

Cow's Milk Allergy: Where have we Come from and where are we Going?

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Abstract: Since the 1930's the scientific literature on cow's milk protein allergy (CMPA) has accumulated. Over the last decade new diagnostic tools and treatment approaches have been developed. The diagnosis of reproducible adverse reactions to cow's milk proteins (CMP), i.e. CMPA, still has to be confirmed by controlled elimination and challenge procedures. Advanced diagnostic testing using epitope and microarray technology may in the future improve the diagnostic accuracy of CMPA by determination of specific IgE against specific allergen components of cow's milk protein. The incidence of CMPA in early childhood is approximately 2-3% in developed countries. Symptoms suggestive of CMPA may be encountered in 5-15% of infants emphasizing the importance of controlled elimination/milk challenge procedures. Reproducible clinical reactions to CMP in human milk have been reported in 0.5% of breastfed infants. Most infants with CMPA develop symptoms before 1 month of age, often within 1 week after inter introduction of CMP-based formula. The majority has two or more symptoms from two or more organ systems. Approximately 50-70% have cutaneous symptoms, 50-60% gastrointestinal symptoms and 20-30% respiratory symptoms. Symptoms may occur within 1 hour after milk intake (immediate reactions) or after 1 hour (late reactions). The prognosis of CMPA is good with a remission rate of approximately 45 to 50% at 1 year, 60 to 75% at 2 years and 85 to 90% at 3 years. Associated adverse reactions to other foods develop in up to 50% and allergy against inhalants in 50 to 80%.

The basic treatment of CMPA is avoidance of CMP. In early childhood a milk substitute is needed. Documented extensively hydrolysed formulas are recommended, whereas partially hydrolysed formulas should not be used because of a high degree of antigenicity and allergenicity associated with adverse reactions. In case of intolerance to extensively hydrolysed formulas and multiple food allergies a formula based on aminoacids is recommended. Alternative milk substitutes such as sheep's and goat's milk should not be used because of a high degree of cross reactivity with CMP. Milk from other mammals such as mare and donkey may be tolerated by some children with CMPA. Soy protein is as allergenic as CMP and soy formula is not recommended for young children with CMPA because of a great risk of development of allergy to soy, whereas soymilk is normally tolerated in older children with CMPA.

Recent treatment modalities are oral immunotherapy (OIT) involving the ingestion of increasing amounts of milk allergen on a regular basis to desensitize and potentially permanently tolerize patients to CMP. OIT can increase the reaction thresholds to CMP, but questions about safety and long-term efficacy remain. Anti-IgE therapy with Omalizumab may improve the safety and efficacy of OIT and may provide benefit in monotherapy.

Keywords: Childhood, cow's milk allergy, diagnosis, infancy, prognosis, treatment.

INTRODUCTION

Since the 1930's the scientific literature on cow's milk protein allergy has accumulated. Over the last decade new diagnostic tools and treatment approaches have been developed. According to a revised nomenclature for allergy [1, 2] reproducible adverse reactions to foods may be classified as food hypersensitivity, which may be divided into non-allergic food hypersensitivity and food allergy when immunological mechanisms have been demonstrated (or strongly suspected). Similarly, cow's milk protein allergy may be divided into IgE-mediated food allergy (and non-IgE mediated food allergy, mainly type III (immune-complexes) and type IV (cell-mediated) reactions [1-3]. Most often,

allergic reactions to cow's milk proteins (CMP) are IgE-mediated causing symptoms from the skin, the gastrointestinal tract, or the respiratory tract. The gastrointestinal manifestations of food allergy may be classified as a continuum from clearly IgE-mediated to mixed reactions dominated by eosinophilic granulocytes as effector cells to clearly non-IgE mediated reactions [3]. In many studies on "milk allergy" the immunologic basis of the clinical symptoms has not been investigated. Based on clinical symptoms alone, a differentiation between IgE-mediated and non-IgE mediated reactions to CMP is not possible. Importantly, a diagnosis of lactose intolerance should be suspected in cases with restricted gastrointestinal symptoms and this diagnosis should be confirmed by a lactose tolerance test or by genetic testing for the gene coding for this disease entity [4].

This review on cow's milk protein allergy (CMPA) will concentrate on incidence, etiological aspects, clinical features, prognosis, cross reactivities to beef and milk from other mammals, recent advances in diagnostic testing using

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epitope and micro array technology, and advances in treatment regarding oral immunotherapy (OIT) and anti-IgE-therapy.

