

Immunoglobulin E to cow's-milk protein in breast-fed atopic children

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Over a 3-yr period, 18 children, ages 10 mo to 5 yr, were discovered to have IgE to cow's-milk protein (CMP). They were compared with 18 age-matched patients for having been primarily breast fed during the first 6 mo of life. All were new allergy clinic asthmatic patients with a strong family history of atopy and evidence of IgE to multiple allergens. Analysis of the data on this allergic population revealed that both a history of breast feeding and of milk-induced immediate reaction in patients with CMP-specific IgE was significantly higher ($p < 0.03$) than in those patients without IgE to CMP. Inadvertent sensitization to food antigens can occur in some atopic breast-fed infants.

It has been suggested that breast feeding of infants decreases the incidence or delays the onset of atopic disease.¹⁻⁴ The suggested mechanisms of this beneficial effect of breast feeding include the action of protective antibodies in mother's milk and the avoidance of potential allergen, cow's milk, which might trigger the expression of the atopic state.

Various clinical studies indicate a trend toward less severe manifestations of allergy, and perhaps a decreased incidence of expression of the atopic state, in those infants not fed cow's milk.^{5, 6} Food allergy is more commonly implicated in infants and young children than in older individuals,^{2, 7} and IgE to food allergens often precedes IgE to inhalants in infants.⁸ This indicates that food allergens have a special importance for infants.

Many of the studies on the relation of breast feeding to the development of allergy are now several years old and were performed at a time when infants in this country were almost exclusively bottle fed. In addition, many of the problems seen in these bottle-fed infants, such as diarrheal disease, frequent colds and bronchitis, and various rashes, may not be etiologically related to the IgE response. Now that large

numbers of women are breast feeding their infants again and our tools for diagnosing IgE-mediated responses have improved, it is time to objectively reexamine the development of food allergy in infants.

Although breast-fed babies undoubtedly gain many benefits, they are unavoidably exposed to food antigens long before these are intended for their diets. The following study indicates that this type of exposure may actually predispose breast-fed atopics to develop IgE to cow's-milk protein and to other foods.

SUBJECTS AND METHODS

Over a 3-yr period (September, 1973, to September, 1976), 18 patients between the ages of 10 mo and 5 yr receiving initial consultation in our allergy clinic were discovered to have IgE to CMP. They were compared with 18 age-matched patients having no IgE to CMP for method of feeding during infancy, history of immediate reaction to cow's milk, and IgE to other common food allergens. All 36 patients in the study group were new allergy clinic patients with a diagnosis of bronchial asthma, a strong family history of atopy, and evidence of IgE to multiple common inhalant allergens. All of the mothers of breast-feeding infants were on unrestricted diets. When a patient with IgE to CMP was identified, the next new patient with the same year of birth, fulfilling all of the above criteria but who did not have IgE to CMP, was assigned to the control group. The classification of feeding was done prospectively at the time of the initial consultation.

Definition of clinical immediate hypersensitivity to cow's milk

Only reactions of urticaria, wheezing, or severe diarrhea, cramping, or vomiting that occurred within 40 min after ingestion of cow's milk were considered evidence of clinical

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Presented at the American Congress of Allergy and Immunology, March 28-31, 1977, New York, N. Y.

Received for publication October 30, 1978.

Accepted for publication March 13, 1979.

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cal immediate hypersensitivity. This information was obtained by clinical history, except for 2 cases in which the patients were seen for treatment shortly after milk ingestion. In one case, because the history was not confirmed by serologic or prick test, the patient was challenged by touching cow's milk to the lips in a double-blind fashion. Symptoms of isolated nasal congestion, delayed wheezing, eczematous rash, or other complaints were not considered in this study.

Except for the case described, the patients were not re-challenged with cow's milk. In contrast to other studies in which reported adverse reactions to foods were largely delayed, subtle, or atypical, the reactions to cow's milk in this study had been clear-cut, immediate, and of the classic IgE-mediated type. Most important, the patients had frequently become quite ill as a result of cow's-milk ingestion, and it would have been inappropriate to rechallenge these young patients for the sake of the study.

