

Cow milk allergy within the spectrum of atopic disorders

D. J. HILL, D. G. BANNISTER, C. S. HOSKING and A. S. KEMP

Department of Allergy, Royal Children's Hospital, Parkville, Australia

Summary

In order to examine the relationship between cow milk allergy (CMA) and atopic disorders in childhood, a consecutive group of 42 infants with IgE mediated CMA was followed for at least 2 years. The incidence of sensitization to common food and inhalant antigens and the development of eczema, asthma, and food allergies was examined for the cohort and compared between patients whose CMA remitted and those with persistent disease. In this cohort the prevalence of eczema was 57%, asthma 69%, egg allergy 67%, peanut allergy 55%, and 83% of infants demonstrated positive skin-prick tests to three or more allergens. At the end of the study CMA had remitted in 13 patients (median age 44 months) whereas in 29 patients it persisted (median age 44 months). Although there was no significant difference in the incidence of eczema or asthma during the study between these two patient groups, the incidence of allergy to egg and peanut butter was significantly greater for children with persistent CMA. Consistent with our hypothesis that children with persistent CMA have a more severe dysregulation of IgE synthesis than those whose disease remits, patients with persistent CMA had a significantly higher incidence of and level of skin sensitivity to inhalant and other dietary allergens. Sensitization to the inhalant allergens *Dermatophagoides pteronyssinus*, cat dander and rye grass was frequently seen in early infancy and increased during the study period. Thus, children with IgE mediated CMA frequently generate IgE responses to multiple dietary and inhalant allergens in infancy and early childhood and develop immediate hypersensitivity to other foods as well as clinical eczema, and asthma.

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Introduction

Atopic individuals have been defined by their capacity to generate IgE antibodies in response to environmental allergens [1]. Most studies which have investigated the relationship between atopy and clinical disease have examined IgE responses to inhalant allergens in older children and adults with allergic respiratory tract diseases. In asthma, the higher the atopic status, the greater the incidence of multiple skin reactions, and the earlier the onset and severity of this disease [1]. However, dietary proteins are among the first antigens infants, including potentially atopic children, encounter. It is generally accepted that IgE-mediated food allergies are probably

related to other atopic disorders [2], but few studies have prospectively examined the IgE responses to ingested and inhaled allergens in a large group of children with proven IgE mediated food allergy.

Cow milk proteins are among the first dietary antigens infants encounter. Allergy to cow milk proteins (CMA) affects between 2 and 7.5% of infants [3–5]. Studies from this department of infants and young children with CMA, have identified three groups of patients (termed groups 1, 2 and 3) [6], described their immunological features [7–9], the natural history of the disease [10], and the high incidence of other food hypersensitivities, and the atopic disorders, like eczema, asthma and rhinitis, which they develop [10]. Recently, Host described a similar spectrum in disorders in a prospective study of CMA in Danish infants [11].

From our studies it was unclear whether children with IgE mediated CMA were part of the atopy spectrum or

Correspondence: Dr D. J. Hill, Director, Department of Allergy, Royal Children's Hospital, 151 Flemington Road, Parkville, North Melbourne 3052, Australia.

whether they represented a distinct group of infants with a single allergic manifestation, i.e. IgE hypersensitivity to cow milk proteins.

In order to clarify this issue, children with IgE-mediated hypersensitivity to cow milk were examined prospectively for at least 2 years to follow the development of IgE sensitization to common food and inhalant antigens. Our previous studies suggested that children with persistent CMA have a more severe dysregulation of IgE synthesis than those whose disease remitted [12] in that the IgE isotype response to milk proteins in children with persistent CMA is significantly higher from the time of diagnosis than that of children whose CMA remits. Based on these observations we hypothesized the incidence of, and level of, IgE sensitization to common food and inhalant antigens would be greater in children whose CMA persisted than those whose disease remitted as would the incidence of associated atopic clinical disease.

