

Primary and secondary dietary prevention

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Introduction

The development and phenotypic expression of atopic disease depends on an interaction between genetic factors, environmental exposure to food and inhalant allergens and nonspecific adjuvant factors (e.g. tobacco smoke, air pollution and infections). The expression of allergic diseases may vary with age, and symptoms may disappear and be replaced by other symptoms. In infancy, the main atopic symptoms are atopic dermatitis, gastrointestinal symptoms and recurrent wheezing, whereas bronchial asthma and allergic rhinoconjunctivitis are the main problems later in childhood. Adverse reactions to foods, mainly cow's milk protein, are most common in the first year of life, whereas allergy to inhalant allergens mainly occurs later. Correspondingly, specific IgE antibodies against milk and egg are most frequent during the first 2–3 years of life, whereas specific IgE against inhalant allergens is predominant later in childhood (1). Thus, it is very important to take into consideration the natural course of the disease when evaluating the results from interventional studies on prevention of allergic diseases. At present it is estimated that genetic factors account for around 50% of atopic diseases (2). An evaluation of the influence of genetic factors is beyond the scope of this review, where the influence of dietary factors on the development of atopic diseases, especially food allergy/intolerance (FA/FI) will be elucidated.

The development of FA/FI depends on several factors including early exposure to allergenic proteins (time, dose, frequency), food protein uptake and handling and development of toler-

ance. The development and rather high incidence of FA/FI and especially cow's milk protein allergy/intolerance (CMPA/I) 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 immunological 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 (3).

In prospective studies, the incidence of CMPA/I in infancy has been estimated to be 2–3% (4). Allergic reactions are also reported frequently for egg white, fish, cereals, nuts and soybean. Even exclusively breast-fed infants may react against food proteins transferred from the mother's diet into her breast milk. The incidence of confirmed food allergy during exclusive breast feeding is around 0.5% (4). When evaluating possible risk factors for the development of allergic diseases and the possible effect of preventive measures, it is important to stress some factors. The study design of both non-interventional and interventional studies should be prospective (true) studies including well-defined diagnostic criteria, a sufficient duration of follow-up and a substantial enough sample size for adequate statistical evaluation. Besides, interventional studies should include proper randomisation, double-blinding and a control for confounders, as well as proper registration of compliance and follow-up of dropouts.

Due to recall bias and selection bias, retrospective studies should not be used for evaluation

of predictive/risk factors for the development of allergic diseases. Similarly, cross-sectional studies are not suitable for assessment of cause–effect relationships between exposure to allergens/adjuvant factors and development of allergic diseases. Generally, it should also be borne in mind that prospective non-interventional studies can be used to generate hypotheses on the relationship between cause and effect in the development of allergic diseases. However, proper confirmation of a possible cause–effect relationship requires demonstration of the causative mechanism and effect of elimination/prevention of the suspected causative factor. Therefore, in the following discussion, mainly the results of proper prospective studies will be considered.

Non-interventional studies

From prospective studies, many possible predictive factors of the development of allergic diseases have been identified. Although it is well documented that atopic heredity is associated with an increased risk of the development of allergic diseases (5–7), it has also been demonstrated that most children who develop atopic diseases during the first years of life come from families without an atopic heredity. Thus, the majority of children who become atopic do not belong to groups at high risk of developing atopic disease (5).

Breast-feeding

Dietary factors. More than 60 years ago, Grulee and Sanford (8) reported that undiluted cow's milk caused a sevenfold increase in the risk of eczema at 9 months of age in a huge cohort of children compared with babies that were breast fed and fed mixed food. One cohort study has demonstrated an association between early feeding of cow's milk formula and development of cow's milk protein allergy (9). In a Finnish study of non-selected, non-high-risk neonates followed until 17 years of age, breast-feeding was associated with lower rates of eczema and food allergy at 1 and 3 years, as well as a lower "score of respiratory allergy" up to 17 years of age, than in those fed cow's milk formula (10). Another prospective study (11) found that non-atopic children (negative skin prick test) at the age of 6 years who had not been breast fed had increased risk of wheezing recurrently as compared with breast-fed children (odds ratio 3.03, 95% CI 1.06–8.69), but the same association was not found for atopic children. In a recent

Australian study (12) introduction of milk other than breast milk before 4 months of age was a significant risk factor for all asthma and atopy outcomes in children up to 6 years (odds ratio 1.25, 95% CI 1.02–1.52), and for current asthma (odds ratio 1.31, 95% CI 1.05–1.64). Breast feeding has also been shown to reduce the risk of wheezy bronchitis during infancy (13, 14), as well as the need for hospital admission due to bronchitis or asthma up to 4 years of age, as shown in a case–control study (15).