Evidence of allergen-specific IgE

A 3+ or 4+ prick test (convincingly positive) with commercial extracts (Hollister-Stier Labs., Livermore, Calif.) of food antigens to 1/50 w/v (cow's-milk casein, cow's-milk whey, egg white, soybean, peanuts, wheat, corn, rice, and oats), and/or positive radioallergosorbent test (RAST)* of 1+ or greater on the serum reaction (α -lactalbumin, casein, egg white, egg albumin, soybean, peanuts, wheat, corn, rice, and oats) were considered evidence of allergen-specific IgE. A serum specimen was scored as 1+ or greater if there was at least a twofold binding of ^{125}I -labeled horse antihuman IgE over nonspecific or background control. The background was obtained from the uptake of radioactive material by pooled cord serum. The α -lactalbumin and β -lactoglobulin were purchased from Sigma Chemical Company (St. Louis, Mo.). The other antigens were crude commercial extracts purchased from Hollister-Stier Labs.

Classification of feeding in infancy

Based on information derived from the parents at the time of initial consultation, each patient was classified as having been breast fed, soy-formula fed, or fed with cow's-milk formula.

The patient was considered primarily breast fed within the first 6 mo of life if given breast milk as the major source of nutrition until 4 mo, not completely weaned until 6 mo, and not given cow's-milk supplement or milk products on a regular basis.

If the patient received cow's milk regularly in the first 2 wk of life, he was placed in the cow's-milk-fed category, regardless of any subsequent change to soy formula. All infant formulas derived from cow's milk, evaporated milk, and regular homogenized milk were categorized together. No patient in the study had been fed a hydrolyzed, purified casein formula.

*RAST performed by Dr. Donald Hoffman,⁹ Department of Pathology, East Carolina University School of Medicine, Greenville, N. C.

TABLE I. Patients with IgE to CMP

Type feeding	Number of patients	Clinical history of reaction	IgE to eggs	IgE to other foods*
Breast fed	14	13†	10	7
Cow's milk	2	1‡	2	2
Soy formula	2	1†	1	0
Total	18	15	13	7

*Excluding eggs and CMP.

†One additional patient had not ingested milk by history.

‡Other patient was drinking milk at time of consultation.

TABLE II. Patients without IgE to CMP

Type feeding	Number of patients	Clinical history of reaction	IgE to eggs	IgE to other foods*
Breast fed	8	1	1	1
Cow's milk	9	0	1	4
Soy formula	1	0	1	0
Total	18	1	3	5

*Excluding eggs and CMP.

Statistical analysis

The p values were calculated using the Pearson, chi-square method (one degree of freedom) with 2×2 table. This treatment was used to make an effective comparison of proportions in two independent sets of data.

RESULTS

Among the 18 patients with IgE to CMP, 14 were breast fed, 2 received cow's-milk formula, and 2 received soy formula (Table I). In the 18 control patients without IgE to CMP, 8 were breast fed, 9 received cow's-milk formula, and 1 was soy-formula fed (Table II).

Thirteen of 14 patients with IgE to CMP who were breast fed had immediate clinical reactions to milk; 11 reacted with urticaria and/or wheezing, and 2 reacted with severe abdominal pain, diarrhea, or vomiting (Table III). One patient with IgE to CMP was still being breast fed and by history had not received pure cow's milk. One of the 13 patients in this study with intractable asthma and severe IgE-mediated milk allergy showed dramatic improvement in bronchial symptoms after the mother stopped using powdered milk for other family members.

Of the 2 soy-formula-fed patients with IgE to CMP, 1 had developed urticaria and wheezing from ingestion of cow's milk and the other allegedly had not received pure cow's milk.

