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REGULAR ARTICLE

Extensive protein hydrolysate formula effectively reduces regurgitation in infants with positive and negative challenge tests for cow's milk allergy

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ABSTRACT

Aim: Cow's milk protein allergy (CMPA) is treated using an elimination diet with an extensive protein hydrolysate. We explored whether a thickened or nonthickened version was best for infants with suspected CMPA, which commonly causes regurgitation/vomiting.

Methods: Diagnosis of CMPA was based on a positive challenge test. We compared the efficacy of two casein extensive hydrolysates (eCH), a nonthickened version (NT-eCH) and a thickened version (T-eCH), using a symptom-based score covering regurgitation, crying, stool consistency, eczema, urticarial and respiratory symptoms.

Results: A challenge was performed in 52/72 infants with suspected CMPA and was positive in 65.4%. All confirmed CMPA cases tolerated eCH. The symptom-based score decreased significantly in all infants within a month, and the highest reduction was in those with confirmed CMPA. Regurgitation was reduced in all infants (6.4 ± 3.2–2.8 ± 2.9, $p < 0.001$), but fell more with the T-eCH (-4.2 ± 3.2 regurgitations/day vs. -3.0 ± 4.5, ns), especially in infants with a negative challenge (-3.9 ± 4.0 vs. -1.9 ± 3.4, ns).

Conclusion: eCH fulfilled the criteria for a hypoallergenic formula, and the NT-eCH and T-eCH formulas both reduced CMPA symptoms. The symptom-based score is useful for evaluating how effective dietary treatments are for CMPA.

INTRODUCTION

Cow's milk protein allergy (CMPA) is a major food allergen in infants (1–3) and is defined as an adverse health effect arising from a specific immune response that occurs after exposure to a cow's milk allergen (4). This immune reaction may be IgE or non-IgE-mediated or both. Symptoms of CMPA are not specific and most frequently involve the skin (atopic dermatitis), the gastrointestinal tract (regurgitation, vomiting, diarrhoea, constipation) and the airways (wheezing, sneezing) or are more general (colic) (1). The diagnosis of CMPA remains a topic of debate and controversy (5). To date, the diagnosis of CMPA requires a food challenge, which is often refused by parents (6).

Correct diagnosis enables parents to give an appropriate diet to their affected infants in order to sustain normal growth and development. Guidelines define a therapeutic hypoallergenic formula as one that is tolerated by at least 90% of CMPA infants with a 95% confidence interval (1,7,8). These criteria are met by several extensively hydrolysed protein formulas, based on whey or casein. The aim of this study was to evaluate the hypoallergenic properties of an extensively hydrolysed casein formula (eCH) and to compare the efficacy of a thickened (T-eCH) versus a nonthickened (NT-eCH) version of the eCH in infants presenting with troublesome regurgitation.

Abbreviations

CMPA, Cow milk protein allergy; eCH, Extensively hydrolysed casein formula; eHF, Extensively hydrolysed protein formula; GI, Gastrointestinal; NT-eCH, Nonthickened extensive casein hydrolysate; SBS, Symptom-based score; T-eCH, Thickened extensive casein hydrolysate.

METHODS

This prospective, randomised, double-blind trial comprised 72 infants being cared for by 18 paediatricians from the Allar Study Group in hospitals in Belgium, Greece, Kuwait, Lebanon and Slovenia. Formula-fed infants were eligible for inclusion if they were <6 months of age with symptoms

Key notes

- Diagnosing cow's milk protein allergy (CMPA) symptoms is a challenge, especially in infants with troublesome regurgitation.
- The extensive casein hydrolysates we tested fulfilled the criteria for a hypoallergenic formula, and both the thickened and nonthickened versions reduced CMPA symptoms.
- Both were equally effective in reducing regurgitation in infants with a positive challenge test, and the thickened formula was more effective in reducing regurgitation in infants with a negative challenge test.

suggesting CMPA, including frequent, troublesome regurgitation and/or vomiting of more than five episodes a day. Infants already fed with an extensively hydrolysed protein formula, or who had experienced previous anaphylactic reactions, were not eligible for inclusion.

