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Diagnosis and Management of Cows' Milk Protein Allergy in Infants

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1. 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 5-15% of infants (2), while most estimates of prevalence of CMPA vary from only 2 to 5 % (1). Confusion regarding CMPA prevalence is often due to differences in study population, and a lack of defined diagnostic criteria for CMPA. The importance of defined diagnostic criteria needs to be emphasised. It precludes infants from an unnecessary diet (3) and avoids delay in diagnosis, which can lead to malnutrition (4).
The intention of this manuscript is to help diagnose and manage CMPA. Most of the recommendations are based on recently published guidelines on CMPA diagnosis and management (3, 5-9).

2. Manifestations

CMPA may develop in breastfed (BF) and in cow's milk formula (CMF) 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 1).
There are two clinical types of CMPA: the immediate and the delayed type. The immediate type presents shortly after ingestion of cow's milk protein (CMP) (urticaria, angio-oedema, 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 $\geq$3 mm) or positive serum specific Immunoglobulin e (IgE) (10). 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 prove by specific testing.

SEVERE MANIFESTATIONS	
Organ Involved	**Manifestation**
Gastro-intestinal tract	Failure to thrive
	Iron deficiency anemia
	Enteropathy
Skin	Exudative/Severe atopic dermatitis
Respiratory tract	Larynx oedema
General	Anaphylaxis
MODERATE-MILD MANIFESTATIONS	
Organ involved	**Manifestations**
Gastrointestinal tract	Regurgitations and vomiting
	Diarrhea
	Constipation
	Colitis
	Colic/Abdominal pain
Skin	atopic dermatitis
	Angio-Oedema
	Urticaria
	Swollen lips
Respiratory tract	Rhinitis
	Conjunctivitis
	Wheezing
General	Irritability

Table 1. Clinical Manifestations suggesting CMPA.

3. Diagnosis

None of the diagnostic tests available in routine clinical situations prove or exclude 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 cows' milk or whole CMP extracts), determination of specific IgE, or patch tests, but they merely indicate sensitisation to the substrate and are not necessarily proof of an allergic reaction. The rate of outgrowing CMPA varies between 30-79% in IgE mediated CMPA (13); consecutive IgE measurements can be indicative in this process (14). 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, persistant 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.

3.1 Diagnostic challenge procedures

The double-blind placebo-controlled challenge is considered the gold standard in CMPA diagnosis, but in practice only an open challenge is often performed.(3) 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.(15) 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.(16)

Medical supervision during a challenge is necessary because the severity of symptoms cannot be predicted (17, 18). 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 (19), but in patients with a history of severe reactions or high IgE levels, a hospital setting with an established protocol is indicated. 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 new challenge is then performed. Children who do not develop allergy-related manifestations during 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. (20) Whereas in the same patient recurrence of symptoms after a challenge with normal cow's milk formula might be more likely.

3.2 Differential diagnosis

The list of potential differential diagnoses for CMPA is long including repetitive viral infections and transient lactose intolerance. Concurrent conditions can also be present: troublesome regurgitation occurs in 20 % of all infants, with or without CMPA. On the other hand, gastro-oesophageal reflux has been mentioned as a possible manifestation of CMPA. (21) CMPA has also been related to infantile colic; CMPA contributes to colic in about 10% of colicky infants (22).

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 (23).

Reactions to other foods - especially egg and soy, wheat, fish and peanut – occur frequently and often in combination with CMPA (24). Therefore, complementary feeding and, preferentially, all supplementary feeding should be avoided during the diagnostic elimination diet.

4. Management of CMPA

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

4.1 Management of CMPA in exclusively breastfed infants (Figure 1)

Breastfeeding is the gold standard feeding in infant nutrition and is recommended exclusively at least for the first four months of life.(25) 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 breast-fed infants are extremely rare, but severe cases with protein losing enteropathy and atopic dermatitis have been described. (24) Any other underlying disease should be looked for in severe cases.

