

Milk allergy/intolerance and atopic dermatitis in infancy and childhood

Adverse reactions to cow's milk proteins are usually indicated as cow's milk allergy/intolerance (CMPA/CMPI) because no differentiation is possible on the basis of symptoms, and there is no reliable single laboratory test available for the diagnosis of CMPA or CMPI. Elimination and challenge tests for cow's milk proteins using strict, well-defined diagnostic criteria are required for the diagnosis of CMPA/CMPI. Atopic dermatitis (AD) is one of the most common symptoms of CMPA/CMPI. Approximately one third of AD children have a diagnosis of CMPA/CMPI according to elimination diet and challenge tests, and about 40–50% of children <1 year of age with CMPA/CMPI have AD. Many children with AD and CMPA/CMPI develop a complete tolerance to CMP in a few years. Children with persisting forms of CMPA/CMPI have a more frequent history of familial atopic disease, change in CMPA/CMPI manifestations over time and very high frequency of multiple food intolerance and allergic diseases. Many children who outgrow their AD develop other allergic diseases, such as rhinitis or asthma. The simultaneous development of allergic tolerance in one organ and the intolerance or atopic disease in another organ suggest that genetic, immunologic and environmental factors play a complex role in the natural history of AD and other atopic diseases.

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In a recent classification, adverse reactions to food have been divided into toxic and non toxic food reactions. Toxic food reactions derive from some substances which contaminate or are naturally present in food. Non toxic food reactions depend on an individual susceptibility to certain foods and are divided in immune-mediated (food allergy) and non immune-mediated (food intolerance) reactions (1). Likewise, adverse reactions to cow's milk proteins can be divided in cow's milk protein allergy (CMPA) and cow's milk protein intolerance (CMPI). The definition of CMPI leads to some confusion, as CMPI is also used in cases in which the immunological etiology of the reaction to cow's milk cannot be confirmed, either due to a lack of immunological investigations or to negative results of the performed analyses. Moreover, CMPA and CMPI cannot be differentiated on the basis of symptoms, and there is no reliable single laboratory test available for the diagnosis of CMPA or CMPI. Therefore, adverse reactions to cow's milk proteins are indicated as CMPA/CMPI, and the diagnosis of CMPA/CMPI must be based on cow's milk protein elimination and challenge test, using strict, well-defined diagnostic criteria. These criteria include a significant reduction of symptoms after elimination of milk from the diet, recurrence of identical symptoms after challenge with cow's milk, disappearance of symptoms after re-elimination of cow's milk, and exclusion of lactose intolerance and coincidental infections. (2–4).

CMPA/CMPI is one of the most common adverse food

reactions in infancy and early childhood. Symptoms suggestive of CMPA/CMPI are seen in about 5–15% of infants, but the "true incidence" ranges from 2% to 3% when strict diagnostic criteria are used (5).

CMPA/CMPI may induce a broad diversity of symptoms, mainly cutaneous (atopic dermatitis, urticaria, angioedema), respiratory (rhinitis, asthma, cough) and gastrointestinal (vomiting, diarrhea, colic, gastroesophageal reflux). General symptoms include food refusal, failure to thrive and irritability. In some cases, anaphylaxis can also occur (2). Based on clinical and challenge data, three groups of children with CMPA/CMPI were identified (6). Children in the first group, some of whom had a history of anaphylactic reactions to ingestion of milk proteins, were IgE sensitized and demonstrated immediate (within 30–40 min from the challenge) cutaneous and respiratory reactions. The second group, including non IgE-sensitized children, developed gastrointestinal symptoms more than 1 h but less than 20 h after milk challenge. The third group of patients developed symptoms affecting the skin, gastrointestinal and/or respiratory systems more than 20 h after ingestion of milk. This classification is useful for practical purposes, but patterns of reactions may vary due to different exposure levels and different time intervals between exposures.

Atopic dermatitis (AD) is one of the most common cutaneous symptoms of CMPA/CMPI.

AD is a chronic inflammatory disease in which genetic,

environmental, pharmacologic, psychologic and immunologic factors contribute to the development and severity of the disease. Immunologic findings in AD include increased IgE levels, eosinophilia, increased spontaneous histamine release, decreased CD8 suppressor/cytotoxic number and function, increased expression of CD23 on mononuclear cells, expansion of IL-4 and IL-5 secreting Th2 cells, decreased numbers of IFN- γ secreting Th1 cells, increased serum levels of secretory IL-2 receptor, eosinophil cationic protein, eosinophil-derived neurotoxin and eosinophil major basic protein (7).

