

Original article

Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets

Background: Food allergy is not always correctly diagnosed in children with atopic eczema dermatitis syndrome (AEDS) and treatment with an avoidance diet is not without danger.

Methods: After admission to our clinic, 11 children with a prolonged cow's milk (CM) elimination diet because of AEDS and sensitization underwent double-blind placebo-controlled food challenge (DBPCFC). Retrospectively, the exposure to CM, sensitization and reactions to accidental ingestion were carefully documented. The DBPCFC was used to evaluate the children's current status.

Results: Before the elimination period (median 2.3 years; started before the admission) all 11 children with AEDS were sensitized and had ingested CM (four bottle-fed; seven breast-fed without CM diet of the mother) without the development of acute reactions. The diagnosis of CM allergy was not confirmed by DBPCFC previously. After elimination the AEDS had not improved, but nevertheless the diet was continued. During the elimination period, eight of 11 children developed severe acute allergic reactions to CM after accidental ingestion. In evaluation, in our clinic all 11 children experienced acute allergic reactions to CM during DBPCFC.

Conclusion: There is a considerable chance of developing acute allergic reactions to CM after elimination in children with AEDS without previous problems after CM intake.

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Food allergy has been recognized as a part of the atopy syndrome, besides atopic eczema dermatitis syndrome (AEDS), asthma and rhinoconjunctivitis (1). The prevalence of food allergy in infants with AEDS has been estimated at 30% (1, 2). Food allergy is characterized by acute reactions, such as the oral allergy syndrome, urticaria, angioedema, vomiting, diarrhoea, dyspnoea and even shock (3–5). Delayed reactions such as flare up of eczema may occur, but are less frequently reported (6, 7). Generally children with AEDS are screened for atopy, including determination of sensitization to food and inhalant allergens by skin prick tests and determination of specific immunoglobulin E (IgE; 8). Although negative results have an excellent negative predictive value for clinical reactivity, it is well known that positive tests do not necessarily indicate clinical relevance (9). In case of sensitization to cow's milk (CM), a CM-free diet should be implied for some weeks followed by reintroduction, preferably using a double-blind placebo-controlled CM challenge to confirm the diagnosis (10). Despite this, because of several factors, frequently the diagnosis of food allergy is made primarily on the basis of test results of sensitization even without a suggestive history or an elimination/provocation test. In this study

we show that this might imply important risks. Not only there is a risk of an insufficient diet, which contributes to deficiencies and growth retardation (11), the development of eating disorders (11) and impaired psycho-social development (12), but even more importantly: severe allergic reactions may be the result.

In this study we describe 11 children with AEDS that developed severe acute allergic reactions to CM after a relatively long elimination period, but previously tolerated this food without any acute symptoms.

Methods

Selection of patients

In the outpatient department of the Wilhelmina's Children Hospital of the University Medical Center Utrecht, 277 children were routinely screened sensitization to CM. Of these children 63 of 277 were evaluated for CM allergy by double-blind placebo-controlled food challenge (DBPCFC). Data before DBPCFC were studied retrospectively. We included sensitized children with AEDS as reason for prolonged CM elimination. Forty-nine (49 of 63) children were known to have AEDS. In all but two (47 of 63) children, AEDS was the reason given for CM elimination in the past (by a general practitioner). In 15 of 47 children the sensitization to CM was not

known retrospectively. After arrival at our clinic they appeared not sensitized to CM and the CM was introduced in all 15 patients without problems at home. Thirty-two (32 of 47) children were sensitized to CM. During DBPCFC with CM, 11 of 32 (34%) children responded with an acute reaction to CM. These children were further evaluated.

Study design

Retrospective data. In the history of all 11 children with AEDS who developed acute allergic reactions after CM elimination the sensitization and the type of feeding before and during elimination of CM and the total length of the elimination period was registered retrospectively. Moreover, parents were asked for the symptoms after CM ingestion before the start of the elimination period and during it. We used both patient files and telephone calls with parents to complete and confirm these data (Table 1).

Prospective data. After referral to our outpatient clinic a complete diagnostic procedure was performed: sensitization to CM was confirmed in all 11 children before evaluating CM allergy by DBPCFC.

Patients

Prospective data. The 11 patients were composed of eight boys and three girls with a median age of 4.0 years (range: 1.8–10.3; Table 1). Initially, they were referred to our department for evaluation of the role of CM allergy and for treatment of the AEDS. The diagnosis of AEDS was confirmed in all patients using the criteria of Hanifin (13). Ten children needed intermittent use of topical steroids to control their AEDS; one child no longer needed topical steroids. In addition, six children demonstrated symptoms of bronchial hyperreactivity. Three of these used inhalant steroids regularly in combination with inhalant β -mimetics; the other three children only used intermittent inhalant β -mimetics. Seasonal rhinoconjunctivitis was not present in this group. All children were sensitized to CM, hen's egg and peanut, as confirmed by skin prick tests, specific IgE, or both. Besides these three major food allergens, nine of 11 were also sensitized to soy, eight of 11 children to hazelnut and one of 11 to sesame. Sensitization to

hazelnut was associated with reactivity to birch pollen in four children. Ten of 11 children had positive skin prick tests and/or specific IgE to inhalant allergens, cat and dog dander accounting for the majority (eight of 11 and nine of 11, respectively). Besides CM, dietary restriction based on sensitization included hen's egg, peanut and tree nuts in all patients. In addition, three patients had a soy-free diet, whereas one child eliminated sesame seed after an obvious acute allergic reaction.

