

Cow's Milk Allergy

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By the end of the last century prevention of waterborne infections by chlorination of water supplies, pasteurization of cow's milk (CM) and production of suitable, easily cleaned bottles and nipples for infants had made artificial infant feeding a relatively safe procedure. But in the early years of the present century unexplained difficulties were reported in infants fed with cow's milk; some of them had continuous diarrhoea and failed to thrive (103). It was speculated that such infants had difficulty in digesting foreign proteins, although they could readily assimilate those in breast milk. In the following years cases of anaphylactic shock caused by CM were described, one of them with a fatal outcome (29). Animal studies showed that one species produced precipitins to proteins of milk from another species, and this type of reaction to the foreign structure of CM proteins was presumed to account for the symptoms seen in infants (29). In 1906, precipitins to CM were found in blood from a marasmic infant fed with CM (80). A year later reports appeared describing successful desensitization: injections of small quantities of cow serum cured and prevented hypersensitivity to oral CM and its symptoms (102). This was not a solution to the problem, however, as treatment with serum caused severe reactions (95). The mechanism and components of CM causing these reactions were debated. Wernstedt suggested that the symptoms were due to altered reactivity to CM because of earlier contact with it, and proposed that it should be called allergy (119). Subsequently, the intestinal symptoms were shown to be caused by the whey fraction of CM (42). They were noted to vary in severity and disappeared with increasing age. A decade later (1921) urticaria was described as a symptom of CM hy-

persensitivity (104). By the 1930's and 40's however, CMA was considered a rare disease (112), but the decrease in breast feeding in most developed countries has made cow's milk allergy (CMA) an important cause of infant morbidity and one of the best known and most frequently encountered problems in current infant feeding practices.

DEFINITION

The majority of infants can be reared on CM formulas without untoward effects. However, sensitive immunochemical methods show that they do react to the foreign proteins in CM. When the immunologic reactions to CM are associated with clinical symptoms, the child can be said to be allergic to CM (89). Obviously, the simplest and the most convincing way to verify cow's milk allergy (CMA) would be to demonstrate this either abnormally strong or qualitatively altered immune reaction to CM proteins. As yet, however, this cannot be done by any single test or combination of tests. Therefore the diagnosis of CMA has to be based on the clinical response to CM. In most cases it is enough to observe a favourable response to elimination of CM, reappearance of symptoms during one challenge test and their disappearance on renewed elimination. When symptoms are severe it is unethical to perform more than one challenge.

Other mechanisms besides allergy to proteins of CM can cause recurrent symptoms on CM challenge, the most common being osmotic diarrhoea caused by failure to absorb lactose. Lactose malabsorption is due to the deficiency of a specific hydrolyzing enzyme (β -galactosi-

Table 1
Incidence of CMA

Study	Population		Number with CMA	Incidence %
Prospective studies				
(3)	304	Healthy babies	4	1.3
(31)	400	Healthy babies		0.5
(33)	787	Healthy babies	59	7.5
(43)	1084	Healthy babies, CM in the diet from birth	20	1.8
	669	Healthy babies, no CM in the diet before 6 months of age	6	0.9
(58)	240	Healthy babies	2	0.8
(55)	1079	Healthy babies	20	1.9
Retrospective study				
(108)	4311	Babies born in the hospital in a year	25 Number admitted to the hospital	0.58

dase or lactase), a condition which in infants may be congenital, secondary or acquired (57). Lactase deficiency has to be excluded as the cause of symptoms in CM challenge; this can be done by finding a normal response in the lactose tolerance test, or by feeding the infants with breast milk before challenge. If infants show no diarrhoea on BM, which has a higher lactose content than CM, a positive reaction to challenge with CM cannot be due to lactose. There is always a possibility that allergic reactions in infants may be due to additives in CM or foreign proteins in the cow feeds passing into CM.

Incidence

In 1948 the incidence of CMA in Stockholm, Sweden, was given as 1:7500 (112) and in 1979 the same city was reported to have an incidence of 1:200 (108). The marked variation in the figures in Table 1 is due to the fact that the diagnosis is clinical and even today there is no general agreement about what symptoms are to be attributed to CMA. Furthermore, the challenges are performed in different ways: some are done at home, others in hospital; another variable is the amount of CM given during challenge.

Time of appearance of symptoms

In some cases symptoms of CMA are seen even during breast feeding; such symptoms have been speculated to be due to intrauterine sensitization and exposure to CM proteins in breast milk (55, 108). This covert sensitization (or unauthorized feeding of CM) leads to symptoms after the first feed with CM in 7–15% of cases (24, 55, 81, 108) and the majority show symptoms within a month (33, 81) or less than 2 months (24).

The chronological age of the baby when the symptoms start depends greatly on the length of the initial period of breast feeding; when this is short, all (90) or most infants have symptoms during the first month of life, and ca. 90% by 3 months of age (33, 35). In recent studies from Sweden ca. 30% showed symptoms in the first month and 60% by 3 months of age (55, 108). At that time 45% of infants were entirely breast-fed for the first 3 months (55).