CMPA was suspected based on the presence of a combination of the following symptoms (1,9):

- General discomfort: persistent distress or colic (crying/irritable ≥3 h per day, at least 3 days/week over a period of >1 week)
- Gastrointestinal symptoms: regurgitation score (10), vomiting, diarrhoea, constipation (with/without perianal rash), blood in stools
- Respiratory symptoms (runny nose, otitis media, chronic cough, wheezing (unrelated to infection)
- Dermatological symptoms (atopic dermatitis, angio-oedema, urticaria unrelated to acute infections, drug intake and others).

Each symptom was assessed on a scale of zero to six, with the exception of respiratory symptoms, which were rated from zero to three (Table 1). The sum of all items resulted in a symptom-based score, which could range from zero to 33 (6). Paediatricians evaluated the symptom-based score at inclusion and after 1 month. Global, specific IgE and skin prick tests were not part of the protocol, as they are not required to diagnose CMPA, according to the most recent guidelines (1,9).

The aims of this study were to assess whether the eCH was well tolerated by at least 90% of the infants with CMPA and to compare the efficacy of a T-eCH and NT-eCH, overall and for each symptom; the composition of each formula is given in Table 2. The T-eCH formula was based on the same hydrolysed proteins as the NT-eCH, thickened with a specific complex containing fibres, mainly originating from pectin, to reduce regurgitation and to help regulate intestinal transit. The fibre content was 3.6 g/100 g, and the viscosity was pH dependent with a viscosity of approximately 500 cP at pH 4.0–4.5 and 150 cP at pH 6.0, measured with a Brookfield viscosimeter at 12 rotations per minute.

We performed computer randomisation for each of the 18 participating physicians to allocate the 72 patients enrolled in the study to one of four product codes, with two codes assigned to each of the two study formulas to help the randomisation process and avoid clinical bias (Figure 1). This random allocation was made in blocks of four to obtain groups of a similar size. Participating physicians had to open an unmarked envelope to find out which group the patient was allocated to. Both formulas were packed in identical tins with indeterminate labels, showing the product code and information on how to prepare it. At the end of the study, the results from the two identical thickened formula groups and the two identical non-thickened formula groups were combined.

To demonstrate that a given formula was tolerated by more than 90% of infants with proven CMPA, with a 95% confidence interval (CI), at least 28 infants had to be included (7,8). Additionally, to detect a difference of 1.5 in the regurgitation score, with a standard deviation of two, 80% power and a type I error of 0.05, 29 patients per group were needed. To allow for a 15% possible premature dropout or withdrawal rate, 35 patients were required for each of the two main thickened or nonthickened groups.

Patients were fed *ad libitum* for 1 month with the thickened or nonthickened study formula. After 1 month, a milk challenge was performed under medical supervision with a standard infant milk formula. The challenge was performed according to recommendations (1,9) and started with a small quantity of standard infant formula that was increased every 30 min if no reaction occurred. At the end

Table 1 Symptom-based score

Symptom	Score		
Crying (*)	0	≤1 h/day	
	1	1–1.5 h/day	
	2	1.5–2 h/day	
	3	2–3 h/day	
	4	3–4 h/day	
	5	4–5 h/day	
	6	≥5 h/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)	
Skin symptoms	0–6	Atopic eczema	
		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 lasted for 1 week or more, as assessed by the parents, and without any other obvious cause.
†From ref. (10).
‡From ref. (18).

Table 2 Formula composition (/100 gr powder)*

For 100 g of powder	Unit	T-eCH	NT-eCH
Proteins (caseins) (N × 6.25)	g	12.1	12.0
Lipid	g	26.2	27.1
Linoleic acid	g	4.5	3.3
α linolenic acid	mg	450	465
Carbohydrates	g	52.7	55.0
Maltodextrin/Glucose syrup	g	51.7	55.0
Starch	g	1.0	–
Fibres	g	3.6	–
Minerals			
Sodium	mg	230	240
Potassium	mg	610	500
Chloride	mg	340	320
Calcium	mg	620	515
Phosphorus	mg	340	330
Magnesium	mg	50	46
Iron	mg	6	6
Zinc	mg	4.0	4.6
Iodine	μg	70	77
Copper	μg	350	385
Selenium	μg	10	13
Manganese	μg	50	160
Vitamins			
A	μg ER	450	540
B1	μg	400	450
B2	μg	800	700
B6	μg	300	300
B12	μg	1.5	1.2
C	mg	60	70
D3	μg	7.5	9.3
E	mg a-ET	10	6.7
K1	μg	30	39
Niacin	mg	4.5	7.4
Pantothenic acid	mg	2.4	2.5
Folic acid	μg	60	80
Biotin	μg	15	11
Choline	mg	60	105
Inositol	mg	25	30
Taurine	mg	44	46
L-Carnitine	mg	8	15
Osmolarity	mOsm/L	156	145