Diagnostic Criteria

No single laboratory test or combinations of tests are diagnostic of CMPA. Therefore, the diagnosis of CMPA still has to be based on strict, well defined food elimination and challenge procedures including double-blind placebo-controlled food challenges (DBPCFC) in children older than 2-3 years [5, 6]. In young children, open controlled challenges have been shown to be reliable when performed under professional observation in a hospital setting [7, 8]. As oral challenge is time consuming, relatively expensive, and not always without a risk for the patient, an alternative to oral challenge with a high sensitivity and specificity would benefit daily practice in diagnosis of food hypersensitivity. Quantification of specific IgE to food has been suggested as an alternative to oral challenge in diagnosis of food allergy [9-11]. Another study demonstrated no significant relationship between quantification of specific IgE and the challenge threshold dose in food allergic children [12]. Recent epitope studies and micro array technology promise to improve the accuracy of diagnostic testing and may also allow a better prediction of reactions' severity and the likelihood of recovery from CMPA. In a recent study, currently used serum IgE testing to whole milk extract versus specific IgE against the milk protein components casein, β -lactoglobulin and α -lactalbumin in detecting challenge proven CMPA it was shown that casein-specific IgE was superior to whole milk extract as well as the other proteins and a cut-off of 6.6 kU/l resulted in 100% specificity. These results are in agreement with previous studies that show that casein-specific IgE was more prevalent in persistent CMPA [13-15]. Previous studies have suggested that the atopy patch test (APT) might make oral challenge superfluous in children with atopic dermatitis and suspicion of food allergy (primarily delayed-onset reactions) [16, 17]. In another study, APT could not predict food allergy to cow's milk and hen's egg not predicted by skin prick test, histamine release or specific IgE in unselected children with and without atopic dermatitis [18]. Therefore, the diagnosis still has to be based on strict well-defined elimination and milk challenge procedures. To avoid overdiagnosis the following minimum diagnostic criteria should be noted: 1) disappearance of symptoms after each of two dietary eliminations of cow's milk or cow's milk products; 2) recurrence of identical symptoms after one challenge and 3) exclusion of lactose intolerance and coincidental infection particularly expected in case of monosymptomatic gastrointestinal symptoms.

In solely breastfed infants elimination and challenge procedures should be performed *via* regulation of the mother's intake of cow's milk. A well defined standardized schedule should be followed [7, 19]. In unusual or not so well known manifestations of CMPA such as allergic eosinophilic esophagitis and allergic proctitis (inflammation of the rectum) with constipation, the challenge schedule may have to be modified to register the relevant symptoms. In older children and adults, DBPCFC will often be necessary to exclude psychologic or other reactions [5, 7, 19]. However,

in patients with delayed reactions, DBPCFC will often not be practical. Therefore, a negative DBPCFC should always be followed by an open, controlled challenge including normal amounts of intake of cow's milk.

Incidence

Food allergy is primarily a problem in infancy and early childhood. Most often infants develop food allergy in the same order as that in which the foods have been introduced into the diet. Thus the prevalence of reactions to different foods depends in part on the eating habits on a given population.

Before 1950 CMPA was rarely diagnosed. Since 1970 widely varying estimates of the incidence from 1.8% to 7.5% have been reported [8] mainly reflecting differences in diagnostic criteria and study design. Based on strict diagnostic criteria the incidence of confirmed CMPA in infancy seems to be about 2-3% in developed countries. The symptoms suggestive of CMPA may be encountered in about 5-15% of infants emphasizing the importance of controlled elimination/milk challenge. In breastfed infants reproducible clinical reactions to CMP in human milk have been reported in about 0.5% [20, 21]. CMPA is the most common confirmed food protein allergy in early childhood with an incidence in the first year of life approximately 2 to 3% in well conducted prospective studies compared with an incidence of 0.8% of allergy to peanut, 0.8% to soy, 0.6% to egg and an incidence of 0.2% to wheat [22]. Adverse reactions to cow's milk is the most frequent parentally perceived adverse reaction to food reported with a point prevalence of 7.5% at 12 months, 5% at 24 months and a cumulative incidence of 11.6% in a large Norwegian birth cohort of 3,623 infants followed from 0 to 2 years by questionnaires at 6-12 months intervals [23]. Therefore, proper diagnostic procedures are important in order to avoid overdiagnosis and overtreatment.

