

Primary prevention of food allergy in infants who are at risk

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Purpose of review

Allergic diseases represent a major burden of health problems in industrialized countries. Though several studies have focused on possible preventive measure and strategies much controversy still exists on this topic. The aim of this review is to discuss the recent literature on primary prevention of food allergy.

Recent findings

In prospective observational controlled studies of high quality of birth cohorts, exclusive breastfeeding for at least 4 months combined with introduction of solid foods after 4 months of age is associated with a reduced risk of food allergy and atopic dermatitis, particularly in high-risk infants. When breastfeeding for 4–6 months is not possible or insufficient, randomized controlled trials have shown a significant reduction in food allergy and atopic dermatitis in high-risk infants fed a documented hypoallergenic hydrolysed formula.

Summary

Breastfeeding should be encouraged for 4–6 months. In high-risk infants a documented hypoallergenic hydrolysed formula is recommended if exclusively breastfeeding is not possible for the first 4 months. As regards primary prevention of food allergy there is no evidence for preventive dietary intervention during neither pregnancy nor lactation. Likewise, preventive dietary restrictions after the age of 4–6 months are not scientifically documented.

Keywords

food allergy, high-risk infants, primary prevention

Introduction

In this critical review we focus on primary prevention of food allergy in infants at high risk for development of allergy. Much controversy still exists on this topic, in part due to different use of diagnostic criteria and nomenclature as regards both food allergy and risk for development of food allergy.

Furthermore, it is important to be aware that retrospective and cross-sectional studies are not suitable for evaluation of possible cause–effect relationships in the development of allergic disease. The randomized controlled study is the gold standard when possible. However, randomization to breastfeeding or exposure to tobacco smoke is unethical and not possible. Consequently, high quality controlled observational studies may provide useful knowledge for evidence based recommendations on allergy prevention [1^{••}] when proper adjustment for confounds including avoidance behaviour and disease-related modification of exposure are considered [1^{••},2,3^{••}].

Therefore, in this review we will discuss both the results from controlled observational studies of high quality and randomized, controlled trials on allergy prevention following the recommendations for evidence based guidelines [1^{••},4^{••}], including original articles and metaanalyses/systematic reviews published between March 2003 and January 2005.

Food hypersensitivity

Food hypersensitivity defined as reproducible adverse reactions to foods can be divided into food allergy and non-allergic food hypersensitivity, with the former subdivided into IgE and non-IgE-mediated food allergy [5,6^{••}]. No symptoms are pathognomonic for food allergy, and no single laboratory tests are diagnostic. Therefore, the diagnosis has to be based on controlled elimination and challenge procedures [1^{••}].

Food allergy is often related to atopic dermatitis and vice versa in early childhood. In many studies atopic dermatitis has been evaluated and reported without a proper evaluation of a possible coexisting and causal food allergy. Much confusion has existed on the definition of atopic dermatitis, and recently in a revised nomenclature World Allergy Organisation [6^{••}] replaced the previous term ‘atopic dermatitis’ with the term ‘eczema’, which could be divided into atopic eczema (IgE-associated) and non-atopic eczema (non-IgE-associated). In this review

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the term 'atopic dermatitis', as used in the articles cited, has been used.

The development of allergic diseases, including food allergy, depends on an interaction between genetic factors and several environmental factors, such as exposure to allergens and non-specific factors (e.g. tobacco smoke, air pollution, infections, and dietary factors). Our knowledge is still incomplete and many other unknown factors may play a role.

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 and hen's egg, are most common in the first years of life, and correspondingly sensitization to these allergens occurs early in life. In general, sensitization and development of clinical food allergy develop in the order of exposure [7,8].

Early exposure to food proteins (time, dose, frequency), food protein uptake and handling and development of tolerance play a major role in the development of food allergy [9^{••}]. The development and rather high incidence of food allergy and especially cow's milk protein allergy 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 allergens by means of specific secretory IgA and other protecting factors [9^{••}].

High-risk infants

From prospective studies many possible predictive factors of development of allergic diseases have been identified. Although it is well documented that atopic heredity is associated with an increased risk for development of allergic diseases, it has been demonstrated that many children with recurrent wheezing/asthma in early childhood do not belong to high-risk groups for development of atopic disease, whereas a higher proportion of children with allergic disease, including manifestations other than asthma, will have atopic heredity [9^{••},10–12].

Varying definitions of high-risk infants have been used. According to a recent joint statement high-risk infants are defined as infants with a well defined increased risk of developing allergic disease, i.e. infants with at least one first-degree relative (parent or sibling) with documented allergic disease (asthma, rhinoconjunctivitis,

atopic dermatitis or food allergy) [9^{••}]. In some studies the optimal high-risk group was defined by double parental atopic predisposition or single atopic predisposition, the latter combined with cord blood IgE level of 0.3 kU/L or higher [11,13^{••}].

Prevention

Prevention may consist of a variety of prophylactic measures and can be directed to the avoidance of sensitization, the avoidance of development of disease manifestations in an asymptomatic individual and the avoidance of disease manifestations and progression of disease in a symptomatic individual. Considering food allergy, primary prevention addresses prevention of sensitization and development of clinical allergic symptoms.

