REVIEW ARTICLE

Transfer of Dietary Allergen in Human Milk

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ABSTRACT The presence of dietary allergens in breast milk have been studied either in animal model or human milk. Transfer of these allergens to the infants have been proven qualitatively and quantitatively. Maternal dietary allergen transfer can also be detected by the presence of antibody response in the infants. The relationship of maternal dietary allergens and sensitisation to the infants can be observed in prolonged breastfed infants. The benefit of maternal dietary avoidance may be found either early from the beginning of pregnancy or in the lactation period. Factors predicting the onset of atopic disease are the nature of dietary protein in breast milk, IgA in breast milk, family history of atopy, allergen exposure, cord blood IgE and contributory factors. Evaluation of infants with sensitivity to dietary allergen in breast milk mainly is DBPCFC. Preventive measure is still avoidance of maternal dietary allergen. The mainstay of treatment is avoidance of the offending foods obtained from food challenge.
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Introduction

Unlike allergic reactions to ingested food which are now widely accepted, allergic reactions to specific protein from the mother's diet to breast fed infant are less well appreciated. Cow's milk accounted most often, and beta lactoglobulin (BLG) in human milk may contribute to, but does not alone explain, the development of cow's milk allergy in breast fed infant.[1] Other foods such as egg, fish and peanut in the mother's diet also implicate in ensuring of infant allergy in studies based on maternal and infants food allergen avoidance.[2,3] Less commonly implicated foods are oranges, apple, banana, strawberry and tomato. It has recently been suggested that allergen delivered to the

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infant in low quantities during breast feeding may favor the development of IgE antibodies. In many studies all over the world comparing exclusively breast fed infant and formula fed infant to determine the risk of sensitization, it is always advised to the mothers to restrict their own milk intake, although the study is not designed to lessen the effect of maternal allergen transfer, indicating that the issue is actually exist.[2] In this paper, we want to review information on the transfer of allergen via human milk and its association with the risk of allergic illnesses in the breast fed infants.

Evidence for the Presence of Dietary Allergen in Breast Milk in Animal Model

Study in animal model indicates the transfer of dietary protein into milk.[4] Intravenous injection of ^{125}I-Bovine Serum Albumin (125I-BSA), 125-Bovine gamma globulin (125I-BCG), 125I-Bovine beta lactoglobulin (125I-BLG), 125I Ovalbumin (125I OVA) in lactating mice shows co-precipitable radioactivity of manually expressed milk 4 hours later. 125I-BSA and 125I-BGG are 8 to 10 fold greater transferred into milk compared with 125I-BLG and 125I-OVA.[4] The same study in rat milk the marked differences in transfer between BSA and BGG compared with OVA and BLG might be explained by preferential clearance of antigen into maternal tissues other than the mammary gland or by the existence of specific transport mechanism for certain protein within the mammary gland.[5]

Transfer of protein into milk was also studied by Halsey et al by injecting of radiolabelled IgG, IgA and IgM. This study found a greater transfer of radioactivity after injection of IgA or IgM compared with IgG, suggesting that a specific transport system for polymeric immunoglobulin might be involved.[6]

Evidence for the Presence of Dietary Allergen in Human Milk

The presence of ovalbumin, BLG and gliadin after a considerable time postprandial has been demonstrated by sensitive immunoassay[7-10] in the following concentration.

Protein	Breast milk concentration
Ovalbumin	200 pg-6 ng/ml
BLG	5-800 ng/ml, 200 pg-4 ng/nl
Gliadin	5-95 ng/ml

Studies in mothers who ingest cow's milk, raw egg and gluten 2 to 6 hours before breast milk sampling indicate that dietary antigens are transferred into human milk, and the concentration of the protein detected varies widely.

Several studies have suggested that an unidentified cow's milk protein other than blg and casein might play a pathogenic role in infantile colic. Clyne et al[11] analyzed breast milk and infant formula using a radioimmunoassay for the presence of bovine IgG. The study recruited 59 mothers with infants in the colic-prone 2 to 7 week age group, compared with 30 mothers of non-colicky infants. The 29 mothers of colicky infants had higher levels of bovine IgG in their breastmilk. Most cow's milk based formulas contained bovine IgG with concentration comparable with levels found in many non-colicky human milk samples. The results suggest that appreciable quantitaties of bovine IgG are commonly present in milk from mothers of colicky infants and that bovine IgG may possibly be involved in the pathogenesis of infantile colic.

