

Prevention of allergic disease. Exposure to food allergens and dietetic intervention

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Pediatr Allergy Immunol 1996; 7 (suppl 9): 102–107. © Munksgaard 1996.

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Key words: food allergy; sensitization; dietary prevention

Food allergy (FA) is principally a problem in infancy and early childhood, and most often the infants will develop FA in the same order as that in which the foods have been introduced into the diet.

Reproducible clinically abnormal reactions to food protein(s) may be due to the interaction between one or more immune mechanisms, possibly any of the four basic types of hypersensitivity reactions. Immunologically mediated reactions, mainly IgE-mediated reactions, are defined as food protein allergy (FA). Non-immunologic reactions are defined as food protein intolerance (FI).

In prospective studies the incidence of cow's milk protein allergy/intolerance (CMPA/CMPI) in infancy has been estimated to be about 2–3% based on strict diagnostic criteria (1, 2). Other FA/FI also commonly seen are to egg white, fish, cereals, peanut and soybean. The total cumulative incidence of FA/FI during the first 3 years of life has been found to be about 7–8% (3).

Development of food allergy/intolerance

The development of FA/FI depends on several factors, especially genetic allergy predisposition, early "foreign" food protein exposure (time, dose, frequency), allergen (food protein) uptake and handling. The rather high incidence of FA/FI and especially CMPA/CMPI in infancy has been suggested to be due to an incomplete mucosal barrier, increased gut permeability to large molecules and immaturity of local and systemic immunologic responses. Human colostrum/milk facilitates maturation of the gut and provides a passive protection against bacteria and antigens (allergens) by means of specific secretory IgA and other protecting factors (4–6). Sensitization to food protein, e.g. milk-protein, may occur prenatally or postnatally.

Sensitization to food allergens

Prenatal

Food antigens may cross the placenta eliciting an immune response in the fetus. Previously only a few studies demonstrated specific IgE antibodies against whole milk/egg proteins by means of RAST analysis in 2–3.7% of unselected and atopic predisposed newborns (Table 1). Recently, specific IgE against individual cow's milk proteins (CMP) in cord blood was demonstrated by means of Magic Lite SQ system in 11% and 9% of newborns with and without atopic predisposition respectively (14), indicating that prenatal formation of specific IgE may be more frequent than previously suggested. By means of CRIE analysis another prospective study (15) has demonstrated specific IgE against individual CMP in cord blood in 76% of a selected group of infants with later development of CMPA/CMPI. Thus, prenatal sensitization may play a role in the pathogenesis of FA. Perhaps a weak intrauterine induction of a low IgE response may need to be "boosted" neonatally in order to cause clinical disease?

Postnatal

Postnatal sensitization to foods and reproducible clinical reactions to foods are principally a problem of early infancy. Neonatal exposure to and uptake of food proteins may be increased due to several factors such as incomplete mucosal barrier, increased gut permeability to macromolecules and immaturity of local and systemic immunologic response. As intestinal permeability is more pronounced in preterm neonates and causes increased absorption of macromolecular bovine milk proteins, an increased frequency of CMPA/CMPI among these infants might be expected. However, two prospective studies (2,

Table 1. Specific IgE antibodies (RAST) in cord blood. Newborns without and with atopic predisposition

	Disp	Incidence	Specific IgE
Michel 1980 (6)	No	3/136 (2.2%)	milk
Croner 1982 (7)	No	0/120	milk, egg
Delespesse 1983 (8)	No	2/96 (2%)	milk, grass
Kjellman 1976 (9)	Yes	0/99	foods
Hamburger 1983 (10)	Yes	0/55	egg, milk, peanut
Businco 1983 (11)	Yes	1/101 (1%)	milk
Fälth Magnusson 1987 (12)	Yes	0/139	milk, egg, (BLG, OA, ovomucoid)
Chandra 1991 (13)	Yes	9/245 (3.7%) 9/234 (3.8%)	milk soy

BLG = beta-lactoglobulin, OA = ovalbumin

16) did not report an increased incidence of CMPA/CMPI in preterm infants.

