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Safety of a thickened extensive casein hydrolysate formula

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ABSTRACT

Objectives: Cow's milk allergy (CMA) is treated in formula-fed infants with an extensive protein hydrolysate. This study aimed to evaluate the nutritional safety of a non-thickened and thickened extensively casein hydrolyzed protein formula (NT- and T-eCHF) in infants with CMA.
Methods: Infants younger than 6 mo old with a positive cow milk challenge test, positive IgE, or skin prick test for cow milk were selected. Weight and length were followed during the 6 mo intervention with the NT-eCHF and T-eCHF.
Results: A challenge was performed in 50/71 infants with suspected CMA and was positive in 34/50. All children with confirmed CMA tolerated the eCHF. The T-eCHF leads to a significant improvement of the stool consistency in the whole population and in the subpopulation of infants with proven CMA. Height and weight evolution was satisfactory throughout the 6 mo study.
Conclusions: The eCHF fulfills the criteria of a hypoallergenic formula and the NT- and T-eCHF reduced CMA symptoms. Growth was within normal range.

Introduction

Cow's milk protein is a major food allergen in infants [1–4]. A food allergy is defined as an adverse health effect arising from a specific immune response that occurs after exposure to the responsible food allergen [5]. This immune reaction may be IgE or non-IgE mediated. Symptoms of cow's milk allergy (CMA) are not specific and most frequently involve the skin (e.g. atopic dermatitis), the gastrointestinal (GI) tract (regurgitation, vomiting, diarrhea, and constipation), the respiratory tract (wheezing or sneezing) or are more general (colic or anaphylaxis) [1]. To date, the diagnosis of CMA requires an elimination diet followed by a food challenge, which sometimes causes concern to (and is often refused) by the parents [6].

Correct diagnosis enables appropriate feeding of affected infants to sustain normal growth and development. Guidelines define a therapeutic hypoallergenic formula as one tolerated by

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Table 1
Formula composition (/100 g of powder)

For 100 g of powder	Unit	T-eCHF	NT-eCHF
Protein (casein) (n x 6.25)	g	12.1	12.0
Lipid	g	26.2	27.1
Carbohydrates	g	52.7	55.0
Starch	g	1.0	–
Fibres	g	3.6	–
Energy	kcal	510	512

NT-eCHF, non-thickened extensive casein hydrolysate formula; T-eCHF, thickened extensive casein hydrolysate formula; n, number of subjects

at least 90% of CMA infants with a 95% confidence interval [1,2,7]. These criteria are met by several extensively hydrolyzed protein formulas, based on whey or casein. The hypoallergenicity of this extensively hydrolyzed casein formula (eCHF) was published before [8]. This paper reports the anthropometric evolution over 6 mo feeding with the test formulas.

Materials and methods

Formula-fed infants were eligible for inclusion in this prospective, randomized, double-blind trial if they were less than 6 mo old with symptoms suggesting CMA, including frequent, troublesome regurgitation and/or vomiting at a frequency of more than 5 episodes a day [8]. Two formulas were compared: a non-thickened and a thickened casein extensive hydorlysate formula (NT- and a T-eCHF); the composition of the tested formulas is listed in Table 1. Infants already fed with an extensively hydrolyzed protein formula, or having experienced previous anaphylactic reactions, were not eligible for inclusion [8]. The trial was registered at ClinicalTrials.gov under Identifier NCT01985607, and the 1 mo results in 72 infants were published prior [8]. Criteria used to suspect CMA, inclusion, and exclusion criteria can be found in the first report (Supplement 1) [8].

The primary goal of this paper is present anthropometric data over a period of 6 mo in infants fed both versions of the eCHF. Anthropometric data (weight, length, and head-circumference), were collected at 1, 3, and 6 mo and the corresponding z-score were calculated according to the World Health Organization Child Growth Standards [9].

Secondary aims were to confirm the hypoallergenicity and the efficacy of two NT- and T-eCHF. The cow milk symptom score (CoMiSS) was used to assess the efficacy of each formula at the end of the 1 mo feeding period with the formula [10].

Before any statistical analyses, the normality of the quantitative variables were tested using the Shapiro-Wilk's test. In case of normality ($P > 0.05$) or number of patients >30 per group, continuous variables were tested using a Student *t* test. In case of non-normality and number of patients ≤30 per group, the non-parametric Mann-Whitney-Wilcoxon test were used instead. The categorical variables were tested using Chi^2 test (expected frequency >5), otherwise using Fisher exact test.