During the last decades an increased incidence of allergic diseases such as asthma and rhinoconjunctivitis in childhood has been reported. Concerning possible changes in the incidence of CMPA the investigations of 2 Danish birth cohorts 14 years apart in the municipality of Odense in Denmark, have not shown an increase in the incidence of CMPA. On the contrary, the one-year incidence of CMPA among newborns born in 1985 was 2.2% (95% CI, 1.5-2.9%) versus 1.0% (95% CI 0.1-1.7) among newborns born in 1999. Considering the use of similar study and diagnostic procedures a decrease in the incidence of CMPA has occurred [24, 25].

Etiological Aspects

The development of CMPA depends on several factors, particularly genetic allergic predisposition, early CMP exposure and CMP uptake and handling. Uptake of high molecular food proteins through the intestinal mucosa is a normal phenomenon and formation of antibodies against cow's milk protein is a normal physiological response [8]. 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 diseases is unclear. However, the development of CMPA primarily seems to depend on the exquisite immune responsiveness in predisposed individuals. A significant association between early neonatal exposure to CMP *via* CMP based formula feeding and subsequent development of CMPA has been documented in large birth cohorts [8, 26]. Findings of specific IgE to individual CMP's in cord blood of the majority of infants with a later development of CMPA may indicate intrauterine sensitisation playing a role in the pathogenesis. Perhaps a weak intrauterine priming including a low IgE response, which needs to be boosted postnatally in order to cause clinical disease, particularly in infants with a marked atopic predisposition. Furthermore, it should be emphasized that sensitisation to CMP during exclusively breastfeeding may be due to "unknown breaks" in the dietary regiment, contact with contaminated hands or inhalation of food proteins rather than due to sensitisation caused by the minute amounts of CMP in human milk (range 0.9-150 ng/ml) [8].

Clinical Features

Most infants with CMPA develop symptoms before one month of age, often within one week after introduction of cow's milk based formula. The majority have ≥ 2 symptoms

and symptoms from ≥ 2 organsystems. About 50-70% have cutaneous symptoms, 50-60% gastrointestinal symptoms and about 20-30% respiratory symptoms. In exclusively breastfed infants with CMPA severe atopic eczema is a predominant symptom. Debut of CMPA after 12 months is extremely rare [3, 8]. Clinical features of CMPA in children are listed in Table 1.

Symptoms may occur within a few minutes to 1 hour after milk exposure (immediate reactions, mostly IgE-mediated) or after 1 hour (late reactions) and in a few cases after several days. Most often the late reactions are non-IgE mediated. Anaphylaxis attributable to CMP may occur in up to 9% in infants with CMPA [8]. Patterns of reactivity may vary because of different exposure levels and different time intervals between exposures. During the last decade some organ specific manifestations of cow's milk allergy such as gastroesophageal reflux, allergic eosinophilic gastroenteritis and constipation as a manifestation of allergic eosinophilic proctitis have become of increased interest [3, 27, 28]. There is some controversy on the underlying mechanism for constipation caused by CMPA, but in selected patient with CMPA, allergic eosinophilic colitis has been demonstrated [28]. Gastrointestinal hypersensitivity to foods including cow's milk represents a pattern depending on the age of the

Table 1. Clinical features of food protein allergy in children.

Cutaneous reactions	
IgE-mediated	Atopic dermatitis Urticaria, acute or chronic (rare) Angioedema
Non-IgE-mediated	Contact rash Atopic dermatitis
Gastrointestinal reactions	
IgE-mediated	Oral allergy syndrome (local reactions) Nausea/vomiting Colic Diarrhoea
Non-IgE-mediated	Enterocolitis syndrome Colitis Allergic eosinophilic gastroenteritis Transient enteropathy (mimicking celiac disease) Protein-losing enteropathy Constipation
Respiratory reactions	
IgE-mediated	Rhinoconjunctivitis Asthma (wheeze, cough) Laryngeal edema Otitis media (secondary to allergic rhinitis and eustachian tube dysfunction)
Non-IgE-mediated	Pulmonary hemosiderosis (Heiners syndrome, rare)
Other reactions	
Systemic anaphylaxis	
Food dependent exercise induced asthma	
Unknown mechanisms	Anemia (not attributable to colitis) Arthritis (rare) Henoch Schönlein purpura (Type III?, rare) Irritability/sleeplessness? Migraine (rare)

individual (infants to children), the anatomical sites (esophagus, ventricle, small intestine, colon, rectum) and the continuum of reactivity from IgE-mediated reactions to non-IgE mediated reactions [3]. There is some evidence that otitis media with effusion in rare cases may be caused by allergy in the middle ear because of CMPA [29].