Materials and methods

Study protocol

The 42 patients (25 men) were a consecutive group of CMA patients who had follow-up data available at least 2 years from the time of diagnosis. At the initial evaluation the mean age was 15 months (5–24 months) and at final follow-up, 51 months (25–102 months). All patients remained under the care of a paediatric allergist who identified the development of CMA, non-cow-milk food allergies, eczema and asthma during the study. The diagnosis of CMA was based on procedures described below. Evidence of allergy to non-cow-milk foods was restricted to egg and peanut; this diagnosis was based on a history of immediate hypersensitivity reactions to egg or peanut which developed within 30 min of ingestion and associated with high positive skin-prick test (SPT) (>4), to an extract of these foods. Eczema was identified on clinical examination. Asthma was diagnosed when three or more episodes of wheezing which responded to beta-agonist treatment occurred in the 12 months prior to the final assessment.

All patients underwent SPT annually. If indicated, on the basis of history and skin-test reactivity, a cow milk challenge was conducted at 12-month intervals until tolerance to cow milk was demonstrated or the study concluded. Children who tolerated cow milk for 1 month were regarded as cow milk tolerant.

Identification of CMA patients

Patients were included in the study if they had CMA demonstrated by one of the following procedures:

Cow milk challenge There were 13 patients who demonstrated CMA on formal challenge. This challenge procedure has been previously described in detail [12]. In summary, the protocol required exclusion on non-protein causes of cow milk intolerance and the demonstration of unequivocal relapse of symptoms after challenge. The procedure was an open one and wherever possible a schedule was followed which required patients to ingest CMA up to 65 ml on day 1, 120 ml on day 2, and 240 ml to normal intake on day 3. The initial challenge was conducted in the Department of Allergy, but after day 2 milk ingestion continued at home and patients were formally reviewed at the time of any adverse reaction, on day 7, and after 1 month. All children whose reactions were in doubt or whose symptoms developed more than 24 h after the start of milk ingestion demonstrated an adverse response to milk challenge on two or more occasions before their responses were regarded as positive.

The 13 patients who underwent open cow milk challenge developed symptoms 1–20 min after ingestion of 1 drop to 60 ml of cow milk and induced peri-oral urticaria (13 cases), cough (three cases), wheeze (one case), rhinorrhoea (two cases) and pruritus with erythema (one case).

High skin-test reactivity to whole cow milk extract (WCME) Our previous studies have demonstrated that all children with a high skin-prick test (SPT) ≥ 4 to the whole cow milk extract (WCME) in use have CMA [13].

Twenty-nine patients had SPT ≥ 4 to WCME. Twenty-seven had a recent history (within 4 weeks) of a severe adverse reaction, within 5–10 min of ingestion of small volumes of cow milk. Reactions included peri-oral urticaria (18 patients), eczema (six patients), anaphylactic shock (four patients), cough (one patient), and vomiting (four patients). The remaining two patients with SPT > 4 had not ingested cow milk but had a history of severe immediate hypersensitivity reactions to egg, soy milk, and wheat.

Skin tests

The following allergen extracts and control solution were purchased from Dome Hollister Stier, Spokane, WA, USA: whole cow milk, egg white, cod fish, wheat, soy milk, peanut, *D. pteronyssinus* (house dust mite), cat fur, dog fur, and *Lolium perenne* (rye grass pollen). An attempt was made to skin test with this complete panel at both the initial and final assessments but in a small number of children this was not possible. Of the possible 840 SPT at the initial and final assessment on the 42

patients there were 812 test results available for analysis. There was no difference in the number of SPTs performed at the initial assessment (94% persistent, 98% remission) or at the final assessment (98% persistent, 99% remission) between the two patient groups. While allergens of different batches were used during the study they were purchased from the same company and reported to be of the same potency.

Skin-prick tests were performed by one of three specially trained allergy nurses as follows. One drop of the extract, control solution, and histamine were placed on the subject's skin, 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 extracts was compared with that of histamine acid phosphate, 1 mg/ml and the control solution. The size of weal of the control solution was subtracted from that of each allergen before the test score was given. The mean diameter (taken at right angles), of the weal and pseudopodia elicited by the histamine was designated as 3, and the reactions to the extracts graded by reference as follows [14]:

>4 reaction => twice the area of histamine standard;

4 reaction = from the area of the histamine standard up to twice the area of that standard;

3 reaction = from one half of the area of the histamine standard up to the area of the histamine;

2 reactions = from one quarter to one half of the area of histamine standards;

1 reaction = up to one quarter of the area of histamine standard, and greater than the control solutions.

Criteria for positive skin tests For the purposes of this study a positive skin-test was defined as an SPT > 2 to any allergen. In all cases these exceeded the control weal by 2 mm or more.

