

Natural history of cow milk allergy: Clinical outcome

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Of an initial cohort of 100 children with challenge-proven cow milk allergy, 97 were reviewed after 5 years to determine the effect of prolonged cow milk avoidance on clinical features, the reported frequency of adverse reactions to other foods, and the reported emergence of other atopic disorders. The mean age at diagnosis was 16 months, and at final follow-up 99 months. Cow milk tolerance by challenge was demonstrated in 28% of patients by 2 years of age, 56% by 4 years, and 78% by 6 years. Only 25% of children were allergic to cow milk alone; parents reported associated adverse reactions to many other foods, including egg (58%), soy milk (47%), and peanut (34%). Exclusion of cow milk from the diet of infants and young children with cow milk allergy did not prevent the subsequent development of atopic disorders. At final follow-up, 40% of patients reportedly had asthma, 21% atopic eczema, and 43% allergic rhinitis. It is unclear whether independent mechanisms control the development of cow milk allergy and other atopic conditions. (J PEDIATR 1990;116:862-7)

Cow milk allergy affects between 2% and 7.5% of infants.¹⁻³ Our previous studies described the clinical and immunologic features of CMA in infants and young children.⁴ From the first 100 patients with challenge-proven CMA, three clusters of patients were identified. In group 1, the immediate reactors, anaphylaxis or exacerbations of eczema or urticaria, or a combination of these, developed within 45 minutes of the ingestion of small volumes of cow milk. In group 2, the intermediate reactors, symptoms of vomiting or diarrhea, or both, developed within several hours of the ingestion of larger volumes of cow milk. In group 3, the late reactors, eczema, bronchitis, or diarrhea, or a combination, developed after the ingestion of normal volumes of cow milk for 24 to 72 hours.⁵

Compared with a control population, all patient groups had low total serum concentrations of IgG and IgA, but only group 1 patients had elevated levels of IgE.⁴ The IgA and

IgM anti-cow-milk-specific antibody levels were similar to those in a control population, but all patient groups had low IgG anti-cow-milk antibodies, a phenomenon we attributed to the exclusion of cow milk from their diet. The IgE anti-cow-milk antibody levels were increased in the immediately reacting group 1 patients only.⁶ The production of leukocyte-migration inhibition factor was measured as a marker of in vitro delayed-type hypersensitivity. The lymphocytes of patients from groups 2 and 3 produced more of this fac-

CMA	Cow milk allergy
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tor in response to α -lactalbumin, β -lactoglobulin, and α -casein than did the lymphocytes from the group 1 patients.⁷

In this longitudinal study of our initial cohort of 100 patients with challenge-proven CMA, we (1) examined the effect of prolonged cow milk avoidance on clinical features, (2) documented the reported frequency of adverse reactions to other foods, and (3) recorded the reported emergence of other atopic disorders.

METHODS

Patients. Thirty-four girls and 63 boys were reviewed after an average period of 5 years; three children could not be located. From the time of diagnosis, patients had been ad-

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vised to avoid all cow milk-containing foods until clinical tolerance had been demonstrated by formal challenge. The mean age of children at initial challenge was 16 months (1 to 98 months) and at the final challenge was 60 months (11 to 135 months). The mean age of all the patients at the final review was 99 months.

Conduct of study. After the diagnosis of CMA by challenge, all patients remained under the care of the chief investigator (D.J.H.), who reviewed them every 4 to 6 weeks until a stable diet was achieved, and then every 3 to 6 months. Formal milk challenges were conducted in the allergy unit at yearly intervals until tolerance was demonstrated. If milk tolerance developed, patients continued to be assessed by the chief investigator at 3- to 6-month intervals if they had evidence of adverse reactions to other foods or if other atopic diseases developed. Patients who demonstrated milk tolerance on challenge and were tolerant to all foods tested, and who had no atopic diseases, were discharged to the care of their family practitioner.

At the time of this study, 5 years after the commencement of the investigation, 30 of the original cohort of 100 CMA patients remained under the care of the chief investigator. At the 5-year follow-up, the parents of 97 of the initial cohort of 100 patients were interviewed by one of us (J.M.B.). At this interview the following were documented: (1) the volume of dairy products ingested daily, (2) the incidence and nature of adverse reactions to other foods, (3) the presence or absence of atopic diseases such as eczema, asthma, rhinitis, and urticaria, and (4) the results of the most recent formal cow milk challenge conducted in the allergy unit. This and other information were recorded on a standardized questionnaire and entered into a computer data base. Patients who had CMA at challenge, within 12 months of the current study, were regarded as still having the disease at the time these data were collected.