A possible protective effect of breast feeding on the development of atopic diseases may be due to either 1) the protective effect of human milk (the constituents) or 2) avoidance of a "high dose" of cow's milk proteins.

The question of whether breast feeding helps prevent allergy remains controversial due to the lack of evidence in some studies and because infants cannot, ethically, be assigned randomly to breast feeding or formula feeding to enable a definitive study (16, 17). However, common factors apparent in studies reporting a benefit of breast feeding were as follows: 1) prolonged breast feeding (>4–6 months) and 2) late solid food introduction (>4 months). Recent studies on the possible allergy-preventing effect of breast feeding indicate that variations in the composition of human milk – e.g. low levels of alpha-linolenic acid and disturbed relationship between the n-3 and the n-6 fatty acids (18), or varying concentrations of cytokines (19) – may explain some of the controversies regarding the protective effect of breast feeding against allergy. No association between nucleotide and polyamine levels in human milk and atopic development during the first year of life has been found (20). However, prospective long-term follow-up studies with a substantial sample size are needed to confirm these possible relationships.

Solid foods. As for the introduction of cow's milk proteins before 4 months of age, the introduction of complementary foods (solid foods) before 4 months of age has been associated with a higher risk of atopic dermatitis until the age of 10 years (21).

Other dietary factors. The results of cross-sectional studies (22–24) suggest that dietary factors such as low intake of fresh fish and omega-3 fatty acids, high sodium intake or inadequate intake of antioxidants may influence respiratory symptoms and asthma. However, prospective studies are needed to elucidate and confirm these possible causal relationships.

Interventional studies

Dietary measures

Unselected/non-high-risk infants. Only a few prospective intervention studies have been performed in infants without a hereditary atopic predisposition. In premature unselected infants, Lucas et al. (25) found no difference in development of atopic symptoms or cow's milk allergy (CMA/I) whether the infants were fed *human bank-milk* or *cow's milk*-based formula. Other studies (26–28) have concluded that cow's milk-based formula given during the first few days of life did not increase the risk of atopic disease until the ages of 2 (28), 4–6 (26) and 14 years (27). However, these studies included intervention diet only for the first few days of life, one (26) included only low-birth-weight infants, and one (27) was not randomised, and its outcome was based on data from medical files and questionnaires obtained at 7, 11 and 14 years. In one study (28) the diagnostic criteria were unspecific, and outcome measures were based mainly on questionnaires. A recent randomised study including a large number ($n=6209$) of full-term unselected neonates (29) indicated that feeding of cow's milk-based formula at maternity hospital increased the risk of CMA when compared with feeding an extensively hydrolyzed whey formula, but exclusive breast feeding for 8 weeks did not eliminate the risk of CMA/I. However, the dietary intervention included only the first 4 days of life, and no data on the diet after that period were given.

High-risk infants. As reviewed in a position paper of ESPACI (30) and a recent joint statement of ESPACI and ESPGHAN (3), prospective studies on high-risk infants have shown a preventive effect of different dietary allergy-prevention programmes on the cumulative incidence of food allergy (FA), especially CMA/I and atopic dermatitis. An effect of dietary allergy prevention has been demonstrated only in high-risk infants, i.e. infants with at least one first-degree relative (parent or sibling) with documented atopic disease (doctor-diagnosed), possibly combined with elevated cord-blood IgE in the case of single atopic predisposition. Due to great variations in study design and diagnostic criteria, it is difficult to compare the effect of these programmes.

