

Cow's milk allergy

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Reproducible adverse reactions to cow's milk (CM) were first described more than 2360 years ago by Hippocrates, who is said to have observed that CM can cause urticaria and gastric upset¹. About 500 years later a case of milk allergy was described by Galen². In the first years of this century, reports on adverse reactions to CM were published in the German literature³. In these early reports adverse reactions to CM were described as 'idiosyncrasy' to CM. In Scandinavia, Wernstedt from Sweden was the first to propose the term 'allergy' to supposing a changed reactivity to CM⁴. The American paediatrician, Talbot, described in 1916, the relation between 'idiosyncrasy' to CM and anaphylaxis to CM⁵. These reactions were reported to occur after ingestion of CM. In 1938 allergic reaction due to inhalation of cow's milk protein was described in a Danish dairy worker⁶. Cow's milk allergy was considered an infrequent disease, but since the 1950s an increasing frequency of this disease has been noted, possibly caused by a decrease in breast-feeding and a more frequent use of CM-based infant formula feeding^{7,8}. During the last decades cow's milk allergy has become the most common food allergy in early childhood, and much attention has been paid to this disease, as elucidated in extensive reviews^{3,7–14}. However, much controversy still exists, probably because of a lack of agreement on standard terminology and lack of reliable diagnostic tests³.

DEFINITION AND DIAGNOSTIC CRITERIA

The term, cow's milk allergy (CMA), is commonly used for immune-mediated reactions, while non immune-mediated reactions are classified as cow's milk intolerance (CMI). Like food allergy in general, CMA can be divided into IgE-mediated, type I, and non IgE-mediated reactions, mainly type III (immune-complexes) and type IV (cell-mediated)¹⁵. Most studies on 'milk allergy' have not investigated the immunological basis of the clinical symptoms. Differentiation between CMA and CMI is not possible solely based on clinical symptoms, and no single laboratory test is diagnostic of CMA or CMI. Therefore, the diagnosis of CMA or CMI still has to be based on strict, well-defined food elimination and challenge procedures including double-blind placebo-controlled food challenge (DBPCFC) in children older than

1–2 years¹⁶. In young infants, open-controlled challenges have been shown to be reliable when performed under professional observation in a hospital setting¹⁷. It is beyond the scope of this paper to deal with adverse reactions to milk due to a lack of the enzyme lactase. According to the new classification of the European Academy of Allergy and Clinical Immunology (EAACI) Subcommittee on Adverse Reactions to Foods¹⁵ reproducible adverse reactions to cow's milk proteins can be classified as CMA, i.e. immune-mediated reactions (IgE-mediated and non IgE-mediated reactions) or CMI, i.e. non immune-mediated ('undefined', but non pharmacological and non enzymatic reactions). In order to avoid overdiagnosis the following diagnostic criteria should be fulfilled as a minimum:

- (1) Definite disappearance of symptoms after each of two dietary eliminations of cow's milk and cow's milk products.
- (2) Recurrence of identical symptoms after one challenge.
- (3) Exclusion of lactose intolerance and coincidental infection (especially suspected in the case of mono-symptomatic gastrointestinal symptoms).

In young infants these diagnostic criteria will usually be sufficient provided that challenge procedures are performed under professional observation in a hospital setting³. In solely breast-fed infants, elimination and challenge procedures should be performed via regulation of the mothers' intake of cow's milk. A well-defined standardized challenge schedule should be followed, including a description of the time intervals between increases in the amounts of cow's milk and the total amount of cow's milk before reaction³. In older children and in adults DBPCFC will often be necessary in order to exclude psychological or casual reactions^{16–18}. However, in patients with delayed reactions DBPCFC will hardly be practicable. Therefore, a negative DBPCFC should always be followed by an open-controlled challenge including normal intake of the food protein in question. For practical purposes the challenge recommendations given by Niggemann *et al.*¹⁹ are useful.

