

Dissertations

Human Milk Immunology in Relation to the Development of Cow's Milk Allergy in the Breast-fed

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SUMMARY

In the light of epidemiologic studies up until now, the effect of breast-feeding on the development of allergic diseases and cow's milk allergy (CMA) in the breast-fed had remained controversial. This may in part be due to individual variations in the levels of immunological constituents in mother's milk. To investigate the impact of distinct immunological factors in human milk on the breast-fed infant's risk for developing CMA, the presence of several immunologic components in the colostrum and milk of the mothers of newborns and infants was studied prospectively. Levels of various immunological factors were correlated with the offspring's clinical response to cow's milk challenge. Further, clinical manifestations of CMA in addition to the immune responses to cow's milk evoked were measured during a cow's milk challenge performed through mother's milk.

The proportions of distinct leucocyte subsets in human milk were studied in mothers of infants with CMA and

in those of healthy infants. In the milk of the latter, the predominant leucocyte was the macrophage, whereas in the former, the proportion of macrophages was significantly smaller, and large proportions of eosinophils and neutrophils were found more often. These abnormalities in mothers' milk were in relation to an imbalance in the CD4+ and CD8+ T-cell ratio and with disturbed B-cell function that were associated with development of CMA in the breast-fed infant. When HLA-DR expression on milk macrophages was investigated in a subgroup of mothers, it was less frequent in those with infants with CMA. These results imply that sufficient numbers of func-

tional milk macrophages may be critical in development of oral tolerance to food antigens in the offspring. Since HLA-DR is necessary for the presentation of antigens to T cells, the central role of the milk macrophages may be the presentation of foreign food antigens to the breast-fed infant's relatively naive and immature immune system. Moreover, these findings suggest that the presence of high numbers of eosinophils and neutrophils in mother's milk may be harmful to the breast-fed, since their cytolysis may potentially lead to the release of high amounts of highly cytotoxic mediators including ECP in the infant's gut. This may lead to an immunoinflammatory process similar



Dr Kirsi-Marjut Järvinen (*right*) defended her thesis on September 1, 2000 at the Hospital for Skin and Allergic Diseases, University of Helsinki. Faculty Opponent was Professor Stephen Strobel (*left*), Institute of Child Health and Chairperson was Professor Annamari Ranki from the Department of Dermatology, University of Helsinki (*centre*). Dr Kirsi-Marjut Järvinen is currently working at the Department of Pediatrics, at the Mount Sinai Medical Center in New York.

to that seen in asthma and to increased gut permeability, and may thus contribute to development of CMA.

Further study of the function of human milk leucocytes required examination of the production of certain cytokines *in vitro*. Consistent with our findings of a low number and less frequent expression of the HLA-DR of milk macrophages, the level of TNF- α in milk was lower in mothers having babies with CMA. TNF- α , a cytokine involved in the maturation process of dendritic cells necessary for presentation of processed antigen to T cells, may be an important factor in regulating development of oral tolerance in the gut mucosa of breast-fed infants. These results indicate that any lack of TNF- α in human milk may downregulate the differentiation of dendritic cells in the breast-fed, thereby playing a role in development of CMA.

The levels of total IgA in colostrum and milk were significantly lower in those mothers whose babies later developed CMA, whereas levels of IgA antibodies to cow's milk were comparable in the two groups of mothers. Since secretory IgA is considered the most important protective factor at mucosal level, its lack in milk may lead to an increased exposure of the intestinal mucosa of the breast-fed infant to potential allergens and thus enhance the risk for development of food allergies.

Clinical symptoms and immune responses in the peripheral blood of the breast-fed were evaluated during a cow's milk challenge performed through mother's milk. After a 2- to 4-week cow's milk elimination diet of both mother and infant, increasing doses of cow's milk or other dairy product were given at 1-hour intervals to the breastfeeding mother. Transfer of β -lactoglobulin (BLG) in mothers' milk was assessed. Most of the infants with CMA reacted to this untraditional cow's milk challenge procedure by showing typical symptoms of CMA, and the level of BLG was simultaneously increased in the milk of a subgroup of mothers. At the same time, there was a significant rise in total number of immunoglobulin-secreting cells of the IgA and IgG classes in the peripheral blood of infants. These findings give reason to believe that allergic reactions to food antigens transferred in the mothers' milk to the breast-fed, may be more common in infants with CMA than previously thought. They further imply that a strict elimination diet for the breast-feeding mother may be required in most cases of an infant with food allergies.

The present study may be the first to report that several aberrations in the cellular, cytokine, and immunoglobulin composition of human milk are related to development of CMA in the breast-fed. It therefore provides

fresh insight into the etiopathogenesis of CMA. Measuring such components of mother's milk may become a useful tool for assessing those newborns at an increased risk for developing CMA. Although human milk is the best source of nutrition for healthy infants, the present study questions the general recommendation of prolonged breastfeeding in the prevention of development of food allergies in allergic families.

List of original publications

This thesis is based upon the following original papers.

- I Järvinen K-M, Suomalainen H. Leucocytes in human milk and immune responses in cow's milk-allergic infants. Submitted.
- II Järvinen K-M, Juntunen-Backman K, Suomalainen H. Relation between weak HLA-DR expression on human milk macrophages and cow milk allergy (CMA) in suckling infants. *Pediatr Res* 1999; 45: 76-81.
- III Järvinen K-M, Laine S, Suomalainen H. Defective tumour necrosis factor-alpha production in mother's milk is related to cow's milk allergy in suckling infants. *Clin Exp Allergy* 2000; 30: 637-643.
- IV Järvinen K-M, Mäkinen-Kiljunen S, Suomalainen H. Cow's milk challenge via human milk evokes immune responses in suckling infants with cow's milk allergy. *J Pediatr* 1999; 135: 506-512.
- V Järvinen K-M, Laine S, Järvenpää A-L, Suomalainen H. Does low IgA in human milk predispose the infant to the development of cow's milk allergy? *Pediatr Res* 2000, in press.