
Manifestations of milk allergy in infancy: Clinical and immunologic findings

In a study of the manifestations of cow milk allergy in 100 young children (mean age 16 months), 30 items of historical data and information relating to the effects of a standardized milk challenge were entered into a computer data base. Three clusters of patients were derived using a K-means algorithm. In group 1 were 27 patients with predominantly urticarial and angioedematous eruptions, which developed within 45 minutes of ingesting cow milk. They had positive skin test reactions to milk and elevated total and milk specific IgE serum antibody levels. In group 2, 53 patients had pallor, vomiting, or diarrhea between 45 minutes and 20 hours after milk ingestion. These children were relatively IgA deficient. The 20 patients in group 3 had eczematous or bronchitic or diarrheal symptoms; in 17 symptoms developed more than 20 hours after commencing milk ingestion. Of the patients in group 3, only those with eczema had a positive skin test reaction and elevated IgE antibodies to milk. The patients in group 3 were the most difficult to identify clinically; they had a history of chronic ill health, and symptoms developed many hours or days after commencing milk ingestion in the challenge situation. In view of the heterogeneous clinical and immunologic findings in our patients, it is unlikely that a single laboratory test will identify cow milk allergy in all susceptible patients. (J PEDIATR 1986;109:270-276)

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Cow milk allergy may be defined as an adverse reaction to cow milk resulting from an immunologic hypersensitivity to one or more milk proteins. Epidemiologic studies suggest that it affects 2% to 7.5% of infants.^{1,2} Several well-defined but uncommon syndromes, including pulmonary hemosiderosis and bronchitis,³ iron⁴ and protein-losing enteropathy,⁵ colitis,⁶ and neonatal thrombocytopenia,^{7,8} have been associated with cow milk allergy. In our experience, these syndromes affect about 5% of infants with adverse reactions to milk protein. We believe that the multiplicity of poorly defined illnesses and the variability of pathologic lesions elicited by milk ingestion in sensitized

children has caused difficulties in the recognition of the more common forms of cow-milk allergy.

Previous studies have identified two broad groups of children allergic to cow milk: the first, an immediate-reacting, IgE-sensitized group, and the second a so-called late-reacting, gastrointestinal responding population.^{1,9,10} In these studies, patients appear to have been assigned to

PRIST	Paper radioimmunosorbent test
RAST	Radioallergosorbent test

one of these two groups on the basis of time to reaction to milk ingestion, although the identification of this reaction time appears to have been arbitrary. Furthermore, investigations of cow milk allergy have concentrated on one particular aspect of patients within these two groups rather than identifying the broader manifestations of milk allergy in childhood. Finally, the association between various

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immunologic abnormalities and the nature of the adverse response to milk ingestion remains confused; some workers have associated IgE hypersensitivity with immediate reactions,⁹ others with the late response.¹¹ IgA deficiency has been implicated in the pathogenesis of gastrointestinal forms of cow milk allergy.¹²

The purpose of our investigation was to use simple clinical methods to identify groups of patients with cow milk allergy, and to document the symptoms of their disease, the effect of milk ingestion, and the immunologic features.

METHODS

Sixty-six boys and 34 girls participated in this investigation. The mean age at the time of diagnosis was 16.2 months; only five children were older than 3 years at the age of diagnosis. Seventeen patients were included in an earlier report,¹⁰ and other data for this population have been published elsewhere.¹³

Cow milk allergy was defined as an unequivocal, adverse reaction to cow milk protein. Milk intolerance caused by disaccharidase deficiency and other gastrointestinal tract diseases was excluded by jejunal biopsy. Milk aspiration as a cause of recurrent bronchitis was excluded by a normal barium swallow examination and by demonstrating a reproducible relapse of symptoms following milk ingestion but not following the ingestion of other infant formulas. Details of this protocol have been published elsewhere.^{10, 13} Patients were given a milk-free diet and were asymptomatic for 6 to 12 weeks prior to milk challenge. They were hospitalized in a specialized hospital unit.

