

Prevention of childhood allergy by dietary manipulation

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Introduction

Allergic asthma and rhinitis, atopic dermatitis (AD), urticaria and gastrointestinal allergy, are common diseases of infants and children. The phenotypic expression of these illnesses varies widely, being very mild in some cases, severe and frustrating in many, and even life-threatening in others.

Specific IgE to foods and positive challenge test to a number of food allergens are frequently present in children with these disorders. Cow's milk appears to be the most common offending food both in gastrointestinal (vomiting, diarrhoea, etc.) and in cutaneous manifestations (urticaria and AD). About 2% of infants suffer from more or less adverse reactions to cow's milk.

Human milk has been for centuries the only way of feeding human neonates. Since the beginning of this century cow's milk formulae became a common breast-milk substitute when mother's milk was not available. Over this century and especially in the last decade other formulae have been developed in order to reduce the antigen load and therefore the risk of sensitization. Therefore, paediatricians and paediatric allergists are now confronted with a difficult but important selection among differing so-called 'hypoallergenic' formulae when breast milk is not available for babies at high risk of atopy.

In this presentation, current knowledge on the dietary measures during pregnancy, lactation and infancy which should be addressed for the prevention of atopic diseases, and the nutritional adequacy and the allergenicity of 'hypoallergenic' formulae will be reviewed. In addition, some guidelines for the use of hypoallergenic formulae for feeding babies with cow's milk allergy will be given.

Dietary measures during pregnancy

Although several data suggest that antenatal sensitization to food antigens may occur, this phenomenon is rather rare. No specific IgE antibodies to the most common offending foods (cow's milk and egg) were recently detected in cord blood of babies, even if their mothers had a high intake of these foods (at least one egg and one litre of cow's milk daily) during the last three months of pregnancy [1].

Antenatal sensitization to different food antigens may be explained not only by the transfer of nutrients via the placenta, but also by the transfer of anti-idiotypic antibodies from the mother to the foetus.

In order to reduce the risk of antenatal sensitization, different approaches have been suggested recently, including modifying the mothers' diet during pregnancy. Chandra *et al.* have shown that the complete exclusion of

milk and dairy products, eggs, fish, beef and peanuts throughout pregnancy was associated with a reduced prevalence of AD and also a significant reduction in the severity score of skin lesions [2]. More recently, Fälth-Magnusson *et al.* in a randomized study, were not able to confirm the protective effect of dietary measures during pregnancy [3]. However, we would like to emphasize that in this study the dietary measures were advised only in the last trimester of pregnancy and the mothers were encouraged to drink a casein-hydrolysed formula (Nutramigen) during the dietary restriction period. We can speculate that the shorter period of dietary restriction and the use of this formula may have influenced the negative result (see section on hydrolysate formulae).

Prolonged breast feeding

As discussed in detail in recent reviews, the preventive effect of breast-feeding on allergy development in high-risk infants has been shown by several prospective studies [4,5]. There is a general agreement that high-risk babies

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should be exclusively breast-fed for the first 6 months of life. Human milk provides the infants not only with homologous proteins which are not allergenic but also with a number of immunological factors which can prevent the absorption of macromolecules. Therefore the preventive effect might be antigen non-specific.

Dietary measures during lactation

About 70 years ago American paediatricians documented that AD in fully breast-fed infants could be related to foods ingested by their mothers, and that eczema cleared up when the mothers avoided the offending food(s). In addition, it was shown that exclusively breast-fed babies with AD had positive skin tests to foods never ingested. It was therefore suggested that food antigens ingested by the mothers might pass into breast milk, thus sensitizing the babies. This passage was first demonstrated by Stuart [6] who found that egg white was present in breast-milk to a dilution of 10^{-9} .

The excretion of foreign proteins in human milk was a distinct possibility and this was later shown by the finding of skin tests positive to egg in 21% of breast-fed infants, but only in 7% of bottle-fed babies [6]. Furthermore, IgE antibodies to different foods such as cow's milk (CM), egg, etc. have been shown in fully breast-fed babies. Recently a number of studies (review in [7]) reported that fully breast-fed babies can experience a variety of allergic symptoms related to CM, soy milk, goat's milk, eggs and fish, the components of which passed from mothers to infants via the breast-milk. In addition, several reports have demonstrated the presence of β -lactoglobulin (BLG), casein, ovalbumin, and gliadin in breast-milk. The transfer of BLG from the mother's gut lumen to breast-milk appears to take place during the whole lactation period and BLG levels varied remarkably intra- and interindividually, correlating with babies' symptoms (review in [7]). We have evaluated the clinical and immunological features of 21 children with food allergy followed up to 19 years, in whom the sensitization appeared to be related to foods present in breast milk. During the follow-up, only five (23%) of the children (median age 14 years) developed tolerance toward the offending food and eight (38%) children developed asthma. Breast-milk may be not only a route of IgE sensitization but the natural history of food allergy due to this unusual route appears to be less optimistic than common food allergy [7].