Prognosis

In prospective observational studies of primarily unselected infants the overall prognosis of CMPA is good with a total recovery of 45-56% at 1 year, 60-77% at 2 years, 84-87% at 3 years and approximately to 90-95% at 5 and 10 years (reviewed in [30, 31]). In selected groups of infants with CMPA a very high recovery rate of 100% in children with cow's milk protein gastroenteropathy before 2 years of age has been reported [32]. In a long term follow-up study up to 15 years a recovery rate of 98% was reported. In other selected studies with a shorter follow-up period varying recovery rates between 33-87% have been found possibly reflecting differences in a composition of the materials (severity of disease), study design, diagnostic criteria, age at entry into the studies and the duration of follow-up period. It is evident that with increasing age at inclusion, a lower proportion of children will develop tolerance to CMP because those with a mild disease and a very good prognosis normally develop tolerance to CMP before the age of 2-3 years. Furthermore, some studies have demonstrated that infants with high IgE levels to CMP have a lower rate of recovery than infants with non-IgE mediated reactions [8, 30, 31]. Adverse reactions to other foods have been reported in 41-75% of children with CMPA. The most frequent reactions are against egg, soy, peanut, citrus, fish and cereals [8, 30, 31]. The varying frequencies of associated food hypersensitivity mainly reflect different eating habits including age at introduction of certain foods. Furthermore, development of allergy against inhalant allergens often occurs in infants with CMPA, especially in those with high levels of specific IgE to CMP (up to 50 – 80%) [33]. Inhalant allergy particularly develops against allergens to which the children have been exposed from early infancy, i.e. house dust mites, cat and dog [8]. Finnish follow-up studies of children with CMPA have confirmed these findings [34, 35]. In one study there was a recovery rate of 96% among children with delayed type of CMPA versus a recovery rate of 63% among children with immediate type (IgE-mediated) CMPA at follow-up at 4 years of age. In the latter study skin prick test reaction with a mean wheal diameter of less than 5 mm and a low s-IgE of less than 2 kU/l to CMP were predictive of development of tolerance to CMP whereas high levels of IgE to CMP and larger skin prick test reactions were associated with an increased risk of persisting CMPA, persisting allergy to other foods and development of inhalant allergy. In several studies quantification of the reaction of skin prick test and/or quantification of specific IgE to milk and other foods have been suggested as an alternative to oral re-challenge in order to evaluate development of tolerance [9-11]. Such investigations have described predictive decision points above which oral re-challenge can be avoided. However, such results will strongly depend on the selection of patient materials and cannot be transferred to other patient materials.

In a recent Finnish review on development of natural tolerance in cow's milk allergy [36] it was concluded that the most documented prognostic characteristic is that intense specific-IgE response predicts persistence of CMPA. Natural development of tolerance involves an immunologic shift where TH2-responses diminish and TH1 as well as T-regulatory cell responses strengthen. Recent studies have reported that extensively heated milk may accelerate the natural resolution of milk allergy compared with strict avoidance. However, it is well-known that heat treatment denaturates most of the whey proteins in cow's milk, whereas the caseins are not destroyed by heat treatment. Those who "develop" tolerance may be those who are primarily sensitized to whey proteins, whereas those primarily sensitized to caseins may have longer lasting CMPA [37].

Cross-Reactivity

Cross-reactivity occurs when 2 or more allergens share epitopes and therefore are bound by the same IgE antibodies. Thus, patients sensitised to one of the allergens may also react to the other without previous exposure and sensitisation.

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%). Individual whey proteins are beta-lactoglobulin, alpha-lactalbumin, proteose-peptones, blood proteins (bovine serum albumin and bovine immunoglobulin). Because of a micellar structure casein can easily be separated from whey. The curd produced during cheese-making is primarily casein.

