
High sensitization rate to food allergens in breastfed infants with atopic dermatitis

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Background: The differences in the characteristics of breastfed and formula fed individuals with allergy have been addressed in few studies and remain controversial.

Objective: To evaluate the effect of breastfed on the development of food allergy and sensitization against food allergens in infants with atopic dermatitis (AD).

Methods: We reviewed 143 infants (77 boys and 66 girls) with AD who were younger than 6 months and were classified into the following 3 groups based on the type of feeding they received: breastfed, mixed feeding, and formula fed. All infants had never been fed egg or soy. The total and specific IgE levels were then assessed using a commercially available assay.

Results: The total IgE level ($P = .004$) and egg specific IgE level ($P = .002$) were significantly higher in the BF group than in the FF group. The rate of sensitization to egg ($P = .001$) was also significantly higher in the BF group when compared with the FF group, as was the egg allergy rate ($P = .004$).

Conclusion: Our results suggest that breastfeeding might not always be beneficial in allergy prevention in some high-risk infants.

Ann Allergy Asthma Immunol. 2009;103:332–336.

INTRODUCTION

It has been reported that breastfeeding prevents wheezing and atopic dermatitis (AD); however, this preventive effect remains controversial. The results of 2 systematic reviews suggested that breastfeeding plays a protective role against the development of asthma and allergic rhinitis.^{1,2} In addition, according to the results of a meta-analysis of 18 prospective studies,³ exclusive breastfeeding during the first 3 months of life is associated with a lower incidence of AD in children with a family history of atopy than in the general population.

However, the results of a cross-sectional study revealed that Japanese junior high school students who were breastfed had a higher prevalence of AD than those who were exclusively formula fed during infancy.⁴ It has also been shown that high-risk women who avoid dietary antigens during lactation may reduce their children's risk of developing atopic eczema.⁵ Taken together, these results suggest that BF does not always prevent the development of AD.

In clinical practice, AD is occasionally seen in exclusively breastfed infants, is usually associated with a high level of food specific IgE, and responds to switching from breastfeeding to a single formula. Such infants appear to have a food allergy that occurs via breast milk. Indeed, several studies have revealed the presence of food allergens, such as cow's milk, egg whites, and wheat, in the breast milk of lactating

mothers.^{6–8} Furthermore, a 4 month-old infant who was exclusively breastfed reportedly experienced severe anaphylactic shock in response to a fish allergy after ingestion of his mother's milk.⁹ Therefore, this study was conducted to identify food allergy and/or sensitization features against food of early infants with AD based on their feeding type and to investigate the association between AD and breastfeeding.

METHODS

Participants

Infants 6 months or younger with AD were enrolled in this cross-sectional study. All infants were fed either breast milk or formula milk and had never eaten any solid food other than rice-vegetable gruel. All of the lactating mothers did not restrict ingestion of any specific foods until their infants developed AD. After the development of AD, only 26.0% (33/127) of breastfeeding mothers tried to avoid ingestion of egg or milk (but not very strictly). All infants fulfilled the Hanifin and Rajka criteria for AD,¹⁰ and its severity was evaluated by the Six Areas, Six Signs in Atopic Dermatitis (SASSAD) score.¹¹ The mothers were asked to complete a questionnaire that contained information such as feeding pattern, sex, age, birth weight, and age at the onset of AD. To determine if families had a history of allergic diseases or AD, the mothers were asked whether a physician had ever diagnosed any family member as having "allergies." The infants were then divided into the following 3 groups according to their feeding patterns: breastfeeding (BF), mixed feeding (MF), and formula feeding (FF). All infants in the FF group were fed cow's milk-based formula, and 3 of them were fed soy-based formula as well.

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Disclosures: Authors have nothing to disclose.

Received for publication January 27, 2009; Received in revised form April 15, 2009; Accepted for publication April 27, 2009.

This study was approved by the institutional review board at Samsung Medical Center, Seoul, Korea, and written informed consent was obtained from the mothers of each patient before participation in this study.