Statistical analysis

Fishers exact test, chi-squared test, and Mann-Whitney U-test were used where relevant to compare the incidence of positive SPTs to allergens between different patient groups. The Wilcoxon signed rank test compared the significance of the change in the incidence and the degree of sensitization to antigens at the initial and final assessment for the different patient groups. The null hypothesis was rejected when P was <0.05.

Results

Table 1 summarizes the clinical and skin-test findings according to whether CMA remitted or persisted.

Clinical outcome

Reactions to cow milk challenge During this study a number of patients underwent remission of CMA. At the final follow-up 13 patients tolerated normal volumes of cow milk (seven boys, six girls) median age 44 months (25–66 months).

By contrast, 29 patients (18 boys, 11 girls) median age 44 months (25–68 months) had persisting CMA at the end of the study. Of these, 17 underwent formal cow milk challenge. In 16, symptoms including urticaria (13 cases), vomiting (two cases), anaphylaxis (one case) developed within 60 min of ingestion of 15–200 ml of cow milk. The remaining patient (SPT > 4), developed diarrhoea over 48 h following ingestion of 600 ml of cow milk over this period. In seven patients the diagnosis of persisting CMA was based on an SPT ≥ 4 ; all of these patients reported immediate hypersensitivity reactions following accidental ingestion of up to 15 ml of cow milk in the 12

Table 1. Comparison of clinical features of children whose CMA remitted or persisted during the study

Clinical features	Remitting CMA	Persisting CMA	Fishers Exact Test
Number	13 (7 M 6 F)	29 (18 M, 11 F)	–
Clinical reaction to peanut during study	4	19	0.04
Clinical reaction to egg during study	5	23	0.01
Eczema at study start	5	19	0.1
Eczema at study end	2	13	0.06
Asthma at study start	1	4	0.50
Asthma at study end	7	22	0.29*
+SPT to $\geq$ three allergens at study start	10	25	0.73*
+SPT to $\geq$ three allergens at study end	7	29	0.003
Eczema and asthma at study end	2	13	0.06

* Chi-squared test. +SPT. SPT-positive. M. Male. F. Female.

months prior to final assessment. A further five patients accidentally ingested up to 30 ml of cow milk in the 4 weeks prior to the final assessment and developed immediate urticaria (four patients) and vomiting, diarrhoea and irritability (one patient); three of these had SPT > 4.

Reactions to other foods At the final assessment the incidence of reported adverse clinical reactions to egg and peanut in children with persisting CMA was significantly greater for those whose disease remitted; egg ($P = 0.01$), peanut ($P = 0.04$) (Table 1).

Development of eczema and asthma At the outset, 24 children had a history of eczema and at final follow-up eczema persisted in 15 of these. There was no significant difference in the incidence of eczema irrespective of whether the children showed persistent CMA or the disease remitted ($P > 0.05$ in all instances) (Table 1).

Overall, 29 children developed asthma by the end of the study. The incidence of asthma at the initial assessment and final assessment according to remission or persistence of CMA was not different ($P > 0.05$) (Table 1). Of the 22 patients with persistent CMA and asthma 13 required long-term asthma prophylaxis (10 inhaled steroids, three cromoglycate) and the remaining nine intermittent bronchodilators. Three of the seven patients with asthma whose CMA remitted needed asthma prophylaxis (one inhaled steroids, two cromoglycate) but the remaining four patients used bronchodilators intermittently. The incidence of inhaled steroid use in

the patients with persistent CMA was not statistically greater than in children whose CMA remitted ($P = 0.07$).

At the end of the study 15 children were being treated for eczema and asthma; there was no significant difference in the incidence of eczema and asthma in those with persistent CMA (13 cases) compared with those who were milk tolerant (two cases) ($P = 0.06$).

Skin-prick tests and CMA

Overall the total number of positive SPTs at the start of the study was 320/400 and at the final assessment was 219/412. The mean number of positive SPTs per patient was 7.6 at the initial assessment and 5.2 at the final assessment. Of the 42 children in the study 35 (83%) at the initial assessment, and 36 (86%) at the final assessment showed positive SPTs to three or more allergens (Table 1). Only two patients were SPT-positive to cow milk alone and CMA remitted in both.