Many clinical studies have shown that food allergy plays a role in AD. Indeed, the elimination of the relevant food allergen can lead to improvement in the skin lesions, while the reintroduction and the controlled challenge can lead to the recrudescence of symptoms (8).

In studies in children with food-related AD where oral controlled food challenges were used (9–11), cutaneous reactions occurred in three fourths of the positive challenges and consisted of pruritic, morbilliform or macular eruptions in the predilection sites for AD. Most of the reactions occurred within an hour after beginning the oral challenge. Egg, peanut and milk were the most common foods responsible for the reactions. Milk-induced reactions were 10–40% of the positive responses (9, 10). In a small proportion of cases the exacerbations of symptoms can occur after 2–5 days of regular ingestion of milk (6).

We have recently studied a group of infants and children (mean age 17.6 months) with AD and no other allergic manifestations. According to elimination diet and challenge tests, 20/54 children (37%) had a diagnosis of CMPA/CMPI, and 7/41 children (17%) had milk-induced symptoms after a 2-year follow-up. Children with persisting AD at 2 years more frequently had positive skin-prick tests (SPTs) to milk proteins compared to children with resolving AD at follow-up (85.7 vs 38.4%; $P < 0.05$). The prevalence of asthma, rhinitis and conjunctivitis at the final follow-up was 39%, 24.3% and 31.7%, respectively, and 30 children (72.5%) still had AD.

Many *in vivo* and *in vitro* tests may be useful in demonstrating an IgE-mediated food-induced reaction. The value of SPTs and circulating IgE antibodies to cow's milk in the diagnosis of food allergy is debated.

May et al. (12) found that AD patients with positive immediate food SPTs did not always have positive challenges to the foods implicated by IgE responses. In food-related AD, Sampson & Albergo (13) reported that children with SPTs > 3 mm to various foods developed rapid exacerbations of atopic dermatitis on challenge, while Atherton (14) did not find SPTs of value in identifying foods that exacerbated childhood eczema.

It has been suggested (15) that SPTs should be supplemented with patch tests. These tests are particu-

larly useful in investigating delayed reactions and improve the accuracy of SPTs in the diagnosis of food allergy in infants with atopic eczema.

Hoffman et al. (16) suggested that the measurement of specific IgE antibodies to foods by RAST might be a useful indicator of food allergy in childhood eczema, but Sampson & Albergo found these measurements were not superior to SPTs. Hill et al. (17) confirmed the value of SPTs and RAST in identifying cow's milk allergic patients with urticarial, eczematous, respiratory or anaphylactic responses to milk ingestion, although these tests did not identify patients who developed gastrointestinal, eczematous and/or respiratory symptoms after several hours or days. It has been recently suggested (18) that, when compared with the outcome of a double-blind food challenge (DBFC), results of CAP System FEIA are generally comparable to those of SPTs in predicting symptomatic food hypersensitivity. The concentration of milk-specific IgE antibodies > 32 kU/l could predict clinical reactivity with greater than 95% certainty. This could eliminate the need to perform a DBFC in a significant number of patients suspected of having IgE-mediated milk allergy.

However, about half of the reactions following the ingestion of milk are not mediated by specific IgE antibodies to cow's milk proteins (2). Therefore, positive SPTs and high serum levels of milk-specific IgE may suggest an immediate IgE-mediated clinical response to ingestion of milk, but elimination diet and a challenge tests are required for a correct diagnosis of CMPA/CMPI.

Development of AD in children with CMPA/CMPI

Few studies based on strict elimination/milk challenge procedures in clinical settings have focused on the development of AD in infants with CMPA/CMPI (Table 1).

In a prospective study of CMPA/CMPI in Swedish infants, Jacobsson & Lindberg (19) found that 20/1079 infants (1.8%) had CMPA/CMPI. Symptoms from the gastrointestinal tract and skin predominated. Only two subjects had respiratory symptoms. Nine of the 20 children (45%) presented atopic dermatitis in the first year of life and in seven (35%) AD persisted in the second year.