Challenge procedure. The following volumes of cow milk were administered: day 1, 5, 10, 20, 30, and 60 ml at 30-minute intervals; day 2, 120 ml; day 3, 240 ml up to normal intake; day 4, normal milk intake.

Every effort was made to follow this schedule, but in some cases of suspected profound hypersensitivity, one drop was used as the first dose; if parents were reluctant to increase milk intake rapidly, a slower incremental dose was used. Seven children were given the normal volume of milk from the outset of the challenge.

The time of onset of reactions was taken from the time the milk challenge procedure commenced on day 1. Patients with an apparent immediate response following ingestion of large volumes of milk after day 1 were assigned reaction times according to the time of commencement of challenge from Day 1. Patients were examined at the time of any adverse reaction and at 1 week, and 1 month after commencement of milk ingestion in those who appeared to tolerate it. In an attempt to minimize the possibility that nonimmediate reactions were the result of intercurrent infection or accidental exposure to other

dietary or environmental allergens, in all children whose reactions were in doubt or whose symptoms developed more than 24 hours after commencing milk ingestion, adverse responses to milk challenge were demonstrated on two or more occasions before being regarded as positive.

The volume of milk administered up to the time of the specific reaction has been documented.

Hematologic studies. Studies were performed in 67 patients at the time of milk challenge. A routine hemoglobin and total white cell count was done on a Coulter counter (Coulter Electronics, Hialeah, Fla.). Eosinophil counts were performed on a peripheral blood film.

Immunologic studies. Serum immunoglobulins IgG, IgA, and IgM were measured using a AutoAnalyzer fluoronephelometer (Technicon Instruments Corp., Tarrytown, N.Y.). The results were expressed as percentile values for age.¹⁴ Total IgE were measured using Phadebas IgE PRIST kit (Pharmacia Diagnostics, Uppsala, Sweden). Milk-specific IgE antibodies were measured with the Phadebas RAST kit. The RAST scoring scale was used. Any RAST score $\geq 1+$ was regarded as positive for the purposes of this study.

Skin tests. Prick tests were done with a 23-gauge needle on the patient's back. The skin wheal diameter was measured at 15 to 20 minutes and compared with the size wheal elicited by histamine 1 mg/ml control. Any wheal diameter that exceeded that of the control and was more than one fourth the size of the histamine wheal was regarded as positive.¹⁵

Identification of clinical profiles by statistical methods. In an attempt to group patients with certain common features, 30 items of historical data and information relating to milk challenge were entered into a computer data base. The historical details included acute or chronic skin, gastrointestinal tract, respiratory, and behavioral disorders that may or may not have been related to milk ingestion. Data regarding the effect of milk challenge included the volume of milk ingested and the time of onset of symptoms provoked by this on the skin or gastrointestinal or respiratory tracts and behavioral changes. This information was recorded on data sheets and then entered into the data base.

To identify clinical recognizable groups of patients with cow milk allergy, clusters of patients were obtained using a K means algorithm.¹⁶ In the initial cluster analysis, symptoms at presentation and the nature of symptoms elicited by milk challenge were the variables used. This analysis revealed that patients appeared to cluster naturally into three groups: one with skin eruptions, another with gastrointestinal disturbance, and a third with both gastrointestinal and respiratory symptoms following milk challenge. These groupings, provided by the K means program, were

Table 1. Initial features in cow milk allergy

	Group 1 (n = 27)	Group 2 (n = 53)	Group 3 (n = 20)	P*		
				a	b	c
Median age (mo)	10 ^a	10 ^b	17 ^{ab}	0.015	0.002	
Urticaria, acute	20 ^{ab}	11 ^{ac}	0 ^{bc}	<0.001	<0.001	<0.001
Eczema, chronic	5	6 ^a	9 ^a	0.003		
Vomiting						
Episodic	10 ^a	27 ^b	2 ^{ab}	0.036	0.006	
Persistent	1	10	3			
Diarrhea						
Episodic	2 ^a	21 ^{ab}	3 ^b	0.002	0.04	
Persistent	9	17	9			
Wheeze, episodic	7 ^a	2 ^a	2	0.006		
Wheeze/bronchitis, persistent	6 ^a	7 ^b	11 ^{ab}	0.02	<0.001	
Weight <3rd centile	4 ^a	10	8 ^a	0.05		
Height <3rd centile	1	4	1			

