

SPECIAL ARTICLE

Food allergy in childhood. Hypersensitivity to cows' milk allergens*

Introduction

Cows' milk allergy (CMA) may be defined as a set of immunologically-mediated adverse reactions which occur following the ingestion of milk. The diagnosis of CMA is made only when a relationship between ingestion of milk and the onset of symptoms can be shown and when the symptomatology can be demonstrated to be the consequence of an immunological reaction. Although several immunological mechanisms, such as those mediated by cellular and immune complex reactions, may also be involved in the pathogenesis of CMA, the most readily demonstrated immunological reaction in clinical practice is that mediated by IgE. When an immunological reaction cannot be demonstrated, the symptom complex is usually termed cows' milk intolerance.

Clinical aspects

A large spectrum of manifestations may be associated with CMA. Some are immediate and severe occurring within minutes (e.g. angioedema, shock); others are of a more insidious nature occurring within hours; and still others are of a more chronic nature occurring over a period of a day or more [1]. The major shock organs which are commonly involved in CMA include the gastrointestinal tract, skin and respiratory tract. It should be stressed that although the offending food allergen, i.e. cows' milk, first encounters the gastrointestinal tract which may be the first organ affected, the respiratory tract and particularly the skin, i.e. atopic dermatitis may be the sole target organs involved. Moreover, some symptoms of CMA are less commonly recognized and may masquerade as other disorders (e.g. gastro-oesophageal reflux and pyloric stenosis) [2,3].

Diagnosis

Since the manifestations of CMA are not pathognomonic and since there is no specific diagnostic test available, the

diagnosis should be made on the basis of a careful history, physical examination and appropriate *in vivo* and *in vitro* tests. A family history of atopy and/or CMA in other family members strongly supports the diagnosis of CMA. It should be emphasized, however, that the vast number of adverse reactions to cows' milk in infancy are not related to CMA. The common clinical practice of change of infant formula followed by clinical improvement is not *prima facie* evidence of CMA.

It is generally agreed that the diagnosis of CMA should be confirmed by the use of an oral challenge test which should be performed after a period of 2–4 weeks of cows' milk elimination with improvement of symptoms. The provocation of symptoms following milk challenge, although suggestive of CMA, leaves open the question of a possibility of other clinical disorders (e.g. lactase deficiency, infections, anatomical anomalies), which may also be elicited by challenge. A positive response to the challenge test, unaccompanied by appropriate immunological tests, suggests cows' milk intolerance and other diagnostic possibilities should be considered. The diagnosis of CMA should only be made when both challenge and immunological tests are positive.

Oral challenge tests

The oral challenge tests (OCT), as originally described by May *et al.* [4], consist of the ingestion of the suspected offending food antigen followed by the reappearance of symptoms. A variety of OCT are available for the diagnosis of CMA. These not only include a variety of procedures (e.g. open, single-blind or double-blind), but also the use of a variety of preparations of cows' milk (e.g. fresh or processed: pasteurized, lyophilized or hydrolysed preparations), or components of cows' milk (e.g. casein, beta-lactoglobulin, etc.). The double-blind method of May *et al.* [4] is the research method of choice. However, its clinical applicability is limited and its universal use may not be necessary, particularly in infants where an open challenge may be satisfactory.

No unanimous consensus exists concerning the choice or the performance of challenge tests in infancy. We propose the following guidelines:

- 1 The test should always be performed under strict medical supervision because of the risk of severe allergic reactions (e.g. anaphylactic shock, angioedema).

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- 2 The test should not be performed in children with documented life-threatening manifestations associated with the ingestion of milk.
- 3 In infants with persistent gastrointestinal symptoms, it is advisable to delay the challenge test until there is a period of improvement in nutritional status.
- 4 If the response to an open challenge test is positive, no further challenge tests need to be performed. However, in cases where the response is not clear, a double-blind challenge is recommended.
- 5 No unanimous agreement exists concerning the amount of milk to be administered in the challenge test nor the precise method of administration. In the blinded food challenge tests the cows' milk antigen is commonly administered in gelatin capsules to disguise the nature of the test antigen. In the small infant and in the child unable to ingest the capsule, no standardized methodology exists concerning the preparation (e.g. use of whole milk, milk components) or the exact method of masking the taste or appearance of the test antigen.

It is generally advisable to begin with small quantities of the test antigen gradually increasing the amount. In the majority of cases symptoms will occur within 4 hr. In other cases where the symptomatology of CMA may be less clear or where the initial challenge tests were negative, increasing the dose of the test antigen over a prolonged period may be necessary [1].

