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Prophylaxis of Cow's Milk Allergy

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Cow's milk allergy (CMA) is a common cause of illness in infants [1], and the severity of symptoms varies widely, according to the patient's age and the disease presentation. Many infants may experience only mild symptoms, but others may exhibit life-threatening manifestations (anaphylactic shock) after ingesting a minute amount of CM. The natural history of CMA is variable, and the phenotypic expression of symptoms usually changes with age. In many infants symptoms disappear completely, whereas in others the disease persists for life, and, in addition, other atopic diseases may occur in a high proportion of children previously affected by CMA.

It has recently been estimated, by a prospective study performed in a cohort of 1,749 newborns, that 2% of children suffer from CMA [2]. A number of previous studies showed that the prognosis of CMA is excellent with up to 80% of the infants acquiring the tolerance in the first year of life [2]. However, another study performed with more definite diagnostic criteria reported a less optimistic outcome [3]. In addition, a quite high proportion of infants (80%) with CMA developed other atopic diseases before puberty, thus stressing that CMA is a hallmark of the atopic constitution. We have shown that 73% of infants with gastrointestinal symptoms due to CMA, followed up to 14 years, experienced other atopic diseases and 34% developed asthma [4]. These figures are in agreement with another recent follow-up study, which indicates the same prevalence of asthma in children with CMA [3]. The atopic status of these infants plays an important role for sensitization to other foods and inhalant allergens, thus modulating the onset and the severity of other atopic diseases [4].

Positive family history for atopic disease in parents and/or siblings has been reported in 40-80% of children with CMA. Host et al. [2] reported a double

parental atopic heredity in 23% of the children with CMA in comparison to 3% of the children in the control group. A number of experimental and clinical data indicate that early exposure to CM is a risk factor for CMA [2–5]. It has been shown by a recent prospective study on a large population of newborns that the babies fully breast-fed who developed CMA, received some CM formulae in the nursery [5].

Primary Prevention

Primary and secondary prevention is antigen specific, therefore avoidance of CM proteins is the prerequisite for prevention of CMA. Due to the peculiarity of the atopic status, even minute amount of CM proteins may provoke sensitization in not already sensitized babies or trigger symptoms in babies with CMA.

Dietary Measures during Pregnancy

According to several observations, prenatal sensitization to food antigens may occur. IgE antibodies to CM and soy proteins have been detected in both amniotic fluid and cord blood in a few cases [6]. In order to reduce the risk of sensitization to food antigens, it has been suggested that the intake of CM, eggs, peanuts and fish be reduced during the last trimester of gestation. However, two recent randomized studies did not show any preventive effect of dietary manipulation during pregnancy [7, 8].

Dietary Measures Early in Life

Since the pioneering study of Grulee and Sandford [9], which showed that atopic dermatitis (AD) was 7 times more frequent in bottle-fed babies than in breast-fed babies, and the early studies by Glaser and Johnstone [10] and Johnstone and Dutton [11] on the use of soy formulae for the prevention of atopic disease, a large debate occurred on the influence of early feeding in the development of CMA and of other atopic diseases. Forty years following the study by Grulee and Sandford [9], Matthew et al. [12] conducted a prospective study on the development of AD in infants of atopic parents who were either subjected to an allergen-avoidance regimen from birth to 6 months or were managed conventionally. The dietary measures included breast-feeding for 6 months and soy formula when breast-feeding was not sufficient. The group on the allergen-avoidance regimen had less AD at 6 months and 1 year than did the control group ($p = 0.017$). We have studied 174 high-risk babies followed up to 52 months [13]. At the last follow-up (52 months), only 1 child (0.5%) had AD and 2 (1%) had symptoms due to CMA. In a randomized prospective study on preterm infants by Lucas et al. [14], it was shown that only babies with a family history of atopy