CLINICAL MANIFESTATIONS

Gastrointestinal disease

The majority of children with CMA have gastrointestinal symptoms (33, 35, 50, 55, 108).

Many of these infants have additionally dermatological symptoms and some respiratory symptoms; in about 10% anaphylactic shock is indicated by the history.

The mode of onset is often acute diarrhoea and vomiting, as in acute infectious gastroenteritis. This type of onset is more common in very young infants, aged less than 1 month (90). In these the disease may resemble neonatal necrotizing enterocolitis. In somewhat older infants (mean age at onset of symptoms 2 months) the disease starts as chronic diarrhoea with vomiting in the majority and visible blood in the faeces of about 10% (69). Severe dehydration is more common in the acute form. Growth failure is frequent in both forms; young infants are often below their birthweight, and in older infants weight is more strongly retarded than height (24, 38, 69). Other common symptoms are protuberant abdomen, muscular hypotonia and hypotrophy. Paralytic ileus is seen in 10% of infants with severe intestinal CMA and oedema in some cases (25, 69).

Laboratory findings indicate iron deficiency anaemia in 20–70%, and hypoproteinaemia in approx. one third (6, 25, 69). Half to two thirds of infants with chronic diarrhoea have moderate to severe steatorrhoea (6, 25, 69), and about the same number have an abnormal xylose test. In many the steatorrhoea leads to a deficiency of vitamin-K-dependent coagulation factors and less than half of these patients have a prolonged coagulation time. Laboratory indications of vitamin D deficiency are common, though clinical rickets is not seen (6, 25, 69). In many cases lactose is not digested and therefore lost in the stools as long as CM is taken (47). This secondary lactase deficiency is cured rapidly when CM is eliminated (24, 47).

These functional abnormalities are associated, being mostly due to the intestinal damage, which is most pronounced in the proximal jejunum. The findings in the jejunal biopsy specimens are like those in coeliac disease, though less pronounced. There is varying villous atrophy with hyperplasia of the crypts and inflammation both intraepithelially and in the lamina propria (6, 53, 68, 69, 106, 118). The number of mitoses in the crypts is increased, as

in coeliac disease (67, 68). Often the disease may also involve other parts of the gastrointestinal tract. There may be gastric mucosal atrophy and reduced gastric acid output (66). Sigmoidoscopy of the rectal and colonic mucosae showed that inflammation was always present and in every case there was either gross or occult bleeding (38). Intestinal blood loss without other gastrointestinal symptoms related to CM ingestion was documented in a high percentage of 20 iron-deficient infants (122), more than half of whom were hypoproteinaemic. Faecal loss of red blood cells tagged with Cr⁵¹ was 5–6 times higher during CM feeding than when it was eliminated. This type of blood loss is not seen after 2–3 years of age (122).

Abdominal colic is a common symptom of intestinal CMA. Relief of colic was observed in 13 out of 19 breast-fed infants after the mothers were placed on a diet free of CM (54). In another study, however, only two out of 52 colicky babies were sensitive to CM (4).

It has been claimed that CM provokes acute attacks of ulcerative colitis (110). Among patients with ulcerative colitis a higher proportion were reported to have a high haemagglutinating titre to CM than among healthy persons (109). However, later studies did not support these findings, and clinically very few patients appear to benefit from dietary restrictions (56, 77).

Dermatologic symptoms

Atopic dermatitis (AD), urticaria, angioedema and minor exanthemas may be due to CMA. They are seen in one third to one half of children with CMA (4, 33, 35, 50, 55, 108). However, the role of CMA and other food allergies as causes of AD is disputed. Food allergy in general is held to be uncommon in AD (83, 91) and the role of CM especially decreases with increasing age. The frequency of AD was reported to be 7-fold in artificially fed babies and 2-fold in babies on mixed feeding as compared with babies who were wholly breast-fed (37). Among children with AD, half of those under 2 years of age were sensitive to CM (4), whereas in the range 2 to 5 years the history indicated CM sensitivity in only 17 of 134 children (11). In 15 of

81 children under 5 years of age CM challenge caused deterioration of AD (44). Exclusion of egg and CM significantly improved the healing of AD in young infants (2). Acute urticaria is less common, this symptom appearing in only about one third or fewer patients as compared with AD (35, 55, 78); it can also be caused by contact with CM (76).

Respiratory symptoms

The relative incidence of respiratory symptoms in CMA differs widely in different reports: in earlier studies they were seen as frequently as gastrointestinal and dermatological symptoms (4, 33, 35) while in recent surveys they were noted in only about 10% of children with CMA (50, 55, 108).

In seven infants aged 13 days to 6 months, Heiner et al. (49) described a syndrome of chronic respiratory disease, including pulmonary infiltrates, wheezing and tachypnoea, chronic rhinitis and recurrent otitis media. These infants had multiple precipitins to CM. In addition, they had poor gain in weight, gastrointestinal symptoms and hypochromic anaemia. Four of the seven had signs of idiopathic pulmonary hemosiderosis. In a later review the incidence of pulmonary hemosiderosis was estimated at 10% of children with the pulmonary form of CMA (71). Similar cases with respiratory symptoms were found in the survey of Holland et al. (51), but Peterson et al. (88) saw benefit from a CM-free diet in only one of six infants with recurrent pulmonary infections and precipitins to CM. Recovery on a milk-free diet took place within days (9). After this initial response many patients no longer reacted to CM (5, 49).