It has long been accepted that cow's milk protein secreted in breast milk may cause cow's milk allergy even during exclusive breast feeding. A study was conducted in 1994 to determine blg levels in human milk of mothers of infants with cow's milk allergy. The results indicated that BLG was found in the 1-2 hour samples in 75% of the mothers. The author concluded that BLG, although not a sole factor, may contribute to the development of cow's milk allergy in breastfed infants.[1] In atopic eczema, other factor may contribute in the development of the disease in infants who are breastfed. Breast milk lipids from mothers of children with newly developed atopic eczema has increased proportions of linoleic acid and significantly decrease proportions of its long chain polyunsaturated derivatives.[12] Increased permeability of intestine to macromolecule contributes the other factor in this issue.[13]

Great intra and interindividual variations in blg levels have been observed in human milk.[14] In a single mother, on whom a longitudinal test was performed, blg level was maximal after 1 hour. Low level cow's milk betalactoglobulin can be measured using sandwich type ELISA. One hour after oral intake of milk, blg could be detected in breast milk of three mothers at concentration about 1-2 micrograms/L.[15]

In other studies in which blg levels in human milk were measured 4 to 24 hours after a cow's milk load, the maximal betalactoglobulin level was found after 8 to 12 hours. This even when assessed after an oral cow's milk load, the presence of blg in human milk seems to be variable.[14,16] The persistence of betalactoglobulin in human milk also seems to be variable. In some mothers betalactoglobulin has been found for 3 days[9] and even for 9 days[17] after elimination of dietary milk. After the mother spent 24 hours on milk free diet, half of the human milk samples contained betalactoglobulin. The level was even high (>0.5 mg/L) in 15%. The secretion of blg in human milk at 1 and 2 hours after oral cows milk load seems to have different patterns in the mothers of infants with CMA. About half of the mothers had an increase in the betalactoglobulin levels. Increase was mild in about 60% of them and high (>0,5 mg/L) in 40%. One third of the mothers of infants with CMA had a decrease in betalactoglobulin

levels. The basal milk samples of these mothers had higher betalactoglobulin levels than basal milk samples of the other mothers. This group of mothers might represent slower metabolizers of observed cases, still reflect the effects of the 24-hour milk free diet and not yet the effects of the cow's milk load. The third group of mothers about 15% had no change and no detectable betalactoglobulin in any of the three samples. Of the six infant with CMA whose mothers had no detectable betalactoglobulin in any of the three samples, two were exclusively breastfed.[1]

Betalactoglobulin, among the other proteins, of cow's milk, is the most widely investigated as the dietary allergen transferred causing allergic disease in infants. Casein, albumin, lactoferrin and immunoglobulins which were not assessed in many studies, might have caused the allergic symptoms in the infants of these mothers. The evidence of dietary allergen in breast milk can also indirectly be proven by the determination of antibodies to these allergen. Breast milk samples were collected from 152 women during the first week after delivery. IgG and IgA antibodies to BLG, ovalbumin and gliadin were assessed with ELISA, although the relationship of sensitisation to the infants was not established in this study.[18]

Evidence for Maternal Dietary Allergen Transfer to Infants

Transfer of maternal dietary allergen to infant was studied by Swedish workers using gut permeability method to human alpha lactalbumin and bovine beta-lactoglobulin in 20 infants from birth to 5 months or until weaning before which they were on a strictly cow's milk free diet. Measurement of the protein was done using a sensitive, solid phase, double sandwich immunofluorometric assay. Median levels of serum alpha-lactoalbumin on days 3-4 after birth, and at 1 and 2 months of age were 3 mg/L, 6 mg/L and 2 mg/L serum per gram alpha-lactalbumin/body weight, respectively.

At 3.5 and 8 month of age only trace amounts of alpha lactoglobumin were found. One week after weaning serum betalactoglobulin was found with median 7 mg/L and 4 mg/L at two week after weaning per G betalactoglobulin given per kg body weight.[19] Maternal dietary allergen can be detected by the presence of antibody response of the infants to these allergen during the first year of life. IgE and IgG to egg were detected using RAST in 5% of 1 year old babies. IgG to bovine casein and egg albumin was predominantly detected in these babies, while IgG1 to these allergen was found lower. The results of this study indicated that type I hypersensitivity to egg occured in 5% of babies studied, the predominant IgG class of antibodies to casein and ovalbumin in babies is IgG1 and in the 22% of babies there was substantially lower than in their mothers.20 Milk specific IgE has been demonstrated more frequently in breastfed infants whose mothers ingesting cow's milk rather than in formula fed infant.[21]