Definitions. For the purposes of this study, the following working definitions were adopted:

cow milk allergy a reproducible adverse reaction to formal milk challenge, attributed to an immunologic hypersensitivity to cow milk protein.

cow milk tolerance ingestion of >300 ml of cow milk per day (or equivalent dairy products) without adverse reaction for the 4 weeks after formal challenge.

persistent CMA reproducible adverse reaction to formal cow milk challenge conducted in this allergy unit. Patients who had been challenged in the allergy unit and responded with symptoms of CMA within 12 months of this study were regarded as still having CMA at the time of interview.

remission of CMA remission said to have occurred when children ingested normal volumes of cow milk for 4 weeks after completing a formal cow milk challenge at the unit, with confirmation at their 4-week follow-up in the allergy unit.

adverse reactions to non cow-milk foods an adverse clinical reaction reported by parents and requiring the chief investigator to exclude that food from the diet. Exclusion of the food occurred if symptoms developed after ingestion of food administered by parents at home (1) within 1 hour on one occasion or (2) after more than 1 hour on two occasions or more.

allergic rhinitis more than five episodes per annum of blocked nose, snoring, chronic mouth breathing, or nasal itching, or a combination of these, requiring treatment with antihistamines or topical nasal steroids, or both.

asthma variable cough, wheeze, and shortness of breath requiring and responding to 3 to 5 days of treatment with bronchodilators for more than five episodes per year.

urticaria recurrent wheal-and-flare skin eruptions.

eczema chronic and recurrent pruritic skin eruptions requiring topical steroids for control, with episodes lasting more than 5 days for more than five episodes per year.

Milk challenge procedure. The diagnosis of CMA was determined by cow milk challenge according to a previously published protocol.⁴ This protocol required patients to be free of milk allergy-related symptoms when on a milk-free diet, exclusion of disaccharidase deficiency as a cause of milk intolerance, and the demonstration of an unequivocal relapse of symptoms after milk challenge. The milk challenge was not placebo controlled. It was conducted in a hospital setting during days 1, 2, and 3. Subsequent milk ingestion was continued at home.

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 given as a single morning dose

Day 3: 240 ml as a single morning dose

Day 4: a normal intake (>300 ml per day)

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

The time of onset of reactions was taken from the time the milk challenge commenced on day 1. Patients whose responses developed after ingestion of large volumes of milk after day 1 were assigned reaction times according to the time of commencement of challenge.

Patients were examined at the time of any adverse reaction, at 1 week, and again 1 month after the start of milk ingestion by those who appeared tolerant. To minimize the possibility that nonimmediate reactions were the result of intercurrent infection or accidental exposure to other dietary or environmental allergens, we required that all children whose reactions were in doubt, or whose symptoms developed more than 24 hours after the start of milk ingestion, demonstrate adverse reactions to milk challenge on

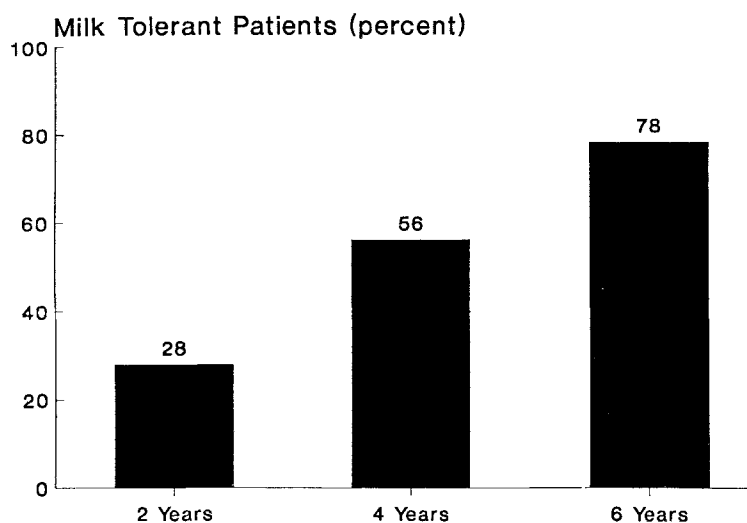


Figure. Percentage of 97 patients with proven cow milk allergy who acquired clinical tolerance to milk challenge at ages indicated.