Cross-reactivity between mammalian proteins have been investigated by methods such as immuno-electrophoresis (sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE)) and immunoblotting and by using animal monoclonal antibodies [38]. Animal monoclonal antibodies specific for cow's milk proteins were able to recognize the major part of milk proteins from mammals such as sheep, goat and buffalo. There was a weak cross-reactivity observed with milk proteins from mares and donkeys. None of the antibodies used reacted with proteins from exotic mammalian species such as camel. Similar cross-reactions were found with human circulating immunoglobulin E from children with CMPA. With regard to beef allergy (meat from cow) monoclonal antibodies specific for bovine serum albumin cross-reacted only with sheep serum albumin. In another study bovine IgG appeared to be a major cross-reacting vertebrate meat allergen that could predict beef allergy [39]. Earlier goat's-milk (evaporated goat's milk) has been recommended to CMPA patients. However, 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 [8]. Thus, persons with CMPA may react at the first exposure to goat's milk. Previous experiences about successful treatment the goat's milk in CMPA may be due to the fact that these goat's milk products were often extensively heat treated (evaporated/boiled) leading to a possible reduction and perhaps elimination of the antigenicity of some of the heat-labile proteins (bovine serum albumin and bovine immunoglobulin), thus explaining the possible benefit in at

least some patients. However, goat's milk is also deficient in certain vitamins, especially folic acid, D, C, B6 and B12 and is rich in minerals salts. Therefore, unmodified goat's milk on several reasons is unsuitable for feeding human infants and should not be recommended as milk substitute to patients with CMPA [8]. Interestingly allergy to goat's and sheep's milk without allergy to cow's milk has been reported [40]. Twenty-eight children with distinct allergic reactions when eating goat and sheep milk/cheese were found to be allergic to the casein fraction of goat's and sheep's milk. Characteristically this food allergy develops later in childhood and not in early childhood as CMPA, and all the children tolerated cow's milk. Previously some case reports on selective allergy to sheep's and goat's milk proteins (and not to cow's milk proteins) have been published.

Among children with CMPA 13-20% also develops allergic symptoms when eating beef. Probably cooking (heat treatment) of beef may destroy some of the allergenicity and some tolerate cooked beef but react to raw beef. Among beef allergic children 26 out of 28 (92%) were also allergic to cow's milk [41]. Those not reacting to cow's milk had negative s-IgE to bovine serum albumin.

In a few clinical investigations the low allergenicity of milk proteins from mare's milk has been confirmed [42]. In that study by Businco L, *et al.*, 24 out of 25 confirmed CMPA children tolerated mare's milk.

Recent advanced diagnostic testing using epitope and micro array technology will enable more accurate testing of the nature of cross-reacting allergen components from different mammals [15].

Treatment

A correct diagnosis is necessary to ensure a sufficient and safe diet. Because of the good prognosis of CMPA it is important to perform re-challenges every $1\frac{1}{2}$ -1 year in early childhood in order to avoid overtreatment and unnecessary diets.

The basic treatment of CMPA is complete avoidance of CMP. During infancy and early childhood an alternative hypoallergenic milk substitute is necessary. Alternative milk substitutes such as goat's milk or sheep's milk should be avoided because of a very high risk of cross-reactivity as discussed above. Another alternative milk substitute is soy bean formula, but these unaltered proteins of soy are potentially allergenic and allergic reactions to them have been documented. Soy proteins is reported to be at least as allergenic as CMP and in young children with CMPA soy protein allergy has been reported with frequencies between 17% and 47% [8]. Some clinicians consider soy formula to be a safe alternative for the majority of children with CMPA [43], because only 14% (13/94) of infants and children with IgE mediated CMPA reacted to soy formula. However, approximately 70% (13/19) of the infants with CMPA below one year of age reacted to soy. Therefore, soy formula should not be recommended to infants and young children with CMPA.

Extensively hydrolysed formulas (EHF) based on casein from cow's milk have been used and regarded safe for treatment of CMPA for several years. Later on EHF based on

whey have been shown to be safe for treatment of CMPA [44]. These formulas are enzymatically extensively hydrolysed and their effectiveness is well documented [44]. The use of EHF is hampered by a poor, bitter taste. This problem would be reduced by a less complete hydrolysis, which may on the contrary result in increasing remaining antigenicity and a higher risk of allergic reactions. Partially hydrolysed whey formulas (PHF) have been used primarily for prevention for some years and should not be used for treatment because of a high risk for adverse reactions [44]. It has been recommended that dietary products for treatment of CMPA in infants should be tolerated by at least 90% (with 95% confidence) of children with documented CMPA [44]. Further, it is recommended that after successful double-blind challenge the products should be tolerated in a controlled open challenge during a period of 7 days. Some EHF and amino acid based products have met these criteria. In contrast, no PHF have fulfilled these criteria and several cases of allergic reactions to these products have been reported in children with CMPA [44]. Documented hypoallergenic EHF are recommended for treatment of infants with CMPA. At present there is no evidence of benefit of the addition of probiotics in hypoallergenic formulas [45, 46].