Double-blind placebo-controlled CM challenge

Clinical reactivity to CM was investigated by DBPCFC (14). Patients received the active or placebo on 1 day either in the morning or the afternoon. The base of both formulas was 250 ml of extensively hydrolysed casein formula (10 of 11) or soymilk (one of 11), depending on what the patient used as a CM substitute, with 4.5 g of CM protein (Protifar, Nutricia, Zoetermeer, the Netherlands) as the active ingredient. Gradually increasing amounts of 10, 20, 30, 40, 60 and 90 ml (this corresponds with a cumulative dose of 10, 30, 60, 100, 160 and 250 ml; 0.18, 0.54, 1.08, 1.8, 2.88 and 4.5 g of CM protein respectively) were given with time intervals of 20–30 min.

Results

Retrospective data

Before initiation of the elimination diet: one of 11 child received regular infant formula; three of 11 children were both bottle-fed with regular infant formulas and breast-fed without CM elimination diet by the mother; seven of 11 children were breast-fed without CM elimination diet by the mother (Table 1).

None of the children had a history of acute reactions upon ingestion of CM prior to the elimination diet. The AEDS combined with sensitization for CM were the main reasons to start an elimination diet. Two patients in addition suffered from recurrent vomiting.

Table 1. General characteristics, details of cow's milk elimination, sensitization and challenge outcome per patient

Patient characteristics			Elimination				Sensitization		Challenge	
Patient number	Age (years)	Sex	Before elimination (type of ingestion)	Type consumed	Length (years)	Accidental ingestion	IgE (kU _A /l)	SPT (mm)	Sympt	ED (ml)
1	2.6	M	Bottle	EHW	2.3	ang, urt, loc	31	16	urt	30
2	5.5	F	Bottle/breast	EHC	5	ang, loc	99	14	rc, dys	30
3	2.6	M	Bottle/breast	EHC	2.3	urt	<0.35	10	urt	20
4	2.5	M	Bottle/breast	EHC	2	urt, vom	29	10	rc, vom	10
5	4.3	M	Breast	EHC	4	urt, vom	18	14	urt, cou	10
6	10.3	M	Breast	Soy	9.5	rc, vom, dia, dys	7.1	–	rc	90
7	1.8	M	Breast	EHC	1.4	–	32	14	urt, hoa	20
8	9.0	M	Breast	EHC	8.5	dys	6.7	10	urt, rc	90
9	2.2	M	Breast	EHC	1.4	–	26	12	urt, rc	10
10	2.0	F	Breast	EHC	1.8	urt, rc, vom, dia	3	8	rc	20
11	2.2	F	Breast	EHC	1.9	–	27	–	cou, hoa	20

M, male; F, female; bottle, infant formula; breast, breast feeding; EHW, extensively hydrolysed whey formula; EHC, extensively hydrolysed casein formula; soy, soy-based formula; Sympt, symptoms; cu, contact-urticaria; ang, angioedema; urt, urticaria; rc, rhinoconjunctivitis; vom, vomiting; dia, diarrhoea; cou, cough; hoa, hoarseness; dys, dyspnoea; loc, loss of consciousness; ED, eliciting dose.

The AEDS did not resolve after eliminating CM from the diet. In addition, two children suffered from recurrent vomiting, which did not resolve either. Nonetheless, the elimination diets with CM were continued without further evaluation of their clinical relevance.

Before referral to our outpatient clinic, eight children developed an acute reaction after accidental ingestion with CM during the elimination period (varying from 1.4 to 9.5 years; median 2.3 years). The last accidental exposure to CM occurred more than a year before the challenge was performed. After a CM elimination period patients were referred to our outpatient clinic.

Symptoms during double-blind placebo-controlled CM challenge

Double-blind placebo-controlled CM challenge was met with an immediate reaction to CM in all 11 children (Table 1). Five children developed symptoms within 5 min after ingestion, four within 30 min and two after 60–90 min. In seven children, more than one organ system was involved. After discontinuing the challenge, seven children received antihistamines. One child with stridor needed additional inhalation of steroids. Six children received placebo without reaction. Five patients did not receive placebo because the challenge was discontinued because of an immediate reaction. In the same day all patients were discharged in good health. At home, none of the patients developed symptoms in the first 24 h following the CM challenge. The AEDS did not deteriorate in any of the patients.

