

Food allergen avoidance in primary prevention of food allergy

Approximately 5–10% of children suffer from allergy to one or more foods. Primary prevention through a hypoallergenic diet may reduce the prevalence of food allergy and associated co-morbidity, such as eczema and urticaria. Breastfeeding has many advantages and should be recommended for all children. Those with a history of atopy in the immediate family are at a higher risk and maternal diet during lactation, avoiding highly allergenic foods, may enhance the benefit. Cow's milk should be strictly avoided, and supplements, if required, should be with a hypoallergenic formula. Delayed introduction of egg, nuts, wheat and fish has also been suggested. Dietary restriction may have nutritional consequences for the mother and child and supervision by a dietician is essential. Maternal diet during pregnancy is not advisable as the benefit is minimal and there may be adverse effects on the foetal nutrition. In high risk infants, a combined approach, where breastfeeding with maternal avoidance of highly allergenic foods, supplemented by extensively hydrolysed formula during the first 6 months of life, in addition to the delayed introduction of solid foods, has been shown to reduce the development of food allergy in infants.

S. Hasan Arshad

The David Hide Asthma & Allergy Research Centre, St. Mary's Hospital, Isle of Wight, UK

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Dr S. Hasan Arshad
The David Hide Asthma & Allergy Research Centre
St. Mary's Hospital
Newport
Isle of Wight
PO30 5TG
UK
Tel: +44 (0)1983 534373
Fax: +44 (0)1983 822928
Email: sha@soton.ac.uk

The burden

Food allergy is relatively common in early childhood, but rare in adults. In children, 90% of reactions are caused by cow's milk, egg, nuts and wheat. Clinical manifestations include acute allergic reactions such as urticaria, angioedema, vomiting, laryngeal oedema, bronchospasm, hypotension and chronic manifestations such as diarrhoea and eczema. Tolerance often develops to cow's milk and egg between the ages of 2 and 4 years. In practice, primary prevention has to be started at, or even before, birth to have a real impact on the prevalence of food allergy.

The prevalence of cow's milk allergy (CMA) during early childhood is reported to be between 2% and 5% (1, 2). Symptoms are usually confined to the gastrointestinal tract and may include diarrhoea, vomiting, colic, rectal bleeding and failure to gain weight. However, acute allergic reactions with systemic symptoms and anaphylaxis may occur.

Sensitisation to egg protein is extremely common in children before the age of 2 years, but clinical allergy occurs in less than 3%. Sensitisation to peanut occurs in about 1% of unselected children, with nearly half having evidence of a clinical reaction (3). Peanut allergy appears early in life, often following cow's milk and egg allergy. Symptoms vary from mild rash to anaphylaxis. Soy allergy is uncommon (1%) in atopic children, including those who have been fed soy milk during the first 6 months of life (4).

Why primary prevention?

There is general consensus that the prevalence of atopic diseases, including food allergies, is increasing. This increase in prevalence has highlighted the need for primary prevention. The concept that the interaction of genetic and environmental factors is responsible for the phenotypic expression of allergic disease is attractive, because children at high risk can be identified, and intervention measures should lead to a reduction in disease prevalence. Food proteins are important allergens in early childhood. A hypoallergenic diet has therefore been suggested as a means of preventing the development of food allergy. The benefit of avoidance, to a great extent, is food specific. Thus, avoidance of cow's milk protein prevents cow's milk allergy and avoidance of peanut may reduce the risk of peanut allergy.

Who should prevention be directed to?

Prophylactic intervention by allergen avoidance should be directed toward those infants at very high risk, who will benefit most. History of atopy in the immediate family is an important risk factor for the development of allergy in children (5). Heritability of peanut allergy using a twin study model was estimated at 81% (6). However, by using family history as the sole criteria for intervention, a number of children will be subjected to prophylactic measures unnecessarily and others will be

missed (7). Unfortunately, other markers such as cord blood total IgE levels lack sensitivity (8). In a recent study, cord blood IgE was found to be a significant predictor for the development of urticaria due to food allergy, but not for other atopic disorders (9). Family history of atopy currently remains the only method available to select infants suitable for prophylactic allergen avoidance.