The main criterion (changes in score of regurgitation between D30 and D0) was compared between groups using an analysis of covariance (ANCOVA), including the baseline value as covariate if the conditions of normality were respected, otherwise using a Wilcoxon test or an ANCOVA based on ranks. This criterion was also analyzed within each group with a paired *t* test if the conditions of normality were respected, otherwise using a Wilcoxon matched-pairs signed ranks test. The secondary criteria were analyzed in the same way. Results are presented as mean +/− standard deviation and/or median (quartile 1–quartile 3).

Full–analysis set (FAS) population was defined as all infants from the safety population having an evaluation of the main criteria.

Moreover, "CMA+" population was defined as all infants from the FAS having a CMA confirmed by either a positive food challenge or positive skin prick test (i.e., a papula to cow's milk at least 3 mm bigger than the negative control) or positive specific IgE (i.e., >0.35 kU/l). Infants with a negative food challenge and infants who did not undergo the food challenge constituted the "CMA?" group.

The study was approved by the Ethical Committee of the UZ Brussels as the primary center and by each participating hospital. Physicians from nine centers in five different countries were selected because of their qualifications and interest in participating in this trial. Informed consent was obtained from parents before randomization.

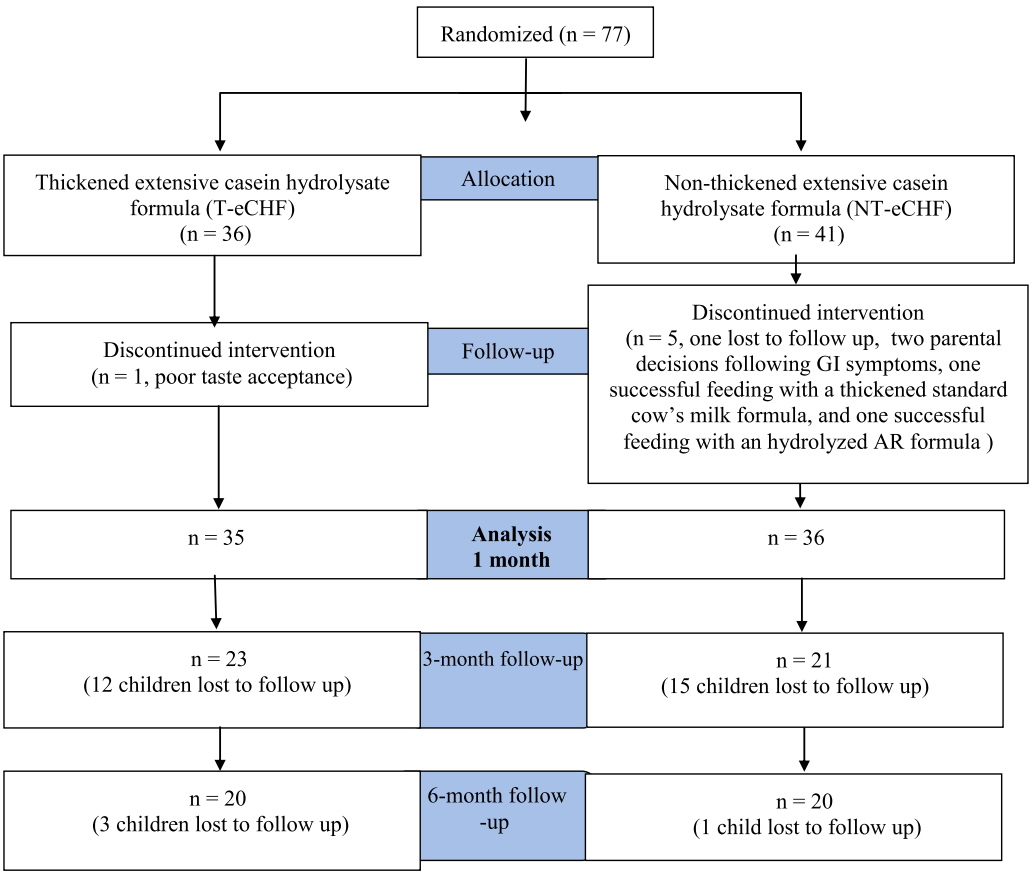

Fig. 1. Flow diagram. n, number of subjects; PPR, per protocol data set for regurgitations; PPA, per protocol data set for allergy; GI, gastrointestinal; AR, antiregurgitation.