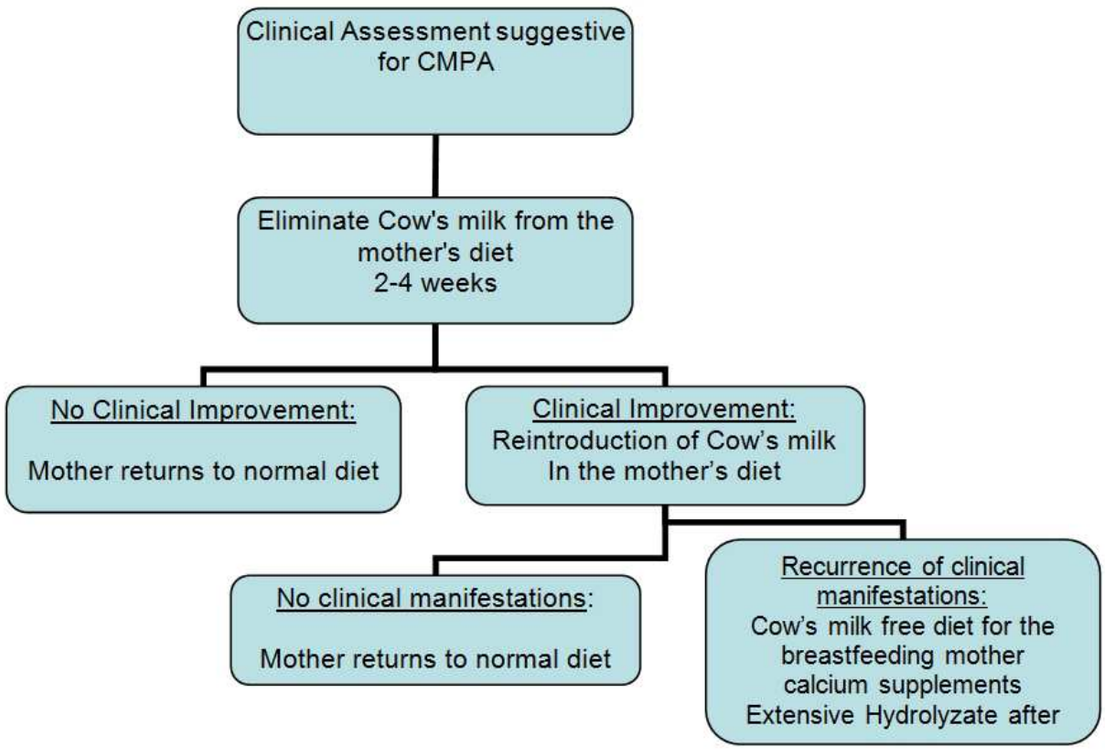

Fig. 1. Decision tree for the diagnosis and treatment of CMPA in Breastfed infants with mild to moderate symptoms

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. (23) 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 have disappeared after two to four weeks, in which case, clinical experience suggests that other food proteins, such as egg, peanut, fish and wheat may as well sensitise an infant through its mother's milk. If so, elimination diet should be adapted 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, cows' 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 extensive hydrolysed formula (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.

4.2 Management of CMPA in formula-fed infants (Figure 2)

4.2.1 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 literature, a therapeutic formula is a formula tolerated by at least 90% (with 95% confidence) of CMPA infants (26, 27). Many eHF's based on whey, casein or another protein source comply to those criteria as well as amino acid based formulae (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.