Breast feeding. Previous studies (25, 31–36) have presumed that breast feeding has an allergy-preventive effect compared with feeding cow's milk formula, but the extent of the pre-

ventive effect remains controversial. In high-risk infants, exclusive breast feeding for at least 4 months in combination with avoidance of solid foods has resulted in a significant reduction of the cumulative incidence of CMA/I and atopic dermatitis during the first 4 years of life. Ethically, infants cannot be randomly assigned to breast or formula feeding to enable a definitive study. Thus, confounding factors may highly influence the results of comparisons. There is no conclusive evidence for a protective effect of a maternal exclusion diet during pregnancy (37–39). A few studies indicate that the preventive effect of breast feeding on the development of atopic dermatitis may be enhanced by maternal avoidance of potential food allergens (milk, egg, and fish) while breast feeding, but other studies do not confirm this finding (39, 40).

Formulas. Some prospective studies have shown that soy formulas are as allergenic as conventional cow's milk-based formulas, and therefore should not be recommended for the prevention of food allergy (30, 34), but contradictory views have been expressed (42–45). Further studies may clarify the allergenicity of soy formula in infants who are at risk of developing allergy. There is no evidence that formulas based on whole proteins other than cow's protein are less allergenic. A few prospective intervention studies (34, 41, 42) have compared the preventive effect of soy with cow's milk-based formula in high-risk infants, but none of these included controlled elimination/challenge procedures in order to diagnose food allergy. One such study (41) found no preventive effect of soy formula, whereas another (42) indicated a possible preventive effect of soy formula but only as regards antigen-unspecific atopic symptoms.

Extensively hydrolysed formulas (eHF) have been investigated in studies on prevention of FA in high-risk infants. Several prospective studies (34, 36, 46–52) show a preventive effect of extensively hydrolysed formulas in combination with avoidance of cow's milk proteins and solid foods for at least 4 months in high-risk infants on the cumulative incidence of atopic dermatitis and FA, especially CMA/I, until the age of 4 years. In two prospective studies (51, 52), the cumulative incidence of FA and CMA/I was significantly reduced until the ages of 5 and 7 years, respectively. Thus, a real prevention, and not only a postponement of the onset of the disease, was documented.

Partially hydrolysed formulas (pHF) (with moderately reduced allergenicity) have been

investigated in randomised prospective studies (33, 35, 53–58) in high-risk infants, and an allergy-preventive effect has been reported. Because of great variations in study design and diagnostic criteria, the relative efficacies of the different interventions tested in the various studies cannot be compared directly with each other. At present, clinical trials are comparing directly the relative preventive effects of products with highly reduced allergenicity (extensively hydrolysed) with those of formulas with moderately reduced allergenicity (partially hydrolysed). Only two such studies (53, 59) have been published. One study reported a lower cumulative incidence of atopic symptoms up to the age of 18 months with both an extensive and a partial protein hydrolysate diet, compared with a cow's milk protein-based formula; a greater effect was reported with the extensive hydrolysate (59). The other study reported a higher cumulative incidence of CMPA/I in infants fed a partially hydrolysed formula compared with infants fed an extensively hydrolysed formula (53). More studies on this issue are needed.

Solid foods. The introduction of complementary foods during the first 4 months of life has been associated with a higher risk of atopic dermatitis (60). A preventive effect of breast feeding or hydrolysed formulas has been shown only in studies including avoidance of complementary foods during at least the first 4 months of life.

Duration of the diet. The duration and the dietary restrictions vary in different studies. All studies showing a preventive effect have included solely breast feeding or extensively hydrolysed formula and avoidance of cow's milk and solid foods for at least 4–6 months. Studies including restrictive diets for over 12–14 months and studies with dietary restrictions for only 4–6 months have shown comparable results. In one recent study (61), no significant effect of supplement with hydrolysate formula after the age of 6 months in breast-fed high-risk infants was found. Controlled studies of the possible preventive effect of avoidance of other potential

food allergens such as egg and fish after the age of 4–6 months of life have not been published. Thus, there is no evidence of restrictive diets having an allergy-preventing effect after 6 months of age (Table 1).

Secondary dietary prevention

In children with symptoms suggestive of FA/FI the diagnosis has to be based on strict, well-defined food elimination and challenge procedures establishing a causal relation between ingestion of a particular food (or food protein) and a subsequent obvious clinical reaction. Thus, a correct diagnosis is necessary in order to ensure the right treatment/diet and to avoid malnutrition and hazard situations due to reactions to unknown food allergens.

