

REVIEW

Development of allergic disorders in children with cow's milk protein allergy or intolerance in infancy

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Introduction

Adverse reactions to cow's milk, indicated as cow's milk protein allergy or intolerance (CMPA/CMPI), are one of the most common adverse reactions to foods in infancy and early childhood with an incidence ranging from 2% to 5%, when strict diagnostic criteria are used [1,2].

Definitions and diagnostic criteria

In 1995, the European Academy of Allergy and Clinical Immunology proposed a classification of adverse reactions to foods based on mechanism [3]. 'Adverse reaction to food', like cow's milk, is defined as any aberrant reaction following the ingestion of a food or food additive. Adverse reactions can be divided into toxic and nontoxic food reactions. A toxic reaction is an adverse reaction which will occur in every person provided that a sufficient dose has been taken in. Nontoxic reactions can be divided in immune-mediated mechanisms (allergy), and nonimmune-mediated mechanisms (intolerance), and the occurrence depends on the susceptibility of the person. Analogous, adverse reactions to cow's milk protein can be divided in CMPA and CMPI. CMPA can be classified according to the type of immune mechanisms, that is IgE-mediated (type I) reactions, and non-IgE-mediated reactions, as type II (cytotoxic), type III (immune complexes), and type IV (cell-mediated) reactions. The definition of CMPI leads to some confusion. CMPI is defined as reproducible adverse reactions to cow's milk which are not immunologically mediated, e.g. enzyme deficiencies, absorption defects, pharmacological reactions, or infectious reactions. However, the term CMPI is also used in cases in which the immunological aetiology of a reaction to cow's milk protein is not confirmed, either due to a lack of immunological investigations, or negative results of the performed analyses. Therefore, the classification of adverse reactions to cow's milk proteins depends on the extensiveness, and the quality

of the diagnostic tests that are used to investigate the immunological mechanisms.

Since the immunological mechanism of the clinical reaction to cow's milk protein is often not determined and no single laboratory test is diagnostic for CMPA or CMPI, and differentiation between CMPA and CMPI is often not possible on the basis of symptoms, adverse reactions to cow's milk protein are indicated as CMPA/CMPI [1,2].

Several laboratory methods, including skin prick, scratch, and epicutaneous tests, determination of specific IgE antibodies, basophil-histamine release test, leucocyte migration inhibition assay, and lymphocyte transformation test are available as diagnostic tools in immunological mediated CMPA [4,5]. However, none of these tests have proved to be indicative of clinical disease, and none of them reaches sufficient sensitivity, specificity, and positive predictive accuracy. Because there is no reliable single laboratory test available to diagnose CMPA or CMPI, the diagnosis CMPA/CMPI has to be based on a cow's milk protein elimination and challenge test, using strict well defined diagnostic criteria. In most recent studies [1,6–12], the diagnosis CMPA/CMPI is made according to criteria proposed by Savilahti, Bahna and Gandhi, and taken over by the European Society for Paediatric Gastroenterology and Nutrition Working Group for the diagnostic criteria for food Allergy, and the European Academy of Allergy and Clinical Immunology Subcommittee on Adverse reactions to foods [3,13–15]. These criteria include: a definite disappearance of symptoms after elimination of cow's milk from the diet, recurrence of identical symptoms after one cow's milk challenge, disappearance of symptoms after re-elimination of cow's milk, and exclusion of lactose intolerance and coincidental infections. A strict well defined cow's milk elimination and challenge procedure is needed to diagnose CMPA/CMPI [1]. In young infants of age 0–1 years, open controlled cow's milk challenges are recommended, and have been shown to be reliable when performed under professional observation in a clinical setting [9,16,17]. In children older than 1–2 years, and in adults, double-blind placebo-controlled food challenges (DBPCFC) are recommended [7,18,19].

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Clinical manifestations

Symptoms of CMPA/CMPI can appear during early infancy. In most of the infants with CMPA/CMPI the symptoms appear in the first 3 to 4 months of age. Adverse reactions to cow's milk protein include a broad diversity of symptoms. More than 70% of the children with CMPA/CMPI present with two or more symptoms, and with symptoms from two or more organ systems. About 50–70% of the infants have symptoms from the skin (including atopic dermatitis, urticaria, exanthema, angio-oedema, conjunctivitis), 50–60% presents with symptoms from the gastrointestinal tract (including vomiting, diarrhoea, colics, gastroesophageal reflux), and 20–30% have symptoms from the respiratory tract (including rhinitis, wheezing, dyspnoea, cough) [1,6–8,20]. General symptoms like inconsolable crying, refusing food, failure to thrive, and irritability occur frequently, but mostly in combination with other symptoms [1,20]. Severe adverse reactions to cow's milk as anaphylaxis have been found in 5% and 9% of the children with CMPA/CMPI [1].