INCIDENCE

In Sweden the incidence of CMA/CMI in the period 1919–1947 was reported to be about 0.1 to 0.3 per thousand in a retrospective study²⁰. Since 1970 widely

varying estimates of the incidence from 1.8% to 7.5%^{21–27} have been reported, mainly reflecting differences in diagnostic criteria, in study design, different compositions of the materials, and maybe also geographical differences. In prospective longitudinal studies of unselected newborns the primary materials of infants with symptoms suggestive of CMA/CMI have varied between 5% and 15% of infants³. However, in infants suspected of CMA/CMI the diagnosis was only proven in about 1/3 when controlled elimination/challenge was used, resulting in a 'true incidence' of CMA/CMI in infancy of about 2%–5% in developed countries (Table 1). In two of the prospective longitudinal studies an association between the early introduction of cow's milk based formula and the development of CMA/CMI was documented^{21,26}.

In exclusively breast-fed infants the one-year incidence of CMA/CMI was found to be about 0.5% in two studies^{23,26}.

These data confirm the findings by O'Keefe from 1920²⁸ that breast-fed infants may react to cow's milk protein ingested by the mother and transferred to the infant via the breast milk.

CLINICAL FEATURES

A broad spectrum of symptoms in children may be caused by CMA/CMI (Table 2). In early infancy the reactions are mostly localized to the gastrointestinal tract ('gastrointestinal allergy') in about 60%, but CMA/CMI may also cause systemic symptoms such as cutaneous reactions (about 50%–60%) or reactions in the respiratory tract in about 20%–30% of the patients (reviewed in Ref. 3). Anaphylaxis has been reported in up to 9%²⁹. The symptoms may occur from a few minutes to one hour after milk exposure, i.e. 'immediate reactions', or later than one hour after milk exposure i.e. 'delayed reactions'. In some cases the symptoms develop after days, i.e. 'late reactions'. Based on clinical and immunological reactions some authors have classified patients into three groups, as immediate onset

Table 1 Incidence of cow's milk protein allergy/intolerance during the first year of life. Prospective studies

Authors (year)	Incidence
Halpern <i>et al.</i> (1973)	20/1084 (1.8%)
Gerrard <i>et al.</i> (1973)	59/787 (7.5%)
Jakobsson & Lindberg (1979)	20/1079 (1.9%)
Hide & Guyer (1983)	15/609 (2.5%)
Bock (1987)	25/480 (5.2%)*
Høst <i>et al.</i> (1988)	39/1749 (2.2%)
Schrander <i>et al.</i> (1993)	26/1158 (2.3%)

*When DBPCFC were used, 11/480 (2.2%)

Table 2 Clinical features of cow's milk protein allergy/intolerance in children

Cutaneous reactions
IgE-mediated:
Atopic dermatitis
Urticaria, acute or chronic (rare)
Angioedema
Non-IgE-mediated
Contact rash
Atopic dermatitis (some forms?)
Gastrointestinal reactions
IgE-mediated
Oral allergy syndrome (local reactions)
Nausea/vomiting
Colic
Diarrhoea
Non-IgE-mediated
Enterocolitis syndrome
Colitis
Eosinophilic gastroenteritis
Transient enteropathy (mimicking coeliac disease)
Protein-losing enteropathy
Respiratory reactions
IgE-mediated
Rhinoconjunctivitis
Asthma (wheeze, cough)
Laryngeal oedema
Non-IgE mediated
Otitis media (secondary to allergic rhinitis and eustachian tube dysfunction)
Pulmonary haemosiderosis (Heiner's syndrome, rare)
Anaphylactic reactions
Systemic anaphylaxis
Food-dependent exercise-induced asthma
Other reactions
Unknown mechanisms
Migraine (rare)
Arthritis (rare)
Henoch-Schönlein purpura (type III? rare)
Anaemia (not due to colitis)
Thrombocytopenia (rare)
Proteinuria (rare)
Irritability/sleeplessness?

reactors, intermediate reactors or late reactors^{30–33}. Children with IgE-mediated reactions to cow's milk protein mostly show immediate reactions, whereas those with non IgE-mediated reactions mostly develop late or delayed reactions, although some overlap between the groups is seen. It is noteworthy that the majority (75%–92%) of

infants with CMA/CMI have more than one symptom and the majority (more than 70%) have symptoms from more than one organ system³. In exclusively breast-fed infants with CMA/CMI the symptomatology is similar to that seen in other infants with milk allergy, although severe atopic eczema seems to be a predominant symptom³.