*The compositions that are provided are the ones used during the clinical trial. The composition of the commercialised formula may be slightly different (e.g. because of national legislation). Allernova (-AR)® is normally prepared at a concentration of 13.5%.

of the challenge, if the child remained asymptomatic after drinking its normal volume of milk-based formula, the parents were instructed to continue feeding with the standard infant formula. A daily telephone call was made during the first week following the supervised challenge. Whenever the parents reported a reaction, the child was seen again by the paediatrician, who determined whether the challenge was positive or not. If CMPA was confirmed by the challenge, the infant was fed the same study formula for a period of up to 6 months (data not presented). The symptom-based score was used to assess the efficacy of each formula. It was evaluated when the child was included in the study and after 1 month, before the oral food challenge.

Secondary outcomes were anthropometric data, crying time, regurgitation, stool consistency, eczema, urticaria and respiratory symptoms. Anthropometric measures were weight, length, head circumference, body mass index (BMI) and the z-scores. Data were obtained at baseline and after 1 month.

The study was approved by the Ethical Committee of UZ Brussel, as the primary centre, and by each participating hospital. Physicians from nine centres in five different countries were selected because of their qualifications and interest in participating in this trial. Informed consent was obtained from parents prior to randomisation. The trial was registered at clinical trials.gov under Identifier: NCT01985607 (11).

RESULTS

Eighteen paediatricians included 72 infants with clinical symptoms suggesting CMPA. The patient characteristics are listed in Table 3. All infants except one presented with at least three different symptoms. A milk challenge was performed in 52 (72%) infants. Despite initially agreeing to their child undergoing a challenge at recruitment, as part of the informed consent procedure, 20 (28%) parents, 11 from the NT-eCH group and nine from the T-eCH group, changed their minds and subsequently refused (Table 4). The challenge was positive in 15/26 (58%) children in the NT-eCH group and, nonsignificantly, in 19/26 (73%) of the T-eCH group. The infants who did not undergo the challenge, because their parents withdrew consent, were integrated into the CMPA-negative group (Table 3).

At the point of inclusion, the symptom-based score in all infants was 14.1 (±3.5; [10-24] (mean (±SD; [min–max]) in the NT-eCH and 14.1(±3.6; [10–27]) in the T-eCH groups (NS) (Table 5). Four children dropped out before the end of the 1-month period. One was in the T-eCH group and was unable to tolerate the taste of the formula. The other three were in the NT-eCH group. One of these was lost to follow-up, one family decided to stop because of vomiting/liquid stools, and one infant was switched and successfully fed with a nonhydrolysed protein antiregurgitation cow's milk formula. The CMPA diagnosis was not confirmed in any of these four cases. None of the patients with proven CMPA dropped out during the 1-month intervention period.

There was no difference in the symptom-based scores at inclusion, either between the groups receiving the NT-eCH and the T-eCH or between the groups in which CMPA was later confirmed or not. The score decreased significantly after 1 month of dietary intervention. It fell by −7.4 (±5.5) ($p < 0.001$) in the entire group, by −6.3 (±5.4; $p < 0.001$) in the group in which CMPA was not confirmed and by −8.6 (±5.3; $p < 0.001$) in the group in which CMPA was confirmed. The confirmed CMPA score therefore showed a statistically significant stronger decrease ($p < 0.05$). After 1 month of dietary intervention, the mean score in the group with confirmed CMPA was <6 (5.7), while the mean