Comparison between persistent CMA and remission CMA During the study children with persistent CMA showed an increase in the median number of positive SPTs per patient (5, range (2–9) vs 6, range (3–9); $P = 0.02$) whereas patients whose CMA remitted this incidence was unchanged (4 (1–9) vs 3 (0–6); $P = 0.50$).

In Tables 2 and 3 the number of children with a positive SPT, and the median weal size to each allergen at the start and finish of the study is shown according to whether or not CMA persisted. At the initial assessment there was no difference in the number of children with

Table 2. Skin-test data at initial assessment

Allergen	Persistent			Remission			Statistical difference persistent vs remission*	
	Patients tested	Positive SPTs	Median weal size	Patients tested	Positive SPTs	Median weal size	Positive SPTs	Median weal size
Milk	29	28	5 (1–5)	13	13	5 (3–5)	0.89	0.83
Egg	29	29	5 (3–5)	13	11	5 (0–5)	0.12	0.03
Fish	28	6	0 (0–5)	13	2	0 (0–4)	0.80	0.58
Wheat	27	12	1 (0–5)	13	2	0 (0–4)	0.09	0.05
Soy	27	9	0 (0–5)	12	0	0 (0–0)	0.07	0.02
Peanut	28	24	5 (0–5)	13	8	4 (0–5)	0.15	0.10
Mite	29	10	0 (0–5)	13	5	0 (0–4)	0.89	0.88
Cat	24	11	3 (0–5)	12	3	0 (0–5)	0.54	0.49
Dog	23	4	0 (0–4)	12	4	0 (0–5)	0.53	0.42
Rye	29	10	0 (0–5)	13	2	0 (0–5)	0.31	0.21

* P value—Mann-Whitney U -test.

Table 3. Skin-test data at final assessment

Allergen	Persistent			Remission			Statistical difference persistent vs remission*	
	Patients tested	Positive SPTs	Median weal size	Patients tested	Positive SPTs	Median weal size	Positive SPTs	Median weal size
Milk	29	28	5 (0–5)	13	7	2 (0–5)	0.0006	<0.001
Egg	29	27	5 (0–5)	13	9	3 (0–5)	0.025	0.007
Fish	28	6	0 (0–5)	12	0	0 (0–1)	0.791	0.73
Wheat	27	9	0 (0–5)	13	0	0 (0–1)	0.153	0.06
Soy	27	9	0 (0–3)	13	2	0 (0–2)	0.305	0.19
Peanut	29	26	5 (0–5)	13	5	0 (0–5)	0.007	0.003
Mite	29	22	3 (0–5)	13	7	2 (0–5)	0.128	0.112
Cat	28	20	3 (0–5)	13	4	0 (0–3)	0.007	0.005
Dog	28	10	0 (0–4)	13	1	0 (0–2)	0.234	0.158
Rye	29	20	0 (0–5)	13	7	2 (0–5)	0.283	0.26

* *P* value—Mann-Whitney *U*-test.

positive SPTs to any of the allergens although the median weal size for egg, wheat and soy was greater in children with persistent CMA (Table 2). However, at the final assessment the number of children with positive SPT to, and the median weal diameter to milk, egg, peanut, and cat was significantly greater for children whose CMA persisted than those whose disease remitted (Table 3).

The change in the number of, and median weal diameter of, positive SPT for each allergen between the initial and final assessment was also examined (Tables 2 and 3). For children whose CMA remitted the incidence of positive SPT to milk, egg, fish, wheat, peanut and dog decreased and this decrease was statistically significant for milk ($P = 0.004$) and egg ($P = 0.02$); the incidence of rye grass sensitization increased ($P = 0.02$). In contrast, for children with persistent CMA the incidence of sensitization to all the allergens tested increased or did not change (except egg and wheat) and these increases were significant for *D. pteronyssinus* ($P = 0.002$) and rye grass ($P = 0.001$).

Inter-relation between SPT, CMA and atopic clinical disease At the outset the median number of positive SPTs per patient in the 24 infants with CMA and eczema was greater than in the 18 patients without eczema (5 (2–9) vs 4 (1–7); $P = 0.02$). However, the number of positive SPTs per patient was not different for eczema patients with persistent CMA compared with those whose CMA remitted.