Food allergen avoidance

Any primary preventive programme for infants at high risk requires highly motivated parents and close co-operation with the physician and other health care workers. Highly allergenic food or foods are excluded from the infant's diet. In certain situations a replacement food will be required, as it is not always possible to simply eliminate the food, e.g. milk, during infancy.

Cow's milk allergy

Cow's milk is an important food allergen during infancy. Avoidance of cow's milk in early infancy has been shown to reduce the development of CMA in at-risk infants (10–13)

Role of breastfeeding. Most studies show a protective effect of breastfeeding (14, 15). Saarinen & Kajosaari (14) have shown that the prevalence of food allergy was highest in those children of 1–3 years of age, who had been breastfed for less than 1 month. However, not all studies have confirmed this beneficial effect (16). There may be a number of reasons for the relative lack of effectiveness of breastfeeding in preventing cow's milk allergy. Protein ingested by the lactating mother can be secreted in the breast milk and sensitise the infant (17). Another potential source of sensitisation to cow's milk in the so called "exclusively breast fed infant", is the cow's milk formula supplements given in the immediate post natal period, sometimes without the knowledge of the mother (18).

Role of hypoallergenic formula. Allergic reactions require large protein molecules (antigens) to stimulate the production of antibodies. To reduce allergenicity, the source protein can be broken down into small peptide molecules and amino acids by enzyme hydrolysis. This process has been used successfully in the production of hydrolysed formula. These infant formulae are based on animal or vegetable protein (casein, whey, soy and bovine collagen) and are used extensively in children with cow's milk allergy or intolerance. Their role in primary prevention of cow's milk allergy is not unanimously agreed, but there is evidence to suggest that the use of these formulae in

infants at high risk of cow's milk allergy may be beneficial (15, 19). Chandra et al. (10) claimed a reduction in the prevalence of food allergy confirmed by DBPCFC, in children at high risk, who were fed breast milk and whey hydrolysate, as compared to those fed cow's milk formula or soy formula.

There is then the choice between partial and extensive hydrolysate. In extensively hydrolysed formulae, 95% of the peptides have a molecular weight below 1500 Dalton and <0.5% of the remaining peptides above 6000 Dalton. Partially hydrolysed formulae have 2–18% peptides above 6000 Dalton. These larger peptides may elicit an allergic reaction. Partially hydrolysed formulae have a higher capacity to induce positive skin tests, provocation tests and to bind to human serum IgE antibodies of cow's milk allergic children (20). Amino acid based formulae do not have peptides, and therefore are unable to stimulate the immune system (20). As a replacement or supplement to breast milk, extensively hydrolysed formulae during the first 6 months of life are effective in reducing the development of food allergy (15). There are, however, problems of producing suitable hydrolysates that are low in antigenicity and taste good.

Some experts argue for the use of partial hydrolysate for primary prevention, as the taste and nutritional value may be better than an extensive hydrolysate (21). In a study by Vandenplas et al. (19), infants were randomly assigned to receive either a partial whey-hydrolysate formula ($n=28$) or a regular cow's milk formula ($n=30$). At 6 months, the prevalence of cow's milk protein (CMP) sensitivity was significantly decreased in the hydrolysate group (7% versus 43%; $P=0.002$). However, extensive hydrolysate seems to be more effective. In a recent study (22), 595 high-risk infants were either breastfed exclusively or randomised to partially hydrolyzed formula or two extensively hydrolyzed formulae for the first 4 months of life. Partially hydrolyzed formula was found to be less effective than extensively hydrolyzed formula in preventing cow's milk allergy, 0.6% vs. 4.7% ($P=0.05$). Hydrolysed formula milk may also be used for pregnant and lactating women if cow's milk is excluded from their diet.

Role of soy formula. Some authorities have recommended soy formula for primary as well as secondary prevention of cow's milk allergy (13). However, children may develop allergy to soy protein and it is generally not recommended for primary prevention.