It is important to be aware that sensitization to foods may precede development of allergy or may be a normal and often transitory harmless phenomenon especially in early childhood, which may even be present already prenatally [9^{••},13^{••}]. The detection of sensitization depends on many factors, such as the sensitivity of the test. Therefore, the aim of primary prevention must be to prevent development of disease and not only sensitization.

Primary preventive measures may include both exposure to allergens and adjuvant risk/protective factors. Some preventive measures may be beneficial for the general population and supplementary measures may be beneficial and recommendable only for high-risk individuals [4^{••},13^{••},14^{••}].

Dietary factors

As previously reported [13^{••},14^{••}] dietary allergy preventive measures during the first 4–6 months of life result in a reduced risk for development of food allergy, especially cow's milk protein allergy and atopic eczema in high-risk infants (Table 1).

Breastfeeding

Recent extensive reviews on the allergy preventive effect of breastfeeding have been published [4^{••},14^{••},15]. In these the existing literature has been reviewed critically

Table 1. Preventive effect of dietary measures

Intervention	Effect
Exclusive breastfeeding, at least 4 months	↓ Cumulative incidence of CMPA until 18 months ↓ Cumulative incidence of AD until 3 years
Documented hypoallergenic formula ^a combined with avoidance of solid foods ≥4–6 months	↓ Cumulative incidence of CMPA until 5 years and AD until 4 years

AD, atopic dermatitis; CMPA, cow's milk protein allergy.

^aExclusively or as a supplement to breastfeeding.

and an analysis of peer reviewed published studies was performed following the statements of evidence as defined by the World Health Organization [4^{••},14^{••}]. The results indicate that breastfeeding is highly recommended for all infants irrespective of atopic heredity, and the preventive effect is even more pronounced in high-risk infants. In high-risk infants breastfeeding combined with avoidance of solid foods and cow's milk for 4–6 months is the most effective regimen. In the absence of breastmilk, formulas with documented reduced allergenicity should be used [1^{••},4^{••},9^{••},13^{••},14^{••},15].

Recently published results from two prospective well controlled studies of birth cohorts [16,17[•]] confirm these conclusions as regards the protective effect of exclusive breastfeeding for 3 months [16] or 4 months [17[•]] on the development of atopic dermatitis in high-risk infants. In none of these studies was investigation of confirmed food allergy undertaken.

A dual long-term effect of breastfeeding on atopy was reported in a prospective Finnish study of 456 4-year-old children from an unselected birth cohort of 4674 infants [18]. In children with atopic heredity exclusive breastfeeding for 3 months protected against allergic rhinoconjunctivitis and sensitization to pets, whereas in children without atopic heredity breastfeeding was related to increased risk of symptomatic atopy. Validated data on food allergy were not reported.

In a prospective observational study of a large birth cohort ($n = 15\,430$) [19] exclusive breastfeeding for at least 4 months was associated with an increased risk of atopic dermatitis in children with no parental history of allergies. On the contrary a protective effect of exclusive breastfeeding for at least 4 months was found in children with double parental allergic heredity. However, data were obtained by telephone interviews, which were undertaken when the child was 6 and 18 months as regards breastfeeding and atopic dermatitis. A low cumulative incidence of atopic dermatitis of 11.5% at 18 months and a very high frequency of reported parental allergic diseases of 54% might indicate recall bias, selection bias, lack of accuracy and validity of data and disease-related modification of exposure.

Overall, there is no reason not to follow the conclusions of the recent extensive reviews on the allergy preventive effect of breastfeeding (Table 1) [4^{••},14^{••},15].

Possible mechanisms of breastfeeding

The interpretation of the possible protective effect of breastfeeding on the development of allergic disease is difficult due to many factors, such as possible selection bias [13^{••},14^{••},20]; higher social

class; less exposure to tobacco smoke and pets; later introduction of solid foods; composition of human milk [9^{••}]; nutritive foreign proteins/allergens; α -linolenic acid; n3/n6 fatty acid ratio [21[•]]; cytokines (such as TNF- α , TGF- β) [9^{••},22,23]; immunoglobulins, IgA [23]; other factors such as contaminants/pollutants [24].

Most of these observations are interesting, but not conclusive and, prospective long-term follow-up studies with a proper sample size are desirable for confirmation of these possible relationships. Regarding the possible allergenic effect of foreign proteins in human milk it is well known that such proteins may cause symptoms in already sensitized individuals. However, it appears more likely from prospective birth cohort studies that these small amounts (a normal phenomenon) induce tolerance rather than disease [14^{••}].