Measurement of Total and Specific IgE Antibody Level

The levels of total IgE and specific IgE antibodies to 3 common food allergens (egg white, cow's milk, and soybean) were measured using a commercially available system (Uni-CAP system; Phadia, Uppsala, Sweden) according to the manufacturer's instructions. Food specific IgE levels greater than 0.7 kU/L were considered to be positive. Unfortunately, a double-blind, placebo-controlled food challenge was not performed to confirm the diagnosis of food allergy because of parents' refusal. Instead, those who showed a serum egg white specific IgE level greater than 2 kU/L and a cow's milk specific IgE level greater than 5 kU/L were considered to have egg allergy and cow's milk allergy, respectively, based on the diagnostic levels suggested by Sampson.¹² Soy allergy was not evaluated in this study, because individuals with a serum soy specific IgE level of more than 30 kU/L were only 73% likely to show a clinical allergic reaction to soy.¹²

Statistical Analysis

Significant differences among groups were evaluated by using SAS software (SAS Institute Inc, Cary, North Carolina). χ^2 Tests were used to compare sex, family history, extent of sensitization, incidence of food allergy, and severity of AD among groups. A *t* test or Mann-Whitney *U* test was used to identify differences in the serum total IgE and specific IgE levels between groups. *P* < .05 was considered significant.

RESULTS

Of the 143 patients enrolled in this study, 65, 62, and 16 were included in the BF, MF, and FF groups, respectively. The clinical characteristics of the infants are given in Table 1.

Their mean age was 4.4 months, and the mean age of AD onset was 1.3 months; these values did not differ significantly among the 3 groups. In addition, there were no significant differences in the SASSAD scores of the whole body or face. The percentages of patients with severe AD (SASSAD score ≥ 15) were similar among the 3 groups (66.2% [43/65] in the BF group, 67.6% in the MF group, and 62.5% [10/16] in the FF group). The presence of family history of allergic diseases or AD in each group was not statistically different. Maternal AD was present in 12.3% in the BF group, 4.8% in the MF group, and 0% in the FF group, which seemed to be different among the 3 groups, but a χ^2 test revealed that the difference in the family history of maternal AD was not statistically significant (*P* = .13).

The results of in vitro evaluation of the serum IgE level for each feeding group are given in Table 2. In the BF group, the levels of total IgE (*P* = .004) and egg white specific IgE (*P* = .002) were significantly higher than those in the FF group (Table 2). In addition, we also observed significant differences in the egg white specific IgE levels between the MF and FF groups. However, cow's milk and soy specific IgE levels were similar among the 3 groups.

The rate of sensitization to 3 common food allergens and the development of food allergy in each feeding group are given in Table 3. The rate of sensitization and allergy to egg was significantly higher in the BF and the MF groups than in the FF group. However, feeding type during the first 6 months of life did not increase the sensitization to cow's milk and soybean.

DISCUSSION

The development of AD is associated with genetic, immunologic, and environmental factors, as well as defects in skin barrier function. Among them, food allergens have a well-known contribution to disease activity of AD, especially in

Table 1. Clinical Characteristics of the Study Population^a

Characteristic	BF group (n=65)	MF group (n=62)	FF group (n=16)	P value
Age at first visit, mean (SE), mo	4.58 (0.16)	4.31 (0.18)	4.24 (0.38)	.44
Age at onset of AD, mean (SE), mo	1.45 (0.18)	1.26 (0.14)	1.13 (0.22)	.55
M/F ratio	33:32	37:25	7:9	.67
SASSAD score mean (SE)				
Whole body	13.58 (1.48)	12.75 (1.50)	12.18 (2.43)	.87
Face	5.03 (3.11)	3.61 (2.27)	4.27 (2.27)	.98
Family history of allergic disease (at least 1 member of the family)	47 (72.3)	28 (45.2)	10 (62.5)	.11
Mother	19 (29.2)	15 (24.2)	5 (31.2)	.61
Other member	28 (43.1)	13 (21.0)	5 (31.2)	.18
Family history of AD (at least 1 member of the family)	21 (32.3)	12 (19.4)	2 (12.5)	.13
Mother	8 (12.3)	3 (4.8)	0 (0.0)	.13
Other member	13 (20.0)	9 (14.5)	2 (12.5)	.61