Of the 2 patients with IgE to CMP who were fed

TABLE III. Patients with immunologic and/or clinical immediate hypersensitivity to CMP

Patient	Age of consultation	Age sensitivity discovered	RAST	Prick test	Feeding	Clinical reaction	No. challenges*	Positive RAST/prick to other foods
1	10 mo	4½ mo	+	+	breast	urticaria/angioedema	2	Yes
2	10 mo	8 mo	+	ND	breast	urticaria/angioedema	1	Yes
3	3 yr	8 mo	ND	+	breast	urticaria/angioedema	3	Yes
4†	11 mo	11 mo	+	ND	breast	wheezing/urticaria	1	No
5	21 mo	7 mo	+	ND	breast	wheezing/urticaria	2	Yes
6	22 mo	9½ mo	+	ND	breast	wheezing/urticaria	3	Yes
7†	10 mo	10 mo	ND	+	breast	wheezing/urticaria	1	Yes
8	13 mo	9 mo	+	ND	breast	urticaria	1	Yes
9	20 mo	8 mo	+	ND	breast	wheezing/urticaria	2	Yes
10	15 mo	5 mo	+	ND	breast	wheezing/urticaria	3	Yes
11	2½ yr	7 mo	ND	+	breast	urticaria/diffuse erythema	3	No
12	16 mo	10 mo	+	+	breast	abdominal pain, vomiting	2	No
13	3 yr	8 mo	+	ND	breast	abdominal pain, vomiting, diarrhea	2	Yes
14	12 mo	‡	+	+	breast	—	‡	No
15	4½ yr	§	+	+	CMP	—	§	Yes
16	11 mo	2 wk	+	ND	CMP	vomiting, diarrhea	2	Yes
17	14 mo	7½ mo	+	ND	soy	wheezing/urticaria	2	Yes
18	10½ mo	‡	+	+	soy	—	‡	No
19	10 mo	7 mo	Negative		breast	urticaria	3	Yes

ND = Not done.

*Inadvertent ingestion.

†Seen in clinic immediately after CMP ingestion.

‡Not received CMP by history.

§Still drinking CMP at consultation.

||Positive wheal-and-flare test within 10 min after touching CMP to skin.

TABLE IV. Age distribution of patients with immunologic and/or clinical immediate hypersensitivity to CMP

Age*	No. of patients
10-12 mo	8
13-18 mo	4
19-24 mo	3
25 mo-3 yr	1
3-5 yr	3

*Median age, 13 mo.

cow's-milk formula, 1 was changed to soy formula at 2 wk because of vomiting and diarrhea and had an additional reaction of wheezing and hives when given milk at 10 mo. The other child had severe chronic eczema and asthma but was still drinking cow's milk at the time of consultation.

Among the 18 children without IgE to CMP, 1 had a clinical history of immediate reaction to cow's milk.

This patient was a 10-mo-old, breast-fed infant who developed generalized urticaria after ingestion of cow's milk at 7 mo of age. The RAST and prick test with the commercial extract of cow's milk were negative. When the patient was challenged on several occasions by rubbing milk on the lips or forearm, a positive wheal-and-flare reaction was obtained within 10 min each time. The test was done in a double-blind fashion, using soy formula and heat-treated cow's-milk controls. The responses to the testing with soy formula and heat-treated cow's milk were negative.

IgE to other common food allergens occurred in 14 of 18 children with IgE to CMP, and 10 of 14 of the breast-fed ones had IgE specifically to egg protein. One breast-fed baby of Oriental parents with IgE to CMP had developed wheezing and angioedema after ingestion of soy formula; he had a positive RAST to soybean. Of the patients without IgE to CMP, 7 of 18 had IgE to other foods.

The median age for the patients in this study with

IgE or clinical immediate hypersensitivity to cow's milk was 13 mo, and children under 2 yr of age predominated (Table IV).

Analysis of data

Breast feeding in patients with IgE to CMP was significantly higher than in the control group of age-matched patients without IgE to CMP ($p < 0.03$).

The occurrence of IgE to CMP was highly predictive of a history of immediate clinical hypersensitivity to milk. An exception was one of the patients in this study who was drinking cow's milk at the time of the initial consultation, although possibly this was etiologically related to his severe chronic eczema or asthma. On the other hand, a negative RAST or skin test with commercial extracts of cow's milk was not an absolute guarantee against immediate hypersensitivity, as illustrated by one of the patients in this study.

The coincidence of IgE to other food proteins (especially eggs) in patients with IgE to CMP was significantly greater than in those without IgE to CMP ($p < 0.05$). The breast-fed infants were more likely to have IgE to other foods in addition to cow's milk.