Table 2
Patient's characteristics

Patient characteristics	Total	T-eCHF	NT-eCHF	*P*-values	CMA+
n	71	35	36		37
Male/Female	34/37	13/22	21/15	0.074*	17/20
Birth weight-for-age z-score (mean ± SD)	−0.31 ± 1.05	−0.40 ± 1.2	−0.22 ± 0.89		−0.38 ± 0.95
Birth Length-for-age Z score (mean ± SD)	1.1 ± 1.28	−0.25 ± 1.41	0.26 ± 1.11		−0.04 ± 1.17
GA (weeks), mean ± SD	38.38 ± 1.59	38.32 ± 1.89	38.43 ± 1.27	0.786†	38.41 ± 1.62
Fam hist +, mean ± SD	1.80 ± 2.0	2.09 ± 2.28	1.53 ± 1.66	0.242†	1.73 ± 2.22
At inclusion					
Age (days), mean ± SD	90.51 ± 49.02	80.77 ± 43.17	99.97 ± 43.17	0.038†	90.49 ± 43.78
Weight –for –age Z score at inclusion (mean ± SD)	−0.64 ± 1.18	−0.67 ± 1.11	−0.61 ± 1.27	0.835†	−0.68 ± 1.37

BW, birth weight; BL, birth length; CMA+, cow's milk allergy positive; Fam hist +, positive family history for atopy (this score was calculated as follows: a score of 1 was attributed to each member of the family [mother, father, or sibling] having a suspected allergic disease; this score was 2 for each member having a medically diagnosed allergic disease, the family score was the sum of each member score); GA, gestational age; n, number of subjects; NT-eCHF, non-thickened extensive casein hydrolysate formula; SD, standard deviation; T-eCHF, thickened extensive casein hydrolysate formula

* Chi-2.

† Student's *t* test.

Results

Eighteen pediatricians included 77 infants with clinical symptoms suggesting CMA. Six children dropped out before the end of the 1 mo period. One was in the T-eCH group and was unable to accept the taste of the formula. The other five were in the NT-eCH group. One of these was lost to follow up, two families decided to stop because of vomiting/liquid stools (one of those has been later fed Neocate with no improvement), one infant was switched and successfully fed with a non-hydrolyzed protein antiregurgitation formula, and parents of the last one successfully switched to a commercialized extensively hydrolyzed antiregurgitation formula (Allernova AR) (Fig. 1). The CMA diagnosis was not confirmed in any of these six cases. None of the patients with proven CMA dropped out during the 1 mo intervention period.

The patients' characteristics of the full analysis set are listed in Table 2. There were no significant differences between both groups for weight-for-age z-scores at inclusion, gestational age, and family score for atopy. Considering the FAS population, a milk challenge was performed in 50/71 (70.4%) infants. Indeed, despite initial agreement to perform a challenge at recruitment (as part of the informed consent), parents of 21 (29.6%) infants changed their minds and refused the challenge procedure (Table 3). The challenge was positive in 15/36 (41.6%) and in 19/35 (54.3%) children in the NT-eCHF and T-eCHF group, respectively (NS). Additionally, in the population which did not undergo the oral food challenge, one had a positive SPT, one had positive specific IgE, and one had both specific IgE and SPT. Therefore the CMA+ population was made of 37 children, among whom 34 (91.8%) had a positive food challenge.

There was no difference in CoMiSS at inclusion, neither between the groups receiving the NT-eCHF and the T-eCHF, nor between the groups in which CMA was later confirmed or not (Table 4). The CoMiSS decreased significantly after the first month of dietary intervention by -7.5 (±5.2; $P < 0.001$) in the entire group, by −8.4 (±5.2; $P < 0.001$) in the group in which CMA was confirmed and by −6.5+/−4.5 in the group "CMA?", the score remaining above 6 (7.3+/−4) after 1 mo in this group.

The CoMiSS decrease did not differ between both versions of the eCHF (−7.6 ± 5.2 versus −7.4 ± 5.3 in the T and NT group respectively) regardless of the result of the challenge test.

Crying time was significantly reduced in the study population. 42.3% of all infants were crying more than 3 h/d at inclusion, but only 9.9% of them still cried more than 3 h/d at the end of the first month observation period ($P < 0.0001$), without a significant difference between groups (Table 5).

