Pediatr Allergy Immunol 2007: 18: 599–606
DOI: 10.1111/j.1399-3038.2007.00566.x

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PEDIATRIC ALLERGY AND IMMUNOLOGY

Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period

Agostoni C, Fiocchi A, Riva E, Terracciano L, Sarratud T, Martelli A, Lodi F, D'Auria E, Zuccotti G, Giovannini M. Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period.
Pediatr Allergy Immunol 2007: 18: 599–606.
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Observational studies have shown that allergic infants, irrespective of the type of diet, show various degrees of growth depression in the first year of life. We investigated whether the type of milk in the complementary feeding period (6–12 months of age) is associated with differences in the increase of standardized growth indices (weight-for-age, WA; length-for-age, LA; and weight-for-length, WL, *z*-scores) in infants with cow's milk allergy (CMA). Infants with immunoglobulin E-mediated CMA breastfed at least 4 months and progressively weaned in the 5- to 6-month period were randomly assigned to three special formulas, a soy formula (n = 32), a casein hydrolysate (n = 31), and a rice hydrolysate (n = 30). A fourth, non-randomized group was made up by allergic infants still breastfed up to 12 months (n = 32). Groups were compared for WA, LA, and WL *z*-scores at 6, 9 and 12 months of age. All groups showed low WA and LA *z*-scores at 6 months of age. Infants fed hydrolyzed products showed a trend toward higher WA *z*-score increments in the 6- to 12-month period. The use of casein- and rice-based hydrolyzed formulas resulted in higher changes in WA compared with soy formula. Further research should be aimed at optimizing the dietary needs and feeding regimens for infants with CMA.

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Key words: cow's milk allergy; hydrolysate formula; infants' growth; soy formula

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Accepted 23 February 2007

Although allergic disorders are widespread, few studies have evaluated so far the influence on growth. Infants with atopic dermatitis (AD) show depression of growth in the first ages of life (1) but underlying causes are still debatable (2–5). Children with cow's milk allergy (CMA) have been described with vitamin D deficiency rickets as a result of dietary manipulation (6, 7). Recently, the nutritional efficiency of high-degree hydrolysate formulas has been investigated in healthy infants (8). Further clinical trials have investigated growth in infants with AD supplemented with probiotics (9) or with CMA fed different formulas, respectively (10). Indeed, depressed *z*-scores of growth variables in infants with AD are evident in the first 12 months of life, irrespective of the type of diet (11). Interest on growth rates in the first year has been raised by the observation that a 'restricted' growth in this period could affect health outcomes in adulthood (12).

The primary aim of the present study was to investigate whether the type of formula in the complementary feeding period (6–12 months of age) might differently affect growth in infants with CMA.

Subjects and methods

Study design

This was a randomized, prospective, comparative, unblinded trial including infants fully breastfed during the first 4 months of life and diagnosed with CMA within 6 months of age. Infants were consecutively enrolled at the Department of Pediatrics, San Paolo Hospital, and the Department of Child and Maternal Medicine, Melloni Hospital, Milan, Italy during the period June, 2001, through December, 2005.

Infants had to refer at the second-level centers for immune-allergic disorders in both Departments and entered the study according to the following eligibility criteria:

- gestational age, 37–42 wk inclusive,
- Apgar score >7 at 5 min,
- singleton birth,
- birth weight $\geq$2500 g,
- no neonatal disease or congenital malformation,
- having been fully breastfed (13, 14) in the first 4 months of life,
- atopic symptoms occurring within 6 months of life and requiring second-level center care: gastrointestinal (vomiting and/or diarrhea), dermatologic (urticaria, AD), respiratory symptoms (asthma, laryngospasm, rhinitis, conjunctivitis), and/or anaphylaxis, and
- diagnosis of CMA at the second-level center.

In the case of secondary sensitization or bad acceptance/poor compliance to the assigned formula infants had to exit the protocol for the impossibility of being appropriately allocated and evaluated as far as growth.