DISCUSSION

Food allergy has been implicated in a wide variety of medical conditions and patient complaints and while some of the conditions may indeed be food related, the immunologic mechanisms remain quite obscure.¹⁰ Clinical immediate hypersensitivity reactions to food with features of a classical anaphylactic reaction often have a clearly defined immunologic mechanism with demonstrable IgE antibody to a particular food protein.^{9, 11}

The development of IgE to food antigens probably depends on several different factors, which may include an atopic constitution of the individual, immaturity of the digestive system permitting entry of foreign antigens, entry of food antigens through extraenteric mucosal surfaces, maturity of the immune response, allergenicity of the ingested protein, and the type of exposure (frequency and quantity) the individual receives.

This study focuses on standard dietary staples that seem to be of high allergenicity for infants. The patient population in the study was expected to have an increased susceptibility to the development of food allergy if given an appropriate antigenic challenge. These patients were atopic, with an immune system capable of producing allergen-specific IgE. Their youth suggests vulnerability of the gastrointestinal

tract to foreign proteins. The most readily identifiable factor distinguishing the breast-fed babies from those bottle fed is the type of exposure the infants probably received to the food antigens.

There is evidence from animal studies that the IgE response occurs from an initial exposure to a small rather than large amount of antigens and that large amounts of antigen actually inhibit the IgE response.¹² The exposure to minute, intermittent amounts of food antigens is potentially highly sensitizing for stimulating production of IgE to food antigens in infants.^{13, 14}

An infant fed a cow's-milk formula is constantly challenged with huge quantities of CMP antigens. But it is often not recognized that even a "completely" breast-fed infant is exposed to food allergens. Food allergens from the mother's diet can pass into her milk, and it is possible that this can sensitize the infant and even provoke allergic symptoms.¹⁵⁻¹⁸ We believe that the presence of food antigens in the mother's milk quite commonly sensitizes the infant, but frequently this event is transient and inapparent.

Many infants are probably exposed to food antigens by inhalation. Allergists are familiar with bakers' asthma and with patients who develop urticaria and severe allergic respiratory symptoms after exposure to frying fish or eggs.

As pointed out by others,¹⁹ the feeding of proprietary cow's-milk formula the first night in the nursery to infants who will be breast fed might cause subsequent hypersensitivity to cow's milk.

No doubt many breast-fed infants get other large quantities of foreign foods such as the taste of sherbet or pudding. In fact, similar circumstances led to the clinical reaction to milk in most of the patients in this study. Inadvertent exposure is demonstrated by the 2 patients with IgE to CMP who had not yet ingested milk by history. In addition, one breast-fed infant with IgE to CMP who also had a positive RAST and severe immediate reaction to soy formula was identified; this is an Oriental child whose family's daily diet includes soybean products.

This study concerns older infants and early childhood asthmatics. The lower median age of the patient in whom IgE to cow's milk was identified, compared with the age limit of the study group, suggests that the IgE response to cow's milk is frequently a transient phenomenon. This has been observed in many of our patients who have been followed over a few years. In several instances, although food sensitivities have vanished, the clinical course (asthma or nasal allergy) worsens as more inhalant allergies are acquired and respiratory infections recur.

The patient in our study with clinical immediate hypersensitivity to cow's milk and negative RAST and skin tests with commercial extract is unexplained. We have subsequently identified 2 other breast-fed infants with similar reactions to cow's milk that cannot be confirmed by laboratory tests; we now believe this is far more common than initially suspected.

This study did not include nonatopic controls, but the work of others suggests that nonatopic, breast-fed infants may be prone to develop IgE to cow's-milk protein as well.^{14, 19}

We strongly support breast feeding, especially for those infants with an atopic family history. The psychological benefit and the decrease in serious gastrointestinal problems²⁰ in the infant are extremely impressive. Most important for the genetically atopic infant who is breast fed, there is considerable protection against early, severe viral respiratory infection. The enormous benefits of breast feeding do not justify ignoring the possibility that some of these infants may develop immediate hypersensitivity to certain foods.

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