A significant reduction in the number of regurgitation was observed after 1 mo for both versions of the eCHF (−5 [−6; −3]; median [Q1; Q3]; $P < 0.001$ for the T-eCHF and −2 [−5; 0]; $P < 0.001$ for the NT-eCHF), this decrease being significantly more important with the T eCHF ($P = 0.025$) (Table 6). When the CMA was not confirmed ("CMA?" population), the T-eCHF seems to reduce regurgitations more than the NT-eCHF (-5 [−6; −3] versus −3 [−5; 0]; NS) (Table 6). After 3 mo, the number of regurgitations was even more reduced in both groups (data not shown). There was also a significant improvement of the "Vandenplas regurgitation score" for all infants and for all populations (Table 5).

In the total study population, a 1 mo dietary intervention led to a normalization of the stool consistency (12.7% of normal/soft stools at inclusion versus 31% after 1 mo, $P = 0.009$). This normalization was significant in infants fed the T-eCHF in the total population (8.6% to 34.3%, $P = 0.013$) and in the subpopulation of infants with proven CMA (T-eCHF 9.5% to 42.5%, $P = 0.020$) but was not significant with the NT-eCHF formula (total population: 16.7% to 27.8%; CMA+ population: 12.5% to 37.5%) (Table 5).

Cutaneous symptoms' score significantly decreased in the whole population after 1 mo (-1.3 ± 1.6, $P < 0.001$). Similarly, the respiratory symptoms score decreased significantly in the total population (-0.48 ± 0.69, $P < 0.001$) with no difference between both formulas.

In the whole study population, the weight-for-age and BMI-for-age z-scores increased significantly from the first month and during the total intervention period. At inclusion, weight-for-age, weight-for-length, and BMI-for-age z-scores were negative (around −0.5) with no differences between the groups nor according to the diagnosis, indicating a slight growth faltering (Table 7). Weight and length-for-age z-scores increased significantly during the 6 mo study, with no difference between

Table 3
Challenge test results on the FAS population

Patient characteristics	Formulas		
	T eCHF	NT eCHF	Total
	n = 35	n = 36	n = 71
Negative	6	10	16 (32.0%)
Positive	19	15	34 (68.0%)
Refused	10	11	21

NT-eCHF, non-thickened extensive casein hydrolysate formula; T-eCHF, thickened extensive casein hydrolysate formula; n, number of subjects

Table 4
Evolution of the cow's milk related symptom score between inclusion and 1 mo of dietary treatment. Results are expressed as mean ± standard deviation

Patient characteristics	Total	T-eCHF	NT-eCHF	*P*-values between groups	CMA+	CMA?	*P*-values between groups	CMA+			CMA?		
								T-eCHF	NT-eCHF	*P*-values between groups	T-eCHF	NT-eCHF	*P*-values between groups
Baseline	14.1 ± 3.5	14 ± 3.6	14.1 ± 3.4	0.842*	14.1 ± 3.4	13.8 ± 3.0	0.805†	13.8 ± 2.6	14.6 ± 4.3	0.975†	13.9 ± 3.5	13.8 ± 2.8	1.000†
1 mo	6.6 ± 3.8	6.4 ± 4.1	6.7 ± 3.6	0.747*	5.7 ± 3.7	7.3 ± 4	0.153†	5.6 ± 4	5.9 ± 3.3	0.710†	7.9 ± 4.7	7 ± 3.6	0.685†
Evolution	−7.5 ± 5.2	−7.6 ± 5.2	−7.4 ± 5.3	0.919*	−8.4 ± 5.2	−6.5 ± 4.5	0.244†	−8.2 ± 4.5	−8.7 ± 6.2	0.988†	−6.0 ± 4.6	−6.8 ± 4.6	0.820†
P-values vs. baseline	<0.001*	<0.001*	<0.001*		<0.001†	<0.001†		<0.001†	<0.001†		<0.002†	<0.002†	

CMA+, cow's milk allergy positive; CMA?, cow's milk allergy negative or not known; NT-eCHF, non-thickened extensive casein hydrolysate formula; SD, standard deviation; T-eCHF, thickened extensive casein hydrolysate formula

* Student's *t* test.

† Wilcoxon's test.

the T-eCHF and NT-eCHF groups (Figs. 2–5). Growth was normal for all children during the 6 mo trial.

Discussion

Unfortunately, 21/71 (29.6%) parents refused the challenge test despite their initial agreement when signing the informed consent. Three of these children were included in the CMA group because of a positive skin prick test (n:2) and/or a positive specific IgE (n:2). According to literature, both parameters have a specificity, which was 100% in a previous report [6]. However, it is likely that the challenge test would have been positive in some of the 15 infants in whom the test was refused. Therefore, it is likely that some infants included in the CMA-negative group were in fact allergic. The results observed in this study demonstrate that the tested eCHF meets the criteria of the American Academy of Pediatrics (AAP) for hypoallergenic formula, since the formula was tolerated by more than 90% of infants with proven CMA, with a 95% confidence interval [7].

