

SPECIAL REPORT

Dietary products used in infants for treatment and prevention of food allergy.

Joint statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition

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For more than 50 years, many children with food protein allergies and other forms of dietary protein intolerance have been treated successfully with protein hydrolysates with highly reduced allergenicity and, more recently, also with products based on amino acid mixtures. Strategies for the prevention of allergy have been proposed, including the use of products with extensively reduced allergenicity. Products designed to have a moderately reduced allergenicity have also been proposed and marketed in Europe as hypoallergenic formulas. The European Society for Paediatric Allergology and Clinical Immunology (ESPACI) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have commented previously on these issues,^{1,2} and the Commission of the European Union has issued a regulation for the requirements of infant formulas with reduced allergenicity or reduced antigenicity.³

This paper comments on the current developments and unresolved issues in the dietary treatment and prevention of food allergy in infancy to help inform paediatricians and other health care professionals, as well as manufacturers of infant foods.

Adverse reactions to foods

Adverse reactions to foods are a problem, particularly in infancy and early childhood, and can present with a wide spectrum of clinical reactions such as cutaneous, gastrointestinal, respiratory, or other symptoms. Reproducible adverse reactions to food(s) can be the result of one or more immune mechanism(s) or they can be non-immunologically mediated. Immunologically mediated reactions, which are often immediate IgE mediated reactions, are defined as food protein allergy. Non-immunologically mediated reactions can be divided into enzymatic or transport defects (for example, lactase deficiency, or glucose/galactose malabsorp-

tion), pharmacological or other (undefined) reactions.^{2,4} The pattern and threshold of adverse reactions to foods varies. None of the symptoms related to immunologically or non-immunologically mediated adverse reactions to foods are pathognomonic, and no single laboratory test is diagnostic of food allergy. Therefore, the diagnosis has to be based on strict, well defined food elimination and challenge procedures establishing a causal relation between the ingestion of a particular food (or food protein) and a subsequent obvious clinical reaction.^{2,4} In prospective studies, the incidence of cows' milk protein allergy in infancy has been estimated to be ~2-3%.^{5,6} 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 ~0.5%.^{5,6}

Sensitisation and tolerance

The development of food protein allergy depends on several factors, including genetic predisposition, early exposure to allergenic proteins (time, dose, frequency), food protein uptake and handling, and development of tolerance.^{1,2,5,7} It has been speculated that the relatively high incidence of adverse reactions to food proteins in infancy, especially to cows' milk protein, could be the result of an increased gut permeability to large molecules and the immaturity of local and systemic immunological responses. Protective effects of breast feeding have been ascribed to enhancement of the postnatal growth of intestinal epithelium and maturation of mucosal functions in several experimental models.^{1,2,7} Food proteins are absorbed unmodified or partly modified from the gut and can be measured in the serum (in

$\mu\text{g/l}$) both in children and adults.⁵ Likewise, exogenous food proteins are secreted into the breast milk of lactating women.^{1,2} An association between early exposure to cows' milk formula and subsequent development of cows' milk protein allergy and intolerance has been documented^{6,8}; however, this was not confirmed in another study.⁹ Macromolecular absorption is increased in preterm infants, but they do not have an increased risk of developing food allergy.^{5,10} Whether increased macromolecular absorption is part of an allergic constitution or arises from temporary mucosal damage is not clear, and neither is the relevance of increased absorption of macromolecules in the development of clinical allergic disease. Cows' milk β lactoglobulin can be detected in the breast milk of up to 95% of lactating women. Although sensitisation of infants to food proteins has been reported during exclusive breast feeding, it is not entirely clear whether the small amounts of foreign proteins found in human milk are responsible for this, or whether other sources of allergens, such as inhaled food proteins or contaminated hands, may play a role.¹¹ Specific IgE antibodies against cows' milk proteins have been demonstrated in cord blood. A possible role of intrauterine sensitisation in the pathogenesis of food allergy has been suggested because a high frequency of cord blood IgE antibodies to cows' milk proteins was found in infants who later developed cows' milk allergy.¹² This hypothesis is supported by recent findings of proliferative responses to specific antigenic stimuli (both inhaled allergens and food allergens) in mononuclear cells derived from fetal as well as umbilical cord blood.^{13,14} However, intrauterine sensitisation may be a normal phenomenon, as may be the postnatal temporary weak IgE response that occurs in some infants who do not develop allergic disease. Neonatal exposure to high doses of foreign protein (inhaled or ingested allergens) may be necessary for the development of allergic disease. Although much new evidence has been revealed about the development of allergy and the induction of tolerance, especially in experimental animals,⁷ our understanding of a causal association is still incomplete.