CMA diagnosis

Infants were tested at skin prick tests (SPT) using fresh milk, soy, rice, and casein hydrolysates (CHy) according to a protocol described elsewhere (15). Specific immunoglobulin (Ig) E determinations were performed for cow's milk, α-lactalbumin, β-lactoglobulin, and casein. A value $\geq$0.35 kU_A/l was considered positive. UniCAP® 100 (Pharmacia Diagnostics AB, Uppsala, Sweden) was used for the analyses.

A double-blind, placebo-controlled food challenge (DBPCFC) was performed to confirm the diagnosis of CMA in all cases who tested positive at SPT and/or specific IgE determination with cow's milk, except in children with a history of anaphylaxis (16). Fresh, pasteurized cow's milk was administered in seven increasing doses of 0.1, 0.3, 1, 3, 10, 30, and 100 ml at 30-min intervals for three and half hours, using Neocate® (Numico, Liverpool, UK) as placebo. Challenge was discontinued at the first onset of symptoms or in case of negative response after the seventh dose. Our challenge method was limited to reactions occurring within 6 h.

Dietary exclusion of milk protein-containing foods was firstly prescribed to breast feeding mothers. Infants whose mothers had insufficient milk or decided to stop breast feeding in the 5- to 6-month period, either directly or weaned to a standard formula before a diagnosis of CMA, were randomly allocated to three different types of formula based on soy protein, hydrolyzed rice, and hydrolyzed casein, whose composition is shown in Table 1. Children testing positive at SPT and/or showing specific IgE to soy, rice, or hydrolysates were in turn randomly allocated to a different treatment group. A non-randomized group maintained breast feeding in the second semester up to 12 months of age. Within this group, infants whose mothers lacked milk and introduced a formula before 12 months left the study, being excluded from the final analysis. The study protocol was approved by the Local Ethical Committees and parents gave their written informed consent at enrolment.

All groups were given similar advice on the introduction of solid foods from the fifth month onward according to general accepted preventive measures (17) and to the individual sensitivity to the tested food items. Common food allergens (egg, fish, peanuts, nuts) were excluded from the diet throughout the study period in agreement with investigations on allergy prevention (18). Other food products causing any suspected hypersensitivity in infants were also eliminated from the diet, including beef when appropriate. A pediatric dietician formulated the dietary schedules based on both the general and the individual food avoidance prescriptions to obtain

Table 1. Composition of the three study formulas per 100 ml (with powder percentage of standard reconstitution)

	Soy	RHy	CHy
Energy, kcal (kJ)	69 (289)	68 (284)	68 (284)
Protein (g)	2.3	2.1	1.9
Carbohydrate (g)	8	8.5	7.5
Fat (g)	3	3.2	3.4
Calcium (mg)	95	75	64
Phosphorus (mg)	66	60	53
Iron (mg)	1.2	1.2	1.22
Zinc (mg)	0.79	0.6	0.48

RHy: Risolac-2 (13.5%), Heinz; CHy: Nutramigen regular (13.6%), Mead Johnson; soy: Isomil-2 (14.2%), Ross Abbott (all products available in the Italian market through the study period).

a balanced and adequate intake of nutrients according to the recommendations of the National Institute of Nutrition (19).The dietician took care that the prescribed intakes of energy, protein, iron, zinc, calcium, and the major liposoluble and hydro-soluble vitamins fulfill the recommended dietary allowances for the Italian pediatric population, either through the permitted food items or specific supplementations (mainly represented by vitamin D and calcium). In the cases of the most extensive dietary restrictions, the major sources of animal proteins were ensured by alternative meats (20). Mothers were instructed to respect the prescribed amounts of foods in preparing the meals for their infants throughout all the complementary feeding period. At the months 9 and 12 visit mothers were interviewed on the infants' acceptance of the prescribed dietary schedules that was rated as 'good' (no food generally left over), 'average' (some difficulties in getting the meal finished and/or minimal amounts generally left out), or 'poor' (major difficulties in getting the meal finished and/or significant amount generally left out). The interviews included both formula feedings and solids.

