 69 infants who underwent DBPCFC in our study were confirmed to have CMA. This is only slightly lower than the 40–60% observed in other series [12,13], perhaps because of the substantial delay in performing challenges for both groups (6.1 and 21.5 months, on average, for delayed and immediate responders, respectively). It is conceivable that a certain number of our challenge negative patients' CMA resolved by the time of DBPCFC. This is certainly likely for the probable delayed reactor group, whose CMA was confirmed in a minority (28.8%) of cases, compared to the majority (62.5%) of the probable immediate responders. The natural history of CMA suggests that delayed responders' hypersensitivity almost always resolves by age 3, whereas about 25% of the IgE positive, immediate group maintain their allergy by that time [2].

Infants and children with a history of CMA presenting with atopic dermatitis represent a subgroup of potentially food-allergic patients, in whom the time–relationship between food ingestion and appearance of symptoms by challenge outcome is very difficult to define [2,14]. Both immediate and late-phase effects of food antigen hypersensitivity have been documented during DBPCFC in this group [15,16]. Furthermore, multiple food allergies may co-exist, and the elimination of one food is unlikely to completely resolve the dermatitis [2]. Therefore, this subgroup of patients was intentionally excluded in the present study. In the study by Hill *et al.* patients with chronic atopic dermatitis were represented in each of the immediate, intermediate and late reactors groups, although a greater incidence was observed in late reactors [3].

We observed an interesting effect of age on the type of milk hypersensitivity, as previously suggested by Hill and Hosking [20]. Delayed reactors were significantly younger than immediate reactors at the time of the first adverse reaction reported by the parent(s). Furthermore, in our series, a patient with a history compatible with a delayed reaction within the first month of life had a chance of less than 15% to have a positive DBPCFC, if challenged after the age of 1 year. Thus, infants with delayed type CMA tended to outgrow their hypersensitivity much earlier than those with immediate type allergy, as previously suggested [2,20]. These findings may in part explain why in our patient population, the mean age of immediate reactors was significantly higher than in delayed reactors at study entry. However, the mean interval between the last reported adverse reaction and the challenge procedure was also significantly longer

in immediate vs delayed reactors. This may be due to a possible patient selection bias to our tertiary referral centre. Referring physicians may have hesitated longer to refer patients with immediate type of CMA, in whom potentially dangerous reactions are more likely, preferring to continue longer on exclusion diets.

Controversy exists on the interpretation, reliability and significance of elevated antigen-specific IgE antibodies in delayed milk responders. Some studies [3] have reported the presence of reaginic antibodies in up to about 20% of intermediate reactors. However, this may be explained by the fact that apart from studies on chronic atopic dermatitis and food allergy, none used DBPCFC. Furthermore, we used stringent criteria for SPT, defining the test as positive if the weal diameter was at least 3 mm greater than saline control, as suggested by others [6]. In our study, none of the 15 delayed reactors had a positive SPT or EAST, whereas false positive IgE anti-milk antibodies were present in only one of 35 DBPCFC-negative patients in the probable delayed reactor group. Our data thus support the view that patients with a positive delayed response are not associated with milk-specific IgE antibodies [2,4], in agreement with other authors [19,21]. As anticipated, SPT and EAST determinations of IgE antibodies to cow's milk were often positive in DBPCFC-positive immediate reactors. The SPT had a sensitivity and specificity of 70/83% vs 63/83% for the EAST. Both tests had a comparable predictive value for immediate reactors, and were of no diagnostic value for the challenge outcome in delayed reactors (Table 2). Of particular interest is that the type of reaction observed in challenge proven CMA infants was 100% concordant with the clinical history for both immediate and delayed responders. Our data thus support the importance of a thorough clinical history as the most helpful tool to characterize the type of hypersensitivity response, and to predict the outcome of the milk challenge procedure. Extreme caution is therefore mandatory in interpreting negative SPT as a reliable tool in predicting outcome of a milk challenge, especially in young infants, as noted by others [2,20,21]. Host and Halken have shown that SPT are useful as a prognostic indicator of CMA [10].