Allergenicity of food proteins

Allergenicity—that is, the ability of an allergen to induce allergic reactions, may vary considerably because thresholds of reactions against specific food allergens and other allergens differ, both within and between individuals, and with time. Allergenic food proteins or glycoproteins usually have a molecular mass between 10 and 60 kDa, and they tend to be relatively resistant to denaturation by heat or to degradation by gastrointestinal proteases. In foods, the allergens are naturally occurring proteins—for example, in cows' milk the most frequent allergens are native proteins, but new allergenic epitopes may result from technological processing, digestion, or heat treatment.¹⁵ Sequential epitopes are degraded by enzymatic hydrolysis and conformational epitopes are also degraded by heat treatment. Low degree

heat treatment (such as pasteurisation at 75°C for 15 seconds) does not reduce the allergenicity of cows' milk proteins, whereas strong heat treatment (such as 121°C for 20 minutes) destroys the allergenicity of many whey proteins, but only reduces that of caseins.^{15,16} In general, conventional heat treatment reduces but does not eliminate the allergenicity of milk proteins. The allergenicity of food proteins can be reduced by enzymatic hydrolysis or by combining hydrolysis, heat treatment, and/or ultrafiltration.

Products with reduced allergenicity

The available allergen reduced dietary products for infants are derived from several different protein sources (such as bovine casein, bovine whey, bovine or porcine collagen, soy, or mixtures of these) exposed to different procedures of hydrolysis and further processing, such as heat treatment or ultrafiltration, or they are based on amino acid mixtures.

Attempts have been made to classify products according to the degree of protein hydrolysis ("extensive" or "high degree" versus "partial" or "low degree" protein hydrolysates),^{1,2} but there is no unanimous agreement on firm criteria on which to base such a classification. For example, product properties may be characterised by biochemical techniques, such as the spectrum of peptide molecular weights or the ratio of α amino nitrogen to total nitrogen. Reduction of allergenicity of dietary products may be assessed in vitro with various immunological methods (for example, IgE binding tests such as the radioallergosorbent test (RAST), RAST inhibition test, immunoelectrophoresis methods, and enzyme linked immunosorbent assay (ELISA)) and in vivo with skin prick tests, patch tests, and challenge tests. In vitro characterisation of peptide size and determination of allergenicity might be valuable for quality control of the products and assurance of batch to batch consistency as well as for labelling, but on the basis of current knowledge, such data do not predict the immunogenic or the allergenic effects in the recipient infant. The regulations of the European Union for labelling infant formulas as having reduced allergenicity (or antigenicity) are based arbitrarily on a content of immunoreactive protein of < 1% of total nitrogen containing substances,³ but there is no evidence that such a threshold of immunogenic protein would ensure a reduced clinical allergenicity. Only pure amino acid mixtures are considered to be non-allergenic. At present, the potential of a product for treatment and prevention of food allergy can only be determined by clinical trials using scientifically appropriate standards. It has been recommended that dietary products for treatment of cows' milk protein allergy in infants should be tolerated by at least 90% (with 95% confidence) of groups of infants with documented cows' milk protein allergy.¹⁷ These criteria have been met by some products with highly reduced allergenicity (extensive hydrolysates) and amino acid based products.¹⁸⁻²⁰

Nutritional aspects

In addition to the immunological properties of dietary products with reduced allergenicity, their nutrient composition, as well as their nutritional and metabolic effects in infants, need to be characterised. Diets without lactose might have disadvantages for the composition of the infants' colonic microflora and colonic physiological function, and they might compromise calcium absorption.²¹ Moreover, feeding lactose free diets from birth (for example, for preventive purposes), will cause false negative results of most neonatal screening tests for galactosaemia. Nutrient balance studies in term and preterm infants indicated that nitrogen absorption and retention with some diets based on protein hydrolysates are not equivalent to those with whole protein, and decreased weight gain and nitrogen accretion have been observed in infants during feeding with some allergen reduced products.²²⁻²⁴ These observations indicate the need for a careful evaluation of the nutritional adequacy of each product. Furthermore, the potential short and long term effects of exposing young infants to the bitter taste associated with most protein hydrolysates and amino acid mixtures remain to be further elucidated. Therefore, such products should only be used with a clear indication.