The role of CM in provoking allergic rhinitis is controversial. In the series of Goldman et al. (35) and Gerrard et al. (33) rhinitis was present in about one third of patients, whereas in recent series it is rarely seen as a symptom of CMA, if at all (55, 108). Rhinitis has been re-induced in double blind challenges with CM (10).

Anaphylactic shock

This most dramatic symptom of allergy was the first to be definitely connected with CM in 1905

(29). Vascular collapse with all its clinical consequences ensues within minutes of ingestion of CM. Shock can be caused by less than a millilitre. Symptoms of shock are accompanied by other symptoms, in most cases frequent vomiting and diarrhoea, but also cutaneous symptoms. If untreated, shock can cause death. The frequency of anaphylactic reactions varies from none in a mixed group (55) to one third of cases among patients with gastrointestinal symptoms (25, 38, 81). During clinical challenge after a milk-free period anaphylaxis occurs more frequently than would be expected from the history (24, 35).

Other symptoms

Food allergy is claimed to play an important role in the pathogenesis of chronic secretory otitis media. In many patients with this complaint a CM by introducing small amounts of the stomach contents of SID cases (84) into the animals' death (SID) may be caused by inhalation of regurgitated food and subsequent hypersensitivity reaction (84). Parish et al. (84) found that infants who had died of SID had higher titres of haemagglutinating antibodies to CM than age-matched controls. They could also reproduce symptoms of SID in guinea pigs sensitized with CM by introducing small amounts of the stomach contents of SID cases (84) into the animals' larynxes. In another study they demonstrated CM proteins in the lungs in SID cases (85). However, later studies have failed to provide immunological evidence for a local hypersensitivity reaction (15, 111).

During provocations Goldman et al. (35) noted that in 18% of patients the reaction included central nervous system symptoms, such as lethargy, weakness, irritability, excessive crying, restlessness, prolonged pallor or intraorbital pallor. Similar symptoms were seen by Gerrard et al. (33).

During CM challenge, according to Liu et al. (73), children with malabsorption syndrome and CMA frequently display ophthalmological symptoms such as mydriasis, conjunctival injection and eyelid oedema.

In many infants with the syndrome of thrombocytopenia and absent radius CM provokes

gastrointestinal symptoms, accompanied by haematological relapse with thrombocytopenia and anaemia (120).

PATHOGENESIS OF CMA

Protein in CM

CM has at least 18 protein components that can induce antibody formation (46). As shown by studies in which children sensitive to whole CM were challenged with purified protein fractions, beta-lactoglobulin (BLG) provokes symptoms in 62 to 100%, and casein provokes symptoms in nearly as many. In most studies, the number of patients sensitive to alpha-lactalbumin (ALA) is low, and challenge tests seldom reveal sensitivity to bovine serum proteins (albumin or gamma-globulin) (35, 69, 74, 114).

In infants with intestinal CMA, the deterioration of absorptive function has been shown to be caused by protein fractions of CM (22, 74).

When protein fractions were used to study the skin reactivity of persons reacting to whole milk extract, BLG was found to be the most active. In molecular size and stability BLG is similar to the allergens isolated from cod, tomato and egg white (8).

Titres of haemagglutinating antibodies to BLG, casein, ALA and bovine serum albumin have been of the same order (32, 63, 64) or titres against BLG are higher (6). Most of the reaginic antibodies to CM are noted to react with BLG (65, 83). *In vitro* lymphoblast transformation of lymphocytes of children with CMA is usually caused by BLG (6) or equally often by BLB and ALA (25, 101).

In most industrialized countries the last two decades have witnessed a change from home-made and unadapted CM formulas to adapted CM formulas. In these formulas the protein concentration is reduced and the ratio of whey proteins to casein is increased, usually to 60:40. However, no differences in allergic symptoms, skin tests to CM or antibodies to CM were observed between infants receiving adapted and unadapted formulas (12).

IMMUNE REACTION TO CM

Immediate hypersensitivity reaction

(Type I, reagin-dependent reaction (17))

Immediate hypersensitivity is common in CMA, to judge from the time of appearance of symptoms in clinical challenges: in clinical tests up to 40–60% of children with CMA show symptoms within an hour of ingesting CM (19, 35, 50).

IgE antibodies to CM in the serum. The radioactive immunosorbent test (RAST) shows IgE antibodies to CM in the majority of children with AD and CMA (11, 21, 44, 86). With a less sensitive method Kletter et al. (65) found IgE antibodies to CM in seven out of 26 children with CMA. The prick test with CM proteins was more frequently positive. In another series of 28 children with AD, a close correlation was noted between a positive history and RAST to CM (14). The total concentration of IgE was often elevated in AD (14) and in AD with CMA (86).

