

Diagnosis and management of cow's milk protein allergy in infants

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Background: Cow's milk protein allergy (CMPA) is frequently suspected in infants with a variety of symptoms. A thorough history and careful clinical examination are necessary to exclude other underlying diseases and to evaluate the severity of the suspected allergy. Care should be taken to diagnose CMPA adequately to avoid an unnecessary diet.

Data sources: We make recommendations based on systematic literature searches using the best-available evidence from PubMed, Cumulative Index to Nursing and Allied Health Literature, and bibliographies.

Results: Skin prick tests, patch tests and serum specific IgE are only indicative of CMPA. Breastfed infants have a decreased risk of developing CMPA; an elimination diet for the mother is indicated if CMPA is confirmed. If a food challenge is positive in formula fed infants, an extensively hydrolysed formula and cow's milk-free diet is recommended. If symptoms do not improve, an amino acid based formula should be considered. In severe CMPA with life-threatening symptoms, an amino-acid formula is recommended.

Conclusions: Elimination diet by a double-blind placebo controlled food challenge is the gold standard for diagnosis. Elimination of the offending allergen from the infants' diet is the main treatment principle.

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Introduction

Cow's milk protein allergy (CMPA) is defined as an immunological reaction to one or more milk proteins.^[1] A variety of symptoms can be suggestive for CMPA. CMPA is suspected clinically in 1%-17% of infants,^[2,3] while most estimates for the prevalence of CMPA vary from only 2% to 3%.^[1,3] Confusion regarding CMPA prevalence is often due to differences in the study population and a lack of defined diagnostic criteria for CMPA. The importance of defined diagnostic criteria needs to be emphasized. It precludes infants from an unnecessary diet^[4] and avoids delay in diagnosis, which can lead to malnutrition.^[5]

The intention of this manuscript is to help pediatricians to diagnose and manage CMPA. Most of the recommendations are based on the recently published guidelines on CMPA diagnosis and management.^[3,4,6-9]

Manifestations

CMPA may develop in breastfed and cow's milk formula fed infants and usually occurs within the first weeks after cow's milk introduction. The presentation is variable; no symptom is pathognomonic. Manifestations mainly occur at the level of the digestive tract (50%-60%), the skin (50%-60%), and the respiratory tract (20%-30%).^[2] They vary from mild-moderate to severe (Table).

There are two clinical types of CMPA: immediate and delayed types. The immediate type presents shortly after ingestion of cow's milk protein (CMP) (urticaria, angio-edema, vomiting or an acute flare of atopic dermatitis) and is present in slightly more than half of the patients with CMPA.^[10] They are more likely to have positive skin prick test (SPT) (wheel size >3 mm) or positive serum specific immunoglobulin e (IgE).^[10] Another immediate reaction due to food hypersensitivity is food protein induced enterocolitis syndrome. It can be caused by cow's milk protein, but is probably cell mediated with negative specific IgE. It is recognized as a separate allergic entity early in life presenting with severe gastrointestinal symptoms and metabolic acidosis. The amount of cow's milk necessary to elicit

an immediate reaction varies from one drop to more than 150 mL, which shows that some patients tolerate a considerable amount of milk before manifestations develop.^[11] Delayed reactions such as atopic dermatitis or gastrointestinal manifestations like proctocolitis or enteropathy, usually present after hours or days.

Immunologically, CMPA can be IgE or non-IgE mediated.^[12] IgE mediated reactions are clinically more often of the immediate type and can be confirmed with SPT or serum specific IgE. Non-IgE mediated reactions are due to a cellular immune response or to a mixed immune response in which IgE and immune cells play a role. This type of reaction is more difficult to be proved by specific testing.

Diagnosis

None of the diagnostic tests available in routine clinical situations proves or excludes CMPA completely.^[11] A thorough history, including family history of atopy, and a careful clinical examination are therefore the key elements in the diagnostic process. Clinicians may perform SPT (preferable with fresh cow's milk or

whole CMP extracts), determination of specific IgE, or patch tests, but they merely indicate sensitization to the substrate and are not necessarily proof of an allergic reaction. According to a recent study,^[13] the sensitivity and specificity of the SPT is 31.8 and 90.3, respectively, and 20.5% and 88.9% of specific IgE, respectively. In cases where a food challenge can not be executed, both SPT and IgE can be used.^[13] The rate of outgrowing CMPA varies between 30% and 79% in IgE mediated CMPA;^[14] consecutive IgE measurements can be indicative in this process.^[15] If serum specific IgE and/or SPT at time of diagnosis are negative, tolerance is obtained at a younger age and the risk of severe acute reaction is small. On the contrary, persistent high IgE titers increase the risk of developing other atopic conditions like asthma, rhino-conjunctivitis and atopic dermatitis. Patch testing, still a topic of on-going research, can aid in the diagnosis of non-IgE mediated reactions.