Frequency of symptoms at presentation in groups 1, 2, and 3. Level of difference indicated if $P < 0.05$ by chi-square analysis and Fisher exact test. There was no significant difference in frequency between persistent vomiting, persistent diarrhea, or height <3rd centile at presentation between groups. Differences in age at presentation analyzed by Mann-Whitney U test and two-tailed test.

P values derived by comparing two values with same superscript letter (e.g., for episodic vomiting, group 1 is significantly different from group 3, $P = 0.036$; group 2 is also different from group 3, $P = 0.006$).

then further assessed with stepwise discriminant analysis from the Statistical Package for the Social Services, using the original variables. For 29 of the original 100 patients, one or more items of information were unavailable, so this analysis was confined to the remaining 71 patients for whom complete data were available. The 29 patients not able to be assessed by discriminant analysis were left in groups assigned them by the K means program.

Once patients were assigned to one of three groups by cluster analysis, chi-square analysis was used to compare differences in the frequency of various symptoms at presentation or elicited by formal milk challenge. The Mann-Whitney U test was used to compare differences in immunologic abnormalities between the separate patient groups. In this study, because of the large number of variables used, the P value was revised from 0.05 to 0.0017. We believe this to be rather stringent and thought that because these results are tentative a revised P of 0.01 could be more realistic.¹⁷ Thus the detailed results of statistical analysis have been included for the reader's own evaluation.

RESULTS

Identification of groups with cow milk allergy. By use of K means algorithm, patients were classified into three major groups on the basis of their symptoms at presentation and the effects of milk challenge: group 1, 27 patients with predominantly cutaneous reactions; group 2, 53 patients with predominantly gastrointestinal symptoms; group 3, 20 patients with predominantly gastrointestinal and respiratory symptoms, although some had eczematous eruptions.

The time of onset of symptoms after milk challenge was not included in the original assessment. It was noted, however, that these clusters appeared to be related to the time of onset of symptoms after milk challenge and to the nature of the symptoms elicited by that challenge. The following reaction times were noted within each group: group 1, patients responded within 45 minutes of challenge; group 2, 48 of 53 patients responded between 45 minutes and 20 hours after challenge, and five responded at 30 to 35 minutes; group 3, 17 of 20 patients had symptoms more than 24 hours after commencing milk, and three had symptoms 8, 12, and 16 hours, respectively, after the start of challenge.

Using the clinical groupings identified by the original cluster analysis and excluding time of reaction, it was found that 98% of the 71 children for whom complete clinical data were available for analysis were correctly classified by the discriminant analysis program. When time of onset of symptoms from challenge was added to the other variables again, 98% of the patients were correctly classified.

Clinical features of cow milk allergy

Historical. In Table 1 the features of symptoms at presentation in each of the groups are shown. The dominance of acute episodes or urticarial skin eruptions with eczema exacerbated by milk ingestion was noted in group 1, and contrasted with the high incidence of vomiting and diarrhea following milk ingestion in group 2. Chronic eczematous eruptions, chronic diarrhea, chronic bronchitis, and wheezing, often apparently unrelated to milk ingestion, were major features of group 3. Whereas acute skin eruptions were reported frequently in group 1, and

Table II. Effect of milk challenge in cow milk allergy

	Group 1	Group 2	Group 3	P		
				a	b	c
Patients	27	53	20			
Angioedema/urticaria	21 ^{ab}	6 ^a	2 ^b	<0.001	<0.001	
Eczema	3	2 ^a	7 ^b	0.001		
Morbilli	1	4	0			
Vomiting	9 ^{ab}	32 ^{ac}	0 ^{bc}	0.02	0.003	<.001
Diarrhea	4 ^{ab}	32 ^a	12 ^b	<0.001	0.001	
Colic/irritable	10	24	10			
Cough/wheeze	8 ^a	2 ^{ab}	10 ^b	0.002	<0.001	
Stridor	2	0	0			
Rhinitis	2	4	6			

Frequency of symptoms induced by formal milk challenge in groups 1, 2, and 3. Level of difference indicated if $P < 0.05$ by chi-square analysis and Fisher exact test. There was no significant difference in frequency of morbilliform eruptions, colic, stridor, or rhinitis between each of the groups.