In contrast, in intestinal CMA, IgE antibodies to CM are seldom found. In nine challenges with CM which provoked eight chronic reactions, none of the several blood samples was positive in RAST to CM (98, unpublished results). Others have obtained similar negative results for IgE antibodies to CM in intestinal CMA (20, 21, 50). However, in five out of nine children with CMA and chronic intestinal disease, IgE antibodies to CM were found with the enzyme-linked immunosorbent assay (ELISA). RAST to CM was positive in only one of them. One of the seven infants with acute symptoms of CMA had the IgE type of antibodies in the ELISA and two in RAST. Three of eight patients with coeliac disease had IgE antibodies to CM in the ELISA, but none of the 15 in the control group (28).

A positive RAST to CM is relatively frequent in children who are not clinically sensitive to CM; it was seen in 15 out of 117 children with AD but no food sensitivity (11). A positive RAST to CM was found in three of 85 healthy infants (7), none of whom had symptoms of CMA by the age of 3 years (94). Thus a positive RAST is not evidence of CMA. Neither is the titre in RAST an indicator of CMA: only one of five children

with CMA and a positive RAST had a higher titre than some of the 16 atopic children with similar antibodies but no history of CMA (21).

IgE in the intestine. In jejunal biopsy specimens from two children suspected to have CMA, increased numbers of IgE-containing cells and IgE were seen in the basement membranes and in the epithelium and connective tissues (105). In nine jejunal biopsy specimens taken immediately after a positive challenge test with CM, the numbers of IgE-containing cells were low and unchanged as compared with the numbers of specimens taken before challenge (98). Few if any IgE-containing cells were seen in the jejunal biopsy specimens of children with AD and CMA after a positive challenge with CM (86).

Skin tests. A scratch test with CM was positive in 24 out of 33 children with CMA (4). In 20 children with CMA and acute onset of symptoms the frequency of positive prick tests was high, 80% to CM and 85% to BLG, and there was a close association between a positive skin test and a positive RAST (19). The prick test was positive in all seven patients with CMA in whom the presenting symptom was urticaria, while none of eight patients with intestinal symptoms had a positive prick test to CM or a positive RAST (50). The scratch test with CM is frequently positive in subjects without symptoms of hypersensitivity to CM: in healthy infants in 5% (12), in allergic children without CMA in 12% (4). The intracutaneous test with CM extract was more often positive in allergic children without sensitivity to CM (68%) than in children with CMA (59%) (36).

*Damage by antigen-antibody complexes
(Type III reaction (17))*

In CM challenges symptoms have been noted 1 to 24 h after ingestion of CM in 12 to 100% of cases (19, 35, 50, 90). The time of appearance of symptoms in these cases suggests that they are caused by tissue damage due to antigen-antibody complexes.

Antibodies to CM in healthy children. In 50% of newborn infants passive haemagglutination

showed that antibodies to CM were present in the cord blood, but the titres were lower than in the maternal blood (40), and newborn sera contained antibodies of IgG class only (63). Feeding with CM is followed by a rise in the titre of antibodies to CM more than 5 days after the start of feeding (41). In infants receiving CM in the first few days after birth the antibody response is especially strong (41). In infants given CM soon after birth the peak of IgG antibodies to CM is reached at the age of 3 months, and antibodies of IgA type are at their highest at the age of 7 months (63). Initial breast feeding results in lower antibody titres and a later rise (64), but in CM feeding antibody titres did not depend on whether adapted or unadapted CM formula was used (12). According to one study, antibody titres to CM fell after 1 year of age (63); in another study antibodies to CM remained unchanged until the age of 3 years and thereafter fell (75). When less sensitive methods are used for the detection of antibodies to CM (e.g., precipitation in double diffusion in agar) the number of positive findings is lower (Table 2).

Antibodies to CM in disease. Titres of antibodies to CM are frequently high in conditions favouring aspiration (Table 3), such as familial dysautonomia, trisomy 21 and treated oesophageal atresia. The relationship between aspiration, CM antibodies and recurrent pneumonias and other lower respiratory tract infections is difficult to determine, but at least in some cases aspiration is important in the pathogenesis of infections (71).

In intestinal diseases where there is mucosal damage in parts of the gastrointestinal tract, as in coeliac disease and ulcerative colitis, the frequency of antibodies to CM is high (Table 3), but after the damage has healed the antibodies disappear (60).