None of the above mentioned symptoms is specific for CMPA/CMPI, however, the presence of a combination of symptoms from two or more organ systems increases the suspicion of CMPA/CMPI. Furthermore, the combination of one of the mentioned symptoms and a positive family history for atopic disorders also increases the suspicion of CMPA/CMPI.

Treatment

The treatment of CMPA/CMPI is based on the principle of elimination of cow's milk protein from the infants diet, or in breast-fed infants from the mothers diet.

At present many commercialized infant feeding formulas are available, which differ in origin of the proteins, and in degree of hydrolysis. Second generation products are formulas with a highly reduced allergenicity, in which the protein is hydrolysed, but the carbohydrates and fats are intact, and are recommended in children with CMPA/CMPI without severe enteropathy. Whey and casein hydrolysate based infant formulas are on the market and are the treatment of choice in infants with CMPA/CMPI [22–24]. In CMPA/CMPI, second generation protein hydrolysate based formula can be the only diet up to 6 months of age [14]. From 6 months of age solid foods can be introduced. A dietician is needed to guide the parents in introducing solid foods in order to guarantee a cow's milk protein free diet, and to guarantee a nutritional balanced diet. Highly allergenic foods such as egg, soy, peanut, fish, citrus fruits, tomatoes, chocolate, and wheat are recommended to be avoided until the age of 12 months is reached [14]. Controlled re-introduction of cow's milk protein in the diet can

be performed from 12 months of age at intervals of three to six months [1].

Development of additional allergic disorders later in childhood

Following dietary treatment, the prognosis of CMPA/CMPI with respect to the recovery rate is good. The recovery rate is about 45–55% at 1 year, 60–75% at 2 years, 85–90% at 3 years, and 92% at 5 and 10 years of age [1]. It has been shown that infants with IgE-mediated reactions against cow's milk protein have a lower rate of recovery than infants with non-IgE mediated reactions [7,11,25].

Only a few long-term prospective follow-up studies (Table 1) have focused on the prognosis of CMPA/CMPI with respect to the development of additional allergic disorders later in childhood. It has been demonstrated that the development of asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, and food intolerance later in childhood is substantial [6,7,10,12,25–27]. In 1958, Clein reported on the outcome of allergy in children with CMPA/CMPI in infancy [26]. He found that 80% of the children with CMPA/CMPI developed other major allergic ailments before they reached the age of puberty.

Development of asthma and allergy against inhalant allergens

Høst *et al.* found in a prospective study that 28% of the children with challenge proven CMPA/CMPI had developed allergic symptoms to inhalants before the age of 3 years [7]. The most important inhalant allergenes were dog, cat, and house dust mite, allergens to which the children had been exposed to from early infancy. The majority (91%) of the children who developed symptoms of inhalant allergy had an IgE-mediated CMPA in infancy. Hill *et al.* found at a median age of 3.7 years, that 69% of the children with IgE-mediated CMPA in infancy had developed asthma [12]. Bishop *et al.* found in a prospective study at a mean age of eight years, that 40% of the children with challenge proven CMPA/CMPI had developed asthma, and 43% had developed allergic rhinitis [11]. A higher incidence of asthma was found in children with challenge proven persistent CMPA/CMPI. In addition, they found a significantly higher prevalence of asthma, and allergic rhinitis in children with an immediate type hypersensitivity to cow's milk, than in children with an intermediate or delayed type hypersensitivity to cow's milk during or after the challenge. In 1997 Høst *et al.* observed a significantly higher prevalence of asthma in children with IgE-mediated CMPA than in children with a non-IgE-mediated CMPA/CMPI [25]. Among the children with IgE-mediated CMPA, 62% developed asthma, whereas among children with a

Table 1. Prognosis in children with CMPA/CMPI in infancy with respect to the development of allergic disorders later in childhood