Diagnostic challenge procedures

A double-blind placebo-controlled challenge is considered the gold standard in CMPA diagnosis, but in practice only an open challenge is often performed.^[4] The patient with suspected CMPA will follow a cow's milk free diet for 2-4 weeks. Formula-fed infants get an extensively hydrolyzed formula (eHF) and breastfeeding mothers follow a cow's milk free diet. If CMPA is present, clinical manifestations will disappear. Cow's milk protein is reintroduced progressively thereafter and clinical symptoms are monitored. The risk of an open challenge is an overestimation of the diagnosis.^[16] A double-blind placebo-controlled challenge will blind the parent and the doctor as for the introduction of cow's milk protein and is the only objective measure to make the diagnosis. Unfortunately, it is expensive, requires extensive preparation, is time-consuming, and is difficult to perform.^[17]

Medical supervision during a challenge is necessary because the severity of symptoms cannot be predicted.^[18,19] When additional allergy testing (serum specific IgE, SPT) is negative, life-threatening manifestations are extremely rare and a non-hospital setting with medical supervision is often sufficient,^[20] but in patients with a history of severe reactions or high IgE levels, a hospital setting with an established protocol is indicated. The challenge can be postponed in case of severe symptoms or when the patients are still recovering on an elimination diet. In case of an unequivocal history of recent anaphylactic reaction to cow's milk, a challenge is debatable. When CMPA is confirmed, the infant should be maintained on an elimination diet until the infant is between 9-12 months or at least for 6 months, whichever occurs first. A

Table. Clinical manifestations suggesting cow's milk protein allergy

Severe manifestations

- Gastrointestinal tract
 - Failure to thrive
 - Iron deficiency anemia
 - Enteropathy
- Skin
 - Exudative/Severe atopic dermatitis
- Respiratory tract
 - Larynx edema
- General
 - Anaphylaxis

Moderate-mild manifestations

- Gastrointestinal tract
 - Regurgitations and vomiting
 - Diarrhea
 - Constipation
 - Colitis
 - Colic/Abdominal pain
- Skin
 - Atopic dermatitis
 - Angio-edema
 - Urticaria
 - Swollen lips
- Respiratory tract
 - Rhinitis
 - Conjunctivitis
 - Wheezing
- General
 - Irritability

new challenge is then performed. Children who do not develop allergy-related manifestations during the challenge and up to one week thereafter can resume their normal diet.

If the patient with CMPA is on amino acid formula (AAF) because of ongoing allergic manifestations under an eHF, the debate whether to challenge with an eHF or standard infant formula is still ongoing. After the initial phase, allergic symptoms may not recur on an eHF challenge and the formula can be used as a less expensive and more palatable treatment.^[21] Whereas in the same patient, recurrence of symptoms after a challenge with normal cow's milk formula might be more likely.

Differential diagnosis

The long list of potential differential diagnoses for CMPA includes repetitive viral infections and transient lactose intolerance. Concurrent conditions can also be present, for example, troublesome regurgitation occurs in 20% of all infants, with or without CMPA. On the other hand, gastroesophageal reflux has been mentioned as a possible manifestation of CMPA.^[22] CMPA has also been related to infantile colic; CMPA contributes to colic in about 10% of colicky infants.^[23]

Although in some young infants, a correlation between atopic dermatitis and CMPA is suggested, many cases of atopic dermatitis are not related. The younger the infant and/or the more severe the atopic dermatitis, the stronger the association appears to be.^[24] Reactions to other foods (especially egg and soy, wheat, fish and peanut) occur frequently and often in combination with CMPA.^[25] Therefore, complementary feeding and,

preferentially, all supplementary feeding should be avoided during the diagnostic elimination diet.

Management of CMPA

The principles for the management of CMPA differ in breastfed and formula fed infants.

Management of CMPA in exclusively breastfed infants (Fig. 1)

Breastfeeding is the gold standard feeding in infant nutrition and is recommended exclusively at least for the first four months of life.^[26] Only about 0.5% of exclusively breast-fed infants show a reproducible clinical reaction to CMP, mostly mild to moderate.^[2] Life-threatening symptoms due to CMPA in breastfed infants are extremely rare, but severe cases of protein losing enteropathy and atopic dermatitis have been described.^[25] Any other underlying disease should be looked for in severe cases.