Abbreviations: AD, atopic dermatitis; BF, breastfeeding; FF, formula feeding; MF, mixed feeding; SASSAD, Six Areas, Six Symptoms in Atopic Dermatitis.

^a Data are given as number (percentage) of each group unless otherwise indicated.

Table 2. Serum IgE Levels of Each Feeding Group

Variable	Serum IgE, kU/L ^a			P value ^b	
	BF group	MF group	FF group	BF vs FF	MF vs FF
Total IgE	107.68 (26.35)	69.04 (22.18)	24.64 (8.56)	.004 ^c	.07
Specific IgE					
Egg white	8.43 (2.52)	7.97 (2.45)	0.09 (0.07)	.002 ^c	.002 ^c
Cow's milk	2.75 (1.57)	1.34 (0.84)	0.57 (0.14)	.12	.22
Soybean	2.88 (1.57)	2.04 (1.83)	0.00 (0.00)	.07	.27

Abbreviations: BF, breastfeeding; FF, formula feeding; MF, mixed feeding.

^a Data are given as mean (SE).

^b A *t* test was used to identify differences in serum total IgE and specific IgE when the BF group was compared with the FF group and the MF group was compared with the FF group.

^c Significant difference.

Table 3. Food Allergen Sensitization and Food Allergy of Each Feeding Group^a

Allergen variable	Food	BF group (n=65) ^b	MF group (n=62) ^b	FF group (n=16) ^b	P value	
					BF vs FF	MF vs FF
Sensitization	Egg	26 (40.0)	25 (40.3)	1 (6.2)	.01 ^c	.01 ^c
	Milk	19 (29.2)	7 (11.3)	3 (18.8)	.40	.43
	Soy	11 (16.9)	8 (12.9)	0 (0.0)	.08	.13
Food allergy	Egg	24 (36.9)	21 (33.9)	0 (0.0)	.004 ^c	.006 ^c
	Milk	3 (4.6)	2 (3.2)	0 (0.0)	.38	.47

Abbreviations: BF, breastfeeding; FF, formula feeding; MF, mixed feeding.

^a Specific IgE levels of greater than 0.7 kU/L by a commercially available assay (UniCAP) were considered to be positive. Infants with an egg specific IgE level of greater than 2 kU/L and a cow's milk specific IgE level of greater than 5 kU/L were considered to have an allergy to egg and cow's milk, respectively.

^b Data are given as number (percentage) of each group.

^c A *t* test was used to identify differences in the sensitization and food allergy between the BF and FF groups and between the MF and FF groups.

infants and young children.^{13–18} The overall prevalence of IgE-mediated food allergy in infants with AD has been found to range from 33% to 81% in various studies, although it is generally estimated to be 30%.^{14,15} Furthermore, Lack et al¹⁶ found that severe AD and younger age are risk factors for food allergy. It has also been reported that the presence of eczema during the first 6 months of life is associated with an increased risk of peanut allergy and that the risk of egg, milk, or peanut allergy is twice as high if eczema occurs during the first 6 months of life than if it occurs between 6 and 12 months of life.^{16–18}

According to meta-analytic data,^{1,2} breastfeeding is beneficial for most allergic diseases. However, there appears to be a subgroup of patients who may not benefit from BF and are instead adversely affected.^{19–21} In the present study, we attempted to investigate the role of breast milk on developing sensitization to food allergens and food allergy during early infancy. We enrolled the infants younger than 6 months to exclude the effects of food allergens that had never been eaten by the infants. Our results revealed that breastfed infants with AD showed a higher serum egg white specific IgE level, a higher rate of sensitization to egg, and more egg allergy than infants in the FF group. Furthermore, the levels of cow's milk and soy specific IgE were higher in the BF

group than in the FF group, although these differences were not statistically significant. Our data suggest that breast milk may play a certain role in sensitization to food allergens.