Human milk

Food proteins are absorbed from the gut and can be measured in the blood in quantities of micrograms per liter serum both in children and adults. Likewise, "foreign" food proteins are secreted into the breast-milk of lactating women as reviewed by Høst (2). FA may occur in exclusively breastfed infants. In a Danish study (2) the 1-year incidence of CMPA/CMPI in "exclusively" breastfed infants was found to be 0.5%. However, all of these infants had been given supplements of cow's milk based formula in the first few days of life. The CMP betalactoglobulin can be detected in the breast milk of 95% of lactating women (0.9-150 µg/l, median value 4.2 µg/l) when consecutive testing of breast milk is done (2). Considering the low frequency of CMPA/CMPI in exclusively breastfed children these small amounts of CMP and other "foreign" food proteins in breastmilk may rather induce tolerance than allergic sensitization and development of allergic disease.

Sensitization to foods, also during exclusive breastfeeding, may rather be due to "unknown breaks" in the dietary regimen, inhalation of food proteins or contact with "contaminate" hands.

Formulae

Previous retrospective studies (17, 18) and prospective studies (1, 2, 16) have demonstrated an association between cow's milk formula feeding and development of CMPA/CMPI. A significant association between early neonatal exposure to cow's milk formula feeding and subsequent development of CMPA/CMPI has been documented as reviewed by Høst (2).

Soy protein is reported to be at least as allergenic as CMP, and in infants fed soy milk a high incidence of soy protein allergy has been reported (19-23).

Table 2. Dietary intervention in "high-risk" infants. Prospective studies including control group

Infant diet Breastfeeding ≥ 4 months				
Study	Number	Follow-up (months)	Diet	Effect
Chandra et al, 1985 (33)	121	24	BF:	AD, Wh ↓
Miskelly et al, 1988 (23)	487	12	BF:	Atopy ↓
			CM=Soy:	Atopy →
Chandra et al, 1991 (13)	263	18	BF:	AD, Atopy ↓
			CM=Soy:	Atopy →
Chandra et al, 1989 (34)	221	18	BF:	AD ↓
			CM=Soy:	AD →
Vandenplas, 1988 (35)	45	4	BF:	Atopy ↓
				CMPA ↓
Lucas et al, 1990 (16) (777 preterms)	160	18	BF:	Atopy ↓
				CMPA ↓
Halken et al, 1993 (36)	141	18	BF:	CMPA ↓
Hypoallergenic formula ≥ 4 months				
Vandenplas 1988 (35)	45	4	pHF:	CMPA, Atopy ↓
Chandra 1991 (13)	263	18	pHF:	AD, Atopy ↓
Vandenplas 1992 (37)	67	12	pHF:	CMPA 15.6% Atopy 21.8%
			CM:	CMPA 42.8% Atopy 48.6%
Chandra 1989 (34)	221	18	eHF:	AD ↓
Zeiger 1989, 1992 (38, 39)	225	48	eHF:	FA ↓
Halken 1993 (36)	141	18	eHF:	CMPA ↓ (3.6%)

pHF = partially hydrolysed formula = low degree of hydrolysis

eHF = extensively hydrolysed formula = high degree of hydrolysis

BF=breastfeeding, CM=cow's milk based formula, AD=atopic dermatitis,

Wh= wheeze, FA=food allergy, CMPA=cow's milk protein allergy

Solid foods

Early introduction of solid foods before 4 months of age in high-risk infants is associated with a higher incidence of atopic dermatitis in early childhood (24-29).

Dietary allergy prevention

Prophylactic measures can be directed to avoid sensitization and development of disease and to avoid disease manifestation in an individual with the disease.

Primary prevention

In prospective studies, an effect of dietary allergy prevention has only been demonstrated in high-risk infants, i.e. infants with at least one first-degree relative (parent or sibling) with documented atopic disease (doctor's diagnosed), eventually combined with an elevated cord blood IgE.