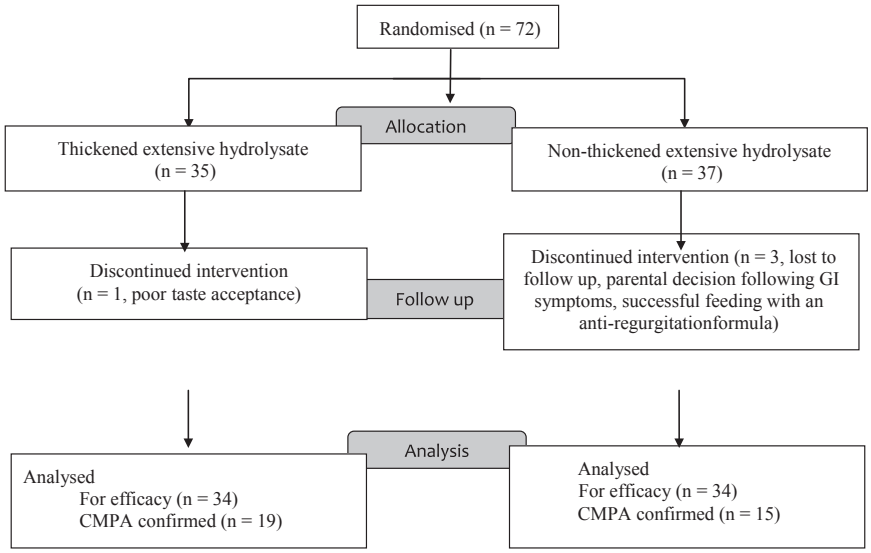

Figure 1 Flow diagram.

Table 3 Patient characteristics

	Total	T-eCH	NT-eCH	CMPA+	CMPA−
N	72	35	37	34	38
Male/Female	36/36	14/21	22/15	15/19	21/17
BW (kg)	3.2 ± 0.5	3.1 ± 0.6	3.2 ± 0.4	3.2 ± 0.4	3.1 ± 0.6
BL (cm)	49.4 ± 2.4	48.9 ± 2.7	49.9 ± 2	49.6 ± 1.9	49.2 ± 2.9
GA (weeks)	38.3 ± 1.6	38.3 ± 1.9	38.3 ± 1.2	38.4 ± 1.6	38.3 ± 1.6
Fam hist+	1.8 ± 2.0	2.1 ± 2.3	1.5 ± 1.7	1.4 ± 1.9	2.1 ± 2.1
At inclusion					
Age (days)	87.5 ± 46.2	80 ± 44	94.7 ± 47.7	86.2 ± 38.9	88.7 ± 52.4
Weight (kg)	5.4 ± 1.2	5.2 ± 1.1	5.7 ± 1.3	5.4 ± 1.3	5.4 ± 1.2

BW = Birthweight; BL = Birth length; GA = Gestational age; Fam hist + = Positive family history for atopy (number of family members); T-eCH = Thickened extensive casein hydrolysate; NT-eCH = Nonthickened extensive casein hydrolysate; CMPA+ = Cow's milk protein allergy positive (positive challenge test); CMPA− = Cow's milk protein allergy negative (negative challenge test or refused challenge test).

Table 4 Challenge test results

Challenge	Not done	Done	Positive	Negative
Number patients	20	52	34	18

NT-eCH = Nonthickened extensive casein hydrolysate; T-eCH = Thickened extensive casein hydrolysate.

score in the group where CMPA was not confirmed was >6 (7.4).

The decrease in the total symptom-based score did not differ between the two formulas and was nonsignificant (−7.7 ± 5.5 vs. −7.2 ± 5.7 in the T and NT groups, respectively), regardless of the result of the challenge test. However, in the group where the diagnosis of CMPA was not confirmed, the thickened formula led to an even more marked, but still nonsignificant, reduction in the score (−7.1 ± 5.9 vs. −5.7 ± 5.1).

Crying for more than 3 h a day was significantly reduced in the study population, from 43.5% at inclusion to 11.6% at 1 month ($p < 0.0001$). The reduction in crying time was similar in all subgroups.

A significant reduction in the number of episodes of regurgitation was observed in the whole study population after 1 month of dietary intervention (from 6.4 ± 3.2 to 2.8 ± 2.9; $p < 0.001$) as well as in all the subpopulations (CMPA confirmed or not, T-eCH or NT-eCH). The thickened formula reduced regurgitation more than the nonthickened formula, but this was not statistically significant (−4.2 ± 3.2 regurgitations per day vs. −3.0 ± .4.5). The difference was larger, but not statistically significant, in the infants who did not have a positive CMPA challenge (−3.9 ± 4.0 vs. −1.9 ± 3.4). Infants receiving the T-eCH formula showed a greater improvement when it came to the

Table 5 Evolution of the symptom-based scores between inclusion and 1 month of dietary treatment (ITT dataset)