P values derived by comparing two values with same superscript letter (e.g., for diarrhea, group 1 is significantly different from group 2, $P = <0.001$, and group 3, $P = 0.001$).

Table III. Immunoglobulins in cow milk allergy

	Group 1	Group 2	Group 3	P	
				a	b
IgG percentile	23	32	33		
IgA percentile	16	13 ^a	40 ^a	0.034	
IgM percentile	29 ^a	33 ^b	65 ^{ab}	0.019	0.019
IgE I-U/ml	77 ^a	12 ^{ab}	48 ^b	0.012	0.012

Median IgG, IgA, IgM percentiles and IgE (IU/ml) levels for groups 1, 2, and 3. Differences between each group indicated only where $P \leq 0.05$ using Mann Whitney U test and Fisher two-tailed test for significance.

P values derived by comparing two values with same superscript letter (e.g., for IgE levels, group 1 is significantly different from group 2, $P = 0.012$; group 2 is different from group 3, $P = 0.012$).

gastrointestinal complaints predominated in group 2, group 3 patients had a high incidence of multisystem symptoms of long duration.

In group 3 there were three patients with chronic eczema, recurrent bronchitis with cough and wheeze, and diarrhea; two with diarrhea and recurrent bronchitis; two with recurrent bronchitis and eczema; and two with chronic eczema and chronic diarrhea. The remaining 11 children in group 3 had symptoms confined to one system: five had chronic diarrhea, two had eczema, and four reported recurrent bronchitis and wheezing. Although failure to thrive, measured by weight less than the 3rd percentile, affected more than 20% of the whole population, this abnormality was most frequently seen in the group 3 patients.

Effects of milk challenge. In Table II the frequency of symptoms induced by formal milk challenge in each group is shown, together with the levels of difference in frequency of these symptoms between each patient group. In group 1 patients, acute urticaria and angioedema were the most striking features, although acute onset of coughing and vomiting was also seen. The predominance of vomiting or diarrhea within hours of commencing milk characterized

patients in group 2. The slow onset of eczema but not urticaria, diarrhea but not vomiting, and insidious onset of coughing and wheezing over more than 20 hours characterized group 3.

Although acute urticaria and angioedema characterized group 1 skin eruptions, eczema and morbilli developed in a few patients; vomiting and wheezing were significantly more frequent in this group than in group 2. Of the patients in group 2 with gastrointestinal symptoms, 16 had vomiting alone, 16 had diarrhea alone, and 16 patients had both diarrhea and vomiting after milk challenge. The cluster analysis placed 12 patients with skin eruptions in group 2; four of these developed morbilliform eruptions several hours after commencement of milk.

In group 3, nine of the 20 patients had symptoms that affected two or more of the gastrointestinal, respiratory, and skin systems. In particular, eczematous skin lesions but not urticaria developed after milk ingestion in group 3 patients. The milk challenge precipitated cough with wheezing and diarrhea in four patients, eczema and diarrhea in three, and eczema with cough and wheeze in two. Of the remaining patients in group 3, diarrhea developed in five, eczema in two, and coughing and

Table IV. Milk specific antibodies in cow milk allergy

	Group 1	Group 2	Group 3	P	
				a	b
Rast ≥ 1	18/26 ^{ab}	19/52 ^a	4/19 ^b	0.006	0.002
Prick test ≥ 1	16/18 ^{ab}	7/26 ^a	1/7 ^b	<0.001	0.001

Frequency of RAST ≥ 1 and skin prick test ≥ 1 in group 1, 2, and 3 patients. Difference in frequencies between each group is indicated where $P < 0.05$ by chi-square analysis and Fisher exact test.