Table I. Percentage of children with CMA with an adverse reaction to individual foods

Food	Children with CMA	
	No. who reacted/ No. exposed	%
Egg	56/97	58.0
Wheat	16/97	16.0
Soy milk	37/78	47.0
Casein hydrolysate	13/58	22.0
Banana	17/93	18.0
Apple	5/97	5.0
Pear	8/96	8.0
Orange	33/93	35.0
Strawberry	10/90	11.0
Tomato	11/90	12.0
Fish	12/95	13.0
Peanut	34/97	34.0
Lamb	7/97	7.0
Beef	14/96	14.5
Chicken	9/96	9.0

two or more occasions before being regarded as allergic.

Identification of clinical profiles in CMA. The three clusters of patients with CMA previously identified⁴ were, for the purposes of analysis, retained in their original groupings, which were defined on clinical grounds. In summary, certain historical information and the effect of formal cow milk challenge conducted in the allergy unit were noted and then entered into a computer data base, and the three groups of patients with common features were identified by means of a K-means algorithm.⁴ Once a patient was assigned to group 1, 2, or 3 at the outset, he or she remained in that group throughout this longitudinal study.

Identification of adverse reactions to non-cow-milk foods.

The diagnosis of adverse reactions to non-cow-milk foods was based on symptoms reported by parents to the chief investigator during follow-up assessments. These assessments were initially conducted every 4 to 6 weeks while new foods were being introduced but were conducted every 3 to 6 months once a stable diet was achieved. An adverse reaction to a non-cow-milk food was said to have occurred when the chief investigator excluded that food from the child's diet because the parents reported an adverse reaction after the introduction of an individual food in a home challenge. The diagnosis of an adverse reaction to a non-cow-milk food was made by the chief investigator if (1) one unequivocal reaction reportedly developed within 1 hour of ingestion or (2) two or more reactions developed more than 1 hour after ingestion of the food.

Identification of atopic diseases. The diagnosis of atopic diseases was based on the assessment conducted during the follow-up by the chief investigator and was confirmed by the assessor at the time of final data collection. When an atopic disease developed after discharge from the allergy unit, diagnosis was based on information provided by the parents in accordance with the strict criteria defined above.

Analysis of data. Comparison between groups of patients was made with the use of appropriate nonparametric statistical methods.

RESULTS

In the Figure, the numbers of CMA patients tolerant at 2, 4, and 6 years of age are shown. Of the 19 children with persistent CMA at the completion of the study, six were girls and 13 boys; 11 of these patients were younger than 6 years of age, 6 were aged 6 to 8 years, and 2 were older than

Table II. Comparison of reported incidence of common adverse reactions to foods in CMA children from group 1, 2, or 3

	Group 1 (n = 27)		Group 2 (n = 52)		Group 3 (n = 18)	
	No.*	%	No.*	%	No.*	%
CMA alone	2/27	7	19/52	36	4/18	22
Egg	23/27	85	21/52	40	12/18	67
Soy milk	12/25	48	17/46	37	8/15	53
Orange	13/26	50	14/50	28	7/18	39
Wheat	4/27	15	9/52	17	3/18	17
Fish	7/27	26	5/50	10	1/18	6
Peanut	11/24	46	10/47	21	6/16	38

*Total number of children reacting to each food compared with total number exposed to food.

Table III. Reported incidence of atopic diseases in children with persisting CMA (intolerant) or remission of CMA (tolerant) at final follow-up

	Group 1*		Group 2†		Group 3‡	
	Intolerant (n = 9)	Tolerant (n = 18)	Intolerant (n = 7)	Tolerant (n = 45)	Intolerant (n = 3)	Tolerant (n = 15)
Asthma	9	5	4	17	3	3
Eczema	5	4	1	7	2	2
Urticaria	3	0	0	3	1	1
Rhinitis	8	8	2	18	2	4

*Immediate reactors.