Because of the possibility of residual antigenicity/allergenicity even in EHF [47], highly sensitised individuals to CMP may react to these products. Therefore, before starting treatment with a hypoallergenic formula a skin prick test should be performed to evaluate a possible reactivity and if negative followed by an oral challenge in a clinical setting. Hypoallergenic formulas are not non-allergenic products.

Only pure amino acid mixtures are non-allergenic and should be used in case of multiple food allergy or intolerance to EHF [48].

A new treatment modality in food allergy is oral immunotherapy (OIT) which involves the ingestion of small, increasing amounts of food allergen on a regular basis to desensitize and potentially permanently tolerize patients to the implicated food. Most studies on OIT have involved an initial day of multiple dose increases, called a rush escalation day. This is followed by gradual dose escalation period until a daily maintenance dose is given for a long period. OIT with CMP induces desensitization in most cases where spontaneous recovery has not yet occurred. Data on long-term tolerance induction are still scarce. According to current research data, the immunologic changes induced by OIT resemble those seen during natural development of tolerance [36]. In some studies, the regular ingestion of small amounts of food in oral immunotherapy (OIT) has been shown to dramatically increase reaction thresholds. However, a subset of patients have developed significant side-effects, particularly gastrointestinal symptoms requiring discontinuation of the treatment. Another drawback of this treatment is that the effect may be transient if milk protein is not given continuously every day [15]. In a recent study, the efficacy of sublingual immunotherapy (SLIT) was compared with OIT in a study of milk allergic children [49]. In that study, OIT was more efficacious than SLIT, but also associated with a higher risk of serious adverse events.

An allergen non-specific treatment is the injectable anti-IgE therapy with omalizumab, which has been shown to

benefit in conjunction with OIT. Preliminary data have also suggested that it may be effective as mono therapy in food allergic patients. Clinical trials using omalizumab in patients with food allergy resulted in achieving tolerance to high amounts of the allergen in some patients. When used as an adjunct therapy during immunotherapy in trials with patients with food allergy and anaphylaxis, omalizumab allowed more rapid and higher doses of immunotherapy to be given. Omalizumab has also been reported to be effective in a few patients with idiopathic anaphylaxis and mast cell disorders. However, large multicentre trials are needed to confirm the findings and to identify the patients that would benefit the most from this treatment [50].

CONCLUSION

Over the last decade, new diagnostic tools and treatment approaches have been developed. Advanced diagnostic testing using epitope and micro array technology may in the future improve the diagnostic accuracy of cow's milk protein allergy (CMPA). Based on the results from prospective birth cohorts, most infants with CMPA develop symptoms before 1 month of age, often within 1 week after the introduction of CMP-based formula. The majority has 2 or more symptoms from 2 or more organ systems, and approximately 50-70% have cutaneous symptoms, 50-60% gastrointestinal symptoms and 20-30% respiratory symptoms. Symptoms may occur within 1 hour after intake of milk (immediate reactions) or after 1 hour (late reactions). The prognosis of CMPA is good with a remission rate of 85-90% at 3 years. Associated adverse reactions to other foods develop in up to 50% and allergy against inhalants in 50-80%. The basic treatment is avoidance of CMP. In early childhood a milk substitute is needed and documented extensively hydrolysed formulas are recommended. In case of intolerance to extensively hydrolysed formulas and multiple food allergies, a formula based on aminoacids is recommended. Soy protein is as allergenic a CMP and soy formula is not recommended for young children with CMPA. Recent treatment modalities are oral immunotherapy (OIT) involving the ingestion of increasing amounts of milk allergen on a regular basis to desensitize and potentially permanently tolerize patients to CMP. OIT can increase the reaction thresholds to CMP, but questions about safety and long-term efficacy remain. Anti-IgE therapy with Omalizumab may improve the safety and efficacy of OIT and may provide benefit in monotherapy.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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