

Treatment of Cow's Milk Protein Allergy

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The diagnosis and treatment of cow's milk protein allergy (CMPA) is still a challenge. A systematic literature search was performed using Embase, Medline, The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials for the diagnosis and treatment of cow's milk allergy (CMA). Since none of the symptoms of CMPA is specific and since there is no sensitive diagnostic test (except a challenge test), the diagnosis of CMPA remains difficult. A "symptom-based score" is useful in children with symptoms involving different organ systems. The recommended dietary treatment is an extensive cow milk based hydrolysate. Amino acid based formula is recommended in the most severe cases. However, soy infant formula and hydrolysates from other protein sources (rice) are gaining popularity, as they taste better and are cheaper than the extensive cow's milk based hydrolysates. Recent meta-analyses confirmed the safety of soy and estimate that not more than 10-15% of CMPA-infants become allergic to soy. An accurate diagnosis of CMA is still difficult. The revival of soy and the development of rice hydrolysates challenge the extensive cow's milk based extensive hydrolysates as first option and amino acid formula.

Key Words: Infant, Cow's milk protein allergy

INTRODUCTION

The prevalence of allergic diseases worldwide is rising dramatically in both developed and developing countries. These diseases include asthma; rhinitis; anaphylaxis; drug, food and insect allergy; eczema; urticaria and angioedema. This increase is especially problematic in children, who are bearing the greatest burden of the rising trend which has occurred over the last two decades.

A food allergy is "an adverse health effect arising

from a specific immune response that occurs reproducibly on exposure to a given food". Cow's milk protein allergy (CMPA), which is also commonly referred to as cow's milk allergy (CMA), is the leading cause of food allergy in infants and children younger than three years [1]. While there is indirect data favoring an increase in CMA prevalence, knowledge of the time trend of CMA prevalence is very limited and there are no unequivocal data to suggest an increase [2].

An important differentiation in the management of milk hypersensitivities is that of allergy or intoler-

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ance [3]. Allergy is the adverse immune response to constituents within the milk, whereas intolerance is a non-allergic food sensitivity as the result of lactase deficiency, the dietary enzyme required to digest lactose, the predominant sugar in milk.

ETIOLOGY

Food allergens are defined as the specific components of food or ingredients within food recognized by allergen-specific immune cells which then elicit specific immunologic reactions, resulting in characteristic symptoms. Food allergens are typically proteins, but sometimes also chemical haptens.

Food allergy symptoms commonly associated with immunoglobulin E (IgE)-mediated reactions include urticaria, angioedema, vomiting, diarrhea, eczema, rhinitis and anaphylaxis. Symptoms associated with non-IgE mediated reactions include vomiting, constipation, hemosiderosis, malabsorption, villous atrophy, eosinophilic proctocolitis, enterocolitis and eosinophilic esophagitis. However, in some infants, irritability and colic may be the only symptoms of food allergy [4,5].

Allergy to cow's milk is due to an immunologic response to milk protein with a Danish cohort study suggesting that 54% of milk allergies are IgE-mediated, and the remaining 46% are classified as non-IgE mediated [6]. This however depends on definition of non-IgE-mediated allergy; while approximately 3-5%, a larger percentage of infants (10-15%) manifests gastrointestinal discomfort which sometimes could be classified as allergy.

The risk of developing allergic sensitization, atopic dermatitis and asthma is increased in children with a positive family history for atopy in first-degree relatives; however it has not been demonstrated that there is an increased risk for CMA if there is a positive family history.