Breast feeding mothers on diet deprived of products containing cow's milk proteins after infants' CMA diagnosis received daily supplements of vitamin D (400 IU/day) and calcium (1000 mg/day). Infants were also supplemented with 400 IU/day vitamin D and 250 (6–9 months) – 500 (9–12 months) mg/day calcium to reach the daily recommended dietary allowances for 6- to 12-month Italian infants (19), and according to general practice in Italy.

Measurements

The birth parameters (body weight and length) of infants with CMA were obtained from the records shown by parents at recruitment. The following data were further recorded: infants' birth date, mother's age, mother's pre-pregnancy body weight, height (directly measured), and gestational age at delivery (based on obstetrical clinical records shown by the mother) and parity.

Growth parameters were then measured for all the subjects at 6, 9, and 12 months with standardized techniques. The permissible time interval around the actual chronological age for nominal age was ± 14 days for all the visits. The naked infant was weighted on an electronic Sartorius scale (Sartorius AG, Gottingen, Germany) accurate to ± 5 g. Crown-heel length was measured on a portable measuring board to the nearest 0.1 cm. Experienced personnel performed the measurements in both centers. In particular, the longitudinal growth measurements were performed according to a standardized procedure by the same four experienced pediatricians (two per each center). At any time three measurements were taken for each growth parameter and the average value was then considered for the analysis. The coefficient of variation of the weight measurements ranged from 0.7% to 1.2% (observer 1), 0.9% to 1.3% (observer 2), 0.6% to 1.1% (observer 3), and 0.8% to 1.2% (observer 4). The corresponding ranges of the coefficient of variation of the length measurements were 0.8–1.4% (observer 1), 0.8–1.1% (observer 2), 0.7–1.2% (observer 3), and 0.9–1.3% (observer 4). The observed low coefficients of variations together with interobservers' comparability make growth measurements reliable. Actual chronological decimal age was used to calculate the standardized anthropometric indices (z-scores). The weight-for-age, length-for-age, and weight-for-length z-scores (on the following also called WA, LA, and WL z-scores, respectively) were calculated by means of the Version 1.0, May 1990 ANTHRO PEDIATRIC ANTHROPOMETRY Software Program, Version 1.01 (Centers for Disease Control and Prevention, Atlanta, GA), to allow for comparisons with our previous report (11). At the 12-month visit mothers were asked to bring a form previously filled with the exact quantities of formula effectively ingested (as controlled with graded bottles supplied by the centers) the 3 days before the visit.

Statistical analysis

The sample size was determined to detect a $+0.4$ relative change difference (Δ) of WA z-score, with an expected s.d. of 0.55 (9), in the 6- to 12-month period among formula groups and controls, assuming a type-I error of 5% and a power of 80%. Accordingly, 29 subjects per feeding group were required. On the basis of an estimated drop-out rate of 20% in formula-fed infants, at least 35 infants per formula group were recruited, while at least 50 breastfed infants with CMA were required at 6 months, based on an estimated rate of 60% maintaining breast feeding up to 12 months (personal observation).

Descriptive data are shown as mean (s.d.) or number of observations, with 95% confidence intervals (CI). Values of reported z-scores have been truncated to two decimals. The z-scores are expressed as mean values and 95% CI. As the growth data and the relative z-scores in each group were normally distributed comparisons of

continuous variables among groups were performed by one-way ANOVA with *post hoc* bivariate analysis (Student's *t*-test) and Bonferroni's adjustment. Multivariate analyses were performed with ANOVA. Comparisons of discrete variables were performed by means of the chi-squared test or Fisher's exact test, as appropriate. The p-values of <0.05 were considered to indicate statistical significance (two-tailed tests). The SPSS 14.0 Package for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