The study provides evidence that the eCHF was well tolerated by infants with confirmed CMA. All the growth parameters improved within 6 mo for the whole population in the study. The development of anthropometric parameters was normal [11,12].

Table 5
Evolution after 1 mo of secondary outcomes contributing to the cow's milk related symptom score

Patient characteristics	Total	T-eCHF	NT-eCHF	*P*-values between groups	CMA+		
					T-eCHF	NT-eCHF	*P*-values between groups
Regurgitations score evolution, (Vandenplas score)							
Mean ± SD	−2.2 ± 1.4	−2.3 ± 1.4	−2.1 ± 1.5		−2.3 ± 1.3	−2.2 ± 1.8	
Median – [Q1; Q3]	−2 [−3; −1]	−2 [−3; −1]	−2 [−3; −1]	0.538*	−2 [−3; −1]	−2 [−3; −1]	0.837†
P-values vs. baseline	<0.001*	<0.001*	<0.001*		<0.001†	<0.001†	
Crying score evolution							
Mean ± SD	−2.1 ± 2.8	−2.1 ± 2.3	−2.2 ± 2		−2.8 ± 2.4	−1.9 ± 2.0	
Median – [Q1; Q3]	−2 [−4; −1]	−2 [−4; 0]	−2 [−3; −1]	0.964*	−3 [−5; −1]	−1 [−3; −1]	0.290†
P-values vs. baseline	<0.001*	<0.001*	<0.001*		<0.001†	<0.001†	
Proportions of patients (%) crying ≥3 h/d							
Baseline	42.3	54.3	30.6	0.043‡	61.9	31.0	0.065‡
1 mo	9.9	17.1	2.8	0.055§	9.5	6.3	1.000§
P-values vs. baseline	<0.0001‖	0.0008‖	0.0016‖		0.0009‖	0.045‖	
Proportions of patients (%) with normal stools (type C, D, and E)							
Baseline	12.7	8.6	16.7	0.478§	9.5	12.5	1.000§
1 mo	31.0	34.3	27.8	0.553‡	42.9	37.5	0.742‡
P-values vs. baseline	0.009‖	0.013‖	0.248‖		0.020‖	0.157‖	
Respiratory symptom score evolution							
Mean ± SD	−0.5 ± 0.7	−0.5 ± 0.7	−0.4 ± 0.7		−0.6 ± 0.7	−0.6 ± 0.7	
Median – [Q1; Q3]	0 [−1; 0]	0 [−1; 0]	0 [−1; 0]	0.448*	0 [−1; 0]	−1 [−1; 0]	0.959†
P-values vs. baseline	<0.001*	<0.001*	<0.001*		0.002†	0.002†	
Cutaneous symptoms score evolution (eczema at both body sites)							
Mean ± SD	−1.3 ± 1.6	−1.0 ± 1.3	−1.6 ± 1.7		−0.8 ± 1.3	−1.9 ± 1.6	
Median – [Q1; Q3]	−1 [−2; 0]	−1 [−2; 0]	−1 [−3; 0]	0.5161‖	0 [−2; 0]	−2 [−3; −1]	0.6913‖
P-values vs. baseline	<0.001†	<0.001†	<0.001*		<0.011¶	<0.01*	

CMA+, cow's milk allergy positive; NT-eCHF, non-thickened extensive casein hydrolysate formula; SD, standard deviation; T-eCHF, thickened extensive casein hydrolysate formula

* Student test.

† Wilcoxon test.

‡ Chi-2 test.

§ Fisher's test.

‖ MacNemar test.

¶ Ancova.

Table 6
Evolution of the daily number of regurgitations during the first month

Patient characteristics	Total	T-eCHF	NT-eCHF	*P*-values between groups*	CMA+			CMA?		
					T-eCHF	NT-eCHF	*P*-values between groups*	T-eCHF	NT-eCHF	*P*-values between groups*
Mean ± SD	−3.65 ± 3.98	−4.36 ± 3.06	−2.91 ± 4.70	0.025	−4.82 ± 2.55	−4.14 ± 5.22	0.185	−3.50 ± 3.87	−2.22 ± 3.47	0.144
Median [Q1; Q3]	−4 [−6; −2]	−5 [−6; −3]	−2 [−5; 0]		−5 [−7; −3]	−3 [−5; −2]		−5 [−6; −3]	−3 [−5; 0]	
P-values vs. baseline*	<0.001	<0.001	<0.001		<0.001	<0.001		0.0074	0.019	

CMA+, cow's milk allergy positive; CMA?, cow's milk allergy negative and not known; NT-eCHF, non-thickened extensive casein hydrolysate formula; SD, standard deviation; T-eCHF, thickened extensive casein hydrolysate formula
* Wilcoxon's test.