Allergic symptoms often develop in a common sequence and pattern in what is termed the "allergic march" with progression of atopic disease from eczema to asthma, and then to allergic rhinoconjunctivitis [7]. It is thought to be the result of regional allergic

response which then leads to systemic allergic inflammation. While genetic and environmental factors predispose to developing the allergic march; data support four possible interventions to prevent progression of the allergic march [8]:

- Exclusive breast feeding during the first few months of life, or, alternatively
- Use of hydrolyzed infant formulae
- Supplements of dietary prebiotics or probiotics
- Treatment with inhalant allergen immunotherapy (subcutaneous or sublingual)

EPIDEMIOLOGY

Comparable international epidemiological evidence on CMA prevalence is lacking, predominantly due to methodological and geographical differences in clinical evaluation [5]. European prospective cohort studies from the last 15 years suggest that the prevalence of CMA is between 1.9% and 4.9%; this is consistent with a 2002 meta analysis of 229 articles on CMA which found that CMA is the most common food allergy in early childhood with an incidence of 2% to 3% in the first year of life [9].

Interestingly, the perception of milk allergy is much higher than confirmed CMA, with patient reports suggesting hypersensitive reactions to cow milk in preschoolers ranging between 1% and 17.5% [3]. As a result, it is desirable to undertake controlled elimination or milk challenge procedures before switching to more expensive formulae.

Most infants with CMA develop symptoms within the first month after introduction of CMP-based formula. The majority has two or more symptoms from two or more organ systems. Prognosis of CMA in infancy is good with a remission rate of approximately 85% to 90% at 3 years. In particular, gastrointestinal symptoms show a good prognosis [8]. While the majority of infants present with two or more symptoms, this may be an artifact of practitioners not identifying allergy in the presence of only a single symptom.

It is interesting to note however, that the vast majority of data come from specialized centers, and the

epidemiology of CMA in primary care is unclear.

SYMPTOMS

The most frequent symptoms are listed in Table 1. Except for anaphylaxis, there is not one symptom that is specific for CMA. CMA rarely develops after the age of 12 months, and most of the time develops within two months after the introduction of cow milk in the diet. CMA is also more likely if more than one organ system is involved. Recently, a symptom-based score was developed, what may contribute to diagnose CMA since an initial score >12 decreasing to <6 under elimination diet was related with a positive predictive value of 80% to have a positive challenge test (Table 2) [10,11]. A challenge test is considered as the golden standard diagnostic test, but does in fact not proof that the immune system is involved. Although a double-blind challenged test is more accurate, most guidelines accept an open challenge to confirm the diagnosis of CMA.

Table 1. Symptoms and Signs Related to Cow's Milk Allergy

Gastro-intestinal symptoms
• Dysphagia, dyspepsia
• Colic, abdominal pain
• Vomiting, regurgitation, nausea
• Anorexia, refusal to feed, early satiety
• Diarrhea±intestinal protein or blood loss
• Constipation±perianal rash
• Failure to thrive
• Occult blood loss; Iron-deficiency anemia
• Food impaction
Respiratory symptoms
• Runny nose
• Chronic coughing
• Wheezing/stridor
• Breathing difficulties
Skin symptoms
• Urticaria
• Atopic eczema
• Angioedema
General symptoms
• Anaphylaxis
• Shock like symptoms with severe metabolic acidosis, vomiting and diarrhea (food protein induced enterocolitis syndrome)

TREATMENT

Where infants are formula fed, either exclusively or as a supplement to breastfeeding, it is common for pediatricians to change the formula when symptoms of intolerance occur [4]. A number of alternatives to cow's milk-based formulae exist and include [3]:

- Amino acid formula (AAF)
- Partially hydrolyzed formula (pHF)
- Extensively hydrolyzed formula (eHF), casein or whey
- Rice partially and/or eHF
- Soy formula
- Soy hydrolyzed formula
- Other mammalian milks (e.g., sheep's milk, goat's milk, camel's milk); some adapted to the nutritional needs of infants, others not