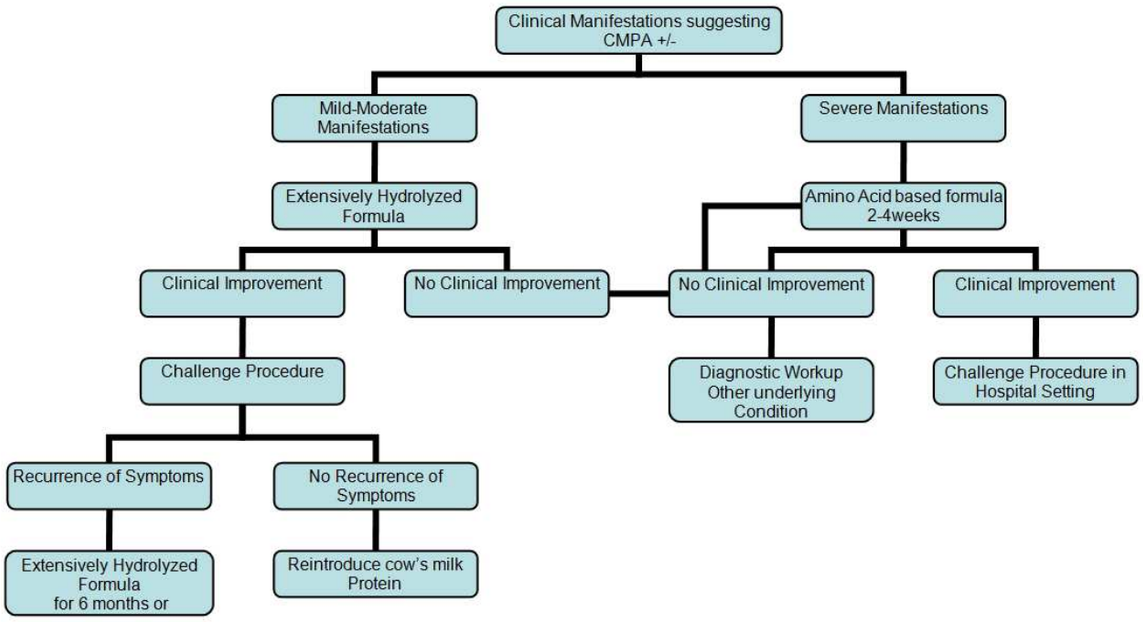

Fig. 2. Decision tree for diagnosis and treatment of formula fed infants with suspected CMPA

Because of high cross-reactivity (up to 80%) and nutritional inadequacy, the use of most animal milk is precluded (28-30). Rice based hydrolysates, available in certain countries, may offer an alternative approach in the treatment of CMPA. (31-33) 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 mechanisms (20). Failure on eHF may be up to 10% in CMPA children in tertiary care centres (20). There are no data available from primary health care centres.

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 CMPA diagnosis should be questioned.

4.3 Severe manifestations

Formula-fed infants with severe CMPA should be given AFF, "the most effective" elimination diet. There is no specific evidence for the use of AAF in severe symptoms, but the risk to aggravate further weight loss and nutritional deficiencies is hereby minimised. Patients with life-threatening, particularly respiratory symptoms or anaphylaxis need immediate referral to the nearest emergency department.

4.4 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 cows' milk formula-fed babies (34). Cross reactivity to soy has been reported in 10 to 35% 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 (35). Therefore, different specialist groups have different standpoints on the use of Soy formula for CMPA, but is generally not recommended before the age of 6 months (26, 34, 36, 37). 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.

5. Prevention

Genetic predisposition, environmental factors and the influence of allergen exposure early in life may play a role in the development of allergy (38). 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 (39) combined with the avoidance of solid food and cow's milk for the same period. (25)

6. Conclusion

CMPA can present in BF and FF 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 (3, 6, 40), the ongoing debate on CMPA management is still dependent on the primary outcome measure chosen: most

efficient or cheapest solution. BF remains the best and cheapest option to feed healthy infants, even in CMPA. When BF is not an option, eHF in CMPA is recommended as by European consensus.

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EDG, TD, BH and YVDP wrote paper. YVDP had primary responsibility for final content. All authors have read and approved the final manuscript.

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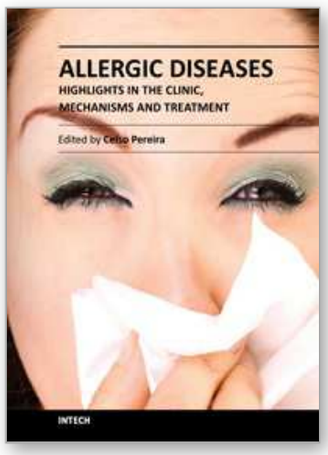

Allergic Diseases - Highlights in the Clinic, Mechanisms and Treatment

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The present Edition "Allergic diseases - highlights in the clinic, mechanisms and treatment" aims to present some recent aspects related to one of the most prevalent daily clinical expression disease. The effort of a group of outstanding experts from many countries reflects a set of scientific studies very promising for a better clinical care and also to the treatment and control of the allergy. This book provides a valuable reference text in several topics of the clinical allergy and basic issues related to the immune system response. The inflammatory reaction understanding in allergic disease is clearly evidenced, as well as new strategies for further researches.

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