Due to the many benefits of breastfeeding, clinicians should advise to continue, even if the infant has CMPA. A cow's milk elimination diet for the mother is then indicated. The maintenance of a strict avoidance of CMP is mandatory if supplementary feeding is being given to the infant.^[24] The elimination diet for breastfeeding mother and child should be continued for a minimum of two (to four) weeks. In cases of atopic dermatitis, symptoms may not disappear after two to four weeks. Clinical experience suggests that other food proteins, such as egg, peanut, fish and wheat may well sensitise an

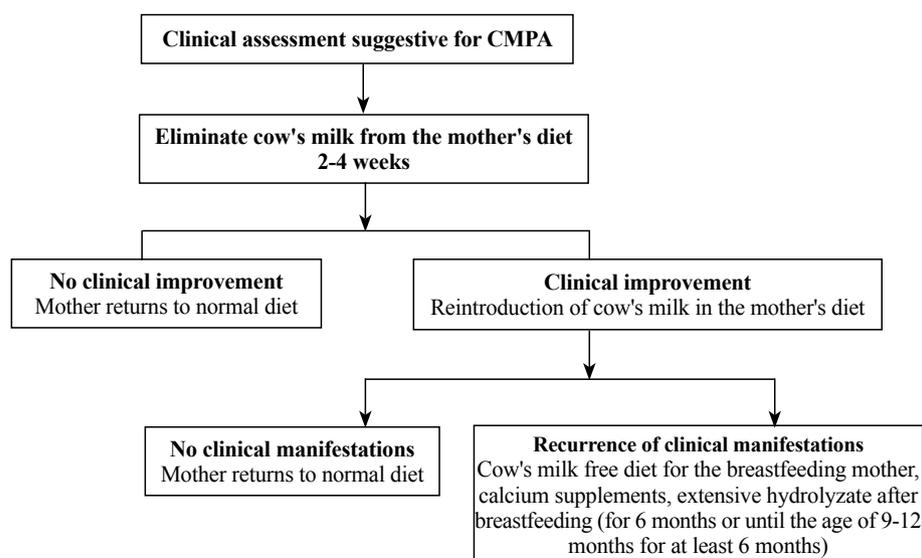


Fig. 1. Decision tree for the diagnosis and treatment of cow's milk protein allergy (CMPA) in breastfed infants with mild to moderate symptoms.

infant through his or her mother's milk. If so, elimination diet should be adopted accordingly. Advice of a dietician is often required in order to help the mother to keep a nutritionally balanced diet; an adequate calcium intake (1000 mg per day) needs special attention.

If symptoms disappear, cow's milk should be reintroduced in the mother's diet after 2 to 4 weeks. If symptoms relapse, the milk should be eliminated from the mother's diet as long as she is breastfeeding. When the mother wants to wean, the infant should receive an eHF. When the elimination diet fails to improve the symptoms or when the patient remains asymptomatic on reintroduction of specific food proteins, the mother should resume her normal diet.

Management of CMPA in formula-fed infants (Fig. 2)

Mild-moderate manifestations

In formula-fed infants with mild to moderate symptoms related to CMPA, a "therapeutic formula" is the first choice. According to consensus in the literature, a therapeutic formula is a formula tolerated by at least 90% (with 95% confidence) of CMPA infants.^[27,28] Many eHF based on whey, casein or another protein source comply to the criteria as well as amino acid-based formula (AAF). During a diagnostic elimination diet, all other food intake should be stopped to avoid misinterpretation of manifestations due to other allergens. The CMP-free diet should be maintained for

at least 6 months. To maintain a balanced therapeutic diet, help of a dietician is often needed.

Because of high cross-reactivity (up to 80%) and nutritional inadequacy, the use of most animal milk is precluded.^[29-31] Rice based hydrolysates, available in certain countries, may offer an alternative approach in the treatment of CMPA.^[32-34] However, any protein hydrolysate, independent of its origin, has a certain residual allergenicity. Residual symptoms on eHF is often due to a non-IgE related mechanism.^[21] Failure of eHF may be up to 10% in CMPA children in tertiary care centers.^[21] There are no data available from primary health care centers.

Although eHF is the treatment of choice in formula-fed CMPA infants, AAF can sometimes be indicated if symptoms persist beyond 2-4 weeks on eHF. AAF has the advantage of no residual protein allergenicity, since AAF is a pure chemically made formula, not derived from cow's milk (or any native protein) containing isolated amino-acids instead of peptides. If symptoms persist on an AAF, the diagnosis of CMPA should be questioned.

Severe manifestations

Formula-fed infants with severe CMPA should be given AAF, "the most effective" elimination diet. There is no specific evidence for the use of AAF in severe