One-hundred and sixty infants with diagnosis of CMA entered the study in a 5-yr period, 108 formula-fed and 52 still breastfed at 6 months. At diagnosis, SPT with milk was positive in 140 children, SPT with soy in 15, with rice in 13, with hydrolyzed casein formula in six cases, respectively. Specific IgE determinations (UniCAP, Pharmacia) returned positive with cow's milk (n = 148), α-lactalbumin (n = 89), β-lactoglobulin (n = 81), and casein (n = 105). Eliciting symptoms at challenge were: vomiting in 12 cases; lip edema in 27 cases; urticaria in 87 cases; AD exacerbation, defined as a worsening of SCORAD >10%, in 11 cases; asthma in four cases; rhinoconjunctivitis in six cases; anaphylaxis (defined as an acute reaction involving multiple organ systems; 21) in 13 cases.

Within this population, 52 children were still breastfed at 6 months. Among them, 32 children were breastfed through 12 months, and were separately evaluated as non-randomized fourth group, while 20 required the introduction of a formula on medical advice for insufficient human milk before 12 months and left the study. The 108 infants with CMA who stopped breast feeding between the fourth completed month and the end of the sixth completed month of life were randomized to soy formula (soy, n = 37), a CHy (n = 35), and a rice-hydrolyzed formula (RHy, n = 36).

The median age at CMA diagnosis in the 160 infants was 5.3 months (range: 3–6). In the soy group, five children showed gastrointestinal and/or cutaneous symptoms of food allergy within 2 wk after introduction. Three of them showed a positive SPT with soy, and all were excluded from the study for the suspicion of secondary sensitization to soy. Six children in the rice hydrolysate and four in the casein-hydrolyzed group, respectively, left the study because of bad acceptance/poor compliance within 4 wk after starting the treatment. Therefore, the final analysis of the randomized groups included 32 subjects with the soy formula, 31 with CHy, and 30 with RHy. Fig. 1 shows the flow diagram of the trial.

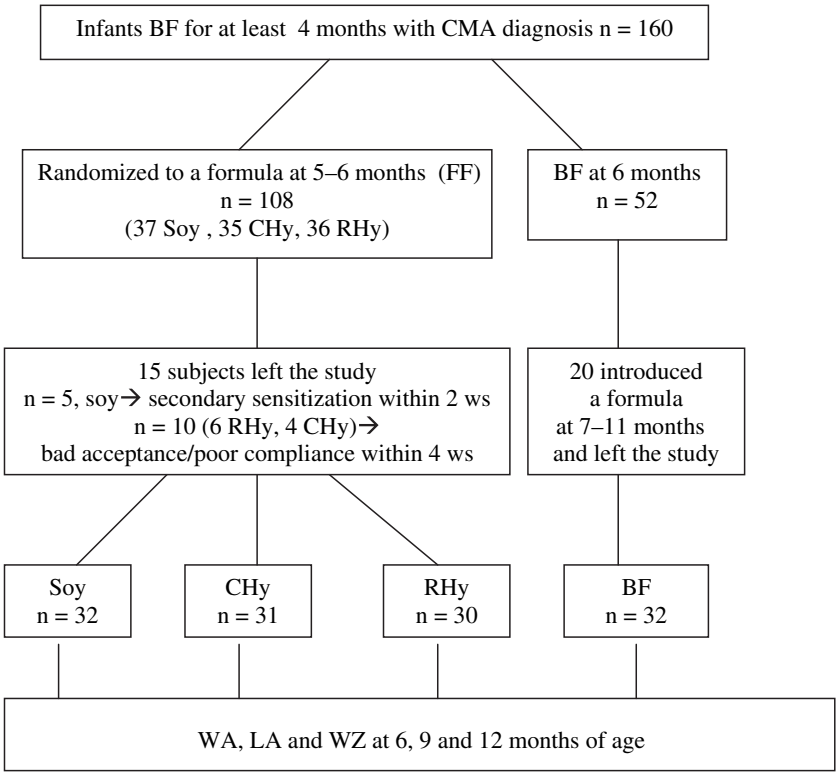

Fig. 1. Flow diagram of subjects progress through the study.

Table 2. Basic characteristics of the four groups of infants (mean, s.d.)