	Global	T-eCH	NT-eCH	p	CMPA+	CMPA−	p	CMPA+			CMPA−		
								T-eCH	NT-eCH	p	TeCH	NT-eCH	p
D0	14.1 (3.5)	14.1 (3.6)	14.1 (3.5)		14.3 (3.3)	13.9 (3.8)		13.6 (2.5)	15.1 (4.1)		14.7 (4.6)	13.4 (3)	
D30	6.7 (4)	6.4 (4.1)	6.9 (3.8)		5.7 (3.7)	7.6 (4)		5.5 (4.0)	5.9 (3.5)		7.5 (4.2)	7.7 (4)	
Evolution	−7.4 (5.5)	−7.7 (5.2)	−7.2 (5.7)	0.60**	−8.6 (5.3)	−6.3 (5.4)	0.04**	−8.1 (4.7)	−9.2 (6.1)	0.66**	−7.1 (5.9)	−5.7 (5.1)	0.88**
p	<0.001*	<0.001*	<0.001*		<0.001*	<0.001*		<0.001*	<0.001*		<0.001*	<0.001*	

D0 and D30 = Mean (standard deviation) of the symptom-based score at baseline and after 1 month; CMPA+ = Positive food challenge; CMPA− = Negative or no food challenge. NT-eCH = Nonthickened extensive casein hydrolysate; TeCH = thickened extensive casein hydrolysate.
* = Student's t-test.
**ANCOVA.

Vandenplas regurgitation score (10) (Table 6). In the total study population, the number of infants with normal/soft stools increased from 13% at inclusion to 30.4% after the 1-month dietary intervention ($p = 0.02$). This normalisation was only significant in the subpopulation of infants fed the T-eCH formula (8.8% to 35.3%, $p = 0.013$) and not the NT-eCH. Cutaneous symptoms present at inclusion improved in more than 80% of patients. Similarly, respiratory symptoms improved in 71.1% of infants affected at inclusion.

In the whole study population, the weight-for-age and BMI z-scores increased significantly during the first month of intervention. At inclusion, all z-scores (weight-for-age, weight-for-height, BMI) were negative (around −0.6) with no differences between the groups or according to the diagnosis, indicating a slight growth faltering. Weight-for-age and BMI z-scores increased significantly during the 1-month feeding intervention with any one of the formulas. The evolution of all growth-related parameters (weight, length, head circumference and BMI z-scores) did not differ between the two formulas or according to whether or not the diagnosis of CMPA was confirmed (Table 7).

DISCUSSION

The results observed in this study demonstrate that the e-CH tested meets the criteria of the American Academy of Pediatrics (AAP) for hypoallergenic formula, that it should be tolerated by more than 90% of infants with proven CMPA, with a 95% confidence interval. Our study provides evidence that the infants with confirmed CMPA showed very good tolerance of both the thickened and nonthickened formula. In the subpopulation with suspected or confirmed CMPA, only one of the 54 patients dropped out due to GI symptoms.

All patients except one had more than three symptoms involving at least two organ systems, and all had at least five episodes of regurgitation a day. At baseline, the symptom-based score in each infant was ≥10. Within 4 weeks, this had improved significantly in all groups with both formulae. Changes in anthropometric data were similar in all groups, with weight and BMI z-scores improving significantly within 1 month ($p < 0.001$ and $p = 0.005$, respectively).

An oral challenge test is considered the gold standard for diagnosing CMPA (1). However, many parents refuse the challenge (6). In this study, 28% of the parents refused, despite initially agreeing, as the challenge was part of the informed consent process. This percentage was similar to a previously reported incidence in a comparable study design and study population (6). The symptom-based score was specifically developed to assess the evolution of symptoms during dietary intervention. Nevertheless, although the score plays a role in confirming the diagnosis of CMPA, the extent to which the score decreases would appear to be more highly predictive than the baseline score. In line with previous research (6), it was not possible in this study to detect a clinically useful difference between the score at baseline in children with and without CMPA. However, the results of both this current trial and a previous study (6)

Table 6 Secondary outcomes contributing the symptom-based score (ITT dataset)