†Intermediate reactors.

‡Late reactors.

8 years. Of the 27 patients in group 1, nine had persistent CMA (33%); of 52 in group 2, seven had persistent CMA (13%); and of 18 patients in group 3, three had persistent CMA (17%). The incidence of persistent CMA was significantly greater in group 1 compared with group 2 ($p = 0.04$, chi-square test). There was no difference in the incidence of remission between the other group comparisons. The mean age of the 19 patients with persistent CMA at follow-up was 91 months (66 to 129 months), whereas the 78 children who became milk tolerant became so at a mean age of 46 months (11 to 144 months).

Adverse reactions to non-cow-milk foods in children with CMA. Only 25 children were reported to be allergic to cow milk alone. A high incidence of soy milk intolerance and peanut allergy was noted. However, of the 34 children said to have peanut allergy, 19 were clinically tolerant to soy milk (Table I).

More patients in group 1 were reported to have adverse reactions to egg, orange, and peanut than in group 2 (chi-square test: $p < 0.05$). More children in group 3 had egg allergy than in group 2 (chi-square test: $p < 0.05$), but no other difference in the incidence of other food allergies was reported (Table II).

Fifty-six patients were reported to have symptoms of egg allergy. Symptoms developed within 1 hour in 45 patients, and included urticaria and angioedema (45 cases), vomiting and diarrhea (7 cases), and stridor (2 cases); 11 reported symptoms including diarrhea (6 cases), vomiting (3 cases), and eczema (4 cases) more than 1 hour but within 24 hours after egg ingestion.

Thirty-seven children were reported to have adverse reactions to soy milk. Of 13 children who reacted within 1 hour of soy milk ingestion, symptoms of urticaria (3 cases), vomiting (8 cases), diarrhea (4 cases), eczema and morbiliform rash (1 case), and wheeze and collapse (1 case) were observed; 24 parents reported symptoms that developed over several hours, including diarrhea (18 cases), vomiting (5 cases), eczema (5 cases), and irritability, cough, and wheeze (1 case each).

Sixteen patients were reported to have adverse reactions to wheat. In five children, symptoms of urticaria (2 cases), diarrhea (3 cases), vomiting (2 cases), and rhinitis (1 case) developed within 1 hour of wheat ingestion; 11 children were reported to have symptoms, including diarrhea (8 cases), eczema (2 cases), vomiting (2 cases), and rhinorrhea, cough, and wheeze (1 case each), several hours after inges-

tion of wheat products. Four children with wheat-induced diarrhea had normal duodenal biopsy specimens while ingesting wheat products.

Casein hydrolysate was excluded from the diet of 13 children because of reported adverse reactions. In 4 children, reactions were reported within 1 hour of ingestion; symptoms of urticaria (2 cases), colic, distress, and diarrhea (1 case), and vomiting (1 case) were noted. Nine children were reported to have symptoms, including diarrhea (8 cases), vomiting (3 cases), face erythema and eczema (1 case), and irritability (2 cases), within hours of ingestion. One of the patients with adverse reactions to casein hydrolysate tolerated soy milk satisfactorily.

Atopic diseases associated with cow milk allergy (Table III). When the results were analyzed according to whether patients were milk tolerant at final follow-up, higher incidences (chi-square analysis or Fisher Exact Test as appropriate) of asthma ($p < 0.001$), eczema ($p = 0.023$), and urticaria ($p = 0.045$) were seen in patients with persisting CMA.

Milk intake of cow milk-tolerant patients. Nearly 20% of the patients who achieved tolerance to cow milk on challenge were ingesting less than 100 ml of cow milk per day, and only a third of the tolerant patients were ingesting more than 300 ml of cow milk per day.

DISCUSSION

The results of this study show that CMA is not a transient disorder. Less than half of our patients were tolerant to challenge by the age of 2 years, 60% by 4 years, and 80% by 6 years. Two thirds of the patients tolerant to cow milk at challenge were ingesting low volumes (<300 ml/day) at final follow-up. We are unable to say whether this limited milk intake reflects persistent low-grade CMA or simple aversion to cow milk as a result of prolonged avoidance and parental concern and contagious anxiety. Recently Bock,³ reported a prospective study of adverse reactions to foods in the first 3 years of life in 501 consecutively born children. Twenty-five children had CMA and all tolerated cow milk by the age of 3 years. However, his findings are not strictly comparable because it is unclear how many of Bock's patients had true CMA and not lactose intolerance. Moreover, our patients were not drawn from a random sample but were referred for management and probably represent the more severe forms of CMA.