Study	Number of subjects subjects included in study	Age at diagnosis mean (range) in months	Follow-up period in years	Allergic disorders				Dietary intervention
				Asthma	AD	Rhinitis/ conjunctivitis	FI	
Clein [26]	206	not specified	0–puberty	80%*				soy, meat based formula, goat milk
Jakobsson & Lindberg [6]	20	6.5 (2–15)	0–2				60%	soy, Nutramigen®
Hill <i>et al.</i> [10]	28	9.6 (4–24)	0–3				41%	CM free diet: not specified
Bishop <i>et al.</i> [11]	97	16.0 (1–98)	0–>5	40%	21%	43%	75%	soy, casein HF: not specified
Hill <i>et al.</i> [12]	42	15.0 (5–24)	0–2	69%	57%		67% (egg) 55% (peanut)	CM free diet: not specified
Høst & Halcken[7]	39	5.0 (2–12)†	0–3	28%‡			54%	Nutramigen®**
Høst <i>et al.</i> [25]	39	5.0 (2–12)†	0–10	62%§		52%§	33%§	Nutramigen®**
				17%¶		6%¶	0%¶	
Sprickelman <i>et al.</i> [27]	93	2.3 (0.5–4.0)	0–7	31%	37%	19%	31%	Pepti Junior®**, Nutrilon Pepti®**

AD = atopic dermatitis; FI = food intolerance; *80% of the children developed allergic disorders, the disorders were not further specified; †median age; ‡inhalant allergy; §prevalences in children with IgE-mediated CMPA; ¶Prevalences in children with non-IgE-mediated; CM cow's milk; HF hydrolysate based formula. **CMPA/CMPI; also avoidance of introduction of solid foods until 6 months of age, and avoidance of highly allergenic foods until 12 months of age.

non-IgE-mediated CMPA/CMPI 17% developed asthma at the age of 10 years. Furthermore, 52% of the children with IgE-mediated CMPA had developed allergic rhinoconjunctivitis, whereas only 6% of the children with non-IgE-mediated CMPA/CMPI developed this disorder at the age of 10 years. We found in a controlled prospective long-term follow-up study that 31% of the children, with a cow's milk elimination and challenge procedure proven CMPA/CMPI during the first three months of life, had developed asthma and 19% allergic rhinitis/conjunctivitis at a mean age of 7 years [27]. Bronchial hyperresponsiveness was observed in 40% of the children with CMPA/CMPI at a mean age of 7 years. Furthermore, 27% of the children with CMPA/CMPI in infancy had a positive RAST test for inhalant allergens (house dust mite, dog, cat, grass, and tree pollen) at a mean age of 7 years.

Development of atopic dermatitis

Only three prospective follow-up studies focused on the development of atopic dermatitis in children with CMPA/CMPI in infancy. Hill *et al.* found that 57% of the children with IgE-mediated CMPA in infancy had developed atopic dermatitis at a median age of 3.7 years at final follow-up [12]. No significant differences were found in the prevalence of atopic dermatitis between children with remitted CMPA and persistent CMPA at follow-up.

Bishop *et al.* reported that 21% of the children with CMPA/CMPI had developed atopic dermatitis at a mean age of 8 years [11]. A significantly higher incidence of atopic dermatitis was observed in children with challenge proven persistent CMPA/CMPI at final follow-up. Moreover, they found a significantly higher prevalence of atopic dermatitis in children with an immediate type hypersensitivity to cow's milk, than in children with an intermediate or delayed-type hypersensitivity to cow's milk during or after the challenge. Recently, we found that 37% of the children with CMPA/CMPI in infancy had developed atopic dermatitis at a mean age of 7 years [27].

Development of food intolerance

Reproducible adverse reactions to other foods than cow's milk protein have been frequently reported in children with CMPA/CMPI in infancy [6,10,25]. Jakobsson and Lindberg found that 60% of the parents of infants with CMPA/CMPI reported adverse reactions to other foods, especially soy protein, before two years of age [6]. Hill *et al.* found that 41% of the children with challenge proven CMPA/CMPI reported adverse reactions to soy, egg, or lamb during the 3 year follow-up period [10]. Bishop *et al.* found at a mean age of 8 years, that 75% of the children with CMPA/CMPI had developed food intolerance to noncow's milk foods

[11]. In the latter study, the parents reported adverse reactions to many foods, including egg (58%), soy milk (47%), and peanut (34%). In another study, Hill *et al.* found in children with IgE-mediated CMPA that 67% had developed egg allergy, and 67% peanut allergy at a median age of 3.7 years [12]. Adverse reactions to especially egg, citrus, and tomato developed in a total of 54% of children with CMPA/CMPI before the age of three years in the study of Høst and Halken [7]. The highest point prevalence, 43% at 18 months of age, and the highest cumulated prevalence, 62% at two years of age, were found in children with IgE-mediated CMPA. In children with non-IgE-mediated CMPA/CMPI the prevalences were 33% and 44%, respectively. Høst *et al.* found in the same study population at 10 years of age, that among the children with IgE-mediated CMPA 33% developed adverse reactions to other foods, whereas among the children with non-IgE-mediated CMPA/CMPI 0% developed food intolerance [25]. In our study, 31% of the parents of children with CMPA/CMPI in infancy reported adverse reactions to other foods than cow's milk at a mean age of 7 years [27]. The study of Høst and Halken is the only study in which the adverse reactions to noncow's milk foods were based on elimination and challenge of the food in question [7].