IgA-deficient persons frequently have strong precipitating antibodies to CM, but they tolerate CM well (100). When the deficiency state is only partial, the frequency of CM antibodies is lower. Precipitins to CM are also frequently found in patients with cartilage-hair hypoplasia, a T-cell defect (Table 3). Evidently, immunologic deficiencies are associated with increased absorp-

Table 2
Antibodies to CM in healthy children

Study	Method for detection of antibodies	N	Positive, %
(72)	Complement fixation	229	90
(40)	Passive haemagglutination	286	98
(51)	Double diffusion micromethod in agar	380	1.3
(88)	Double diffusion micromethod in agar and/or precipitation in capillary tubes	170	25
	Passive haemagglutination	288	67
(96)	Passive cutaneous anaphylaxis in guinea-pigs	40	10
(93)	Precipitation of I ¹³¹ -BSA-antibody complexes	158	69
(52)	Double diffusion micromethod in agar	150	17
(63)	Radioactive immunodiffusion – IgG antibodies	47	85
	IgA antibodies	47	79

N = Number of children studied

Table 3
Antibodies to CM in disease

Study	Disease	Method for detection of antibodies	No. of children studied	Positive, %
(1)	Marasmic infants	Precipitation in tubes	98	82
(48)	Coeliac disease	Double diffusion micromethod	40	38
(109)	Coeliac disease	Passive haemagglutination	17	100
	Ulcerative colitis	Passive haemagglutination	75	83
(51)	Paediatric hospital patients	Double diffusion micromethod	1618	5.4
(93)	Paediatric hospital patients	Precipitation of I ¹³¹ -BSA-antibody complexes	221	79
(45)	Oesophageal atresia and aspiration	Double diffusion micromethod	4	100
(82)	Trisomy 21	Double diffusion micromethod	14	43
(26)	Familial dysautonomia	Double diffusion in agar	6	83
		Passive haemagglutination	6	100
(13)	Selective deficiency of IgA	Double diffusion in agar	24	75
(100)	Selective deficiency of IgA, paediatric patients	Double diffusion micromethod	26	96
(99)	Partial deficiency of IgA	Double diffusion micromethod	16	38
(113)	Cartilage-hair hypoplasia	Double diffusion micromethod	28	57
(21)	Atopic dermatitis with food intolerance	Radioimmunoassay for IgG antibodies	62	89
		Radioimmunoassay for IgA antibodies	62	100
	Atopic dermatitis without food intolerance	Radioimmunoassay for IgA antibodies	30	100
		Radioimmunoassay for IgA antibodies	30	100

tion of CM proteins and subsequent production of antibodies to them.

Antibodies to CM in CMA. When measured with insensitive methods (Table 4) antibodies to CM are more frequent in children with CMA than in healthy children, and with sensitive techniques, the titres are usually higher in children with CMA (Table 4). In one study, however, passive

cutaneous anaphylaxis in guinea pigs was the only test found to discriminate between allergic and nonallergic children (96), and in another study no significant difference was found between children with CMA and controls either by passive haemagglutination technique for detection of antibodies to CM (16).

Precipitating antibodies to CM are frequently, but not invariably present in children with CMA

Table 4
Antibodies to CM in CMA

Study	Method for detection of antibodies	N	Positive, %
(96)	Passive cutaneous anaphylaxis in guinea-pigs	79	67
(32)	Passive haemagglutination	8	83
	Double diffusion micromethod	6	50
(98)	Passive haemagglutination	7	100
(122)	Double diffusion micromethod	16	88
(69)	Double diffusion micromethod	49	65
(6)	Passive haemagglutination	41	75
(21)	Radioimmunoassay for IgG antibodies	7	100
	Radioimmunoassay for IgA antibodies	7	100

N = Number of children studied

and malabsorption, and during a positive challenge test there is an increase in the titre of haemagglutinating antibodies to CM (6, 32, 69, 98). All patients with recurrent respiratory tract infections and CMA had precipitating antibodies to CM, these antibodies being of IgG and IgM type (49, 107). With any method there is always an overlap in the titre of CM antibodies, and for the immunoglobulin class of antibodies to CM there is no difference between healthy children and those with CMA. The titre is highest for IgG antibodies in CMA and in health; IgA antibodies are found in both, and the occurrence of IgM antibodies is irregular (28, 63).

Serum immunoglobulins A, M and G. Elevation of serum IgA has been noted in 74 to 81% of children with severe intestinal CMA (6, 52, 69), whereas in patients in whom skin symptoms predominate the level is mostly normal (86). When CM is eliminated, IgA falls, and during a positive challenge test it is often seen to rise (52, 98), such a rise being less frequent after short challenges and in patients with AD (86). Recently, low serum IgA had been found in one third of cases with CMA (47, 50); in many other studies, however, such cases have not been seen (6, 69, 86).

In infants with intestinal CMA one study (6) showed that IgM and IgG were often increased, whereas in another study increases in the mean levels of IgM and IgG were insignificant (52). Positive challenges in children with intestinal CMA and with AD and CMA elicited no con-

stant changes in the serum concentrations of IgM and IgG (86, 98).

Antibodies to CM and immunoglobulins in stool extracts and intestinal juice. In four children with intestinal CMA, stools contained CM-precipitating substance, and stool extracts contained IgA; both precipitins and IgA disappeared when CM was eliminated (39). In six out of seven children with CMA these coproantibodies were found after prolonged challenge, but after a few feeds with CM they were present in only one of five patients with CMA (62). In radioimmuno-electrophoresis the CM-precipitating stool factor reacted most often with anti-IgA serum (in four of five specimens), reactions with anti-IgG and IgM sera being infrequent. Such coproantibodies were infrequent in healthy controls, or in patients with trisomy 21 or familial dysautonomia, even when the serum antibody titre to CM was high (62). But precipitins to CM occur frequently in the stools of patients with infectious gastroenteritis (23). During positive challenges with CM in the intestinal juice and stool extracts IgA and IgM concentrations are increased (98).

