

Cow-milk allergy

Erika Isolauri *

Department of Paediatrics, University of Turku, 20520 Turku, Finland

Abstract

Hereditary predisposition is the major denominator of allergy, and hypersensitivity reactions contribute to the expression of the genetic predisposition. The route of sensitization varies with age so that dietary antigens predominate in infancy. The immaturity of the immune system and the gastrointestinal barrier may explain the peak prevalence of food allergies at an early age. The treatment of choice for cow-milk allergy is complete avoidance of cow-milk antigens. The approach to control allergic inflammation by antigen elimination, however, has not been satisfactory. New approaches are urgently needed for the management of patients with cow-milk allergy. These may include: (i) immunotherapy to counteract the immunological dysfunction, and (ii) stabilisation of the gut mucosal barrier to strengthen endogenous defence mechanisms. © 1997 Elsevier Science B.V.

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1. Introduction

Food allergy is defined as an immunologically mediated adverse reaction to dietary antigens. The foods most commonly responsible for such reactions include egg, cow milk, peanut, soy and wheat (Bock et al., 1988). Cow-milk allergy is frequently the first major allergy to manifest itself, since cow-milk proteins represent the first source of antigens encountered in large quantities in infancy (Dreborg, 1995; Isolauri and Turjanmaa, 1996). Cow milk contains numerous protein components, in both casein and whey, all of which may induce sensitisation.

Cow-milk allergy can affect several organ systems and an infant with cow-milk allergy may show more than one symptom or show symptoms in more than one organ system. The symptoms arise from the gut, skin and respiratory tract (Hill et al., 1986). This allergy is diagnosed by clinical response to withdrawal and subsequent challenge with cow milk (Bock et al., 1988). Children with a positive clinical reaction to such a formal elimination–challenge procedure have been di-

vided into subgroups according to the reaction onset time, immediate or delayed-onset reactions (Hill et al., 1986; Isolauri et al., 1990; Isolauri and Turjanmaa, 1996). The acute-onset manifestations include reactions from the skin such as urticaria, pruritus and exanthema, from the bowel for example vomiting and diarrhoea and from the respiratory tract—wheeze and sneezing. Delayed-onset reactions include eczematous skin lesions or gastrointestinal reactions such as loose stools, chronic diarrhoea and malabsorption.

Allergy to cow milk is most prevalent at the age of 1 year and has been reported in 2.8% of the general child population (Schrandt et al., 1993). In infants with atopic dermatitis, however, the occurrence of cow-milk allergy has been shown to be up to 50% (Sampson et al., 1985; Isolauri and Turjanmaa, 1996). Even atopic infants tend to outgrow food allergies, particularly those to milk, egg and cereals (Bock, 1982; Isolauri et al., 1992). However, at the time when they acquire clinical tolerance to cow-milk antigens they have an elevated risk of developing allergic respiratory disease. The phenomenon is known as ‘the atopic march’. Cow-milk allergy may therefore be considered an important initial link in the allergic disease family. This involvement may be due to immaturity of the immune system

* Tel.: +358 2 2611611; fax: +358 2 2611460.

and to immature gut defence mechanisms, where the major load of new antigens is encountered at an early age.

Cow-milk allergy is suggested to be rare in adults and only a few case reports indicate milk protein as the responsible antigen for allergic reactions in adults (Körs et al., 1986; Paganelli et al., 1986; Olalde et al., 1989; Levy et al., 1996; Tabar et al., 1996). Recent data suggests, however, that cow-milk allergy in adults, occurring as gastrointestinal reactions, may be more common than previously thought (Bengtsson et al., 1996; Peltö et al., *in press*).

2. Pathomechanisms of cow-milk allergy

Elevated concentrations of serum IgE to cow-milk antigens may indicate dysregulation of B-cell responses in cow-milk allergy. The conception of T-helper 1- and T-helper 2-like cells producing highly polarised patterns of cytokines controlling IgE responses would imply that aberrant cytokine production may underly the pathogenesis of cow-milk allergy (Romagnani, 1994). Differences in other cell types may also play a role in the pathogenesis (Isolauri et al., 1997). The divergent manifestations of cow-milk allergy have been explained by different immunological mechanisms, IgE-mediated hypersensitivity reactions are the basis for immediate-type reactions whereas cell-mediated reactions may be responsible for delayed-type symptoms.

As elevated antigen-specific IgE can be demonstrated by skin-prick testing, these tests are widely used to disclose cow-milk allergy in patients with atopic dermatitis. In contrast, it has been shown that patch-tests are positive in patients with delayed-onset reactions to double-blind, placebo-controlled milk challenge, though prick tests are frequently negative (Isolauri and Turjanmaa, 1996). In like manner, it has been shown that patients with predominantly delayed-type gastrointestinal reactions to cow-milk challenge have significantly greater cow-milk-induced lymphocyte proliferation than those tolerant to cow-milk (Suomalainen et al., 1994). Intestinal inflammation has been detected in atopic infants with cow-milk allergy. An elevated concentration of eosinophil cationic protein in the faeces was associated with immediate-type reactions to double-blind, placebo-controlled cow-milk challenge, while tumour necrosis factor- α in the faeces was associated with delayed-type reactions (Majamaa et al., 1996).