Chandra *et al.* have demonstrated that the complete exclusion of cow's milk, eggs, fish and peanuts during breast-feeding (six months) significantly reduced the prevalence of AD [2]. In a prospective randomized study, Hattevig *et al.* [8] have shown that the avoidance of cow's

milk, eggs and fish during the first three months of lactation was associated with a statistically significant reduction in the prevalence of AD at the age of three and six months. However, although AD appeared later and with a milder severity score in the infants from the maternal-diet group during the 18-month follow-up, no significant difference in the prevalence of AD and other atopic manifestations was present when the infants were more than six months of age.

We have investigated the sensitizing effect via breast-milk of the partial hydrolysed (whey proteins) hypoallergenic formula (HA). The formula was given (400 ml daily) to 39 nursing 'high-risk' mothers throughout the lactation period (six months). The controls were 39 'high-risk' mothers who consumed 400 ml of cow's milk daily. There was no significant difference in the cumulative incidence of atopic diseases in the babies at one year of age according to the mothers' diet. However, the prevalence of babies at six and 12 months with specific IgE and with total IgE more than 2 s.d. above the normal values for age were significantly higher ($p=0.02$) in the group of babies whose mothers received the hypoallergenic formula. This preliminary study shows that this partially hydrolysed formula not only still contains peptides which are able to sensitize high-risk babies via breast-milk, but it seems even more sensitizing than cow's milk.

It seems crucial from these studies to avoid allergenic foods such as cow's milk, eggs and fish throughout the breast-feeding period in order to prevent sensitization via breast-milk. In addition, it seems from our preliminary data that cow's milk protein hydrolysate formulae, when given to nursing mothers, may sensitize the babies via breast milk.

Soy-protein formulae

Soy-protein formulae have been used for feeding infants with cow's milk allergy since 1929. They contain purified soy proteins, the fat is a mixture of vegetable oils, and carbohydrates are represented by maltodextrines, corn, starch, or saccharose. Soy-protein formulae are accepted well by most infants, and their nutritional adequacy is comparable to that of cow's milk formulae.

Recent studies performed on infants fed a soy formula exclusively during the first six months of life revealed no immunologic abnormality or increase in infection morbidity as previously reported [9]. The daily recommended vitamin requirements are added to soy formulae, including vitamin D, so that problems similar to those found in premature infants have never been found in full-term infants (review in [10]). More recently, carnitine has been added to some soy formulae. Carnitine is a nitrogen quaternary base present in meat and cow's milk and

synthesized by the body from lysine and methionine. Carnitine allows the oxidation of long-chain fatty acids so that they can be transferred from the cytoplasm into mitochondria, where they undergo β -oxidation, which produces energy. Infants can store only limited quantities of carnitine and cannot synthesize adequate quantities of it from lysine and methionine because they lack the enzymes necessary for the biosynthesis. Carnitine deficiency has been reported in infants fed soy formulae without added carnitine and can cause subclinical or clinical manifestations due to a deficiency in the utilization of long-chain fatty acids. These fatty acids can accumulate in the muscle and liver cells, while the concentration of triglycerides increases in the plasma. For these reasons, carnitine has recently been added to various soy formulae in concentrations similar to those found in human milk [10].

Soy-protein formulae are used for different conditions including cow's milk allergy, cow's milk protein intolerance, lactose and galactose intolerance and in the management of infants with severe gastroenteritis. The use of such formulae for the prevention of atopy is rather controversial. Some studies have shown that breast-feeding supplemented with soy formula for the first six months of life significantly reduced the prevalence of atopic diseases [11,12]. Over the last decade we have worked on atopy prevention in high-risk babies. In Table 1 the dietary and environmental measures of our prevention programme are reported. The results of our studies show that the onset of allergic disease is significantly reduced using the prevention measures. Summing up our studies using a soy-protein formula when breast-milk was not available, we did not see an increased prevalence of soy sensitization [13–16]. However, other studies failed to show any preventive effect of soy formulae [17,18]. More recently we have shown, in a multicentre study compris-

ing 2291 babies with the cooperation of many Italian maternity hospitals, that babies fed breast- and/or soy-milk and whose parents strictly followed the environmental measures had at one year of age a lower prevalence of atopic diseases (5%) in comparison with cow's milk formula bottle-fed babies (13%).