TREATMENT

Milk-free diet

The basic treatment of CMA/CMI is a complete avoidance of CM and CM products. Documented hypoallergenic formula is the only suitable diet for infants up to 6 months of age. After the introduction of solid foods after 4–6 months of age it is important to avoid milk proteins in commercially available foods, which may contain small quantities of milk proteins not listed on the labels, even in non-dairy products³⁴ and specialist dietitians are often needed to ensure correct milk-free diets and adequate nutrition.

Soy formulas cannot be generally recommended because adverse reactions to soy have been reported to occur in about 17% to 47% of children sensitive to cow's milk proteins (reviewed in Ref. 3).

Goat's milk should not be recommended as a milk substitute to patients with CMA/CMI because most of the proteins of goat's milk (and also sheep's milk) share identity with those of cow's milk, resulting in cross-reactivity (reviewed in Ref. 3).

'Normal' processing procedures such as pasteurization, spray drying, and evaporation do not eliminate but only reduce the antigenicity and allergenicity of milk proteins. Consequently such products should not be recommended for treatment of CMA/CMI.

In conclusion only documented hypoallergenic formulae should be used in infants with CMA/CMI. The extensively hydrolysed formulae (eHF) have been found to be substantially less antigenic and allergenic than partially hydrolysed formulae (pHF) in patients with CMA, although some individuals highly sensitized to cow's milk protein may react against residual quantities of cow's milk protein even in eHF, confirming the fact that none of the 'hypoallergenic' formulae are 'non-allergenic'³⁵. It has been recommended that a hypoallergenic formula should fulfil the criterion of 90% clinical tolerance (with 95% confidence limits) in infants with proven CMA^{35,36}. Before use, a skin prick test with a fresh sample of the recommended ready-to-feed formula should be done in order to evaluate the allergenicity, followed by an open-controlled challenge with the chosen formula if the skin prick test is positive. In children with reactions against even eHF, an amino acid-derived elemental formula, should be used³⁷.

Because of a favourable prognosis of CMA/CMI it is very important to avoid over-treatment and an unnecessarily long-lasting milk-free diet. Therefore, controlled re-challenges are recommended at intervals of about 6–12 months in early childhood, and above 3 years of age at intervals of 1–2 years.

PROGNOSIS

The prognosis of CMA/CMI has recently been reviewed^{3,38}. The main results are shown in Table 3.

The prognosis of CMA/CMI is good with a remission rate of about 45%–55% at one year, 60%–75% at 2 years and 85%–90% at 3 years³. With increasing age a lower proportion, about 1/3 of still intolerant children, will develop tolerance to CM milk^{3,38}. Infants with CMA (IgE-mediated reactions to cow's milk protein) have a significantly lower rate of recovery than infants with non IgE-mediated reactions^{3,38}. Generally the prognosis for non IgE-mediated reactions, e.g. gastrointestinal reactions, enteropathy, enterocolitis and colitis, is excellent with total recovery within 1–2 years on a milk-free diet.

Development of adverse reactions to other foods occur very often in infants with CMA/CMI, mostly against egg, soy, peanut, citrus, fish and cereals (reviewed in Ref. 3). Widely varying frequencies of associated food intolerances probably reflect differences in eating habits, and particularly the age at which certain foods are introduced. Compared to infants with non IgE-mediated reactions to cow's milk protein, those with IgE-mediated reactions develop adverse reactions to other foods, and especially to egg, significantly more often³.

Development of allergy to environmental inhalant allergens has been reported in about 50% of such children by 3 years and in 80% before the age of puberty (reviewed in Refs 3 and 38).