Despite the wide spectrum of immune effector mechanisms that may be activated in cow-milk allergy, two prerequisites for the development of this disorder have been identified: intraluminal antigens must penetrate the intestine's mucosal barrier and the absorbed antigens must cause harmful immune responses.

3. Gut mucosal barrier functions

Continuous exposure by the enteral route to antigens from food and micro-organisms imposes high demands on the intestine's defence barrier. Protection against such potentially harmful agents is ensured by two opposing functions of the intestinal mucosa, a barrier excluding antigens and controlled transfer of antigens evoking local antigen-specific immunity. The antigens are absorbed across the epithelial layer by transcytosis along two functional pathways (Fig. 1). The first of these, the degradative pathway, entails lysosomal processing of the antigen to smaller peptide fragments (Ducroc et al., 1983), which reduces the antigen load, while a minor pathway allows the transport of intact proteins, which results in antigen-specific immune responses. Peyer's patches, as the source of IgA-committed plasma cells, play an essential role in intestinal immune function. These aggregations of lymphoid follicles are covered by a unique epithelium characterised by rapid uptake and reduced degradation of antigens.

4. Gut mucosal barrier dysfunction in cow-milk allergy

In patients with cow-milk allergy, disturbances in intestinal permeability compared with controls have been reported. It has been shown that during a cow-milk elimination diet the lactulose/mannitol permeability test results are comparable in patients with cow-milk allergy and their age-matched controls, while a rise in the lactulose/mannitol excretion ratio follows a positive oral cow-milk challenge (Jalonen, 1991). The changes in intestinal permeability have been shown to be identical in patients who manifest cow-milk allergy cutaneously and gastrointestinally. As recent observations suggest that no direct correlation exists between permeability tests and antigen transfer (Jalonen et al., 1991), *in vitro* studies have been made of macromolecular absorption. Heyman et al. (1988) detected enhanced absorption of macromolecules across the jejunal mucosa in cow-milk allergy patients, most of whom had predominantly

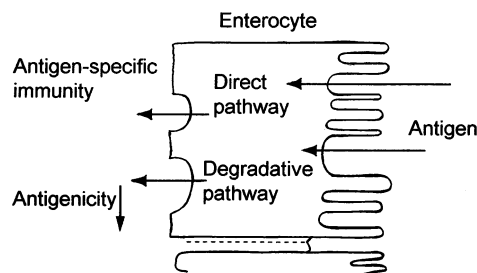


Fig. 1. Dietary antigens are absorbed across the epithelial layer by transcytosis along two functional pathways, (1) the major route, the degradative pathway and, (2) a minor pathway which allows the transport of intact proteins.

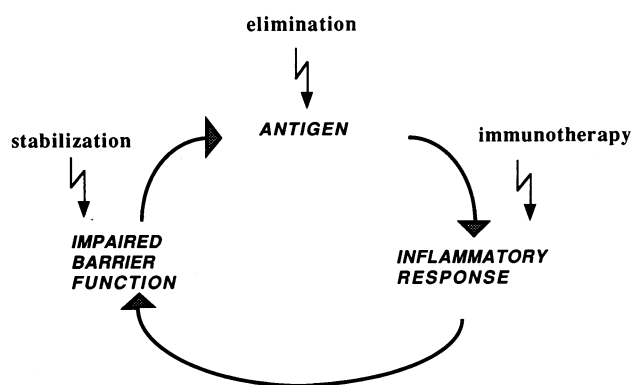


Fig. 2. Cow-milk antigens induce local hypersensitivity reaction that impairs the intestine's barrier function. Mucosal dysfunction may lead to aberrant absorption of intraluminal antigens. Targets of the treatment of cow-milk allergy: elimination of the antigen responsible, alleviation of the immunoinflammatory reaction and stabilisation of the gut mucosal barrier.

gastrointestinal symptoms. The barrier function was normalised when cow-milk antigens were eliminated from the patients' diet. Data on atopic patients with multiple food allergies indicate that altered macromolecular absorption in the gut may proceed even when the patient is on an elimination diet (Majamaa and Isolauri, 1995). In these patients, however, persistent unnoticed intestinal inflammation could have deranged the intestinal barrier (Majamaa et al., 1996). Such results point to the conclusion that, in patients with cow-milk allergy, cow-milk antigens evoke a local hypersensitivity reaction that may or may not induce local symptoms but impairs the intestine's defence barrier (Fig. 2).