Serum complement fractions. Among eight children with CMA five with immediate symptoms showed altered complement in immunoelectrophoresis and a reduced quantity of C3, while three with delayed symptoms showed no change (76). However, later studies have not verified such changes in complement: no reduction in C3 took place during nine challenges in CMA

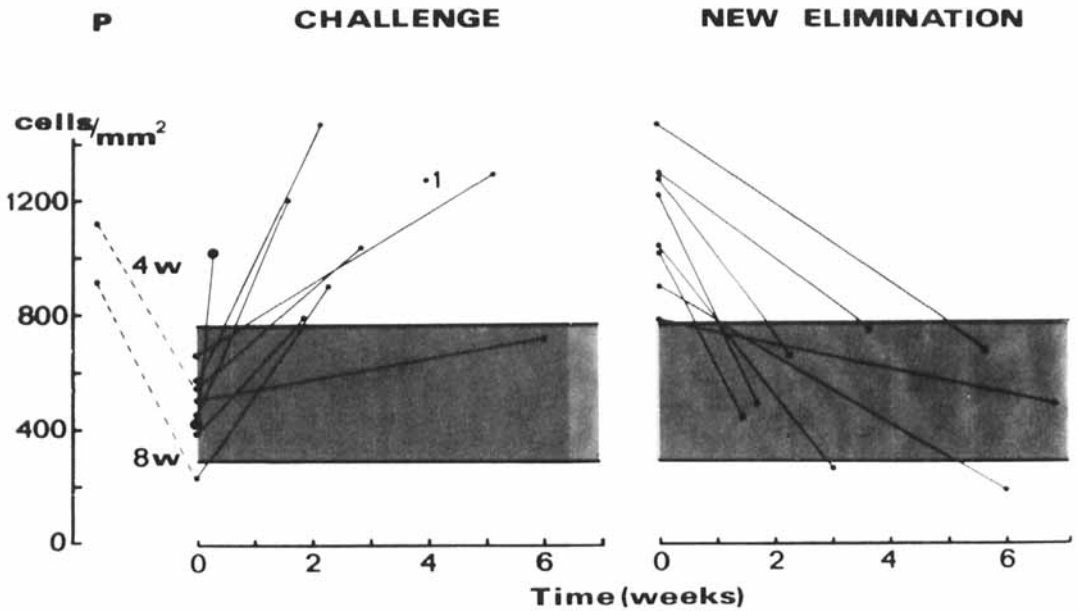


Fig. 1. Numbers of IgA-containing cells in jejunal biopsy specimens of eight patients after nine positive challenges with CM. Every challenge was stopped immediately when the patient displayed symptoms of relapse, and biopsy specimens were taken within a day of the last feed with CM. P – primary biopsies taken before any elimination diet. The interval to the prechallenge biopsy is indicated in weeks (w). .1 – the biopsy before the challenge was not studied. Shaded area: range of numbers of IgA-containing cells in six controls. (This figure is reproduced by kind permission of the editor of "Gut", see (98).)

with malabsorption (98); and in three other series with 43 similar positive challenges with CM the complement fractions measured were unchanged (28, 79, 116). In 13 children with AD and CMA complement fractions 3 and 4 were unchanged during the positive challenge test (86). In nine infants with protracted diarrhoea and CMA in all and soy allergy additionally in six, a significant increase in the mean serum C3 concentration was seen 90 min after the start of 14 positive challenges, with prechallenge serum levels at 5 and 24 h after feeding CM or soy (90).

Immunoglobulins A, M and G and complement fractions in the intestinal mucosa. In seven cases of intestinal CMA and malabsorption, increased numbers of IgA-containing cells were seen in the lamina propria of the jejunum, the numbers of IgM- and IgG-containing cells being normal. Normalization of the numbers of IgA-containing cells took place during CM elimination (59). In children with CMA and malabsorption the

mean number of IgA- and IgM-containing cells being 1.8-fold. On a renewed elimination diet the numbers of IgA- and IgM-containing cells fell to within the normal range. In 10 children with suspected CMA, but no clinical relapse during CM challenge, a mean 1.5-fold rise in IgA-containing cells was seen in specimens taken 2–6 weeks after the start of CM feeding as compared with specimens taken during the preceding breast-milk feeding. The numbers of IgM-containing cells were unchanged (98). In 13 children with AD and CMA, six of whom also had intestinal symptoms, the jejunal mucosa contained significantly larger numbers of IgA- and IgM-containing cells than in 11 controls. In none of these specimens was there positive staining with anti-C3 or -C4 sera (86, 98). In one of two patients with intestinal CMA, the lamina propria of the epithelial cells gave positive staining with anti-C3 serum (106).

