Severe Reactions to Cow's Milk in Very Young Infants At Risk of Atopy

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ABSTRACT

Cow's milk (CM) allergy (CMA) is a disease of infancy, usually appearing in the first months of life. Symptoms triggered by CM at first introduction are not completely defined. The aim of this study was to investigate the prevalence of severe reaction to CM and clinical manifestation triggered by CM administration in the first few months of life. Particularly sensitizing appears to be the exposure to CM formulas in the neonatal nursery. The little doses of allergens are more sensitizing than larger ones. These data provide clear evidence of the immunological effects of oral antigen administration during the neonatal period. Babies at risk of atopy should receive in their first days colostrum and/or formulas appropriate for atopy prevention. In this prospective study, we evaluated 27 babies in order to ascertain the prevalence of CM-induced severe reactions.
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The prevalence of atopic disease, atopic dermatitis (AD), bronchial asthma, gastrointestinal allergy, urticaria/angioedema, and allergic rhinitis (AR) appears to be progressively increasing in the last decades. In recent years, it has been estimated to be about 20%. The cumulated incidence of atopy, moreover, varies from 25% to 35%, according to different criteria for diagnosis, study design, and definition of atopy and ages for evaluation.[1–3]

The clinical manifestations of atopic disease depend on both genetic and environmental factors such as allergen exposure, which may even occur in utero.[4]

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Food allergy in predisposed infants often develops in relation to the order in which the foods have been introduced into the diet, such as CM first, then egg-white, fish, wheat, etc.[3]

CMA/CM intolerance (CMI) is a typical condition of infancy, usually appearing in the first few months of life. Its prevalence in infancy ranges from 0.5% to 7.5%, according to different criteria of atopy, different ages for evaluation, and different quality of the studies.[4]

Further, symptoms triggered by CM at first introduction are not completely defined. In this study we observed the clinical manifestations triggered by CM in 27 babies with CMA.

PATIENTS AND METHODS

To ascertain the prevalence of severe reactions triggered by CM, in particular at the first meal, we have studied 27 children, 14 male, 13 female, aged 4–48 months (median 12 months), attending the Division of Allergy and Immunology of the Rome University La Sapienza, from 1984 to 1990 because of suspected CMA. A positive family history of atopy was investigated, asking whether one or both parents and/or other siblings suffered from food allergy, asthma, AD, or AR. The diagnosis of atopic disease in the children was established on clinical history, physical examination, and positive skin prick test (SPT), and/or RAST to the most common inhalant and/or food allergens.

Skin Prick Test

Skin testing was done by prick method on the volar surface of the forearm. The babies were tested with histamine hydrochloride (1 mg/mL) as positive control and isotonic saline as negative control, whole CM protein, casein, lactoalbumin, *Dermatophagoides pteronyssinus* (Dpt), *Altenaria alternata, Lolium perenne, Olea europea*, and

Parietaria officinalis (Bayropharm, Milano, Italy). They were placed on the volar surface of the forearm as drops through which the skin was superficially abraded with a straight pin. A new pin was used for each prick test. The prick tests were read at 20 minutes and considered positive when the wheal was 4 mm or more larger than the negative control.

Total IgE

The determination of the total serum IgE levels was done by paper radioimmunosorbent test (PRIST, Pharmacia Diagnostics AB, Sweden), and results were expressed in International Units (IU) for mL.

Specific IgE antibodies and determination of specific IgE levels were done by radioallergosorbent test (Phadezym RAST, Pharmacia Diagnostics).

RAST results are expressed in RAST Units (PRU = Phadebas Rast Unit) as follows:

1st class = IgE levels < 0.35 IU/mL,
2nd class = IgE levels between 0.35 IU/mL and 0.70 IU/mL,
3rd class = IgE levels between 0.70 IU/mL and 17 IU/mL,
4th class = IgE levels higher than 17 IU/mL.

Only RAST third and fourth classes were considered positive.

The diagnosis of AD was made according to Hanifin and Rajka criteria.[5] The severity score of AD was recorded with body diagrams in which the front and the rear of the body were each divided into 10 areas for which a score was recorded of 0 to 3.[6] For the diagnosis of asthma, three episodes of wheezing without fever were required. For the diagnosis of AR, nasal discharge and/or blockage occurring continuously for at least 4 weeks plus the typical pale aspect of allergic mucosa on rhinoscopy, without any signs of infective rhinitis in other relatives, was required.

Statistical analysis: Data were statistically analyzed using the chi square test.