In conclusion the overall prognosis of CMA/CMI in infancy is good with a remission rate of about 85%–90%. However, an early increased IgE-response to cow's milk protein is associated with an increased risk of persisting

Table 3 Prognosis of cow's milk protein allergy/intolerance

	Recovery	Other food allergy/intolerance	Inhalant allergy
Prospective unselected series (0–3 years)	84%–87%	54%–60%	28%*
Prospective selected series (2–4 years)	33%–38%	41%–75%	40%–43%†

*Among infants with CMA (IgE-mediated reactions) 48% developed inhalant allergy by 3 years

†In one study 80% developed inhalant allergy before puberty

allergy to CM, development of associated adverse reactions to other foods (especially egg), and development of asthma and rhinoconjunctivitis later in childhood. Early development of cow's milk allergy may be predictive of subsequent development of allergy to common environmental allergens, i.e. pets and house dust mites. Therefore, in such cases preventive measures including avoidance of indoor pets, humid housing and tobacco smoking should be recommended and undertaken.

AETIOLOGICAL ASPECTS

Development of CMA/CMI seems to depend on several factors, especially genetic predisposition, allergen (cow's milk protein) exposure and allergen uptake and handling.

In studies on CMA/CMI increased frequencies of *atopic predisposition* among first-degree relatives have been reported with estimates between 41% and 80%³. In one study double parental atopic heredity was found in 23% versus 3% in the background population¹⁷, and several studies have shown that genetic factors are of great importance for the development of IgE-mediated reactions³⁹. Infants with an increased risk for development of CMA/CMI seem to have a primary immunoregulatory defect⁴⁰ which can be identified by elevated cord blood IgE, high levels of specific IgE, low numbers of T cells⁴¹, disturbed T helper/T suppressor cells^{42,43} or delayed postnatal maturation of T cell competence⁴⁴.

Cow's milk protein antigens/allergens have not been shown to be particularly predisposing to the expression of IgE-mediated or other immune-mediated clinical allergic reactions. Food allergy/intolerance (FA, FI) is principally a problem in infancy and early childhood. Most of the infants will develop FA/FI in the same order as that in which the foods have been introduced into the diet. In developed countries, cow's milk proteins are the first foreign proteins given to infants. All cow's milk proteins, more than 25, can act as allergens. Cow's milk contains 30–35 g/L of total protein, 24–28 g/L caseins (80%), and 5–7 g/L whey proteins (20%). Formation of specific IgG, IgA, IgM antibodies to cow's milk proteins is a normal physiological response and can be demonstrated in normal children (highest levels in infancy) as well as in adults (reviewed in Ref. 3). It can be concluded that cow's milk proteins are antigenic/immunogenic in humans. The humoral immune response due to systemic immunity to foods involving formation of IgG, IgA and IgM antibodies is usually harmless as well as formation of low levels of IgE antibodies, whereas high levels of IgE antibodies to foods are predictive of a present or later development of allergic disease⁴⁵. T cell mediated reactions in the gut have been documented in several reports, and active immune

responses can be detected and measured in humans, as well as in animals. There is evidence that T cell mediated reactions in the small bowel mucosa can cause immune mediated damage and malabsorption. Lymphokine detecting assays and lymphoblast stimulation tests have indicated a pathogenetic role of T cell mediated reactions to individual cow's milk proteins (reviewed in Refs 3,15).

The allergenicity of cow's milk proteins may be altered by technologic processing and/or by digestion. Enzymatic digestion (hydrolysis) denatures the sequential epitopes, whereas low heat treatment (low pasteurization at 75 °C for 15 s) only ensures the bacteriological quality of milk and does not cause any significant reduction of the antigenicity or the allergenicity. However, strong heat treatment (121 °C for 20 min) may destroy the allergenicity of the whey proteins (mainly the conformational epitopes) but only reduces that of caseins. In general heat treatment only reduces but does not eliminate the allergenicity of milk proteins. As regards antigenicity/allergenicity, no significant difference has been found in comparative studies between unhomogenized and pasteurized/homogenized milk in children with CMA/CMI⁴⁶. Based on determination of specific IgE to individual cow's milk proteins in patients with CMA, the major allergens in infancy seem to be bovine serum albumin, beta-lactoglobulin and bovine immunoglobulin, whereas in older children beta-lactoglobulin, caseins and alpha-lactalbumin may be more reactive. In general most patients react to two or more proteins³.