To test this hypothesis, the ELISPOT assay has been used to elicit indirect evidence of gut local immune response (Czerkinsky et al., 1983) in patients with cow-milk allergy and healthy infants (Isolauri et al., 1990, 1992; Kaila, 1993; Kaila et al., 1994). Circulating antigen-specific cells become measurable in the blood at 1 week after initial antigen challenge in the gut and remain measurable as long as the antigen challenge continues. The total number of immunoglobulin-secreting cells (ISC) is an index of antigen-nonspecific immune response and the number of specific antibody-secreting cells (sASC) an index of antigen-specific immune response. The assays revealed that in healthy formula-fed infants IgA sASC to cow-milk antigens were measurable, while the serum IgA antibody level was still low. During oral milk challenge healthy infants mounted a focused sASC response to cow-milk antigens while no antigen-nonspecific ISC response was seen. The pattern of the immune response was different in patients with cow-milk allergy. These evinced a high, antigen-nonspecific ISC response to the oral milk challenge, while the sASC response specifically directed against β -lactoglobulin and casein was

small and inconsistent. By the time these infants acquired cow-milk tolerance, the total numbers of ISC did not increase during provocation, but they had sASC of IgA isotype. These results indicate that in cow-milk allergy immune elimination of cow-milk antigens is ineffective and an unfocused antigen-nonspecific immune response is generated in compensation.

Taking these results together, it would appear that impaired barrier function and defective handling of cow-milk antigens in the gut mucosa may be an important pathogenetic mechanism in cow-milk allergy. Hypersensitivity reactions to cow-milk antigens disturb the gut defence barrier and cause mucosal dysfunction, which consistently occurs in children with cow-milk allergy, irrespective of the focus of clinical reaction.

5. Treatment of cow-milk allergy

The mainstay in the treatment of cow-milk allergy is complete avoidance of cow-milk proteins. Dietary elimination of the antigen responsible has been shown to alleviate symptoms, preserve intestinal integrity, prevent aberrant antigen absorption and reverse the disturbance of humoral and cell-mediated immune response (Isolauri et al., 1992; Agata et al., 1993; Isolauri and Turjanmaa, 1996; Majamaa et al., 1996).

Milk and milk products are of particular nutritional importance in infancy. Therefore, in infants allergic to this source, it is necessary to use substitute formulae during cow-milk elimination diet. For this purpose, the commonest approach is predigestion of bovine casein or whey to provide nitrogen as mixtures of peptides and amino acids (Isolauri et al., 1995). The reduction of antigenic protein in extensively hydrolysed casein or whey formulae is several millions from values in cow-milk and of the same order as in breast milk (Mäkinen-Kiljunen and Sorva, 1993; Isolauri et al., 1995). However, hydrolysis does not render the formulae non-allergenic and their use may result in unidentified continued allergen challenge. The circumstance that clinically significant amounts of immunoreactive cow-milk protein may be contained in extensively hydrolysed formulae underlines the importance of careful evaluation of infants with allergy to cow-milk when the use of these formulae is commenced. Moreover, effective management of cow-milk allergy requires an understanding of the nutritional risks attending elimination diets (Isolauri et al., 1995, 1997). In view of the nutritional hazards that have been associated with empirical elimination diets, it is mandatory to make the diagnosis of cow-milk allergy accurately (Hill et al., 1995). Since the advantage of elimination diets consists in silencing the specific hypersensitivity reaction, only patients with challenge-proven cow-milk allergy will benefit from cow-milk elimination diet.

6. New approaches for the management of cow-milk allergy

The completeness of the antigen elimination may be ensured by synthetic amino acid-derived formulae. These have been shown to be safe for children with multiple food allergies (Sampson et al., 1992) and to promote growth in patients requiring a highly restricted dietary regimen (Hill et al., 1995; Isolauri et al., 1995). However, the control of sensitisation by antigen elimination only has not been satisfactory. The incidence of allergic disorders is steadily increasing. The recognition that cow-milk allergy comprises the first manifestation of such disorders has evoked scientific interest in preventing the progression of the atopic march from food allergy to asthma.

Systemic immune responses to gut-processed antigens are preferentially directed towards suppression (Weiner et al., 1994). Modification of immune responses by such gut-processed antigens may introduce a new approach in the management of cow-milk allergy. Peroral administration of probiotic bacteria has been shown to stabilise intestinal integrity (Isolauri et al., 1993), to promote local IgA production (Kaila et al., 1992) and to dampen intestinal inflammation in atopic patients with cow-milk allergy (Majamaa and Isolauri, 1997). Moreover, recent data demonstrate that hydrolysis of caseins with intestinal bacteria-derived enzymes generates molecules with suppressive effects on lymphocyte proliferation (Sütas et al., 1996a). Considering that cytokines produced by T-helper 2-like cell population are associated with early sensitisation (Romagnani, 1994), it is interesting that *Lactobacillus* GG (ATCC 53103)-hydrolysed casein reduced the production of interleukin-4 (Sütas et al., 1996b). Therapeutically exploiting the intestine's defence mechanisms may provide a new direction in the search for means of treating allergic inflammation at early age.

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