who received a preterm formula rather than human milk had a significantly greater risk of developing AD by 18 months. Strangely enough, babies with a negative family history had significantly less AD and food and drug reactions if they were initially fed the preterm formula with a high protein content than a standard formula with a lower protein content [15]. This data indicates that early diet may influence the onset of allergic disease in preterm babies. A strong interaction between diet and genetic propensity to atopy influences the response to early diet [15]. As suggested by Sigurs et al. [16], the exclusion of CM, eggs and fish during the first 3 months of lactation, with supplementation of a casein extensively hydrolysate formula (eHF), was associated with a statistically significant reduction in both the prevalence and the severity of AD at the age of 3 and 6 months, and a significant lower cumulative prevalence of atopic disease at the age of 4 years. Moreover, Zeiger et al. [17] have shown, by a prospective randomized study, that the avoidance of CM, eggs, fish and peanuts during the first 6 months of lactation, with the supplementation of a casein eHF, significantly reduced the prevalence of AD and food allergy at the age of 1 and 2 years. Nevertheless, these authors did not observe differences in the prevalence of atopic disease at the age of 4 years. These studies, therefore, suggest that the avoidance of allergenic foods in the nursing mother's diet such as CM, egg, fish and peanuts during the breast-feeding period should be considered in order to prevent sensitization via breast milk in high-risk babies. In addition to breast-feeding, the use of eHF is recommended for the prevention of CMA, owing to their reduced allergenicity *in vitro* and *in vivo* [18]. In high-risk babies, early manifestation of atopy, especially AD, may be reduced by the use of eHF, such as in breast-feeding children. Halken et al. [19] demonstrated that feeding breast milk, or an eHF or an ultrafiltrated whey HF, combined with avoidance of solid food during the first 6 months of life in high-risk infants, significantly reduced the cumulative incidence of CMA during the first 18 months of life. Supplementation of breast-feeding with a soy-based protein hydrolysate, in association with a number of environmental measures, significantly reduced AD at the age of 12 months of life [20]. A preventive effect of partially hydrolysate formulae (pHF) on CMA has been supported, but not proven, by several studies in high-risk infants. pHF may possibly be effective in allergy prevention, but the results of several studies, at the moment, cannot be considered definitive. The design shortcomings including inexact definitions of disease, lack of immunological documentation, and omission of double-blind, placebo-controlled food challenge, render it impossible to recommend pHF for the prevention of CMA, at the moment [18]. In addition, it is very difficult to agree with a definition of 'hypo-allergenic' for a product which triggers symptoms in about 50% of children with CMA and which contains significant amounts of intact CM proteins [18, 21–23].

Secondary Prevention

The replacement of CM with a CM substitute should not provoke the recurrence of symptoms in children with CMA. There are now available a wide variety of milk substitutes, including soy-protein formulae, and eHF from casein, whey, soy and beef collagen. Nutritional adequacy and allergenicity, as well as the cost and the taste of these formulae, should be taken into account in the choice of a CM substitute (table 1). Since soy formulae have been available for over 30 years, several long-term studies of their use in infants with CMA have demonstrated normal growth and development [24]. On the contrary, recent studies have shown that HF feeding induces abnormalities in some nutritional parameters (e.g. amino acid profile, nitrogen blood urea, calcium, phosphorus retention and absorption).

Although all these formulae are in wide clinical usage for CMA, they are each capable of inducing allergic symptoms to a varying degree (table 2). It has been demonstrated, for example, that soy formulae can induce allergic reactions in CMA infants with a prevalence ranging from 5 to 10% [25]. Casein eHF, which have been in use for over 40 years for infants with defects in protein digestion and with CMA, are generally well tolerated, as well as whey protein eHF, introduced more recently. However, in a few cases even these products can trigger allergic symptoms [18, 23]. In a recent study [23] it has been shown that pHF can result in allergic reactions in 50% of infants with CMA, and serum IgE-specific antibodies can be demonstrated in such infants whereas casein or whey eHF induced symptoms in 2/20 (10%) and 2/15 (13%) respectively, a soy formula did not give reactions. More recently, an infant formula composed of individual amino acids, fat, carbohydrate, minerals, and vitamins (Neocate) has been well tolerated by patients with hypersensitivity to multiple infant formulae [26].

Meat-based formulae (e.g. lamb, chicken, turkey), from commercial and home-made sources have also been used in the treatment of CMA in infants with varying degrees of success [4]. These formulae have the added advantages of low cost and good taste. Although it is well known from a number of studies that goat's milk is not a suitable CM substitute in children with CMA due to the high degree of cross-reactivity between goat and CM proteins, recently goat's milk formulae have been developed and marketed for feeding children with CMA. We have shown that almost 100% of children with confirmed CMA have positive challenge with goat's milk. Companies providing goat's milk formulae should be encouraged to mark such products which are dangerous for children with CMA, or at least a warning should be labelled on the can.

In conclusion, CMA is not a transient disease as previously claimed, almost 30% of school children previously affected by CMA, still have CMA. Respiratory allergic disease develops in a high proportion of such a population, even

Table 1. Ideal CM substitute for primary and secondary prevention of CMA

Nutritionally adequate
Pleasant taste
Low cost
Easily available
Not allergenic
{ No CM proteins, even in minute amounts
{ No peptides with allergenic epitopes

Table 2. Characteristics of the formulae (available on the market) for primary and secondary prevention of CMA

	Soy	eHF	pHF
Immunogenicity (sensitizing property)	±	—	±
Allergenicity (trigger symptoms)	±	±	+++
CM proteins	—	—	++
Reactive epitopes	—	±	+++
Nutritional adequacy	+	?	?
Pleasant taste	+	—	+
Low cost	+	—	+

eHF = Extensively hydrolysate; pHF = partially hydrolysate.

when the children can ingest milk with impunity. The ideal formula for primary and secondary prevention of CMA should not contain any CM proteins, even in minute amounts, because of the peculiarity of the atopic status, sensitization and symptoms are usually triggered even by a small quantity of the relevant allergen.

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