We analyzed the efficacy and growth data in the CMA-positive and CMA-negative or unknown ("CMA? population") groups, as this represents daily clinical reality in primary health care. Before the diagnosis of CMA can be established, infants are put on an elimination diet as part of the diagnostic procedure. Subsequently, many parents refuse a challenge, which is mandatory to confirm the diagnosis, because the symptoms decreased significantly. Therefore, it is relevant to have efficacy, but even more safety data on growth for these infants, who may be inappropriate for long term consumption of an eHF.

An oral challenge test is considered the gold standard to diagnose CMA [1]. However, many parents refuse a challenge [6]. In this study, 29.5% of the parents refused despite an initial agreement, since the challenge was part of the informed consent, a percentage which is similar to a previously reported incidence in a comparable study design and study population [6]. The CoMiSS was specifically developed as an awareness tool to select infants with a high risk of symptoms related to ingestion of cow's milk and to assess the evolution of symptoms during dietary intervention [10]. A challenge to confirm the diagnosis of CMA remains imperative.

Regurgitation was significantly decreased in all groups but the T-eCHF was more effective for all infants during the first month. In infants with confirmed CMA, the NT-eCHF decreased

Table 7
Evolution of anthropometric parameters during the study period. Results are expressed as mean ± standard deviation

Patient characteristics	Total	T-eCHF	NT-eCHF	*P*-values between groups	CMA+	CMA+		*P*-values between groups
						T-eCHF	NT-eCHF	
Weight-for-age z-score								
Baseline	−0.64 ± 1.18	−0.67 ± 1.11	−0.61 ± 1.27	0.835*	−0.70 ± 1.39	−0.52 ± 1.14	−0.93 ± 1.67	0.510†
1 mo	−0.31 ± 1.09	−0.37 ± 1.01	−0.25 ± 1.17	0.660*	−0.30 ± 1.29	−0.24 ± 1.10	−0.38 ± 1.53	0.890†
P (D30–D0)	<0.001*	0.004*	0.001*	0.691*	<0.001†	0.052†	0.005	0.415†
3 mo	−0.00 ± 1.00	0.04 ± 1.01	−0.05 ± 1.01	0.991†	0.16 ± 1.00	0.23 ± 0.93	0.07 ± 1.11	1.000†
P (D90–D0)†	<0.001	0.002	0.003	0.937†	<0.001†	0.002	0.005	0.123†
6 mo	0.33 ± 0.98	0.52 ± 0.86	0.13 ± 1.08	0.348†	0.59 ± 0.85	0.73 ± 0.58	0.42 ± 0.98	0.482†
P (D180–D0)†	<0.001	<0.001	0.001	0.481†	<0.001†	<0.001	0.003	0.186†
Length-for-age z-score								
Baseline	−0.51 ± 1.34	−0.66 ± 1.32	−0.36 ± 1.36	0.343*	−0.61 ± 1.55	−0.71 ± 1.51	−0.47 ± 1.66	0.425†
1 mo	−0.31 ± 1.27	−0.46 ± 1.31	−0.17 ± 1.33	0.332*	−0.50 ± 1.44	−0.63 ± 1.28	−0.33 ± 1.69	0.319†
P (D30–D0)	0.965*	0.222*	0.141*	0.965*	0.447†	0.720†	0.354†	0.818†
3 mo	−0.07 ± 1.40	−0.21 ± 1.04	0.08 ± 1.73	0.200†	−0.19 ± 1.38	−0.23 ± 1.01	−0.14 ± 1.78	0.340†
P (D90–D0)†	0.021	0.124	0.091	1.000	0.111	0.236	0.303	0.742
6 mo	0.29 ± 1.35	0.31 ± 0.89	0.27 ± 1.71	0.473†	0.17 ± 1.48	0.28 ± 0.97	0.03 ± 1.97	0.984†
P (D180–D0)†	<0.001	0.005	0.026	0.285	0.005	0.017	0.152	0.275
Weight-for- length z-score								
Baseline	−0.25 ± 1.47	−0.08 ± 1.42	−0.42 ± 1.53	0.345*	−0.23 ± 1.78	0.20 ± 1.60	−0.79 ± 1.89	0.133†
1 mo	−0.01 ± 1.30	0.07 ± 1.19	−0.09 ± 1.42	0.601*	0.18 ± 1.49	0.43 ± 1.21	−0.15 ± 1.77	0.319†
P (D30–D0)	0.048*	0.206*	0.075*	0.486*	0.035†	0.187†	0.034†	0.319†
3 mo	0.21 ± 1.29	0.38 ± 1.28	0.02 ± 1.31	0.254†	0.53 ± 0.99	0.67 ± 0.96	0.37 ± 1.04	0.290†
P (D90–D0)†	0.054	0.510	0.051	0.398	0.015	0.283	0.023	0.314
6 mo	0.33 ± 1.26	0.57 ± 0.98	0.08 ± 1.47	0.330†	0.77 ± 0.87	0.88 ± 0.65	0.64 ± 1.10	0.620†
P (D180–D0)†	0.075	0.357	0.137	0.473	0.024	0.258	0.054	0.361
BMI for age z-score								
Baseline	−0.49 ± 1.33	−0.40 ± 1.24	−0.56 ± 1.43	0.614*	−0.48 ± 1.61	−0.15 ± 1.35	−0.92 ± 1.85	0.312†
1 mo	−0.17 ± 1.24	−0.14 ± 1.12	−0.21 ± 1.36	0.816*	−0.02 ± 1.43	0.17 ± 1.14	−0.26 ± 1.74	0.571†
P (D30–D0)	0.003*	0.044*	0.031*	0.656*	<0.001†	0.120†	0.025†	0.319†
3 mo	0.09 ± 1.39	0.27 ± 1.30	−0.12 ± 1.36	0.259†	0.42 ± 1.03	0.56 ± 0.99	0.23 ± 1.09	0.331†
P (D90–D0)†	0.007	0.057	0.053	0.851	<0.001	0.024	0.023	0.555
6 mo	0.24 ± 1.31	0.49 ± 1.00	−0.02 ± 1.55	0.304†	0.70 ± 0.94	0.81 ± 0.66	0.56 ± 1.21	0.606†
P (D180–D0)†	0.010	0.019	0.110	0.925	0.004	0.023	0.054	0.512