Peanut allergy

It has been suggested that exposure to peanut *in utero* and during infancy may increase the risk of peanut allergy in children (23). This notion was supported by a

recent study by Frank et al. (24), who studied 25 peanut allergic and 18 control children. Consumption of peanut by the mother during pregnancy, and its early introduction to the infant's diet, increased the likelihood of peanut sensitisation. However, preventive studies showing a reduction in peanut sensitisation or allergy, following maternal avoidance during pregnancy or lactation, or by children in early years, are lacking. Despite this, the UK Department of Health has issued standard advice to pregnant and lactating women who are atopic themselves, or whose partners or children are atopic, to avoid eating peanuts. Avoidance was also recommended for the child up to the age of 3 years (25).

Egg allergy

The prophylactic effect of allergen avoidance on allergy to egg has not been studied in detail. However, some studies have shown a reduction in egg allergy following avoidance of highly allergenic foods including egg, during early infancy (11, 12).

The period of avoidance

Recognition of milk protein (and other) allergens by cord blood cells indicates that allergen priming occurs prenatally (26). However, avoidance of highly allergenic foods, such as egg, nuts, fish and cow's milk, during the third trimester of pregnancy by atopic mothers, has shown little benefit (11, 27). It is possible that allergen avoidance may have to be commenced earlier in pregnancy to be effective. However, there are concerns about the development and growth of the foetus (11, 27).

Results are more encouraging when avoidance is practised during infancy (10–13, 19, 22). Apart from avoidance of cow's milk, late introduction (4–6 months) of solid foods is recommended. Highly allergenic food such as eggs and fish are not introduced until 1 year and nuts may be excluded for 2–3 years. The benefit of replacing cow's milk with a whey hydrolysate after the age of 6 months seems to be minimal (28).

A combined approach

In infants at risk of developing allergies, maternal avoidance of allergenic foods during lactation, exclusive breastfeeding for 6 months, use of extensive hydrolysate, if required, and introduction of solids after 4 (preferably 6) months of age reduces the incidence of atopic syndromes, particularly atopic dermatitis and food allergy in early childhood (11–12, 29). There is also evidence of reduced sensitisation in the number of positive skin-prick tests and specific IgE antibodies (11, 12).

In the study by Arshad et al. (12) environmental

measures, primarily, house dust mite avoidance, was added to the food allergen avoidance, with a significant reduction in asthma at 12 months, as well as a reduction in food allergy, eczema and skin sensitisation, in the prophylactic group. Food or inhalant allergen avoidance may specifically lead to reduction in food allergy/eczema or respiratory allergy, respectively.

Problems of food allergen avoidance

The prevention through dietary means is not easy in terms of compliance, resources required and expense. Although most hydrolysed and soy formulae meet the fatty acid and protein recommendations for infant formula (30), there remains concern regarding other nutrients (31). Hypoallergenic formulae are more expensive than cow's milk formula. Egg is also a cheap source of protein for both lactating mothers and for weaning infants.

Complete avoidance is difficult because there are small amounts of milk, egg or nut proteins in many packaged or prepared foods. These diets are socially disruptive, which inevitably leads to problems with compliance. Education on avoidance measures is imperative.

Role of the dietitian. Close supervision by a dietitian is required to ensure nutritional adequacy of the preventive diet for both infant and mother, if on an exclusion diet. This should be done with respect to intake of energy (calorific value), proteins, fibre, calcium, iron, vitamins and other minerals (32). Alternatives should be recommended such as a hydrolysate or another cereal. Supplements should be prescribed if alternative sources are liable to be inadequate in a particular nutrient. The dietitian should give a detailed explanation and provide a list of packaged foods that may contain the food to be excluded. A list of foods free from the food allergen is also very helpful. An assessment must be made of the parent's ability to understand and comply with the avoidance diet.

Conclusion

A restricted maternal diet during pregnancy is generally not advisable except for the avoidance of nuts. Exclusive and prolonged (>6 months) breastfeeding should be encouraged. A maternal diet that excludes highly allergenic foods during lactation may enhance the benefits, but should be restricted to mothers of very high risk children and close supervision by a dietitian is essential.

Cow's milk formula should be avoided for at least the

first 6 months of life. This may require hydrolysates or amino acid based formula as replacement or supplement to breastfeeding.

The argument for partial or extensive hydrolysate is

not resolved but, in general, extensive hydrolysate is more effective. Delayed (4–6 months) introduction of solids, avoidance of egg and fish for 12 months and nuts for up to 2–3 years may also be recommended.

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