Relationship of Maternal Dietary Allergen and Sensitization to the Infant

Prolonged exclusive breastfeeding to nine months does not contribute to the prevention of infantile atopy and respiratory tract infections.[21] The results of this study indicate that there is still sensitization to the infants, may be by the presence of allergen in breast milk. Breast milk carries small quantities of food protein in allergenic form.[23] Symptoms of cow's milk allergy also develop in some infants after ingestion of reputedly considered hypoallergenic foods including breast milk. Clinical disappearance of symptoms is observed after removal of milk from mother's diet.[24] Previous studies, a double blind controlled setting, have confirmed the relationship between maternal ingestion of cow's milk and egg and the presence of colic and eczema in their infants. In these studies approximately 50% of babies improved clinically on initial withdrawal of cow's milk and egg from the mother's diet.[25,26]

Other report shows an association of eczema and diarrhoea in an infant whose mother receive cow's milk, soy milk, goat's milk in her diet. The infant's symptoms are reproduced on masked administration of either cow's milk or soy protein to the mother.[27] Opposite result is also possible, protein transfer by breastfeeding can induce tolerance, though in a dose range otherwise associated with priming.[28]

Cow's milk and egg are among foods widely investigated, other foods may also have a contributory role in the sensitization to the infants via breast milk. In a simple survey of peanut consumption during pregnancy and breastfeeding by mothers of these infants either peanut allergy may suggest that they are being exposed to peanut allergens in utero or via breast milk.[29]

Effect of Maternal Avoidance of Dietary Allergen on the Development of Symptoms in Infants

The benefit of maternal avoidance of dietary allergen on the development of disease in infants, can be observed early from the beginning of third trimester of pregnancy. Maternal avoidance of cow's milk, egg, peanut during the third trimester of pregnancy and lactation and infant use of casein hydrolisate and avoidance of commonly allergenic foods result in reduced food associated atopic dermatitis, urticaria, and gastrointestinal disease.[3]

A maternal diet excluding milk egg, peanut fish and beef during pregnancy and lactation coupled with breastfeeding and delaying solid food introduction for 6 months, reduced the incidence of eczema from 31% to 14% in infants at risk of atopy.[30] Modification of the prophylactic treated mother's diet during lactation in this study demonstrating that breast milk may actually be the route of allergens ingested by the mothers to the nursing infants, facilitating exposure and potential sensitization. In

support of this study, Hattevig et al found that the infants of mothers who avoided egg cow's milk and fish during the first 3 months of lactation developed less eczema by 6 months by 11% versus 28% of infants with normal diet mothers.[2]

Factors Predicting the Onset of Atopic Disease Related to Dietary Allergen in Breast Milk

Several factors have to be considered concerning this issue:

1. The nature of dietary protein in breast milk; this includes the concentration of dietary protein in breast milk and molecular character of allergen
2. Total IgA concentartion and cow's milk protein specific IgA antibody in breast milk
3. Family history of allergic disease
4. Allergen exposure
5. Cord blood IgE
6. Contributory factors

An uncontrolled longitudinal study of 25 Swedish mothers and infants indicates that there is correlation of high BLG levels in breast milk with symptoms of allergy in the infants,[16] although this finding does not accord with a study comprising mothers of unsolicited population.[9]

The molecular character of allergen is not widely characteristic of ovalbumin in breast milk, which was found to have the same gel filtration characteristic as native ovalbumin. There is no evidence for the transfer of fragments of ovalbumin into breast milk.[7] Heredity is the only significant predictor of atopy. Atopy was seen in 33% of infants with a positive heredity and in 16% without family history for atopy. The occurrence of atopic disease was not prevented by prolonging exclusive breastfeeding and dietary avoidance.[22] Study of Magnuson finds that maternal elimination during late pregnancy does not prevent the development of allergic disease in the genetically predisposed infant. This indicate that atopy is the most important factor in the development of allergic disease.[31]

In a study comparing the effect of a maternal milk free diet during late pregnancy and lactation, atopic mothers were randomly allocated into an intervention group, or an unrestricted diet group and compared with non atopic mothers following an unrestricted diet. Infants of these three groups mothers were followed up for 18 months postnatally. Single blind allergy assessment by a pediatrician at 12 and 18 months showed that the infants born in the non atopic group had a significantly lower allergy incidence compared with the infants born in the atopic group following an restricted diet. The allergy incidence of the infants born in the atopic diet group was significantly lower compared with that of the atopic group following an unrestricted diet.[32] It was

observed that the atopic nature of the parents significantly affected the allergy incidence in their children, although allergen exposure seemed likely play an important role in this study.