There is no doubt that soy proteins can induce sensitization and different allergic manifestations. However, in the last decade soy allergenicity has been frequently emphasized in the literature, without providing data on the true prevalence of soy allergy in different allergic diseases. Sampson has found that only 5% of 204 patients with AD showed soy sensitivity, as demonstrated by double-blind placebo-controlled challenge tests [19]. We have confirmed that only 4% of 143 children with AD showed positive challenge test to soy [20]. Fomon has recently summed up his 30-year studies on the use of soy-protein formulae for infant nutrition, emphasizing that less than 1% of the soy-formula fed babies show adverse reactions to soy-protein [21].

Soy formulae are often poorly tolerated by infants with chronic diarrhoea and intolerance to cow's milk proteins. Therefore, intolerance to soy proteins is a cause of chronic diarrhoea often coexisting with cow's milk intolerance. Some investigators consider soy intolerance to be caused by sensitivity to soy protein. However, neither a demonstration of soy protein sensitivity nor the mechanisms of this intolerance have been demonstrated. It has been shown that a soy formula with lactose was useful for feeding infants with chronic diarrhoea and secondary multiple protein intolerance, including cow's milk and soy proteins alone (review in [10]).

In conclusion, soy formulae are nutritionally adequate and are well accepted by many infants. Many foods such as cakes, biscuits, ice cream, desserts and beverages can be made with soy-protein formulae, thus offering a varied

Table 1. Dietary and environmental measures

Dietary measures	Environmental measures
Exclusive breast-feeding for the first six months of life	Absolutely no smoking in the house
Total avoidance of cow's milk, dairy products and eggs for the nursing mothers	Strict environmental controls for the elimination of house dust mite
Soy milk supplement when breast-milk is not sufficient	No pets in the house
Selected weaning after the sixth month of life	Day-care centre attendance delayed to after the third year of life
Cow's milk and dairy products gradually introduced after the sixth month and gluten shortly afterwards	

diet to children with cow's milk allergy. Although soy proteins can be sensitizing, they are less allergenic than cow's milk proteins.

Hydrolysate formulae

Hydrolysed formulae have been developed with the aim of decreasing or eliminating the allergenicity of cow's milk proteins. The use of these formulae is based on the premise that predigested protein, when fed as amino acids and peptides, provides nutrients in a non-antigenic form. Thus, protein hydrolysate formulae have been classified as 'hypoallergenic'.

These formulae are processed using two main technologies: heat denaturation and enzymatic hydrolysis for reducing the molecular weight of peptides. Heat treatment eliminates conformational antigenic determinants, while enzymatic hydrolysis affects sequential determinants. These different technical procedures are necessary for obtaining an acceptable palatability. The reduction of the antigenicity (peptides with very low molecular weight) is associated with a reduction of the palatability.

The allergenicity of these formulae is dependent on several factors such as the degree of digestion, post-hydrolysis processing, elimination of the enzymes used for the hydrolysis, and protein source. Extensively hydrolysed formulae are considered the most hypoallergenic, whereas partly hydrolysed formulae are considered less hypoallergenic and even dangerous in children with cow's milk allergy [22,23]. Molecular-weight profiles of protein hydrolysates are an index of the extent of hydrolysis.

According to the protein source there are three types of hydrolysate formulae: bovine casein (Alimentum, Nutramigen, Pregestimil), bovine whey (Alfa-Rè, Prophylic), soy and bovine collagen (Pregomin). In addition, a bovine whey part hydrolysate formula with lactose has been developed (Beba HA, which is called HA in Italy and Good Start HA in the U.S.). However, due to the less extensive hydrolysis this formula should be given only for prevention and not for treatment of infants with cow's milk allergy. These formulae are integrated with vegetable lipids; Alfa-Rè, Alimentum and Pregestimil contain medium-chain triglycerides. All hydrolysate formulae, except Beba HA, are lactose free, and contain a small amount of carnitine. They are rather unpalatable (except Good Start HA) and for this reason the compliance is poor.

Hydrolysate formulae are nutritionally adequate and infants generally gain weight unless they refuse the formula because of its bad taste. However, caution should be taken when these formulae are given for prolonged periods; no data are available on nutritional assessment

of infants exclusively fed with such formulae for many months.

It has been shown in animal models that hydrolysate formulae do not elicit an IgG response nor a cutaneous passive anaphylaxis. In addition, infants fed casein hydrolysates during the first three months of life do not show IgG antibodies to the hydrolysate formula. These data strongly suggest that these formulae are not antigenic. However, they do contain peptides of molecular weight more than 2,500 μ g, which may elicit IgE response in predisposed infants.