Cell-mediated reaction to CM (Type IV reaction (17))

When challenge tests are started with a small quantity of CM, and the amount is slowly increased, it may take several days before the amount of allergen is sufficient to cause symptoms, this being an important cause of the large number of late reactors in some studies. Many children with CMA show no symptoms for more than 24 h after the start of the challenge with CM; in different series the proportion of late reactors has varied widely, from none (19, 90) to 7–81% of cases (35, 50, 69, 81).

The role of cell-mediated immune reactions in the pathogenesis of CMA and the usefulness of these reactions as diagnostic tools have been studied by measuring *in vitro* the degree to which CM proteins cause stimulation of lymphocytes from patients with CMA. Significant reactivity was noted in 14 samples from 33 cases (101), reactivity being even more frequent in two other series (6, 25). The stimulation indices

in the tests were not affected by the length of the CM-free diet or by recent feeding with CM (6, 101). After CM challenge a positive result was associated equally often with acute and with chronic symptoms. In the control group the test was positive in 9.3% of samples (101).

Eosinophils in CMA

Children with CMA frequently have eosinophilia during CM feeding, this sign being present in one third to half of the patients (6, 69). No increase in the numbers of eosinophils has been seen during challenges (79, 90). In the jejunal mucosa in CMA a minority of specimens show an increase in eosinophils (78).

Conclusions on the pathogenesis and aetiology of CMA

As indicated, there is abundant evidence that immediate, IgE-mediated, and antigen-anti-

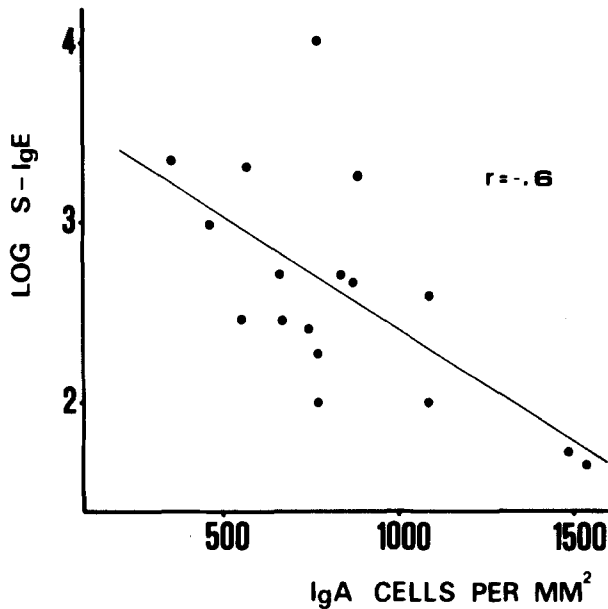


Fig. 2. The negative correlation ($r = -0.6$) between serum IgE and number of IgA-containing cells in the lamina propria of the jejunum in 16 children with AD and food allergy. 13 of these patients had CMA. The biopsy specimens were taken within a day after a positive challenge test with CM. The number of IgA-containing cells is increased in every specimen. (This figure is reproduced by kind permission of the author, see (86).)

body-mediated reactions play a role in the pathogenesis of CMA; cell-mediated immunity is probably also involved. In the individual patient several mechanisms probably operate, one predominating, and the others being weaker (Fig. 2). Compared with the pathogenesis even less is known about the aetiology, i.e., the factors that would explain why a small number of children become allergic to CM although the vast majority grow tolerant to it. These factors are age-dependent, as CMA is acquired in early life and lost later on. A combination of massive exposure to CM proteins and deficient local production of immunoglobulins (87, 97), which takes place when infants are not breast fed at all, favours excessive absorption of CMA antigen (117), and later such children frequently show CMA (25, 108). Other conditions that lead to increased CM antigen absorption have been reported to precede the clinical symptoms of CMA: infective gastroenteritis, prematurity, and surgery of the gastrointestinal tract (47, 92). Additional factors, some of them hereditary, must operate. Atopy is reported to be common (40–70%) in the family members of children with CMA (24, 25, 55). The leucocyte antigens are distributed with the same frequencies in persons with CMA as in the general population (Verkasalo, unpublished observation).

TREATMENT

The basis of the treatment is the elimination of CM products containing CM proteins; they have

to be totally eliminated until the age of 1.5–2 years. We advise that gluten-containing cereals be eliminated from the diet of children who have received them before the onset of symptoms and who have severe intestinal damage. It is also recommended that foods which tend to cause allergy should be avoided until the age of 2 years (e.g., citrus fruits, chocolate, eggs, nuts, peas and fish). Many of these foods are known to have caused symptoms in children with CMA (Table 5 and (33, 55)).

Severely dehydrated infants with intestinal CMA require intravenous therapy initially, and occasional patients may even need prolonged intravenous nutrition, because severe intestinal damage does not allow any oral feeding for several weeks (70). Corrections have to be made for anaemia, hypoproteinaemia and vitamin deficiencies (frequently vitamin K deficiency).

The transfer to oral feeding is best done with breast milk, especially in very young infants and those with severe intestinal disease. The volume has to be increased slowly, because there is often secondary lactase deficiency, but in most cases we have been able to achieve full oral feeding in a few days. Breast milk is continued until the weight gain is satisfactory and the infant can be discharged from hospital. At that time (within 2 weeks to 2 months) he is gradually (during 1 week) placed on a soy-based formula.