							CMPA+			CMPA−		
	Global	T-eCH	NT-eCH	p	CMPA+	CMPA−	p	T-eCH	NT-eCH	p	T-eCH	NT-eCH	p
CMPA													
D0	14.1 (3.5)	14.1 (3.6)	14.1 (3.5)		14.3 (3.3)	13.9 (3.8)		13.6 (2.5)	15.1 (4.1)		14.7 (4.6)	13.4 (3)	
D30	6.7 (4)	6.4 (4.1)	6.9 (3.8)		5.7 (3.7)	7.6 (4.0)		5.5 (4.0)	5.9 (3.5)		7.5 (4.2)	7.7 (4)	
Evolution	−7.4 (5.5)	−7.7 (5.2)	−7.2 (5.7)	0.60****	−8.6 (5.3)	−6.3 (5.4)	0.04****	−8.1 (4.7)	−9.2 (6.1)	0.66****	−7.1 (5.9)	−5.7 (5.1)	0.88****
p	<0.001*	<0.001*	<0.001*		<0.001*	<0.001*		<0.001*	<0.001*		<0.001*	<0.001*	
Regurgitations (daily number)													
D0	6.4 (3.2)	6.6 (2.1)	6.2 (4.0)		6.9 (3.9)	5.9 (3.2)		6.6 (2.3)	7.5 (5.6)		6.7 (2.0)	5.3 (2.3)	
D30	2.8 (2.9)	2.4 (2.3)	3.3 (3.4)		2.4 (2.0)	3.3 (3.6)		2.1 (1.6)	2.8 (2.4)		2.7 (3.1)	3.6 (3.9)	
Evolution	−3.6 (3.9)	−4.2 (3.2)	−3 (4.5)	0.24****	−4.5 (4)	−2.8 (3.7)	0.20****	−4.4 (2.6)	−4.7 (5.6)	0.43****	−3.9 (4.0)	−1.9 (3.4)	0.32****
p	<0.001**	<0.001**	<0.001**		<0.001**	<0.001**		<0.001*	0.002**		0.011**	0.020*	
Regurgitations (Vandenplas score)													
D0	3 (1.3)	3 (1.2)	2.9 (1.3)		3.2 (1.3)	2.8 (1.2)		3 (1.2)	3.5 (1.5)		3.1 (1.2)	2.6 (1.1)	
D30	0.9 (1)	0.7 (1)	1 (1)		0.9 (0.9)	0.9 (1.1)		0.7 (0.7)	1.1 (1.1)		0.8 (1.2)	0.9 (1)	
Evolution	−2.1 (1.5)	−2.3 (1.6)	−2 (1.5)	0.32****	−2.4 (1.5)	−1.9 (1.5)	0.86****	−2.3 (1.4)	−2.4 (1.7)	0.29****	−2.3 (1.9)	−1.7 (1.2)	0.68****
p	<0.001**	<0.001*	<0.001**		<0.001**	<0.001**		<0.001**	<0.001*		<0.001*	<0.001**	
Crying													
D0	3.3 (2.2)	3.6 (2.4)	3 (2.0)		3.7 (2.3)	3 (2.1)		4.2 (2.4)	3 (2.1)		2.9 (2.4)	3.1 (2)	
D30	1.1 (1.6)	1.4 (1.9)	0.8 (1.3)		1.1 (1.6)	1.1 (1.7)		1.2 (1.9)	0.9 (1.3)		1.7 (2)	0.8 (1.3)	
Evolution	−2.2 (2.2)	−2.2 (2.3)	−2.2 (2.1)	0.27****	−2.6 (2.2)	−1.9 (2.1)	0.48****	−3 (2.4)	−2.1 (1.9)	0.88****	−1.3 (1.9)	−2.3 (2.2)	0.07****
p	<0.001**	<0.001*	<0.001**		<0.001**	<0.001*		<0.001*	<0.001**		0.022*	<0.001*	
Crying (≥3 h/d)													
D0	43.50%	55.90%	31.40%		55.90%	31.40%		68.40%	40%		40%	25%	
D30	11.60%	17.60%	5.70%		8.80%	14.30%		10.50%	6.70%		26.70%	5%	
p***	<0.0001	0.0008	0.0067		<0.0001	0.0578		0.0009	0.0253		0.3173	0.1025	
Normal Stools (type C, D, E)													
D0	13%%	8.8%	17.1%		14.7%	11.4%		10.5%	20%%		6.7%	15.0%	
D30	30.40%	35.3%%	25.7%		44.1%	17.1		42.1%	46.7%		26.7%	10.0%	
p***	0.0186	0.01268	0.4054	0.45*****	0.0124	0.5271		0.03	0.153	0.75*****	0.1797	0.6547	0.62*****

*Student's t-test.
**Wilcoxon.
***McNemar's test.
****ANCOVA.
*****Cochran–Mantel–Haenszel.