Treatment

The basic treatment of adverse reactions to food proteins is complete avoidance of the causal protein. Allergen elimination is relatively easy in exclusively breast fed or formula fed infants, if the causal agent is a protein supplied with the milk.

In exclusively breast fed infants with food allergy, a strict elimination of the causal food protein from the diet of the lactating mother might lead to resolution of the allergic symptoms. Bottle fed infants with cows' milk protein allergy should not be fed preparations based on unmodified milk of other species (such as goats' or sheep's milk) because of a high rate of cross reactivity.^{1,2} In general, formulas based on intact soy protein isolates are not recommended for the initial treatment of food allergy in infants, although a proportion of infants with cows' milk protein allergy tolerates soy formula.^{2,25} Products with highly reduced allergenicity based on so called extensively hydrolysed protein, or amino acid mixtures, are recommended for the treatment of infants with cows' milk protein allergy. In contrast, formulas with moderately reduced allergenicity (partially hydrolysed) are not recommended for the treatment of allergy, because they contain substantially higher amounts of residual allergens than extensively hydrolysed products.²⁶ Some infants may react even against the residual quantities of cows' milk protein in products with highly reduced allergenicity, thereby illustrating that none of the so called "hypoallergenic" hydrolysates can be truly regarded as non-allergenic; such highly sensitive patients may require an amino acid based dietary product.^{18,20}

Products with highly reduced allergenicity (extensively hydrolysed) differ with respect to

their contents of lactose and the contribution of medium chain triglycerides. Products with little or no lactose and a large proportion of fat as medium chain triglycerides can be of value in the initial treatment of infants with enteropathy and malabsorption secondary to severe food allergy. However, for the treatment of most infants with food allergy whose digestive and absorptive functions are normal, it is reasonable to use products with highly reduced allergenicity, which apart from the protein modification meet the European Union standards for infant formulas.³ A practical concern is the inclusion of lactose in such formulas, because contamination of lactose with residual cows' milk protein could cause allergic reactions in some infants who are highly sensitive to cows' milk protein. Such patients would require products without lactose, or with lactose processed to remove any residual allergenic protein.

Allergic reactions to the causal food protein may disappear in infants and children after several months or years of allergen avoidance, particularly in children with cows' milk protein allergy.^{2,5} Therefore, controlled rechallenges should be performed at regular intervals to avoid unnecessarily prolonged avoidance diets.

Prevention

It is presumed that breast feeding has an allergy preventive effect compared with cows' milk formula feeding, but the extent of the preventive effect remains controversial.^{1,2,27} The issue remains open because infants cannot ethically be randomly assigned to breast or formula feeding to enable a definitive study. Consequently, confounding factors may highly influence the results of comparisons. In a recent Finnish study of non-selected (non-high risk) newborns followed up to 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 compared with cows' milk formula fed individuals.²⁸

In other recent prospective studies, the allergy preventive effect of breast feeding has only been documented in high risk infants, defined as infants with at least one first degree relative with documented atopic disease. In such high risk infants, breast feeding alone or in combination with avoidance of cows' milk products and avoidance of supplementary foods for the first 4 months of life was associated with a significant reduction of the cumulative incidence of atopic dermatitis and cows' milk protein allergy and intolerance during the first 2-4 years of life. There is no conclusive evidence for a protective effect of a maternal exclusion diet during pregnancy. A few studies indicate that the preventive effect of breast feeding on the development of atopic dermatitis might be enhanced by maternal avoidance of potential food allergens (milk, egg, fish) while breast feeding, whereas other studies do not confirm this finding.^{29,30}

Some prospective studies have shown that soy formulas are as allergenic as conventional cows' milk based formulas, and on this basis

they should not be recommended for the prevention of food allergy,^{1,2} but controversial views exist,^{27,31,32} and further studies may be useful to clarify the allergenicity of soy formula in infants who are at risk of developing allergies. There is no evidence that formulas based on whole proteins other than cows' milk protein are less allergenic.

The introduction of complementary foods (Beikost) during the first 4 months of life has been associated with a higher risk of atopic dermatitis up to the age of 10 years.³³ Thus, it appears prudent not to introduce complementary foods before the 5th month of life and then to introduce only a limited number of foods with low allergenicity, but the basis of such advice is incomplete.