Soy protein formulas are nutritionally adequate and in less severe cases can be used from the beginning of the elimination diet. Soy proteins are quite as antigenic as CM proteins; in in-

Table 5
Clinical symptoms provoked by other foods in CMA

Study	No. in the study	Soy proteins		Wheat (or gluten)		Egg		Lamb		Chicken	
		No. exposed	No. with symptoms	No. exposed	No. with symptoms	No. exposed	No. with symptoms	No. exposed	No. with symptoms	No. exposed	No. with symptoms
(33)	59	51	10	NI	5	NI	7	NI	3	NI	1
(55)	20	NI	7	NI	1	NI	3				
(50)	17	NI	2	NI	–	NI	5	NI	2	NI	–
Studies including patients with intestinal symptoms only											
(69)	54	35	4	19	7						
(24)	30	17	4	25	2	NI	1				
(81)	42	35	3	36	0	NI	1				

NI = not indicated

fants they cause antibody formation similar to that observed to CM proteins (27). When soy formula was fed to healthy infants from birth, it provoked allergy in 0.5% of infants (43). When given to infants with CMA, however, it causes symptoms in a far higher percentage (Table 5). Newborn infants with intestinal CMA are especially liable to become allergic to soy as well (90, 121). Symptoms of soy allergy are closely similar to those of CMA. Of 108 patients with intestinal CMA to whom we gave soy-based formulas, we had to transfer 16 back to breast milk because of suspected soy allergy.

Many centres successfully use formulas with casein hydrolysates as the protein source (27, 31), but these, too, may cause symptoms of allergy (69). The major shortcomings of these formulas are high osmolality, unpalatability and high price.

Meat-based formulas, preferably prepared from chicken or lamb, are useful, but may also cause symptoms (Table 5). Goat milk shares BLG crossreacting with CM antibodies and often gives rise to clinical symptoms if used in elimination diets in children with CMA (24, 33).

Children over 1 year of age do not generally need special formulas; dieticians can advise parents to use a variety of meats and vegetables to meet the protein needs.

We repeat CM challenge at the age of 1.5 to 2 years; in cases in which the initial symptoms were severe, the child is admitted to hospital. A standard small dose (5 ml) of pasteurized CM is given on the first day and the volume of CM is increased at each meal during 3 days to that usually given at meals (1.5 dl). If the child shows symptoms, elimination of CM is continued for another 6 months. In most cases the challenge is done at home in a similar manner and the result is reported to the physician in charge. Other restricted foods are also presented one by one at the age of 2 years. When it is thought possible that the child has coeliac disease, jejunal biopsy is taken at 6 months and, if morphology is normal, again at 2 years, after the reinclusion in the diet of gluten-containing cereal.

Disodium chromoglycate

Given orally, disodium chromoglycate prevented intestinal symptoms of CMA in 4 infants who at the same time were given one meal containing CM proteins daily. When disodium chromoglycate was stopped after one week, only 1 infant relapsed (30). However, an unsuccessful experiment with the same drug has been reported (121). Probably this treatment is best suited for multiple food allergies when it is difficult to find a reasonable elimination diet (18).

PROGNOSIS

The prognosis in CMA is good; today the disease is manageable in its most fulminant forms (70). In the great majority of patients it is transient: in 6–45% of patients the clinical reactivity to CM disappears by the end of the first year (33, 50, 55), and by the end of the second year, according to two clinical follow-up studies, every patient was taking CM without symptoms (69, 81). Others report that from 40 to 73% still show symptoms of CMA at the age of 2 years (33, 55). In a few cases CMA persists even after the age of 3 years (10, 24). Later on however, many children with cured CMA have other allergic symptoms (24, 69).

PREVENTION

In the perinatal period every effort should be made to protect infants from contact with CM proteins. The role of intrauterine sensitization is disputed. Unnecessary feeding with CM formulas are often given in many maternity hospitals. Breast feeding must be encouraged. The length of breast feeding needed to prevent CMA is not known. Prolonged breast feeding reduces the frequency of other forms of allergy, too (94). It is disputed whether artificial feeding with foods other than CM is capable of preventing allergy in general and CMA in particular (34, 43, 58). Glaser & Johnstone (34) saw reduced numbers of children with CMA in a group fed with soy formula or breast milk for a period from birth to a median age of 6 months. In another study the incidence of CMA was lower when infants were

given soy formulas for 6 months (43, Table 1), but no difference in the incidence of childhood allergy as a whole was seen between groups of infants fed with either breast milk, or soy formulas or CM formula. In a recent study of 48 infants with a biparental history of atopic disease, half of the children were given soy formula and the other half CM formula for 9 months; initial breast feeding was equally long in the two groups. In each group four cases of CMA were seen and the frequency of atopy by the age of 4 years was the same (61), indicating that soy formulas do not offer any advantage in the prevention of CMA or allergy in general.

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