The high incidence of adverse reactions to other foods in our patients with IgE immediate-type hypersensitivity reactions to cow milk is consistent with the findings of Sampson and McCaskill.⁸ However, a significant number of our non-IgE-associated CMA patients were reported to have immediate hypersensitivity reactions to other foods. In addition, our patients had a higher frequency of adverse

reactions to foods such as soy milk, wheat, and casein hydrolysate than has been reported in other studies. A similar spectrum of symptoms noted after cow milk ingestion in our CMA patients was reported by parents whose children reacted to these three foods.

In nearly half of our patients, intolerance to soy milk was reported to have developed. In the early phase of this investigation, most soy milk formulas contained sucrose. We documented a high incidence of abnormal sucrase/isomaltase ratios in duodenal biopsy specimens from CMA patients, suggesting intolerance to sucrose.⁹ For the past 5 years, non-sucrose-containing soy preparations have been used, so soy-milk-induced diarrhea in this latter period is likely to be due to true soy protein intolerance. For the wheat-allergic children, the rate of development of symptoms within an hour or days of ingestion of wheat, and the finding of normal duodenal biopsy specimens at the time of adverse reactions to wheat, make it unlikely that these children have celiac disease.

Ingestion of casein hydrolysate preparations as a substitute for cow milk reportedly led to the development of symptoms in 13 children. Recent studies have identified peptides of casein hydrolysate that can elicit an IgE response in animals, supporting the potential immunogenicity of these preparations.^{10,11} Bock¹² reported an infant with an IgE-associated hypersensitivity reaction to casein hydrolysate confirmed by double-blind challenge. Although our patients showed clinical features of hypersensitivity reactions to casein hydrolysate, the possibility that the high osmolarity of casein hydrolysate formulas induced diarrhea in some of our young children with CMA cannot be excluded. Because most of the patients with adverse reactions to non-cow-milk foods were not challenged in the allergy unit, and because we relied on parental observation and assessment of those reports by the chief investigator in an outpatient setting, these results should be interpreted cautiously. However, they suggest that if children with suspected CMA do not respond to exclusion of cow milk from their diet, the possibility should be considered that they are reacting adversely to other food proteins.

A high percentage of our patients reported adverse reactions to fruits and vegetables. Bock³ reported similar findings in young children. Recently, Ortolani et al.¹³ described a high incidence of adverse reactions to fruits and vegetables in adults with the oral allergy syndrome (i.e., perioral urticaria and angioedema after the ingestion of foods to which they are intolerant). In our study the features of the syndrome of oral allergy to various fruits and vegetables were not confined to our group 1, immediate-reacting patients.

Our findings do not support the commonly held view that adverse reactions to foods occur within related food groups.

For example, most of our patients with CMA were beef tolerant, most with egg allergy were chicken tolerant, and most said to have peanut allergy were tolerant to soy milk. The latter findings are contrasted with the findings of Barnett et al.,¹⁴ who found immunologic cross-reactivity among the legumes—soy, peanut, chick-pea, and garden pea.

A high incidence of atopic diseases, particularly in those children with persistent CMA, was noted at final follow-up.¹⁵ Many children became milk tolerant but subsequently had other atopic diseases. These findings do not support a widely held belief that exclusion of cow milk from the diet of CMA patients will protect them from the subsequent development of atopic disorders. Furthermore, atopic diseases reportedly developed in patients irrespective of whether they initially showed an immediate-type hypersensitivity reaction to cow milk. Thus factors that control the development of atopic diseases may be independent from those which control the initial immune response to cow milk protein in patients with CMA.

There are four major conclusions from this study: (1) CMA is not a transient disease; (2) reported adverse reactions to other foods are frequent; (3) it is common for patients with CMA to acquire other atopic disorders; and (4) those patients who do acquire atopic disease do not always have the IgE type of hypersensitivity to cow milk at the outset. From these observations, it is unclear whether independent mechanisms control the development of CMA and atopy.

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