Elimination

The basic treatment of food allergy is complete avoidance of the offending food. Patients and parents often need help of a clinical dietician to avoid potential hidden food allergens. Even the elimination of a single food can be very difficult. For example, milk may be hidden under several other names on the food labels, such as whey, casein, caseinate, lactalbumin, etc. In exclusively breast-fed infants, a strict elimination of milk of the lactating mother is necessary. Bottle-fed infants should not be fed preparations based on milk of other species such as goats or sheep because of a high rate of cross-reactivity (3). In young children formulas based on intact soy protein are not recommended for the initial treatment of milk allergy, although a proportion of infants with CMPA/I tolerate soy formula (3, 62, 63). Products with highly reduced allergenicity based on so-called extensively hydrolysed protein or amino acid mixtures are recommended for the treatment of infants with CMPA/I. Formulas based on partly hydrolysed protein are not recommended, because they contain substantially higher amounts of residual allergens than extensively hydrolysed products (3, 64). Some infants may even react against the residual quantities of

Table 1. Primary prevention

For all infants

No special diet during pregnancy or for the lactating mother

Exclusive breast feeding for at least 4 months

Avoidance of solid food until 4 months of age

Further recommendations for infants with a high risk of allergic disease

If supplement is needed during the first 4 months, a documented hypoallergenic formula is recommended

Non-dietary recommendations for all infants

Avoidance of exposure to tobacco smoke – also during pregnancy

cow's milk protein in products with highly reduced allergenicity, and such sensitive patients may require an amino acid-based formula (65, 66). In infants with adverse reactions to cow's milk protein and an additional malabsorptive enteropathy the use of a formula with highly reduced allergenicity (extensively hydrolysed formula or amino acid mixture) with medium chain triglycerides might be useful until normal absorptive function of the mucosa is regained. Due to the good prognosis of CMPA/I (as well as other food allergies in early childhood except allergy to peanuts, fish, seafood), re-challenges should be performed at regular intervals of 6–12 months before 3 years of age, and at intervals of 1–2 years after 3 years of age, in order to avoid unnecessarily prolonged avoidance diets.

Clinical reactivity to food allergens is very specific, and patients rarely react to more than one member of a botanical family (67, 68) or animal species (69, 70). Therefore, elimination diets should not be based on exclusion of food families, but be based on individual foods proven to provoke allergic symptoms.

Conclusion

In prospective studies the cumulated prevalence of food allergy/intolerance has been shown to be around 7–8% in children less than 3 years of age, with a decreasing prevalence during later childhood and early adulthood with a prevalence around 1.5–2%. A limited number of foods are responsible for the majority of allergic reactions, i.e. milk, egg, fish, peanuts and tree nuts in children. The pattern of food allergy/intolerance changes with age, and in later childhood pollen-related cross-reactivities to foods, occurring in up to 50% of pollen allergic individuals, is the most common form of food allergy (the oral allergy syndrome, e.g. allergy to hazelnuts and apples in birch-allergic individuals). Up to 80% of young children with food allergy, especially those with high-levels of specific IgE to foods, may develop inhalant allergies before puberty.

For primary prevention breast feeding should be encouraged in all infants for 4–6 months. In high-risk infants a documented extensively hydrolysed formula is recommended if breast feeding is not possible for the first 4 months of life. Furthermore, solid food should not be introduced until the fifth month of life. There is no evidence for prenatal dietary intervention during pregnancy. For secondary prevention, treatment of allergic reactions to food proteins, complete avoidance of the offending food is the basic treatment. Thus, a correct diagnosis, based

on controlled elimination/food challenge procedures is necessary in order to ensure the right treatment/diet and to avoid malnutrition and hazard situations due to reactions to unknown food allergens. Patients and parents often need help of a clinical dietitian to avoid potential hidden food allergens. Due to a high recovery rate for most food allergies, except peanuts, tree nuts, fish and seafood, rechallenges are recommended at intervals of 6–12 months before 3 years of age and at intervals of 1–2 years after 3 years of age.

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