RESULTS

Parental History

All children but two had positive family history for atopy (double heredity, or one parent + sibling, or one parent) ($P = 0.0019$).

Feeding Modalities

CM was first introduced in the diet at age of 1–8 months (median, 4 months). Most of the children (25/27) received breast milk for 3–8 months (median, 4.5 months); two of them were breast-fed since birth.

Clinical manifestations at the "first" meal of CMA: At the "first" introduction of CM, all infants had immediate symptoms, as Table I shows.

TABLE I

Clinical Manifestations Presented by the 27 Infants

Symptoms	Number of Cases	Percentage
Anaphylaxis	2	7.4
Skin rash	2	7.4
Vomiting	2	7.4
Respiratory	3	11.1
Diarrhea	4	14.8
Angioedema	6	22.2
Atopic dermatitis worsening	8	29.6

Skin Tests and RAST

All children tested positive for casein and/or lactalbumin. These results were confirmed by RAST. Sixteen (59%) children had positive skin tests for other foods (egg, wheat) and 4 (15%) for inhalants (Tables II, III). The double-blind placebo-controlled food challenge could not be performed in these very young infants.[7]

Association with AD: Twenty-four babies of 27 (89%) had CMA associated with AD ($P = 0.001$).

Data on occasional meals while the babies were in the nursery were examined. Analyzing the clinical records of these infants and interviewing the parents, we learned that 25/27 children (93%) were given a CM formula in the neonatal nursery in the first days of life. The remaining 2/27 babies were CM-fed since birth.

DISCUSSION

In this study we analyzed in 27 babies the reciprocal importance of the severe manifestation of CMA. Twenty-five children of 27 were at risk of atopy according to the family history. Two babies appeared not to have such genetic risk; however, their frequency (7.4% or more) was found in other studies.[8] We have not performed in these babies the cord blood IgE (CB IgE) determination, because the sensitivity and the positive predictive value are very low, as recently stressed.[9] For this reason we relied only on family history.[9] In this study, all neonates at genetic risk of atopy were subjected to a dietetic preventive program including, among others, exclusive breast feeding up to 6 months of life, no more than 150–200 mL of CM/day and no more than two eggs/week to the nursing mothers, soy-

TABLE II

Skin Prick Test in 27 Infants

SPT	Positive	Percentage
Casein	27	100
Lactoalbumin	26	96.3
Egg	13	48
Wheat	3	11
Dermatophagoides pteronyssinus	4	14.8

TABLE III		
RAST Results in 27 Infants		
RAST	**Positive**	**Percentage**
Casein	26	96.3
Lactoalbumin	25	92.6
Egg	15	55.6
Wheat	4	14.8
Dermatophagoides pteronissunus	7	26

milk supplement until the sixth month, when breast milk was not sufficient.[10]

At the first introduction of CM, the infants reacted with the severe symptoms outlined in Table II. These figures are correlated with the data in Figure 1, in which the prevalence of each CM-triggered manifestation was analyzed and plotted.[1,4-6,11-19] However, differences were seen between our data and literature data in the prevalence of clinical manifestation of asthma, skin rash, vomiting, and diarrhea.

Anaphylaxis is the most dramatic symptom, its prevalence being 7.4% of infants. Within minutes of ingestion of CM, vascular collapse ensues, with all its clinical consequences. Infants may react to one milliliter of CM; however, frequently a few drops posed on the lower lip may trigger vomiting (7.4% of the babies in the present study) and diarrhea (14.8%), but also respiratory (11.1%) and skin symptoms (7.4%).

In the present study, none of the infants developed symptoms after the first exposure to CM. In fact, the true first CM-containing meal was administered, in 25/27 infants, in the neonatal nursery, in the first two days of life. When CM was reintroduced, all the infants presented immediate symptoms.

We have therefore demonstrated that all 25 babies fed CM in the nursery and 2/27 breastfed since birth developed severe reactions at the "booster" dose of CM. The two children breastfed from birth were probably sensitized to CM proteins present in breast milk, since they improved when the nursing mothers followed dietetic restrictions.

Intrauterine sensitization and exposure to CM in breast milk may cause symptoms of CMA even during breastfeeding[4,12,17,20-23]; this covert sensitization may induce symptoms after the first feed with CM, and the majority of children have symptoms within 1–2 months after the introduction of CM.[4] Recent studies have stressed that the levels of CM-proteins in breast milk are lower than those previously measured. Host et al.[22] found in breast milk 0.9–150 ng/L of beta-lactoglobulin (BLG) (mean 4.2). Sorva et al.,[24] using more sophisticated methods, found 0.01 ng/L (mean basal) and 0.12 and 0.07 ng/L (mean) 1 and 2 hours after a feed of 400 mL of CM, respectively. This corresponds to a ratio CM/breast milk = 1:400.000.000. For the hydrolysate formula with the least amount of BLG, the ratio is 1:4.800.000 (personal data).