Prospective studies have reported that intervention programmes in high risk infants using dietary products with highly reduced allergenicity (extensively hydrolysed) and avoidance of complementary foods (Beikost) and foods containing cows' milk protein during at least the first 4 months of life (in some studies in combination with other preventive measures) results in a reduction of the cumulative incidence of atopic dermatitis and food allergy, especially cows' milk protein allergy with manifestations in the skin and gastrointestinal tract.³⁴⁻³⁶ The preventive effect of these combined intervention programmes using products with highly reduced allergenicity (extensively hydrolysed) has been reported to be comparable with that of exclusive breast feeding in high risk infants. Intervention using formulas with moderately reduced allergenicity (partially hydrolysed) has been investigated in randomised prospective studies in high risk infants, and an allergy preventive effect comparable with that of exclusive breast feeding has been reported.^{26,37,38} Because of great variations in study design and diagnostic criteria, the relative efficacy of the different interventions tested in the various studies cannot be compared directly with each other. At present, clinical trials are ongoing that compare directly the relative preventive effects of products with highly reduced allergenicity (extensively hydrolysed) with those of formulas with moderately reduced allergenicity (partially hydrolysed).²⁷ Only one such study has been published and 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 cows' milk protein based formula; a greater effect was reported with the extensive hydrolysate.³⁹ More studies on this question are needed.

It has been suggested that the preventive effect of allergen reduced diets is greatest in early infancy when human milk or hypoallergenic formula is exclusively fed from birth, and becomes less clear after the introduction of a mixed diet in the 2nd half of the 1st year of life.^{12,37} With respect to the extent of preventive effects, a few studies have shown that the cumulative incidence of food allergy and cows' milk protein allergy was significantly reduced until the age of 5 and 7 years, respectively,^{12,27,37}

suggesting a true reduction and not only a postponement of the onset of the disease.

Based on the current evidence, dietary allergy preventive measures are only recommended in high risk infants with a well defined increased risk of developing atopic disease; that is, infants with at least one first degree relative (parent or sibling) with documented atopic disease. As in all healthy infants, breast feeding should be encouraged for at least the first 4 months of life. Supplementary foods should not be introduced before the 5th month of life. If exclusive breast feeding is not possible, it is recommended that a hypoallergenic formula (with a confirmed reduced allergenicity in adequate clinical studies) should be used. There is no conclusive evidence for the use of formulas with reduced allergenicity (protein hydrolysate formulas) in infants without a documented hereditary risk. Formulas with reduced allergenicity used for the prevention of allergy should meet the European nutritional standards for infant formulas.³

Summary

TREATMENT OF ALLERGIC REACTIONS TO FOOD PROTEINS

- Infants with confirmed food protein allergy should be treated by complete exclusion of the causal protein
- In exclusively breast fed infants, a strict elimination of the causal protein from the diet of the lactating mother should be tried
- Infants with cows' milk protein allergy who are not breast fed should receive a dietary product with highly reduced allergenicity based on "extensively" hydrolysed protein or, in selected cases, a product based on an amino acid mixture
- In infants with adverse reactions to food proteins and malabsorptive enteropathy, the use of a formula with highly reduced allergenicity (extensively hydrolysed formula or amino acid mixture) without lactose and with medium chain triglycerides might be useful until normal absorptive function of the mucosa is regained
- For the treatment of most infants with food allergy whose digestive and absorptive functions show no major disturbances, products with highly reduced allergenicity based on extensively hydrolysed protein or amino acid mixtures, but whose other compositional characteristics meet the European union criteria for infant formulas, is recommended
- Diets based on unmodified proteins of other species' milk (for example, goats' or sheep's milk), or so called "partially" hydrolysed formulas should not be used for the treatment of cows' milk protein allergy.

PREVENTION OF ADVERSE REACTIONS TO FOOD PROTEINS

- Exclusive breast feeding during the first 4-6 months of life might greatly reduce the incidence of allergic manifestations and is strongly recommended
- Supplementary foods should not be introduced before the 5th month of life

- In bottle fed infants with a documented hereditary atopy risk (affected parent or sibling), the exclusive feeding of a formula with a confirmed reduced allergenicity is recommended because it can reduce the incidence of adverse reactions to food, especially to cows' milk protein
 - More studies comparing the preventive effects of formulas that have highly reduced allergenicity with formulas that have moderately reduced allergenicity are needed
 - Dietary products used for preventive purposes in infancy need to be evaluated carefully with respect to their preventive and nutritional effects in appropriate clinical studies
 - There is no conclusive evidence to support the use of formulas with reduced allergenicity for preventive purposes in healthy infants without a family history of allergic disease.
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