P values derived by comparing two values with same superscript letter (e.g., for RAST ≥ 1 , group 1 is significantly different from group 2, $P = 0.006$, and group 3, $P = 0.002$).

wheezing in four. In all but three patients, these symptoms developed more than 24 hours after commencing substantial volumes of milk. There was a good agreement between the historical information for these children and the effects of a formal milk challenge in the controlled hospital situation with regard to the symptoms elicited by challenge and the rate at which these symptoms evolved. In particular, all patients in group 3 demonstrated one or more of these initial symptoms on repeated milk challenge.

Immunologic data. In Table III various immunologic data are recorded. For the entire population, the median percentile for IgG was 23, for IgA 17, and for IgM 37 IU/ml. The median total IgE was 26 IU/ml. The IgA percentile values were significantly lower in group 2 patients, and IgM levels significantly elevated in Group 3 patients. Although total IgE levels were higher for patients in group 1 than in groups 2 and 3, the comparison is only valid between groups 1 and 2, because these children were of comparable age. No percentile IgE values are available for Australian children, so levels in excess of 100 IU/ml were arbitrarily assigned as abnormal. Levels in excess of 100 IU/ml were seen more frequently in group 1 immediate-reacting and group 3 late-reacting patients with skin manifestations of cow milk allergy. Nine children in group 2 with gastrointestinal reactions to milk without skin eruptions and without respiratory disease had elevated total IgE levels.

Elevated serum anti-milk IgE antibody levels and positive skin test reactions were significantly more frequent in patients in group 1 than in groups 2 and 3 (Table IV). However, in the predominantly gastrointestinal-reacting group 2 patients, in nine of the 52 serum samples tested, and for seven of 26 skin tests, evidence of reaginic antibodies to milk was found in patients without skin manifestations of cow milk allergy. Positive RAST and skin test reactions in group 3 patients were confined to those who had eczematous eruptions.

Although elevated serum IgE antibodies to milk and positive skin test reactions were seen in seven of eight children in group 1 with a respiratory response to milk

challenge, only two of 10 patients in group 3 with a respiratory response to milk ingestion showed these abnormalities; that is, eight of 10 of the respiratory responders in group 3 had no features of atopy in that they had negative RAST and skin test reactions and no evidence of cutaneous reactions to cow milk. These eight patients had wheezing and coughing, or wheeze with cough and diarrhea following milk challenge.

Age at diagnosis. The median age at the time of diagnosis in group 1 and group 2 patients was 10 months, and in group 3 was 17 months. Group 3 patients were significantly older than the patients in groups 1 and 2 (Table I).

Hematologic results. Only one child had iron deficiency anaemia. Ten patients had eosinophil counts of more than 6% at the time of milk challenge during a milk-free diet. There was no significant difference in the incidence of elevated eosinophil counts in the three patient groups.

DISCUSSION

In our study, statistical methods, based on the effect of a standardized milk challenge procedure, identified three groups of children with cow milk allergy who have separate clinical and immunologic features. The first group, an IgE-sensitized atopic population, corresponds to the immediate reactors of other investigations.⁹ Our group 2 patients with gastrointestinal disease correspond with the so-called late reactors and have cow milk protein enteropathy.¹⁸ Analysis identified a third group of patients, the majority of whom took more than 24 hours to respond to milk ingestion. We are aware of only one other study that has identified this third subpopulation.¹⁹ The heterogeneous symptoms and immunologic findings within this group suggest that it may contain subgroups of patients. The patients within group 3 were difficult to identify initially because their symptoms were chronic, affected the skin or respiratory and gastrointestinal tracts, and often appeared unrelated to milk ingestion. Other investigators may not have recognized this group because they restricted the diagnosis of cow milk allergy to reactions occurring up to

24 or 48 hours after commencement of milk ingestion, and the volumes of milk used in their challenge procedures were well below those normally ingested. Our investigations placed no such restrictions on making the diagnosis of cow milk allergy, but the protocol of challenge, which required increasing volumes of milk to be ingested over a certain period, inevitably extended the apparent period between the commencement of milk ingestion and the identification of an adverse reaction.