Characteristic	Soy (n = 32)	CHy (n = 31)	RHy (n = 30)	BF (n = 32)	p-Value
Mother's age (yr)	31.2 (3.1)	30.7 (2.6)	31.0 (2.5)	30.6 (1.5)	0.818
Mother's body weight (kg)	55.0 (3.4)	53.9 (5.3)	54.4 (3.2)	54.0 (0.8)	0.584
Mother's height (cm)	164.3 (4.3)	162.6 (3.2)	163.3 (3.3)	162.9 (3.7)	0.301
Gestational age (wk)	39.3 (1.0)	38.7 (0.8)	39.1 (1.0)	39.2 (0.7)	0.092
Parity					
1st	23	19	17	16	0.307
>1st	9	22	12	16	
Infant's gender					
Female	8	10	10	11	0.842
Male	24	21	20	21	
Infant's birth weight (g)	3265 (237)	3341 (356)	3374 (395)	3246 (445)	0.464
Infants' birth length (cm)	49.7 (0.7)	50.4 (1.3)	50.3 (1.4)	50 (1.7)	0.146

Table 3. Standardized anthropometric parameters in the four groups of infants at 6, 9, and 12 months of age (mean values and 95% CI)

Months	Soy (n = 32)	CHy (n = 31)	RHy (n = 30)	BF (n = 32)	p-Value
Weight-for-age *z*-scores					
0	−0.13 (−0.39 to 0.13)	0.24 (−0.07 to 0.55)	0.28 (−0.06 to 0.63)	−0.03 (−0.38 to 0.31)	0.180
6	−0.45 (−0.71 to −0.19)	−0.44 (−0.74 to −0.13)	−0.41 (−0.76 to −0.06)	−0.36 (−0.63 to −0.09)	0.973
9	−0.60 (−0.82 to −0.38)	−0.45 (−0.77 to −0.12)	−0.28 (−0.68 to 0.12)	−0.43 (−0.71 to −0.15)	0.517
12	−0.61 (−0.90 to −0.33)	−0.27 (−0.59 to 0.04)	−0.23 (−0.61 to 0.14)	−0.47 (−0.79 to −0.15)	0.290
Length-for-age *z*-scores.					
0	−0.24 (−0.41 to −0.07)	0.19 (0.01–0.37)	0.01 (−0.38 to 0.40)	−0.11 (−0.39 to 0.17)	0.113
6	−0.55 (−0.81 to −0.29)	−0.40 (−0.69 to −0.10)	−0.73 (−1.00 to −0.46)	−0.49 (−0.75 to −0.24)	0.355
9	−0.49 (−0.74 to −0.23)	−0.33 (−0.59 to −0.06)	−0.58 (−0.94 to −0.21)	−0.48 (−0.77 to −0.20)	0.676
12	−0.43 (−0.73 to −0.13)	−0.16 (−0.51 to 0.19)	−0.49 (−0.79 to −0.18)	−0.48 (−0.79 to −0.17)	0.395
Weight-for-length *z*-scores.					
0	−0.20 (−0.47 to 0.06)	−0.37 (−0.65 to −0.09)	0.12 (−0.61 to 0.86)	−0.31 (−0.62 to −0.00)	0.375
6	−0.12 (−0.45 to 0.21)	−0.20 (−0.54 to 0.13)	0.04 (−0.34 to 0.42)	−0.01 (−0.29 to 0.25)	0.727
9	−0.18 (−0.47 to 0.09)	−0.25 (−0.59 to 0.08)	0.18 (−0.24 to 0.60)	−0.10 (−0.37 to 0.17)	0.260
12	−0.30 (−0.63 to 0.01)	−0.12 (−0.47 to 0.23)	0.24 (−0.15 to 0.65)	−0.11 (−0.46 to 0.23)	0.163

The basic characteristics of the four groups of infants are reported in Table 2. No significant differences were found. On the whole, the symptoms leading the 125 infants to the second-level centers included atopic eczema (78.6%), urticaria/angioedema (23.1%), asthma, and/or rhinitis (11.9%), gastrointestinal symptoms such as colic, vomiting and/or diarrhea (8.6%), and anaphylaxis (5.4%). The 35 subjects who left the study (20, BF, and 15, formula-fed) were comparable with those remaining in the study as far as basic characteristics and presenting symptoms, whose distribution was equivalent among the four groups (data not shown).