It is presumed that sensitization to food allergens during early infancy could occur via in utero exposure through the placenta, by breast milk, or via cutaneous exposure.^{6–8,22–25} Sensitization via cutaneous exposure was demonstrated in the animal studies in which exposure of mice to ovalbumin or peanut via abraded skin led to significant food specific IgE responses.^{24,25} Furthermore, low-dose exposure to peanut in the form of arachis oil applied to the inflamed skin of human infants was associated with an increased risk of peanut allergy at 5 years of age.¹⁶ It is speculated that sensitization by cutaneous exposure is more likely to occur in the patients with more severe AD, especially in the face. We compared the severity of AD, including facial dermatitis among groups, but there was no difference in the presence and extent of AD.

The proliferation of allergen specific T cells from cord blood in response to proteins present in cow's milk (β lactoglobulin, α -casein, β -casein, κ -casein, and bovine serum albumin) suggests that fetal sensitization is possible.^{22,23} The route of sensitization at this early age is not clear in our study. However, a significantly higher rate of sensitization to egg white was observed in the BF group. Furthermore, the levels

of milk and soy specific IgE were higher in the BF group than in the FF group, although these differences were not statistically significant. Taken together, these findings suggest that breast milk may be a major route of food exposure. Considering that most breastfeeding mothers consumed egg, milk, and soybean, infants might be exposed to food allergen through breast milk. These results are supported by several studies in which food allergens have been detected in breast milk.^{6–8} Furthermore, the role of breast milk in the food sensitization observed in the present study was also supported by the association between the duration of breastfeeding and the egg specific IgE levels.^{19,26}

In this study, the milk specific IgE level in the FF group was not significantly higher than the IgE levels in the BF and MF groups. Based on the amount and frequency of exposure to milk protein, the FF group was expected to have a high level of milk specific IgE; therefore, the risk factors for food allergy beyond food allergen exposure in the BF group were suspected. The effects of maternal origin are believed to play an important role in AD (and other atopic conditions).²⁷ For example, Ruiz et al²⁸ reported that infantile AD was more closely related to maternal than paternal disease status. Allergic inflammation is typically characterized by altered production of mediators, such as cytokines and immunoglobulins, and it has been shown that the allergy history of the mother influences breast milk composition.²⁹ Specifically, breast milk from atopic women has been found to contain higher levels of interleukin 4, interleukin 8, regulated on activation normal T-cell expressed and secreted (RANTES), IgE, and n6/n3 polyunsaturated fatty acids, which are believed to induce sensitization to allergens in the infant recipient. In this study, the BF group had a higher rate of maternal AD than the FF group, although this difference was not significant. However, there still might be a possibility that a difference in genetic susceptibility between the BF and FF groups might contribute to the difference in sensitization to food allergen, because mothers with allergy, especially AD, have a tendency to feed breast milk to their infants.

One limitation of our study is that the FF group was smaller than the other groups. In the present study, the 3 groups (BF, MF, and FF) were not randomly divided but were determined according to parental preferences. That is why the numbers of each group were not evenly distributed. Despite the few infants in the FF group, there were no statistical differences in age at first visit, age at onset of AD, sex, severity of AD, or family history of allergic diseases or AD among the 3 groups. Although the number of infants in the FF group was small, the statistical analysis showed that significantly more infants in the BF group were sensitized to egg and manifested egg allergy than in the FF group.

In conclusion, our results showed that BF patients with AD had a higher rate of sensitization to egg white during early infancy, which suggests that BF might not always be beneficial in allergy prevention in some high-risk infants (ie, maternal AD).

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