Maternal IgE does not cross the placental barrier and detectable IgE in cord serum has been shown to be of fetal origin, indicating an intrauterine sensitisation. Elevated cord IgE levels have been reported to be predictive of later development of atopic disease. This is considered justified to suspect food allergy in infants and small children who in addition to atopic symptoms and/or family history of atopic disease, have elevated serum IgE in relation to age. Measurable IgE in cord serum may indicate an extreme atopic predisposition with an increased risk of developing food allergy.[33] Food by far seems to be the major allergen of the vast number of environmental allergen such as inhalant allergens and other contributory factors. These factors can be immunologic defects, gastrointestinal diseases, infection or non specific irritants such as tobacco smoke, can enhance the development of allergy, perpetuate its chronicity, or facilitate precipitation of symptoms.[34]

Evaluation of Infant with Sensitivity to Dietary Protein in Breast Milk

Because there are few tests that establish a definite diagnosis of allergic illnesses, it is essential that non allergic causes of the presenting symptom complex be firstly eliminated. For example in the case of diarrheal illness, the evaluation included the assessment for an infectious cause of colitis. Another example might involve a child presenting with frequent emesis. In addition to considering the possibility that allergic illness is responsible, gastro-esophaseal reflux, anatomic anomaly, inborn metabolic disease, renal tubular acidosis and intracranial lesions should be considered.

Evaluation of infants with sensitivity to dietary protein in breast milk may comprise the following: (1) Skin test; (2) RAST; (3) Double blind placebo controlled food challenge (DBPCFC); (4) Elimination diet and provocation test; (5) Others.

Although the family history of allergic illness the measurement of the infant's total IgE, RAST and skin testing have not been helpful in the reported series of infants with symptoms related to dietary protein in breast milk, it may be premature to disregard these diagnostic tests in all cases. An elevated RAST titer or positive skin test specific for a dietary antigen would suggest that this antigen should be the one initially eliminated from the mother's diet.

The study of Caffarelli et al comprising 21 infants with food allergy and positive skin test and RAST reaction to egg which they had never previously ingested; the control group of 12 infants had food allergy and negative test results. All subjects underwent double blind placebo controlled food challenges with egg; 61% infants with

positive test and 8% of control subjects had positive reaction to challenges. 93% of positive challenges elicited immediate symptoms, late onset eczema occured in two children. Skin test results showed a high sensitivity (0.92) and negative predicative accuracy (0.92), whereas specificity (0.57) and positive predictive accuracy (0.61) were poor.[35] Because the infants had never ingested egg before challenge, sensitization must have occured either in utero, or more commonly after birth, through breast milk. RAST did not have any diagnostic advantage over skin test. The diagnostic accuracy of skin test and RAST compared with DBPCFC was similar.[36]

Elimination and provocation test is initiated with removal of the suspected dietary allergen form the maternal diet. In more severely affected infants, mother may be placed on a hypoallergenic diet, if the infant are still exclusively breast fed. If other foods have been added, mother and infant must be put on the same diet.

The diet must be continued for three weeks to allow for resolution of symptoms.37 After resolution of symptoms, provocation can be initiated. All previously excluded foods from maternal diet, one by one can be readed to the mother, one at a time in a sufficient amount every day for one week. If no symptom appear, the food can be considered as non allergenic to the infant. On the contrary symptoms reappear, the food should be suspected as allergen, For diagnosis, three provocations are needed.

Other examination introduced by investigators from Japan. Fecal IgE levels were investigated in 165 asymptomatic infants at one month of age under two nutritional regimens: breastfeeding and formula feeding. IgE levels were meassured by time-resolved fluoroimmunometric assay. IgE antibodies were detectable in fecal extract and reported to be increased in food allergy patients after administration of food allergen. Thirty five persent of 105 formula fed infants had high fecal IgE levels, compared with 18% of 60 breastfed infant ($p<005$).[38]