Prospective studies on high-risk infants have shown a preventive effect of different dietary allergy prevention programmes on the cumulative incidence

Table 3. Dietary intervention in "high-risk" infants. Prospective studies including control group

Maternal diet			
Maternal diet during pregnancy			
Study	Number	Follow-up (months)	Effect
Fälth Magnusson 1987 (12)	180	0	Spec. IgE → Total IgE →
Fälth Magnusson 1992 (40)	180	60	Atopy →
Lilja 1989 (41)	163	18	Atopy →
Maternal diet during pregnancy and lactation			
Chandra 1986 (42)	109	12	AD → CM: AD ↑
Zeiger 1989, 1992 (38, 39)	225	48	FA ↓
Lilja 1989 (41)	107	18	Atopy →
Maternal diet during lactation			
Businco 1983 (11)	101	24	BF, Soy: Atopy ↓ CM: Atopy ↑
Chandra 1989 (34)	97	18	BF - D: AD ↓ BF + D: AD ↓↓
Lilja 1989 (41)	81	18	BF + D: Atopy →
Sigurs 1992 (43)	115	48	BF + D: Atopy → AD ↓

BF=breastfeeding, D=maternal diet, CM=cow's milk based formula, AD=atopic dermatitis, Wh=wheeze

of FA, especially CMPA/CMPI and atopic dermatitis. A few studies also showed a reduction in the prevalence of recurrent wheezing until the age of 12–18 months (30–32), but some of these (31, 32) also included environmental measures.

Due to the spontaneous course of FA/FI it is important to evaluate the cumulative incidence of FA/CMPA during the first 3–4 years of life – and not only the point prevalence at the age of 3–4 years. Moreover proper diagnostic criteria are important. Due to great variations in e.g. study design and diagnostic criteria, it is not possible to compare the effect of these programmes.

Breastfeeding – In high-risk infants, breastfeeding in combination with avoidance of CM and solid foods during ≥ 4 months has resulted in a significant reduction of the cumulative incidence of CMPA/CMPI during the first 1–2 years of life (Table 2).

Sensitization to CMP as well as CMPA during the first years of life occurred in breastfed children only if they had been exposed to CMP during the first days of life (1, 2).

A few studies indicate that the preventive effect of breastfeeding on development of atopic dermatitis may be enhanced by maternal avoidance of potential food allergens (milk, egg, fish) during the lactation

Table 4. Contents of beta-lactoglobulin in CM and some HF-products

	Dry weight ($\mu\text{g/g}$)	Ready to use ($\mu\text{g/l}$)	
	Oldaeus, 1991 (47)	Mäkinen-Kiljunen, 1993 (48)	
Cow's milk	117 000	4 000 000	
LHA		200	31 200
Good Start	200	83	12 400
Alfa-Ré	-	0.12	14.5
Profylac	0.066	0.066	8.9
Pregomin	-	0.065	9.7
Pepti-Junior	-	0.0061	0.91
Nutramigen	0.006	0.0056	0.84
Alimentum	0.03	-	

Breast milk
according to Jakobsson, 1985 (49): 5–33 $\mu\text{g/l}$
according to Høst, 1990 (2): 0.9–150 $\mu\text{g/l}$

period. Other studies do not confirm this finding (Table 3). No studies document any protective effect of maternal diet during pregnancy (Table 3).

Hydrolysed formulae – When breastmilk is insufficient or lacking, a substitute formula is needed. More than 50 years ago, extensively hydrolysed formulae (eHF) have been developed in order to decrease the allergenicity of CMP. Hydrolysed formulae are processed by an enzymatic hydrolysis of CMP – eventually combined with an ultrafiltration.

For 50 years extensively hydrolysed casein formulae have been used and have been regarded safe for the treatment of CMPA/CMPI. Recently, an ultrafiltrated whey formula has been shown to be safe for treatment of CMPA/CMPI (44), in contrast to partially hydrolysed formulae (pHF). Hydrolysed formulae have been investigated in studies on prevention/reduction of the incidence of food allergy in high-risk infants. Several prospective studies show a preventive effect of eHF in combination with avoidance of CMP and solid foods during ≥ 4 months in high-risk infants (Table 2) on the cumulative incidence of FA, especially CMPA/CMPI until the age of 4 years. In two prospective studies the cumulative incidence of FA and CMPA/CMPI was significantly reduced until the age of 5 and 7 years (45, 46). Thus, a real reduction and not only a postponement of the onset of the disease was documented. Also, a reduction of the cumulative incidence of atopic dermatitis was demonstrated. Some of these studies showed a significant reduction in the cumulative incidence of recurrent wheezing until the age of 1–1½ years (30–32). However, at follow-up at 4 and 7 years of age, Zeiger et al (39, 46) found no reduction of asthma or rhinitis.