Host & Halken (20) studied a cohort of 1749 newborns from the municipality of Odense and found that 39 infants (2.2%) had CMPA/CMPI. Twenty-five out of these infants (64%) had cutaneous symptoms and 22 (56%) had atopic eczema. Gastrointestinal symptoms were present in 23 (59%) and respiratory symptoms in 13 (33%) children. Twenty-eight children (72%) had symptoms from > 2 organ systems. The overall prognosis of CMPA/CMPI was good, with a total recovery of 22/39 children (56%) at 1 year of life, 30/39 (77%) at 2 years, and

Table 1. Presence of AD in children with CMPA/I

Study	No. of subjects included in study	Age at diagnosis	Follow-up (years)	Presence of AD (% subjects)
Jacobsson & Lindberg 1979 (19)	20	<1 year	2	45% at 1 year, 35% at 2 years
Host & Halken 1990 (20)	39	<1 year	3	56% at 1 year
Bishop et al. 1990 (21)	97	16 months	8	21% at 8 years
Schrander et al. 1993 (22)	26	<1 year	1	35%
Hill et al. 1994 (23)	42	15 months	2	57% at 2 years
Sprickelman et al. 2000 (24)	93	2.3 months	7	37% at 7 years

34/39 (87%) at 3 years. Infants with CMPA/CMPI and early sensitization to cow's milk had an increased risk of persisting CMPA/CMPI, development of persistent adverse reactions to other foods and inhalant allergy before 3 years of age.

In a long-term study of 97 children with challenge proven cow's milk allergy, Bishop et al. (21) found that 21% of patients had AD at the final follow-up (8 years), 40% had asthma and 43% had rhinitis. Exclusion of cow's milk from the diet of infants and children with cow's milk allergy did not prevent the subsequent development of atopic disorders. A significantly higher prevalence of AD was observed in children with challenge proven persistent CMPA/CMPI at the final follow-up.

In another study, incidence and clinical manifestations of CMPA/CMPI were studied in 1158 unselected newborn infants followed prospectively from birth to 1 year of age (22). CMPA/CMPI was proven in 26 patients (2.8%). The most common symptoms in infants with CMPA/CMPI were gastrointestinal (50% of the subjects), dermatological (31%) and respiratory (19%). Eczema was found in nine children (35%).

Hill et al. (23), in a follow-up study of 42 infants with IgE-mediated cow's milk allergy, found that 57% of the children had developed atopic dermatitis at a median age of 3.7 years. Children with remitted CMPA/CMPI and persistent CMPA/CMPI at final follow-up had a similar prevalence of AD.

It has recently been reported (24) that 37% of 93 children with CMPA/CMPI in infancy had AD at a mean age of 7 years.

Development of tolerance in children with CMPA/CMPI and AD

The overall prognosis of CMPA/CMPI is good, with total recovery of about 50% at 1 year, 70% at 2 years, 85% at 3 years and 90–95% at 5 and 10 years (25).

Some studies (20, 26, 27) have demonstrated that the persisting forms of CMPA/CMPI have some similar characteristics. Individual IgE milk-specific antibody concentrations at either the time of negative double-blind placebo-controlled food challenge (DBPCFC) results or the final DBPCFC results were significantly lower in children losing clinical reactivity than in those

remaining allergic (26). The group of children with CMPA/CMPI over 9 years of age have significantly greater concentrations of whole milk and casein-specific IgE antibodies compared with the group of children with CMPA/CMPI under 3 years of age (27).

In another study (20) infants with CMPA/CMPI and early sensitization to cow's milk had an increased risk of persisting CMPA/CMPI, development of persistent adverse reactions to other foods and inhalant allergy before 3 years of age.

Not only circulating antibodies, but also cellular immunity is involved in the immunologic reactions to cow's milk and in determining the clinical course of the disease. It has been reported that in children with a persistent form of CMPA/CMPI there is a more prolonged delay between cow's milk consumption and manifestation of symptoms as an expression of a possible involvement of cellular immunity. Moreover, in children with a persisting form of CMPA/CMPI, familial atopic disease, change in CMPA/CMPI manifestations over time and very high frequency of multiple food intolerance and allergic diseases (28) are considerably important.

Food proteins can enter the circulation and be redistributed throughout the body, including skin sites. Such food antigens may well cause a T cell-mediated response, which leads to worsening of AD. Lymphocyte proliferation in response to food antigens has been demonstrated, with a positive correlation between food-specific activation of IFN- γ and IL-2 secreting CD4+ peripheral blood lymphocytes in children whose AD worsened in response to oral challenge (29). A specific T cell-mediated immune response to casein was also found in the blood of adolescent and adult patients with milk-induced exacerbation of AD (30).

The development of tolerance to foods in the natural history of AD is therefore a complex process which involves both cellular and humoral immune response. Interestingly, as AD patients develop other allergic diseases, such as rhinitis or asthma, they frequently outgrow their eczema. The simultaneous development of tolerance in one organ and the intolerance or atopic disease in another organ system suggests that genetic, immunologic and environmental factors play a complex role in the natural history of AD and other atopic diseases.

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