Prevention

Some studies have favoured to prevent sensitisation of maternal dietary allergen via breast milk to the infants by food allergen avoidance early from the beginning of pregnancy. Zeiger et al, avoided cow's milk, egg and peanut from maternal diet during third trimester of pregnancy and lactation, resulting from reduced food associated atopic dermatitis, urticaria and/or gastrointestinal disease by 12 months. The prevalence of rhinitis, asthma and inhalant skin test were unaffected may be because of other allergen (inhalant allergen) predominantly play a role in these diseases.[3]

Other workers excluded milk, egg, peanut, fish, and beef during pregnancy and lactation complete with breastfeeding and delaying solid food introduction for 6 month reduced the incidence of aczema in infants at risk for atopy.[30] Maternal avoidance of eggs, cow's milk and fish during lactation significantly reduced the incidence of Atopic Dermatitis during 6 months of life in infants of mothers adhering to a hypoallergenic

diet.[2] Prevention of allergic diseases can also be initialed in infants. Some workers reported the effectiveness of dietary manipulation in infants.

The mainstay of this environmental engineering is the avoidance of highly allergenic foods: milk, egg, soy, corn, wheat, peanuts, nuts during the first 2 to 36 months of life and aggressive avoidance of inhalant allergen throughout life. Breastfeeding is strongly encouraged for long periods, prefferably for at least 6 months. Solid feeding is withheld until 6 months of age. Supplemental soybean and cow's milk formulas are totally avoided during the first year because they contain potentially sensitising proteins. Formula containing an enzimatically prepared hydrolysate of casein, which contain added corn oil, carbo hydrate, minerals and vitamins has demonstrated hypoallergenic properties and nutritional adequacy.[39]

Avoidance of cow's milk, egg and fish during first three months of lactation significantly decreased both the prevalence and severity of atopic diseases up to the age of 5 years. The infants in this study were supplemented a soy formula containing sucrose when breast milk was not available, delayed weaning and environmental measures: no smoking, no pet in the house and measures for the elimination of mites.[40]

The effect of allergen avoidance in infancy on allergic manifestations was investigated by Hide et al, comprising one hundred infants, identified before birth as being at high risk for atopy, were prenatally assigned to prophylactic or control groups. The infants in the prophylactic group either received breast milk from mothers on an exclusion diet or on extensively hydrolysed formula. Their bedrooms and living rooms were treated repeatedlt with acaricide, and they used polyvinyl-covered mattresses with vented head areas. The infants in the control group were fed conventionally, and no environmental control was recommended. A significant advantage, first demonstrated at 1 year of age, persists for children in the prophylactic group. They have less of eczema, but the reduced prevalence of asthma is no longer significant.[41] A dual approach to allergen avoidance focusing on foods and inhalant allergens as seen in this study and others seem likely to be benficial in selected high risk infants.

Management

Allergen avoidance is the mainstay of treatment in allergic disease. The offending foods obtained from DBPCFC or open challenges must be restricted from the infants diet. Hypoallergenic formula may be put instead. It may be necessary to make this change in diet on a permanent basis. Fortunately, allergy to cow's milk disappears in most cases by 2 years of age.[42] In an infant who has definite and severe food protein allergy, and who has been treated with a hypoallergenic formula, one should reintroduce the offending food only in the controlled setting of the physician's office.

When food allergen avoidance fails, anaphylaxis may result. An immediate subcutaneous dose of epinephrine may be administered in the event of accidental ingestion.

The dose of 0.01 ml/kg body weight up to 0.3 ml of aqueous epinephrine (1:1000 mg/ml) may be given subcutaneously. Intravenous hydrocortisone may be added during a resucitation. In young children who have no history of asthma or anaphylactic symptoms and whose reaction are strictly convinced to skin symptoms, liquid diphenhydamine in doses of 1 to 2 mg/kg body weight up to 75 mg may be administered for an accidental food allergen ingestion.[43]

The use of cromolyn in combined gastrointestinal allergy was reported effective. Treatment was begun while the children were receiving elimination diets. They were challenged with specific antigen only after 18 hours drug administration. Cromolyn significantly afforded protection in 11 of 13 trials, whereas placebo was effective in only 3 to 9 trials.[44] Oral cromolyn in doses up to 600 mg daily reported to be effective in improving skin lesions in atopic dermatitis due to food allergy, while other study concluded that cromolyn may reduce local intestinal responses in children with cow's milk allergy but does not prevent the extraintestinal reactions.[45]

Pharmacotherapy with a variety of drugs can not replace food allergen avoidance. Some of these medications may modify the milder symptoms but overall they have minimal efficacy, have unacceptable side effects or mask early cutaneous symptoms.

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