Eliciting doses

Three patients reacted after the first dose of CM of 10 ml corresponding to 0.18 g of CM protein (Table 1). So the lowest eliciting dose could not exactly be established, but it was clearly below or at 10 ml. Four children developed the first symptoms after the ingestion of 20 ml and two children after 30 ml. After the last dose of 90 ml, two children developed a reaction. No significant correlation between the eliciting dose and the type of reaction during challenge was observed.

Discussion

We describe 11 children who were on a CM-free diet for a prolonged period because of AEDS and sensitization to CM. All children (one bottle-fed, three bottle- and breast-fed and seven breast-fed without a CM restriction diet of the mother) had ingested CM proteins before the elimination period without the occurrence of any acute reaction. Moreover, during the elimination period the AEDS had not improved. Remarkably, after accidental ingestion of CM, eight of 11 children developed acute symptoms (varying from urticaria to shock). After admission to our clinic all children still had AEDS and

were sensitized to CM. They all experienced acute allergic reactions during DBPCFC with CM. Eliciting doses ranged from <10 up to 90 ml of formula (corresponding to a cumulative dose of 250 ml, which contains 4.5 g of CM protein).

In children with AEDS who previously tolerated a certain food, the development of acute allergic reactions after elimination of that food has been reported only rarely (1, 15–18). The same phenomenon has also been described in children with asymptomatic food sensitization (19, 20). Together these data indicate that avoidance of allergen exposure in patients with chronic symptoms of AEDS or even without any symptoms might result in the occurrence of acute allergic reactions. Apparently the state of tolerance, which is maintained by continuous exposure to the food, was broken down by allergen avoidance. This might be a more common problem. In no less than 34% of the patients (11 of 32; evaluated for CMA by DBPCFC in 1 year) in our clinic moderate to severe acute allergic reactions developed. This study is limited by its retrospective design. There might be a bias in the patient selection because only sensitized patients with CM elimination for AEDS as reason were included. A part of the patients were only breast-fed, making exact calculation of CM intake impossible. Still, 34%, but at least 12.5% (only bottle-fed; four of 32 evaluated for CMA by DBPCFC in 1 year in our clinic) is much higher as mentioned in other studies, mainly case reports (15, 16, 19, 20). The study of David (15), which is the only study describing the original population, reported an acute reaction to CM after elimination in one of 80 (1.3%) patients. Whether this phenomenon is specific for food allergens is uncertain. In inhalant allergy Platts-Mills et al. (21) have observed that continuous exposure to high doses of cat allergen reduces the symptoms of cat allergy. In addition, acute allergic reactions were observed after re-exposure after a period of absence of exposure to cat (T. Platts-Mills, personal communication).

The elimination period in the patients we studied was rather long. It is a question whether this is an important prerequisite, because acute allergic reactions have also been described after the normally advised elimination period of 2 weeks (1, 2, 22).

Another aspect is the amount of allergen that is required to maintain tolerance. Four (four of 11) children were bottle-fed and it can be assumed that they ingested large amounts of CM. Seven (seven of 11) children received breast feeding before elimination. It has been illustrated that breast-milk contains sufficient amounts of CM to induce even severe (like shock) allergic reactions (23, 24). Although small amounts of CM proteins were ingested, because the mother of the breast-fed children (seven of 11) had no restriction in CM intake, it cannot fully be excluded that the exposure in these breast-fed children was below their threshold, resulting in the absence of acute reactions before the elimination period. Elimination of all CM proteins did not improve the AEDS. Despite of this,

elimination diets were prolonged and after elimination all bottle- (four of 11) and breast-fed (seven of 11) children developed acute reactions to CM. A prospective study, including patients tolerating a specific food (i.e. milk) but sensitized, to our opinion, is unethical if the main end point is to assess if acute clinical symptoms develop.

Several studies describe the efficacy of oral desensitization (25–28) as a successful treatment of food allergy in children and adults, with a decrease in allergen-specific IgE and an increase in allergen-specific IgG₄ (25). On the contrary, in most of these oral desensitization studies in part of the patients the treatment needed to be interrupted and discontinued due to the occurrence of uncontrolled side-effects, indicating a different mechanism than present in classical immunotherapy with inhalant allergens. Recently, it has also been described that in some patients symptoms reappeared after a short period of allergen avoidance (29). This suggests that oral desensitization does not alter the course of food allergy and does not induce immunological tolerance towards food, but increases the

threshold dose to elicit allergic symptoms, in case of continuous exposure. Together these data illustrate that continuous exposure might even be beneficial in patients with clinically manifested CM allergy that tolerate relatively small amounts of CM. Apparently, avoiding a food allergen, in this case CM, in patients with AEDS and sensitization may lead to the development of acute allergic reactions, whereas a tolerant state can be maintained by continuous exposure to this allergen. In conclusion, there is a considerable chance of developing acute allergic reactions to CM after elimination of CM in children with AEDS without previous problems after CM intake.

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