Using a two-stage DBPCFC in short-term and prolonged phases, we have clearly identified two groups of infants and young children with CMA of either immediate or delayed type allergy. The prospective comparison between the clinical history of CMA and analyses of specific IgE antibodies (SPT and EAST tests) to milk showed a comparably high, but imperfect predictive value for immediate reactors, and were of no diagnostic value for probable delayed responders. Thus, in the lack of better tests, the diagnosis of CMA still depends upon

the demonstration of a reproducible adverse clinical response to formal milk challenge after exclusion of other, non-immune causes of milk intolerance.

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References

- 1 Anderson JA, Jogn DD, eds. Adverse reactions to foods. American Academy of Allergy and Immunology/NIAID. NIH Publication 1984; 84-2442.
- 2 Bock SA, Sampson HA. Food allergy in infancy. *Pediatr Clin N Amer* 1994; 41:1047-67.
- 3 Hill DJ, Firer MA, Shelton MJ, Hosking CS. Manifestations of milk allergy in infancy: Clinical and immunologic findings. *J Pediatr* 1989; 109:270-6.
- 4 Baehler P, Seidman EG. Gastrointestinal manifestations of food protein induced hypersensitivity. In: Rudolph AM, ed. *Rudolph's Pediatrics*. Norwalk: Appleton & Lange, 20th edition, 1995, in press.
- 5 David TJ. Provocation tests: foods challenges II: limitations. In: *Food and Food Additive Intolerance in Childhood*. David TJ (ed). Blackwell Science, Oxford, 1993:275-80.
- 6 Bousquet J, Michel FB. In vivo methods for study of allergy: Skin tests, techniques and interpretation. In: Middleton E Jr, Reed CE, Ellis EF et al, eds. *Allergy: Principles and Practice*. St-Louis, CV Mosby, 1993, 4th edition, vol. I: 573-94.
- 7 Businco L. Food allergy in childhood. Hypersensitivity to cow's milk allergens. *Clin Exp Allergy* 1993; 23:481-3.
- 8 Moon A, Kleinman RE. Allergic gastroenteropathy in children. *Ann All Asthma Immunol* 1993; 74:5-12.
- 9 Burks AW, Williams LW, Casteel HB, Fiedorek SC, Connaughton CA. Antibody response to milk proteins in patients with milk protein intolerance documented by challenge. *J Allergy Clin Immunol* 1990; 85:921-27.
- 10 Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first three years of life. *Allergy* 1990; 45:587-96.
- 11 Bock SA. Prospective appraisal of complaints of adverse reaction to foods in children during the first 3 years of life. *Pediatrics* 1987; 79:683-8.
- 12 Bock SA, Sampson HA, Atkins PM et al. Double-blind placebo-controlled food challenge (DBPCFC) as an office procedure: A manual. *J Allergy Clin Immunol* 1988; 82:986-97.
- 13 May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J Allergy Clin Immunol* 1976; 58:500-15.
- 14 Damaeus A, Johansson SGO. A follow-up study of infants with adverse reaction to cow's milk. 1. Serum IgE skin test reactions and RAST in relation to clinical course. *Acta Paediatr Scand* 1979; 68:377-82.
- 15 Sampson HA, McCaskill CM. Food hypersensitivity in atopic dermatitis: Evaluation of 113 patients. *J Pediatr* 1985; 107:669-75.
- 16 Burks AW, Mallory SB, Williams LW et al. Atopic dermatitis: Clinical relevance of food hypersensitivity reactions. *J Pediatr* 1988; 113:447-51.
- 17 Sampson HA, Broadbent KR, Bernhisel-Broadbent J. Spontaneous release of histamine from basophils and histamine-release factor in patients with atopic dermatitis and food hypersensitivity. *N Engl J Med* 1989; 321:228-32.
- 18 Minoford AMB, MacDonald A, Littlewood JM. Food intolerance and food allergy in children: a review of 68 cases. *Arch Dis Child* 1982; 57:742-7.
- 19 Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990; 117:561-7.
- 20 Hill DJ, Hosking CS. Some limitations of double-blind, placebo-controlled food challenges in young children. *J Allergy Clin Immunol* 1991; 87:136-7.
- 21 Hill DJ, Duke AM, Hosking CS, Hudson IL. Clinical manifestations of cow's milk allergy in childhood. II. The diagnostic value of skin tests and RAST. *Clin Allergy* 1988; 18:481-90.

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