There was a low incidence of asthma at the outset of the study so the inter-relation between CMA, asthma

and SPTs was examined at the end of the study only. For the cohort, the median number of positive SPTs per patient for the 29 children with asthma, was 6 (1–9) compared with 3 (0–9) for the 13 without asthma ($P = 0.05$). For the children with persistent CMA the number of positive SPTs per patient was similar for the children with asthma, 6 (3–8), as those without asthma, 6 (3–9); this incidence was greater when compared with those whose CMA remitted irrespective of whether, 4 (2–5), or not 3 (2–5), they developed asthma ($P < 0.05$ in both instances).

Discussion

Our findings suggest that CMA is part of the spectrum of atopy in that virtually all children with IgE mediated CMA, irrespective of associated eczema or asthma, demonstrated IgE responses to multiple inhaled and ingested antigens from early childhood. Host [11] described similar findings in a smaller study. While there was reactivity to a broad range of allergens within the group, individuals showed varying degrees of specificity of antigen response. Thus, though most children would have a similar exposure to *D. pteronyssinus* and rye grass pollen, not all patients were sensitized to these allergens by the end of the study. Consistent with our hypothesis that children with persistent CMA have a more severe dysregulation of IgE synthesis than those whose disease remitted, infants with persistent CMA showed the highest number of positive SPTs per patient and level of sensitivity, to several allergens, particularly when it was associated with eczema or asthma.

Our previous studies of children with IgE mediated CMA [6,10], described a high incidence of adverse reactions to non-cow milk foods, eczema and asthma. The results of this study confirms those clinical observations and provides evidence that patients who develop these diseases following CMA are similar in this respect to other children with these atopic disorders.

A high incidence of sensitization to inhalant allergens in our patients was observed. Primary sensitization to specific inhalant allergens involves initial T cell priming in early infancy although the ensuing IgE antibody response may take as long as 2 years before inhalant specific IgE is evident [15,16]. However, our results suggest that some CMA infants acquire sensitization to inhalants like cat dander and house dust mite before 2 years of age which are associated with the development of IgE sensitization to multiple dietary antigens. Whether sensitization to dietary antigens facilitates the IgE response to inhalant antigens, i.e. by a process of molecular mimicry, or is simply the consequence of the natural sequence of exposure to different levels of allergen, initially to dietary and then to inhalant allergens, is unclear.

Williams and McNickol, in studies of Melbourne school children, emphasized that many children with severe chronic asthma suffered from severe eczema in early infancy [20]. These children were likely to have asthma which subsequently has been shown to persist beyond the age of 28 years [21]. The possibility exists that the infants and young children we have described with persisting CMA are those destined to develop severe persisting asthma as they show many of the clinical and immunological features identified by the earlier studies of Williams and McNickol [20]. From an immune perspective our patients with persistent CMA showed a significantly higher incidence of sensitization to *D. pteronyssinus* (76%), cat dander (71%), and rye grass (70%), than other populations of Australian children of similar age; the incidence of sensitization to these allergens was approximately five times that in a random population [18] and three times that of children genetically at risk of developing atopic disease [17]. Sensitization to *D. pteronyssinus* and cat dander is associated with a six-eightfold risk of asthma in older children [19].

We envisage that a spectrum of atopy exists in infancy which ranges from asymptomatic infants [22] who generate transient levels of IgE antibodies to common dietary antigens through to those who generate high levels of IgE antibodies to common dietary antigens and have severe food allergy, eczema and subsequently asthma. Our results suggest this latter group of infants may generate very high levels of IgE responses to both dietary and inhalant antigens within the first 2 years of

life and that it may persist for longer [23]. These children may be analogous to the T cell modulated 'high' IgE responding rat strains described by Tada *et al.* [24]. There is a small group of children with persisting CMA who do not appear to show other features of atopic childhood disorders; further studies are required to determine whether these children have a delayed onset of other atopic disorders or whether they represent a sub-group whose IgE hyperresponsiveness is directed to dietary antigens alone. Because this study only examined children presenting with CMA, the relative size of the group of children who develop atopic diseases like eczema and asthma without previous signs of CMA, and other food hypersensitivity or transient dietary IgE sensitization cannot be accurately assessed. However, we have previously described older children with moderately severe asthma without a reported preceding history of eczema or food allergy who generate high IgE antibody responses to common ingested foods and inhalants when compared with an age-matched control population [23].

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