According to the source of proteins and the degree of hydrolysis, there are several types of hydrolysed formulae. Compared with eHF, partially hydrolysed formulae contain a high proportion of non-degraded proteins in the molecular weight range 8–

40 kDa. As shown in Table 4, the content of beta-lactoglobulin in pHF is very high compared with eHF.

Partially hydrolysed formulae may be effective in allergy prevention, but due to drawbacks of study design, e.g. lack of clear well-defined diagnostic criteria, lack of immunologic documentation, and unclear challenge procedures, pHF cannot be recommended at present (50).

Studies comparing pHF and eHF are not yet available, but presently a prospective, randomized, double-blind, controlled study comparing the preventive effect of 2 eHF's and a pHF is being performed in Denmark.

Solid foods – A preventive effect of breastfeeding or hydrolysed formulae has only been shown in studies including avoidance of solid foods during at least the first 4 months of life (Table 2).

Duration of the diet – The duration and the dietary restrictions vary in the different studies. All studies showing a preventive effect have included a diet with breastmilk or hydrolysed formula and avoidance of CMP and solid foods $\geq$ 4–6 months. Some studies include rather restrictive diets for a long period. In one of these (38, 39), breast/eHF for 12 months, avoidance of solids $>$ 6 months, avoidance of CMP, soy, corn $>$ 12 months, and egg, fish, peanut $>$ 24 months is recommended. In this study a few children developed FA against egg and peanuts at the age of 3 years despite the extensive diet. Other studies (30, 36) only include breastfeeding or eHF for 6 months, avoidance of CM and solids for 6 months. These studies both showed a significant reduction of FA (especially CMPA/CMPI), but due to different study designs the effect of these different regimens are not comparable. In the latter study a recent 5-year follow-up (45) did not reveal development of new FA, and thus this regimen seems to be sufficient. No studies concerning the preventive effect of avoidance of milk and other potential food allergens e.g. egg, fish etc. after the age of 4–6 months of life have been performed.

Duration of the effect – Recent studies show a real preventive effect as regards food allergy – with a significant reduction in the cumulative incidence of CMPA/CMPI – and not only a postponement of the onset of the disease (39, 45, 46). Concerning other allergies, further long-term follow-up of present studies is awaited.

Secondary prevention

Apart from efforts in preventing sensitization and development of atopic disease, it is important and

necessary to prevent symptoms and progression of the disease in patients who already have developed the disease. After diagnostic controlled elimination/challenge procedures have verified the diagnosis, a sufficient elimination diet avoiding the food in question should be established. Due to the natural course of FA/FI, rechallenges should be performed every $\frac{1}{2}$ –1 year until tolerance has developed.

Conclusion

In high-risk infants fed exclusively breastmilk and/or eHF combined with avoidance of cow's milk proteins and solid foods during at least the first 4 months of life, a significant reduction of the cumulative incidence of food allergy, especially CMPA/CMPI, in the first 4 years has been documented. Also a reduction in the cumulative incidence of atopic dermatitis during the first 2–4 years of life is found. As no studies concerning the preventive effect of avoidance of milk and other foods after the age of 4–6 months of life have been performed, recommendation of preventive elimination diets beyond this age is empirically based. In order to reduce the costs and to minimize the risk of stigmatisation and the risk of malnutrition, it is important to avoid unnecessary restrictive and prolonged diets. A diet period of 4–6 months seems sufficient in most infants. At present eHF are recommended for avoidance of cow's milk. The results of studies comparing the preventive effect of eHF and pHF are awaited. A few high risk infants may benefit from maternal diet during lactation, but there is no documented beneficial effect of maternal diet during pregnancy.

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