BMI, body mass index; CMA+, cow's milk allergy positive; NT-eCHF, non-thickened extensive casein hydrolysate formula; SD, standard deviation; T-eCHF, thickened extensive casein hydrolysate formula
* Student's *t* test.
† Wilcoxon's test.

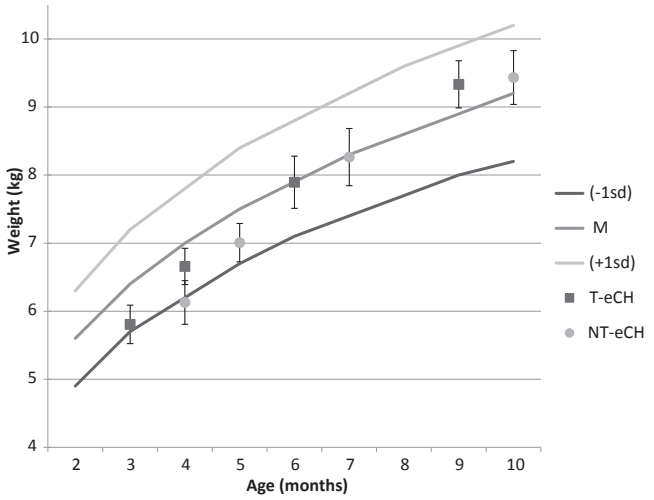

Fig. 2. Weight evolution in boys for both formulas compared to World Health Organization standard chart. NT-eCHF, non-thickened extensive casein hydrolysate formula; T-eCHF, thickened extensive casein hydrolysate formula; M, mean; SD, standard deviation.