A positive result of the challenge test should be based upon solid objective criteria. The symptoms evoked usually take the form of those which are expressed following natural challenge. However, it is important to stress that symptoms not previously experienced may occur after the challenge particularly in children with severe atopic dermatitis, in which symptoms may vary from vomiting, nasal stuffiness, diarrhoea, urticaria, asthma and even anaphylaxis. The objective evaluation of a positive response to the challenge test may be accomplished, for example, by measurement of pulmonary function if bronchoconstriction is evoked, or by quantitation of the area of involvement of the skin by use of specialized charts in the case of evoked skin involvement, i.e. urticaria or atopic dermatitis or by measurement of faecal output or occult blood in the case of gastrointestinal symptoms.

Allergological diagnostic tests

Methods for the *in vivo* and *in vitro* detection of specific IgE antibody to cows' milk consist of the prick-puncture skin test and *in vitro* specific IgE antibody tests, respectively.

Prick-puncture skin tests. When properly performed these tests can be very helpful in the diagnosis of CMA. The presence of a positive skin test very often correlates with clinical symptomatology and the results of *in vitro* IgE tests. A negative skin test, however, does not necessarily negate the diagnosis of CMA since many factors may influence the skin responsivity (e.g. atopic dermatitis, antihistamines, quality of the test antigen, etc.).

In vitro tests for specific IgE antibody detection. The *in vitro* methods used for specific IgE detection show similar sensitivity, specificity and limitations as the prick-puncture skin tests and are not influenced by the factors affecting skin responsivity. Because of their variability and lack of standardization the following tests are not recommended for general clinic use. These include the detection of humoral and cellular mechanisms of CMA such as the measurement of specific antibodies of other isotypes (IgA, IgM), or IgG subclasses (e.g. IgG4); circulating immune complexes; lympho-proliferative responses to milk antigen(s).

Other tests

Other tests which may be helpful in the evaluation of CMA, particularly in infants with gastrointestinal symptoms, include functional tests of intestinal permeability [5], and the measurement of eosinophils in blood and in various secretions. Although intestinal biopsy [6] usually reveals a normal mucosa in IgE-mediated cows' milk allergy, even in infants with gastrointestinal manifestations, the procedure may be useful in cows' milk enteropathy in which case the biopsy may be abnormal.

Dietary management

The first step in the management of the child with CMA is the identification and elimination of the offending cows' milk protein(s). This should be followed by the replacement with cows' milk substitutes which should not provoke the recurrence of symptoms. There are now available a wide variety of milk substitute infant formulae which include soy-protein formulae, and protein hydrolysates (e.g. those made from casein, whey, soy, and beef collagen). Since there are a variety of methods for preparation of these hydrolysates (e.g. digestion with a variety of proteolytic enzymes followed by heat treatment, etc.), the molecular weights of the peptides in the final products are quite variable and range from 100 to 6000. In making a choice of these formulae for use in CMA, there are two important factors to be considered: nutritional adequacy and allergenicity. In addition, the cost and the taste of these formulae should be taken into account. Since soy formulae have been available for over

50 years [7,8], several long-term studies of their use in infants with CMA have demonstrated normal growth and development. Although a limited number of short-term studies of infants fed with hydrolysate formulae have indicated their nutritional adequacy [9,10], longer term studies are awaited.

Careful evaluation of infants with CMA fed with soy or hydrolysate formulae is recommended to assure adequacy of individual nutrients (e.g. minerals). Although all of these formulae are in wide clinical usage for the treatment of CMA, they are each capable of inducing allergic symptoms to a varying degree. It has been demonstrated, for example, that soy formulae can induce allergic reactions in cows' milk allergic infants with an incidence ranging from 5–10% [1,11,12]. Casein hydrolysate formulae, which have been in use for over 40 years for infants with defects in protein digestion and with CMA, are generally well-tolerated [13]. Whey protein hydrolysate formulae have been introduced more recently. There are basically two types: highly hydrolysed and less hydrolysed, which differ in the size of the peptide fragments (6000 in the former, 15 000 in the latter).

Recent *in vitro* [14] and *in vivo* studies [15–18] have shown that hydrolysate formulae can result in allergic reactions in infants allergic to cows' milk and serum IgE cows' milk specific antibodies can be demonstrated in such infants. The data, thus far, suggest that hydrolysate formulae may be effective for the prevention of CMA in the allergic-prone, non-sensitized infant [19]. Although casein and highly hydrolysed whey formulae may be used in infants with CMA, the use of less hydrolysed whey formulae is not recommended [20].

Meat based formulae made from a variety of meat (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 [21]. These formulae have the added advantages of low costs and good taste; no data are available about nutritional adequacy of these formulae.

In summary, a variety of milk substitute formulae are available for the treatment of CMA allergic infants. Each of them show distinct advantages and each are capable of inducing undesirable allergic reactions to varying degrees. All of these formulae belong within the armamentarium of the physician who should have the flexibility to choose among them in any given clinical situation.

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