Table 7 Evolution of anthropometric parameter during the 1st month intervention period

	Global	T-eCH	NT-eCH	p	CMPA+	CMPA−	p
Weight							
D0	5.4 (1.2)	5.2 (1.1)	5.7 (1.3)		5.4 (1.1)	5.4 (1.3)	
D30	6.4 (1.1)	6.2 (1)	6.6 (1.2)		6.3 (1.0)	6.4 (1.2)	
WG	0.9 (0.5)	1 (0.4)	0.9 (0.5)	0.96***	1 (0.5)	1 (0.5)	0.64***
Weight-for-age z-score							
D0	−0.6 (1.2)	−0.7 (1.1)	−0.6 (1.3)		−0.6 (1.4)	−0.7 (0.9)	
D30	−0.3 (1.1)	−0.4 (1.0)	−0.2 (1.1)	0.53***	−0.3 (1.3)	−0.4 (0.8)	0.57***
p	<0.001*	0.009*	0.002*		<0.005*	0.003*	
Height							
D0	58.6 (5)	57.6 (4.8)	59.6 (5)		58.6 (5)	58.7 (5)	
D30	61.8 (4.3)	61.1 (4.2)	62.5 (4.4)		61.7 (4.5)	61.9 (4.2)	
HG	3.2 (1.8)	3.5 (1.9)	2.9 (1.7)	0.51***	3.1 (1.6)	3.2 (2)	0.81***
Height-for-age z-score							
D0	−0.5 (1.3)	−0.7 (1.3)	−0.4 (1.4)		−0.5 (1.4)	−0.6 (1.3)	
D30	−0.3 (1.3)	−0.5 (1.2)	−0.2 (1.3)	0.87***	−0.3 (1.3)	−0.4 (1.2)	0.96***
p	0.085*	0.231*	0.22*		0.258	0.202	
Weight-for-height z-score							
D0	−0.2 (1.5)	−0.1 (1.4)	−0.3 (1.5)		−0.2 (1.8)	−0.2 (1.1)	
D30	0 (1.3)	0 (1.2)	0 (1.4)	0.55***	0.1 (1.5)	−0 (1)	0.51***
p	0.054*	0.428	0.065		0.125*	0.321**	
BMI z-score							
D0	−0.5 (1.3)	−0.4 (1.2)	−0.5 (1.4)		−0.5 (1.6)	−0.5 (1)	
D30	−0.2 (1.2)	−0.2 (1.1)	−0.1 (1.3)	0.61***	−0.1 (1.5)	−0.2 (0.9)	0.54***
p	0.005*	0.074*	0.033*		0.041*	0.056*	
HC z-score							
D0	−0.2 (1.3)	−0.3 (1.2)	−0.2 (1.4)		−0.3 (1.5)	−0.2 (1.1)	
D30	0.3 (2.5)	0 (0.9)	0.5 (3.4)	0.52***	0 (1.5)	0.5 (3.2)	0.40***
p	0.023**	0.07*	0.16*		0.14*	0.06*	

WG = Weight gain; HG = Height gain; HC = Head circumference; BMI = Body mass index.
*Student's t-test.
**Wilcoxon.
***ANCOVA.

show that a score of more or <6 after 1 month of dietary treatment might be predictive of CMPA.

Regurgitation decreased significantly in all groups. Compared with standard infant formula, an extensive (casein) hydrolysate has been shown to enhance gastric emptying (12,13). This could have contributed to the decrease in regurgitation in the subgroup in which CMPA could not be confirmed and which was treated with the NT-eCH. However, the T-eCH was slightly more effective in the same subgroup, confirming that a thickened formula decreases regurgitation. The normalisation of stool consistency is an interesting aspect, because hydrolysates are known to cause soft, liquid stools (14). The development of anthropometric parameters was normal (15,16).

Thickened eHF is a new development. CMPA management should reflect not only basic research, but also newer and better appraisals of the literature in the light of the values and preferences shared by both patients and their caregivers (17). The therapeutic efficacy of the tested e-CH was very good. Thickening is important in nonallergic infants as the protein hydrolysate is important in those who are allergic. In daily practice, many infants with mild-to-moderate symptoms of CMPA may be difficult to distinguish from nonallergic infants. That is why a thickened eHF may be useful, because it treats both conditions effectively.

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CONFLICT OF INTEREST

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APPENDIX 1

Allar study group

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