Two separate atopic populations of patients with exacerbations of eczema after milk ingestion were identified. Eczematous lesions in group 1 patients developed within 45 minutes of milk ingestion, and were usually preceded or accompanied by other skin eruptions, including urticaria, violent flushing, and in one patient, a morbilliform eruption. These skin lesions elicited intense pruritus and scratching, leading to skin abrasions and eczema. The eczematous patients in group 1 appear similar to those described by Sampson et al.,²⁰ who demonstrated increased serum histamine concentrations at the time these skin eruptions occurred. By contrast, the eczema in group 3 patients developed over several days without any apparent preceding urticaria, flushing, or morbilliform eruptions. The finding of high IgE antibodies to cow milk in both the group 1 and group 3 eczematous reactions resolves other apparently conflicting data; Danneus and Johansson⁹ found IgE hypersensitivity to cow milk confined to patients with immediate skin reactions following milk ingestion, whereas Fällström et al.¹¹ found elevated IgE antibodies to cow milk in patients with slow onset of reactions. Our findings suggest they were simply studying different aspects of the spectrum of cow milk allergy.

Although vomiting and diarrhea were the major manifestations of cow milk allergy in group 2 patients, some in group 1 had these symptoms after milk ingestion, but this was part of an anaphylactic response. The children in group 2 correspond to those described by others as having cow milk protein enteropathy; our earlier studies demonstrated mucosal damage in some of them following a positive milk challenge.¹⁰ Miniford et al.²¹ have suggested that such patients do not develop IgE antibodies to cow milk, but 10 of our patients tested in group 2 with gastrointestinal manifestations of cow milk allergy without skin or respiratory involvement did have these antibodies. It is possible that children with gastrointestinal cow milk allergy do have mucosal IgE hypersensitivity to cow milk, but that overflow from the gastrointestinal tract to systemic sites occurs in only some of them. Small bowel mucosal IgE sensitization does occur in some forms of gastrointestinal milk hypersensitivity.²² Studies of other tissues have demonstrated that mucosal IgE hypersensitivity can develop without evidence of systemic IgE hypersensitivity.²³

In a third of the patients respiratory symptoms were attributed to cow milk allergy, but in only two thirds of these could it be demonstrated at challenge. Acute onset of wheezing, stridor, and skin eruptions was common in group 1 patients and was associated with IgE hypersensitivity. Although in some children in group 3 with eczema mild asthma developed during milk ingestion, a striking feature in group 3 patients was the history of chronic respiratory disease, often associated with chronic diarrhea and failure to thrive. Clinical findings resemble those in patients with cystic fibrosis, recurrent aspiration syndrome, or immunodeficiency. These patients are separate from the group of children with Heiner syndrome³ and are similar to those described by Kuitunen.¹⁹ They did not have elevated levels of IgE antibodies to cow milk, nor positive skin tests.

A third of all infants in our study had IgA levels below the 5th percentile, but IgG and IgM percentile values were also low. Furthermore, IgA deficiency was not confined to the atopic group 1 population but also occurred in the group 2 nonatopic patients. Although the role of IgA deficiency in relation to mucosal handling of dietary antigens has received considerable attention in the past,²⁴ our results highlight a relative immunodeficiency of IgG, IgA, and IgM classes in patients allergic to milk. Thus any defect in handling of dietary antigen in cow milk allergy need not be confined to the mucosal level in these patients, but may also occur at a systemic level through IgG-, IgM-, and IgA-dependent mechanisms.

Further refinement of skin testing or measurement of IgE antibodies to cow milk may improve the diagnostic value of these relatively simple tests in accurately identifying one subgroup of patients with cow milk allergy. However, for the present, the diagnosis of cow milk allergy will rely on demonstration of a reproducible adverse response to formal milk challenge after exclusion of other nonimmune forms of milk intolerance. It is unlikely that a single laboratory test will identify all patients with cow milk allergy.

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