We have first reported [24] five infants, aged 3–8 months (median 5 months) with IgE-mediated cow's milk allergy, who experienced anaphylactic reactions when first fed a small amount of a whey hydrolysate (Alfa-Rè). All these infants were successfully fed with a soy-protein formula. All infants had positive skin tests and RAST to cow's milk proteins and to Alfa-Rè. These data show that whey hydrolysate formulae can trigger severe anaphylactic reactions in children with IgE-mediated cow's milk allergy [24]. Anaphylactic reactions have been reported in infants with IgE-mediated cow's milk allergy fed hydrolysate formulae [25]. This is confirmed by a recent study which demonstrated residual casein epitopes in all the hypoallergenic formulae tested: Alfa-Rè, Pregomin and Beba HA [26]. The above data tally well with studies by Strobel *et al.* [22], who showed that antibodies raised against a cow's milk formula recognized epitopes displayed by peptides of some hydrolysate formulae: Pregomin, Alfa-Rè, Nutramigen and Pregestimil. In addition, the same group of investigators showed that hydrolysate formulae in experimental animals induced cell-mediated immunity, and cross-reactivity existed also between IgE antibodies to cow's milk and peptides of hydrolysate formulae in this limb of the immune response. Bauer confirmed that hydrolysate formulae contain protein fractions which resulted in a specific IgE binding after incubation with serum samples from patients allergic to cow's milk [23]. In conclusion, although the proteins of hydrolysate formulae have been processed by heat and enzymatic hydrolysis and therefore contain peptides of lower molecular weight than the native protein source, the peptides still have allergenic potency and can be recognized by the cell-bound IgE of a child allergic to cow's milk. In an elegant study by Lau and Wahn, 9/15 children sensitive to cow's milk and with a positive histamine release from mixed leukocytes also had a positive histamine release to at least one of five tested hypoallergenic formulae [27]. In addition, high positive prick tests to whey (Good Start HA and Alfa-Rè) and casein (Nutramigen and Alimentum) hydrolysate formulae in 26 children with a current history of recurrent acute

respiratory and/or cutaneous reactions to cow's milk, showed that allergenic determinants for humans were still present in commercially available cow's milk casein/whey preparations after hydrolysis [28].

Generally, cow's milk hydrolysate formulae are well tolerated by infants who have gastrointestinal symptoms caused by cow's milk intolerance and who do not have IgE antibodies to cow's milk proteins.

Several groups of investigators have used these formulae (Nutramigen or HA) as breast-milk substitutes in high-risk babies and although these studies have a short follow-up, the results seem to be very encouraging [8,18,29,30].

A recent issue of the Committee on Nutrition of the American Academy of Pediatrics states that no published, well-controlled, double-blind studies exist to support the use of whey hydrolysates either for prophylaxis or treatment of infants with cow's milk hypersensitivity. A so-far-limited clinical experience suggests that a whey hydrolysate formula may be an acceptable alternative to cow's milk and soy protein formulae for infants intolerant, but not allergic, to cow's milk [31].

We conclude that hydrolysate formulae should not be used in infants with IgE-mediated CMA. Further studies are needed to investigate the nutritional adequacy of hydrolysate formulae in babies exclusively fed such formulae for many months.

Weaning

Another important dietary preventive measure is selected weaning after the sixth month of life, which has been shown to be useful for atopy prevention [32]. Weaning is potentially dangerous for the high-risk baby, therefore special care should be addressed when new foods are introduced into the infant diet, and offending foods such as eggs, fish, and peanuts should be further postponed.

Guidelines for dietary measures in secondary prevention of cow's milk allergy

The antigenicity, allergenicity and cross-reactivity with IgE antibodies to cow's milk of hypoallergenic formulae are reported in Table 2. Soy proteins can be antigenic and allergenic but they do not cross-react with IgE antibodies to cow's milk proteins; however, hydrolysate formulae do cross-react with these antibodies. Therefore, soy protein formulae should be given to babies with IgE-mediated cow's milk allergy, while hydrolysate formulae can be given infants with cow's milk protein intolerance.

In conclusion, the possibility of preventing atopic diseases in high-risk babies has been shown by several groups of investigators and we point out that in order to

Table 2. Immunogenicity and cross-reactivity of hypoallergenic formulae

	Hydrolysate		Soy formula
	Whey	Casein	
Antigenicity (IgG A, M Abs)	—	—	+
Allergenicity (IgE Abs)	±?	±?	+
Cross-reactivity with IgE Abs to cow's milk	++	+	—

prevent atopic diseases in high-risk babies not only dietary measures should be given, but also environmental measures. Our prevention programme described so far required profound modifications of both customs and mentality, sometimes a burden on the family. Even our dietary modifications were puzzling for both the families and the paediatricians. Today, to suggest exclusive breast-feeding for at least six months and delayed weaning until after the sixth month, collides with practical problems (e.g. for mothers who work), as well as with the widespread practice of early weaning. In keeping with this, it is to be noted that few young mothers understand much about breast-feeding physiology and most have very little awareness that early supplements can upset a developing balance. It will be a rather long time, if ever, before prenatal and postpartum educational efforts will be sufficiently widespread to modify this.

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