Milk formulae can be hydrolyzed in order to remove allergenic epitopes [12]. pHF have been developed with the aim of minimizing the number of sensitizing epitopes within milk proteins, while at the same time retaining peptides with sufficient size and immunogenicity to stimulate the induction of oral tolerance (and thus, they are not suitable in treatment). eHF have been extensively hydrolyzed in order to destroy allergenic epitopes; in which most of the nitrogen is in the form of free amino acids and peptides $<1,500$ kDa [7]. eHFs are indicated in treatment and in prevention. AAF formulae have been developed to overcome the hypersensitivity that can arise from the residual proteins in eHF. AAF are only indicated in treatment. While eHF and AAF remove allergenicity, in CMA prevention the loss of immunogenicity also prevents the immune system from developing tolerance to milk proteins [12]. As a result, pHF is commonly used for prevention of allergy. In CMA treatment, as pHFs contain larger peptides than eHF, they trigger activation of symptoms in a relatively large percentage of already sensitized infants and are therefore not recommended where there is a risk of severe CMA symptoms [12]. AAF is tolerated by $>95\%$ of those allergic to cow's milk and are therefore hypoallergenic, while pHF is tolerated by approximately 50-66% of milk allergic individuals

Table 2. Symptom-based Clinical Score (Cow's Milk Protein Intolerance Score) (Adapted from Ref. 10,11)

Symptom	Score	
Crying*	0	<1 hour/day
	1	1-1.5 hours/day
	2	1.5-2 hours/day
	3	2 to 3 hours/day
	4	3 to 4 hours/day
	5	4 to 5 hours/day
	6	>5 hours/day
Regurgitation†	0	0-2 episodes/day
	1	>3-<5 of small volume
	2	>5 episodes of >1 coffee spoon
	3	>5 episodes of +half of the feedings in <half of the feedings
	4	Continuous regurgitations of small volumes >30 min after each feeding
	5	Regurgitation of half to complete volume of a feeding in at least half of the feedings
	6	Regurgitation of the "complete feeding" after each feeding
Stools (Bristol scale)‡	4	Type 1 and 2 (hard stools)
	0	Type 3 and 4 (normal stools)
	2	Type 5 (soft stool)
	4	Type 6 (liquid stool, if unrelated to infection)
	6	Type 7 (watery stools)
	0 to 6	Atopic eczema
Skin symptoms		Head-neck- trunk Arms-hands-legs-feet
		Absent 0 0
		Mild 1 1
		Moderate 2 2
		Severe 3 3
	0 or 6	Urticaria (no 0/yes 6)
Respiratory symptoms	0	No respiratory symptoms
	1	Slight symptoms
	2	Mild symptoms
	3	Severe symptoms

*Crying was only considered if the child was crying for 1 week or more, assessed by the parents, without any other obvious cause.

†Vandenplas Y, Hachimi-Idrissi S, Casteels A, Mahler T, Loeb H. A clinical trial with an "anti-regurgitation" formula. *Eur J Pediatr* 1994;153:419-23.

‡Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997;32:920-4.

and are therefore not considered hypoallergenic [13]. However, while pHF is not considered "hypoallergenic" by these criteria, it is acknowledged that they have a reduced allergenicity and therefore have a place, and are frequently used by practitioners, in the prevention of infant allergy. Decisions about when and how formula should be changed can vary between practitioners, and as such a number of guidelines aimed at harmonizing diagnosis and treatment strategy exist. Rice hydrolysates are safe alternatives for eHFs in the treatment of CMPA [14]. Soy infant formula has been shown to be safe [15], and to be effective in 85-90 % of the infants with CMPA [16]. Other mammalian milks are not indicated in the

treatment of CMPA as most of them are nutritionally not adequate as they are no "infant formula". In some countries, goat's milk exists as commercialized infant formula and is adapted to the nutritional needs of infants. However, the cross-reactivity with CMP is about 80% [17]. As a consequence, milk from other mammals cannot be recommended in the treatment of CMPA.

CONCLUSION

It is still difficult to diagnose CMA. Extensively hydrolyzed cow's milk protein based is the preferred treatment option. Amino acid formula should be re-

served for the most difficult cases. Soy and extensive rice hydrolysate formulas are valuable second choice therapeutic options.

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