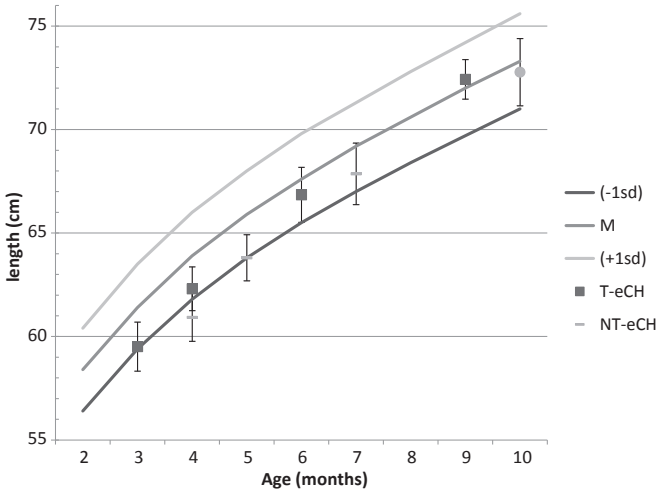

Fig. 4. Height evolution in boys for both formulas compared to WHO standard chart. NT-eCHF, non-thickened extensive casein hydrolysate formula; T-eCHF, thickened extensive casein hydrolysate formula; M, mean; SD, standard deviation.

regurgitation. The normalization of the stool consistency observed only in the subgroup fed the T-eCHF is an interesting characteristic since hydrolysates are known to cause soft, liquid stools [3]. Indeed, the patented thickening complex present in the T-eCHF contains specific fibers selected for their ability to regulate the transit, i.e., to induce neither liquid nor hard stools.

Conclusion

The therapeutic efficacy of the tested eCHF fulfills the requirements to be designated as a hypo-allergenic formula. A thickened extensive hydrolysate is a new development. CMA management should reflect not only basic research but also a newer and better appraisal of the literature in light of the values and preferences shared by patients and their caregivers [13]. Overall, the T and NT-eCHF are effective to alleviate symptoms of CMA. However, in case of CMA suspicion, the thickened hydrolysate is more efficient to reduce regurgitations and also improves the stool consistency. The evolution of the anthropometric parameters was excellent with both variants of the eCHF.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.nut.2015.08.008

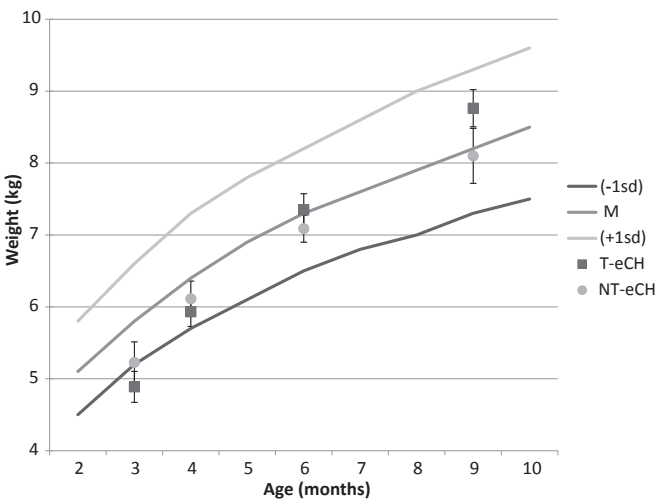

Fig. 3. Weight evolution in girls for both formulas. Compared to WHO standard chart. NT-eCHF, non-thickened extensive casein hydrolysate formula; T-eCHF, thickened extensive casein hydrolysate formula; M, mean; SD, standard deviation.

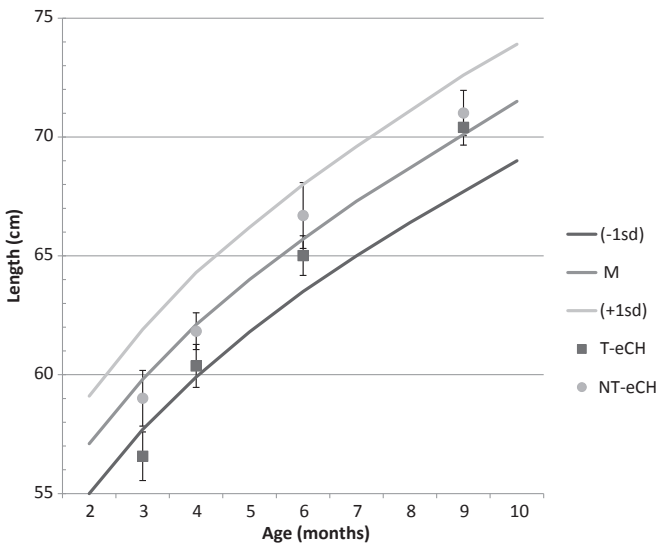

Fig. 5. Height evolution in girls for both formulas compared to WHO standard. NT-eCHF, non-thickened extensive casein hydrolysate formula; T-eCHF, thickened extensive casein hydrolysate formula; M, mean; SD, standard deviation.

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