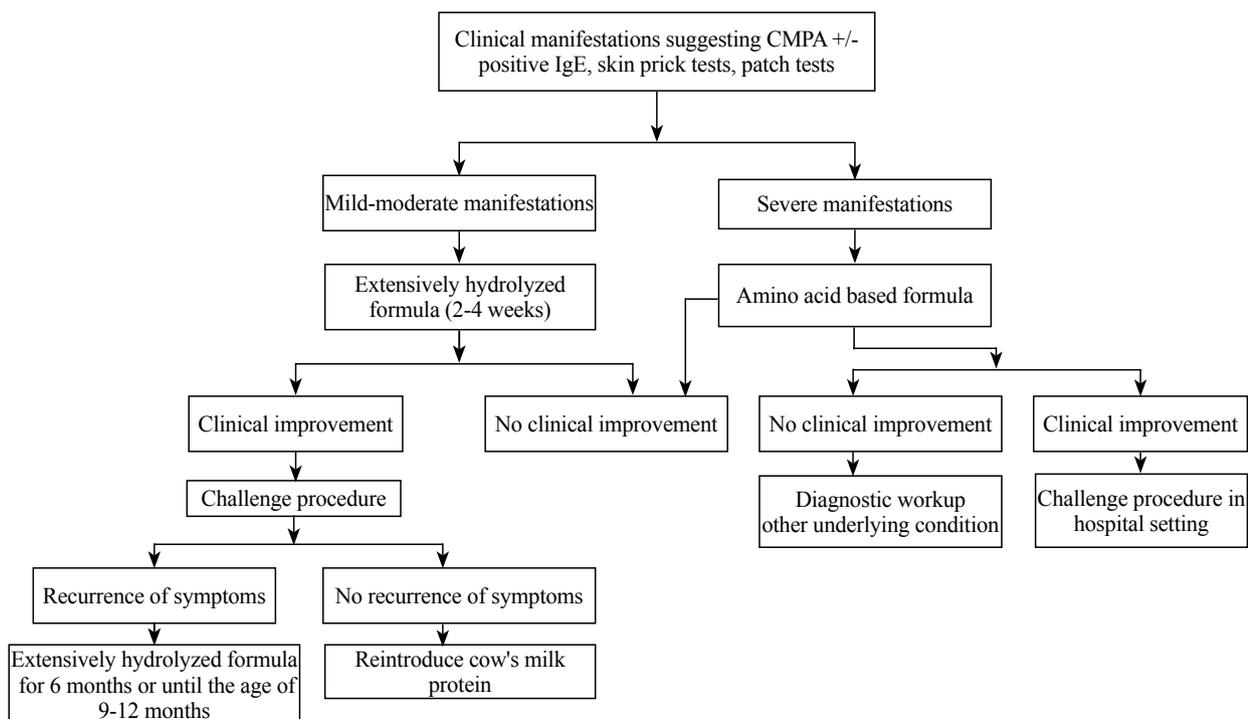


Fig. 2. Decision tree for diagnosis and treatment of formula-fed infants with suspected cow's milk protein allergy (CMPA).

symptoms, but the risk to aggravate further weight loss and nutritional deficiencies is hereby minimized. Patients with life-threatening, particularly respiratory symptoms or anaphylaxis need immediate referral to the nearest emergency department.

Soy formula in CMPA

The discussion on the use of soy-based infant formula is difficult, since scientific societies have different recommendations. There is a broad consensus on the following statements: the incidence of soy allergy in soy formula-fed infants is comparable to that of CMPA in cow's milk formula-fed babies.^[35] Cross reactivity to soy has been reported in 17.3% of infants with CMPA, regardless whether they were positive or negative for specific IgE for CMP.^[10] In particular, infants with multiple food allergies and eosinophilic enterocolitis also react to soy protein.^[36] Therefore, different specialist groups have different standpoints on the use of soy formula for CMPA, but the formula is generally not recommended before the age of 6 months.^[27,35,37,38] Soy could be considered as an alternative, the possible cross reactivity in mind, in cultures where the hydrolyzation process with pork-derived enzymes is considered a problem and beyond the age of 6 months.

Prevention

Genetic predisposition, environmental factors and the influence of allergen exposure early in life may play a role in the development of allergy.^[39] There are no data on the development of CMPA in atopic versus non-atopic families. A comprehensive history (including family history of atopy) and careful physical examination are therefore an important part of diagnosis. Irrespective of the atopic heredity, exclusive breastfeeding remains the best nutrition for all infants up to the age of 4-6 months, even as prevention of CMPA. If breastfeeding is not an option, hydrolysed formulas with proven efficacy are recommended in high risk infants^[40] combined with the avoidance of solid food and cow's milk for the same period.^[26]

Conclusions

CMPA can present in breastfed and formula-fed infants. The manifestations are non-pathognomonic and a comprehensive history and thorough clinical examination form the basis of the diagnosis. Confirmation with SPT, serum specific IgE or patch testing, unfortunately lack specificity and a double blind placebo controlled food challenge, remains the gold standard.

Although several groups have published

recommendations,^[4,7,41] the ongoing debate on CMPA management is still dependent on the primary outcome measure chosen, i.e., most efficient or cheapest solution. Breastfeeding remains the best and cheapest option to feed healthy infants, even in CMPA. When breastfeeding is not an option, eHF in CMPA is recommended by European consensus.

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