The above mentioned studies show that the development of additional allergic disorders in children with CMPA/CMPI is substantial. Differences in prognosis of children with CMPA/CMPI in infancy with respect to the development of subsequent allergic disorders later in life between these summarized studies, reflect differences in definitions, and differences in study design and population, such as the age of the subjects at inclusion, and presence of confounding environmental factors which might have influenced the allergic expression. Therefore, interpreting and comparing the results of these studies lead to some difficulties. In these studies and between these studies there is a considerable variability in the age at diagnosis of CMPA/CMPI, and consequently the age at which a cow's milk protein elimination diet was started. Furthermore, there is no uniformity in type of food intervention between these studies, but also in some studies. Moreover, these studies show a lack of uniform diagnostic outcome definitions.

Due to a lack of prospective follow-up studies in which dietary intervention is started early in life, it is still not clear whether secondary prevention strategies, i.e. early dietary intervention, will influence the prognosis of CMPA/CMPI with respect to the development of additional allergic disorders later in childhood.

It has been hypothesized that early dietary intervention and environmental measures may influence the development of subsequent allergic symptoms. Primary preventive effects of dietary intervention during lactation and in the neonatal period on the development of allergic symptoms

have been demonstrated in high risk infants, i.e. infants with at least one parent or sibling with an atopic disorder [28,29]. It has been hypothesized that secondary prevention, including early dietary intervention with a protein hydrolysate based formula, could modulate the 'atopic march' in infants with CMPA/CMPI. However, it is still a matter of debate whether there is a preventive effect of dietary intervention on the development of additional allergic disorders in children with CMPA/CMPI in infancy, due to the absence of placebo-controlled studies, because of ethical considerations. In our study we have tried to fill in these gaps in the field of CMPA/CMPI [27].

We presented the first controlled prospective follow-up study on the development of additional allergic disorders in children with CMPA/CMPI in infancy in which all infants were treated with an extensive whey protein hydrolysate based formula before the fourth month of age. Our study was not placebo-controlled, however, this problem will probably not be resolved in future studies, because of ethical considerations mentioned above. Our control group consisted of children in whom the diagnosis CMPA/CMPI was suspected, but could be rejected on the basis of the same elimination and provocation procedure during the first three months of life (non-CMPA/CMPI group). Therefore, making it possible to compare the development of allergic disorders in children with CMPA/CMPI. The non-CMPA/CMPI group was comparable with the CMPA/CMPI group in terms of age at diagnosis, presenting symptoms, family history of atopy, and exposure to environmental factors. They only differed significantly in improvement of symptoms during the elimination period, and in deterioration of symptoms up to one week after the cow's milk challenge test. Therefore making it possible to investigate, for the first time, whether CMPA/CMPI is a risk factor for the development of allergic disorders in childhood. We found no significant differences in the development of allergic disorders in children with and without CMPA/CMPI. This may suggest that early dietary intervention might have influenced the allergic outcome in this selected study population. However, hard evidence of a secondary preventive effect of early dietary intervention will only be obtained from a placebo-controlled study.

Furthermore, we found that early diagnosed and treated CMPA/CMPI is not a risk factor for the development of asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, and food intolerance later in childhood. Other factors, like atopy among first degree relatives, substantially determine the allergic outcome in children with CMPA/CMPI in infancy. We hypothesize that a genetic background is more important for an 'allergic march' than the development of CMPA/CMPI early in life, since both our groups had the same allergic heredity load. The results of our study suggest that early diagnosed and treated CMPA/CMPI in

infancy can be considered as the first expression of an allergic constitution, and not as a risk factor for the development of additional allergic disorders later in childhood.

Conclusion

The prognosis of CMPA/CMPI with respect to the recovery rate is good, though, the development of additional allergic disorders as asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, and food intolerance later in childhood is considerable. However, early diagnosed and treated CMPA/CMPI is not a risk factor for the development of these subsequent allergic disorders. Other factors, like a positive family history for atopy, determine the allergic outcome in children with CMPA/CMPI in infancy. CMPA/CMPI in infancy can be considered as the first expression of an allergic constitution, and not as a risk factor for the development of additional allergic disorders. Due to the absence of placebo-controlled studies, it is still not clear whether there is a secondary preventive effect of early dietary intervention on the development of additional allergic disorders in infants with CMPA/CMPI.

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