Solid foods

As for introduction of cow's milk proteins before 4 months of age, the introduction of complementary foods (solid foods) before 4 months of age was earlier associated with a higher risk of atopic dermatitis up to the age of 10 years [25,26]. In a recent study [27] no association between introduction of solids and the development of preschool wheezing, transient wheezing, atopy, or dermatitis was found in an unselected birth cohort followed to the age of 5 years [27[•]]. However, these results should be interpreted with caution because the data on breastfeeding and introduction of solids were obtained at the age of 1 year (recall bias), and the children have not been investigated for food allergy. Importantly, reliable data on early feeding including the duration of exclusive breastfeeding and introduction of solids must be obtained prospectively from birth and onwards [1^{••},14^{••},28]. Otherwise, recall bias may severely influence the results. In another prospective study of 257 premature children, early introduction of solid foods before 4 months was associated with an increased risk of atopic dermatitis in children both with and without atopic heredity [29]. The children in this study were not investigated for food allergy.

Only a few studies have focused particularly on the possible influence of early introduction of complementary foods on development of atopic disease and none has investigated the possible relation between solid foods and properly confirmed food allergy [1^{••},14^{••}]. However, in all the prospective randomized placebo controlled studies showing a preventive effect of hypoallergenic formulas/breastfeeding for 4–6 months in high-risk infants, solid foods were not introduced before the age of 4–6 months. This might indicate that introduction of solid foods after the age of 4–6 months is appropriate in high-risk infants.

Intestinal microbial flora

It has been hypothesized that the intestinal microbial flora may influence the development of sensitization. One prospective study showed a preventive effect of supplementing the diet of high-risk infants by probiotics 2–4 weeks prenatally and for the first 6 months of life as regards mild atopic dermatitis at the age of 2 years, but no effect was found as regards sensitization/proven allergic disease [30]. Preliminary data from the same study at follow-up at 4 years showed similar results [31]. This theory needs confirmatory evidence as concluded in a recently published position paper [32^{••}].

Formulas

When exclusive breastfeeding for the first 4 months is not possible or insufficient a substitute formula is necessary. As previously reviewed [13^{••},14^{••}] prospective, controlled studies have shown that feeding hydrolysed formulas for the first 4–6 months of life resulted in a reduced risk for development of food allergy, especially cow's milk protein allergy and atopic eczema in high-risk infants (Table 1). Besides, it has been discussed whether feeding adapted soy formula has an allergy preventive effect.

Adapted soy formula

Some earlier prospective studies have shown that soy formulas are as allergenic as conventional cow's milk based formulas, and on this basis they should not be recommended for the prevention of food allergy. There is no evidence that formulas based on whole proteins other than cow's milk protein are less allergenic [14^{••}]. A recent meta-analysis (Cochrane review) of five randomized and quasi-randomized trials evaluated the use of an adapted soy formula compared with human milk, an adapted cow's milk or a hydrolysed cow's milk formula in the first 6 months of life in high-risk infants [33^{••}]. There was no preventive effect of soy formula in high-risk infants as regards development of allergy and food allergy.

Table 2. Primary prevention of food allergy: evidence based recommendations

Category	Recommendations
All infants	No special diet during pregnancy or to the lactating mother Exclusive breastfeeding the first 4 months; if supplement is needed conventional cow's milk based formula is recommended for infants without a high risk for allergic disease Avoidance of solid food the first 4–6 months
Infants with a high risk for allergic disease ^a	If supplement is needed during the first 4 months a documented hypoallergenic formula is recommended. After the age of 4 months high-risk children can be nourished like non-high-risk children.

^aHigh-risk infants: infants with a well-defined increased risk of developing allergic disease, i.e. infants with at least one first-degree relative (parent or sibling) with documented allergic disease (asthma, rhinoconjunctivitis, atopic dermatitis or food allergy).

Hypoallergenic formulas

In a recent prospective randomized interventional study the preventive effect, a reduction in the prevalence of atopic dermatitis, was particularly seen in infants with a family history of atopic dermatitis [34]. Meanwhile, children with atopic dermatitis or other atopic symptoms were not investigated systematically for food allergy with controlled elimination/challenge procedures at onset of symptoms.

Recent extensive reviews on the primary allergy preventive effect of hypoallergenic formulas have been published [4^{••},13^{••},14^{••},15]. In these the existing literature has been reviewed critically and an analysis of peer reviewed published studies was performed following the statements of evidence as defined by the World Health Organization [4^{••},14^{••}]. In high-risk infants who are unable to be completely breastfed there is evidence that feeding with a hypoallergenic hydrolysed formula compared to cow's milk formula for the first 4–6 months of life reduces infant and childhood atopic dermatitis and cow's milk protein allergy [35] (Table 1).

Furthermore it is concluded in these extensive reviews [4^{••},13^{••},14^{••}] that there is no evidence for a preventive effect of a diet after the age of 4–6 months, although this needs further investigation. Neither is there convincing evidence for a preventive effect of maternal diet during pregnancy or lactation. Partially hydrolysed formula has an effect, though it seems to be less than that of extensively hydrolysed formula at present. This preventive effect has only been demonstrated in high-risk infants.

Conclusion

Prospective studies have demonstrated a preventive effect of simple dietary measures during the first 4–6 months of life as regards development of food allergy especially cow's milk protein allergy and atopic dermatitis. Present evidence based recommendations on primary prevention of food allergy are shown in Table 2.

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