

# Neonatal Cow Milk Sensitization in 143 Case-Reports Role of Early Exposure to Cow's Milk Formula



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## Abstract

**Objective:** 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 evaluation of infants for possible CMA is one of the more common problems encountered by pediatricians. Purpose of this study was to investigate the prevalence of severe reaction to CM and clinical manifestation triggered by CM administration in the nurseries.

**Materials and Methods:** The series includes 143 prospectively studied CM-allergic babies.

**Results:** At the first introduction of CM, at the age of 1-8 months (median 4 months) all infants had immediate symptoms the babies were probably sensitized during the first days of life. Particularly sensitizing appears to be the exposure to CM formulas in the neonatal nursery.

**Discussion:** Little doses of allergens are more sensitizing than larger ones. We provide clear evidence of the immunological effects of oral antigen administration during the neonatal period, and discuss the possible critical allergen transmission to the nursing baby via breast milk (BM).

**Keywords:** Cow's milk allergy; Neonate; Neonatal nurseries; Severe reactions; CM sensitization; Breast milk

## Introduction

A major cause of sensitization to CM in genetically predisposed neonates is the (in) advertent administration of CM in neonatal nurseries. Neonatal care should include 49-100% of such infants given supplements of CM or hydrolysate formulas (HFs) during the first 3-4 days of life [1-5]. Among these babies CM allergy (CMA) was more frequent [6], until to 100% of infants, none of them had symptoms at the first CM administration [3]. Immediate reactions at the subsequent CM feeding bring into focus a delayed effect of the "hidden bottle" [2]. Høst et al [3] documented that the 40-860 ml of CM received from 39 neonates during the first three days contained 0, 4-7,4 g of  $\beta$ -lactoglobulin ( $\beta$ LG). Feeding half of babies with a CM formula and half with HFs for 1-4 days and then with BM, if necessary supplemented with HFs until the third month, total IgE titres were at the 5<sup>th</sup> day significantly related to the dose and frequency of supplements received (200-500ml) [7], maintaining significances until 12 months [8] especially in at-risk babies.

In at-risk children, prospectively followed-up from birth during 18 months [9] and re-evaluated at age 4-6 [10], the

cumulative prevalence of atopy was 18% in CM-fed or 33% in wholly BM-fed babies, and in at-risk children the incidence was as high as 11 or 61%, respectively [9]. Newborns with 27-42 week gestational age and 2 SDs (standard deviation) below the mean normal weight at birth correspond to prematures responding in a different manner to sensitization and onset of atopic manifestations. During the follow-up, the prevalence of atopy was nearly similar in both groups, yet skin prick tests (SPT) positive for CM significantly correlated with RAST only in CM-fed infants [10]. We have also studied four additional at risk infants who were exposed in the nursery to a first HF dose during their first days of life, and elicited acute allergic symptoms when fed again this HF at the end of an exclusive breastfeeding (data not shown).

Healthy newborns accidentally exposed to CM in a nursery develop a modest and transient antibody production (primary immune response). Such initial responses are self-limited and gradually resolve due to development of tolerance despite unremitting allergen exposures. At the second encounter, CD4

clones from non-atopic infants have a Th1 profile, whereas in atopic infants provide help for IgE synthesis (secondary immune response) [11]. Remarkably, there appears to be a consensus that BM-feeding for at least 4-6 months will delay, if not prevent allergy [12-48], although a case of apparent sensitization via BM has been reported [48].

### Materials and Methods

We have prospectively studied 143 CM-allergic babies, 79 males and 64 females aged 4-8 months (median 5 months) with IgE-mediated CMA, who attended between June 1997 and December 1999 the Allergy and Clinical Immunology Division of Rome University "La Sapienza". The diagnosis was based on SPTs, all positive to CM, and oral food challenges (OFCs) done in a hospital setting which were positive to CM in 74 babies, to egg in one baby, and to a HF in 50. In total, 125 out of 143 babies (87.4%) were positive to OFCs. Parents of each child gave details of their allergic disease (if any) and their informed consent. The babies were defined at risk of atopy when at least one parent had or had had diagnosed and treated atopic disease. Data were statistically analyzed using the Student t and the X2 tests.

### Results

At the first introduction of CM, at the age of 1-8 months (median 4 months) all infants had immediate symptoms, as follows: anaphylactic shock (9 cases), urticaria-angioedema (37 cases = 25.9%), skin rash (13 cases = 9.1%), diarrhea (25 cases = 17.5%), vomiting (19 cases = 13.3%), respiratory manifestations (wheezing or rhinitis) (18 cases = 12.6%), and worsening of atopic dermatitis (AD) (59 cases = 41.2%). Several children had more than one allergic manifestation. All children but twelve (82.8%) had positive family history for atopy ( $p = 0.0001$ ). Only 10/143 infants (14.3%) were fed CM since birth; the other 133 were BM-fed for 3-8 months (median 4.5 months). Two children breastfed from birth were probably sensitized to CM proteins present in BM since their conditions improved when the nursing mothers followed dietetic restrictions. Analysing the clinical charts of the infants and interviewing the parents, we learned that 133 (93%) of the CM-allergic babies were fed a CM formula in the neonatal nursery in the first days of life. ( $p = 0.0001$ )

### Discussion

In this prospective study we learned that as many as 133 newborns were fed CM in the newborn nurseries, and this data tallies well with previously alluded to studies. As a result of OFCs, a larger proportion of babies (41.2%) had a worsening of AD symptoms, however it is remarkable that 12.6% presented with respiratory manifestations. As previously reported, there is a large consensus that BM-feeding for at least 4-6 months will delay, if not prevent allergy [12-48]. A note of caution is their unmatched results owing to methodological differences. Given that CM and egg allergens are present in BM, it was also thought that a maternal diet excluding the above allergens may be important in atopy prevention [13,34,42]. A typical case was

reported by Lifschitz et al [48], an anaphylactic shock due to CM protein hypersensitivity in a newborn who was mistakenly fed BM that had been expressed before CM products were eliminated from his mother's diet, as it is correctly shown in the title [48]. More than 70 years ago Talbot documented that AD in a fully breast-fed infant could be related to chocolate ingested by the mother, and that AD cleared up when the nursing mother avoided the offending food [49], a phenomenon recently confirmed [3]

However, IgE-mediated sensitization through BM is rather rare: 0.042% [50] or 0, 28% [3]. Therefore, inadvertent exposure to CM appears to be far more important than the very low CM amounts transmitted via BM [51]. A note regarding a study based on HFs for allergy prevention [17]: the frequency of BM-feeding was high (98%), and in 232 not randomized such babies the incidence of CMA was 1.3%. The study is far more important because newborns who received a CM formula in the nursery were not included into the program [17]. We have stressed the negative effects of the maternity wards. To avoid the possible risks it should be clearly stated that giving any formula in the first few days of life is strictly forbidden unless prescribed by a pediatrician or de-manded by a mother who is unwilling or incapable to breastfeed her baby [41].

A new front was unexpectedly opened up by the significant report that a 22-week-old fetus responds to a great variety of oral and inhalant allergens including CM  $\beta$ LG, and egg ovalbumin [52]. That is why reducing intake of highly allergenic foods in the last trimester has not been found to be worthwhile in atopy prevention in at-risk babies [51,53-55]. In conclusion, as early as in 1935 Ratner [56] recommended that isolated CM feedings to BM-fed infants should be avoided during the newborn period.

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