These data are in agreement with a study comprising more than 40,000 children that demonstrated that "breast milk allergy" attains a prevalence of 0.042%.[23] Possibly, it is more sensitizing to give CM and/or formula occasionally and in little doses than regularly to newborns.[25] Usually, intact protein entering the circulation does not cause clinical symptoms because most individuals develop tolerance to ingest antigens.[26] Jarret, indeed, suggests that regular exposure to "large" doses induces tolerance, whereas "small" allergen doses may be sensitizing in predisposed individuals.[25] The ability to develop oral tolerance in a mouse takes place around 4 days of life. A single feeding of a protein to a mouse results in suppression of systemic IgM, IgG, and IgE antibody responses, as well as cell-mediated immune responses.[27] In genetically predisposed infants, food antigens may stimulate excessive production of IgE antibodies or other abnormal immune responses.[28]

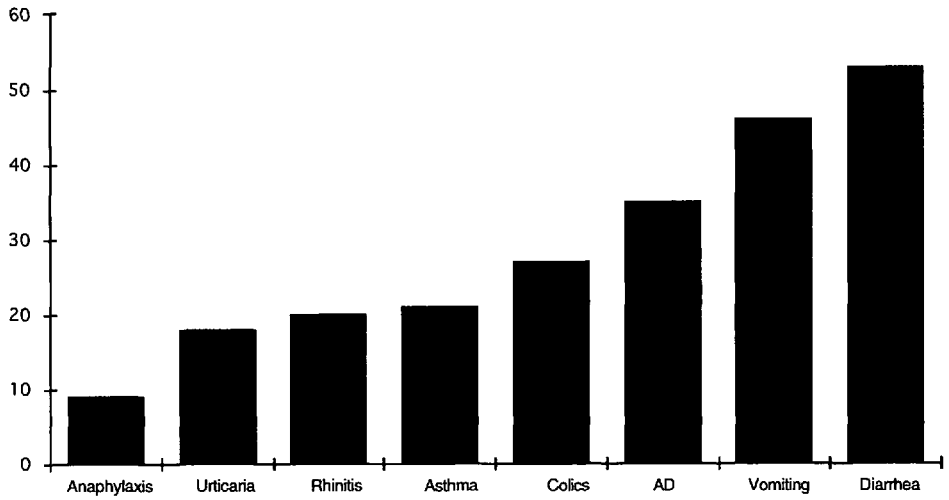

Figure 1. *Prevalence of clinical manifestations (%) of CMA. Asthma = asthma, wheezing, bronchitis, bronchospasm, coughing, etc.; Colic = colic, crying, etc.; AD = atopic dermatitis, eczema.*

In addition, because IgE antibody production appears to be closely regulated by CD8+ T cells, a large initial dose of antigens may promote suppressor activity and suppression of IgE synthesis.[29] In newborns and very young infants, there is a striking reduction of CD8 cells.[30] Therefore, occasional administration of CM in the first days of life initiate sensitization to CM proteins in predisposed individuals.[29] Subsequent exposure to small amounts of CM formula or of CM proteins contained in human milk may trigger allergic manifestations. However, the most consistent way of sensitization is the supplement of CM formula in the nurseries.[4,17,20-23] In this regard, Stintzing et al. were the first to stress that 25 infants with CM allergy were given CM formula significantly more often than 52 controls during the first 4 weeks of life.[17] In addition, Host demonstrated that 39 infants of 1749 received supplements of CM formula among neonates exclusively breast-fed in the nurseries.[1] Only those 39 infants developed CMA.

Sensitization to CM proteins is usually due to ingestion of CM-based formulas. Even more sensitizing are hydrolysate CM formulas given at-risk neonates. Recently, the clinical and immunologic findings were reported of five breast-fed babies, at risk of atopic disease, who experienced anaphylaxis after the ingestion of CM, partially whey hydrolysale formula (PWHF). Again, the sensitization seems to have occurred in the nursery, where the babies received the PWHF for a few days.[31]

In conclusion, the prevalence of clinical manifestations triggered by CM administration during the neonatal period is fairly high. Therefore, babies at risk of atopy should received, in the first days of life, only colostrum or breast milk or, if not available, appropriate formula for atopy prevention.

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