Exposure to cow's milk proteins may occur prenatally considering that high molecular milk proteins may cross the placenta, stimulate the fetal immune system, and elicit a specific IgE response in the fetus indicated by the demonstration of specific IgE antibodies to various allergens in cord blood (reviewed in Ref. 47).

Postnatally infants are exposed to food proteins including cow's milk proteins via human milk, when the mothers are ingesting cow's milk or cow's milk products (reviewed in Ref. 48). Thus, the cow's milk protein, beta-lactoglobulin, can be detected in the breast milk of 95% of lactating women (0.9–150 µg/L, median value 4.2 µg/L) when consecutive continual testing of breast milk is done⁴⁸. However, after introduction of CM-based formula into the infants' diet, the antigenic load of cow's milk proteins may be appreciable (enormous) during the first year amounting to about 10–15 g/day or about 3.6–5.5 kg/year when considering that normal cow's milk formula contains about 15 g/L. Cow's milk proteins are absorbed from the gut and can be measured in the blood in quantities of micrograms per litre serum both in children and adults^{49,50}. Macromolecular absorption is increased in preterm infants

and in newborns, and has also been demonstrated in infants with CMA. Whether an increased macromolecular absorption is a part of an allergic constitution/heredity or is due to temporal mucosal damage is not clarified, and the relevance of an increased absorption for development of clinical disease is unclear³.

Previously only a few studies have reported specific IgE antibodies against cow's milk proteins by means of RAST analysis in 0%–3.7% of unselected and atopic predisposed newborns (reviewed in Ref. 3). Recently, specific IgE against individual cow's milk proteins was demonstrated by means of CRIE analysis in 76% of a selected group of infants with later development of CMA/CMI. By means of a very sensitive method, the Magic Lite SQ-system, specific IgE against individual cow's milk proteins has been detected in cord blood among 11% and 9% of newborns with and without atopic predisposition, respectively⁵¹. These data indicate that prenatal formation of specific IgE may be more frequent than previously suggested and prenatal sensitization may play a role in the pathogenesis of food allergy. Other authors have shown specific T cell proliferative responses from fetal leucocytes to specific inhalant and ingestant allergens supporting the hypothesis of intrauterine sensitization⁵².

Breast-fed infants with CMA may react against the minute amounts of cow's milk protein in human milk, but convincing evidence of allergic sensitization due to these minute amounts has never been documented. Postnatal sensitization due to foods, also during exclusive breast-feeding, may rather be due to 'unknown breaks' in the dietary regimen, inhalation of food protein or contact with contaminated hands. Thus, one should consider that just 1 mL of ordinary cow's milk contains 35 mg of protein, equal to about 3 mg of beta-lactoglobulin (or 3000 µg) corresponding to the amount provided by about 2 months nursing 1 L milk/day. Considering the low frequency of CMA/CMI, the very small amounts of cow's milk protein in breast milk may induce tolerance to cow's milk protein rather than allergic sensitization and development of allergic disease. In contrast a significant association between early neonatal exposure to cow's milk formula feeding and subsequent development of cow's milk protein allergy/intolerance has been documented^{3,21,26}.

AETIOLOGICAL HYPOTHESIS

The recent evidence of sensitization *in utero* to both ingestant and inhalant allergens indicate that intrauterine sensitization occurs more frequently than previously suggested. Prenatal sensitization may play a role in the pathogenesis of allergic disease. However, a weak intrauterine sensitization may be a normal phenomenon like the well known weak IgE-response postnatally in

infants without allergic disease⁴⁵. Neonatal exposure to a 'high dose' of foreign protein (inhalant or ingestant) allergens may be a condition of development of allergic disease, particularly in individuals with a marked atopic predisposition.

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