Even if allergological findings on the efficacy of treatment were not included in the present survey, CMA infants with AD requiring either local therapy with ointments and corticosteroids or oral antihistaminics were equally distributed among the four groups.

In Table 3a–c the standardized WA and LA and WL *z*-scores for all the four groups are reported as far as birth, the 6-month, 9-month, and 12-month assessments. No between-group differences were found at any time-point. In any case, all the four groups showed quite negative values for both WA and LA at 6 months.

As far as compliance with the recommended intakes, no differences were found. At 9 months of age, 96 infants showed 'good', and 29 'average' or 'poor', compliance. At 12 months of age, 103 infants showed 'good', while 22 'average' or 'poor', compliance. The distribution of infants showing good vs. those showing average and poor acceptance of the prescribed diets (inclusive of formula and solids) was similar in the four feeding groups at 9 and 12 months (chi-squared test, $p = 0.641$ and $p = 0.907$, respectively). At 12 months, the contribution as mean daily intake for the three formulas was 525 ± 139 ml/day for the soy formula, 538 ± 121 ml/day for the casein hydrolyzed, and 546 ± 132 ml/day for the rice-hydrolyzed formula. Breast feeding mothers did not weigh their infants before and after the feeding, according to recommendations

Table 4. Six to 12 months differences for WA (Δ WA), LA (Δ LA), and WL (Δ WL) *z*-scores for all the groups (mean and 95% CI)

	Soy (n = 32)	CHy (n = 31)	RHy (n = 30)	BF (n = 32)	p-Value
Δ WA	−0.16 (−0.36 to 0.04)[a]	0.16 (−0.05 to 0.38)[b]	0.18 (−0.02 to 0.38)[b]	−0.10 (−0.28 to 0.07)	0.023
Δ LA	0.11 (−0.14 to 0.37)	0.23 (−0.10 to 0.58)	0.24 (0.01–0.47)	0.01 (−0.20 to 0.23)	0.548
Δ WL	−0.18 (−0.50 to 0.14)	0.08 (−0.17 to 0.33)	0.21 (−0.17 to 0.59)	−0.09 (−0.40 to 0.20)	0.286

Different superscripts ([a, b]) indicate significant between-group comparisons at bivariate analysis.

on breast feeding practice (13, 14) so no inference can be drawn from this group.

On the whole, infants with lower ('average' or 'bad') acceptance showed a trend to weigh less and to be thinner than those with 'good' acceptance, with a significantly lower change in *z*-score for weight (Δ WA: −0.25, 95% CI: −0.46 to −0.05, vs. 07, 95% CI: −0.03 to 0.18, p = 0.013) in the 6- to 12-month period, while changes were not significant for LA (Δ LA) and WL (Δ WL).

Finally, as primary outcome measure of the study, we computed the 6- to 12-month differences for WA (Δ WA), LA (Δ LA), and WL (Δ WL) *z*-scores for all the groups (Table 4). According to the general model, Δ WA yielded a difference among groups (p = 0.023). Crude bivariate comparisons yielded significant differences of Δ WA for infants-fed RHy (mean + 0.34 *z*, p = 0.019) and CHy (mean + 0.32 *z*, p = 0.029) vs. the soy formula group, respectively. After Bonferroni's adjustment, significance levels were 0.090 and 0.120, respectively. In a multivariate model including Δ WA *z*-score in the 6- to 12-month period as dependent variable, feeding group as factor and infants' acceptance at 12 months (good vs. average + poor) as covariate, both were significantly related to changes in Δ WA *z*-score (p = 0.023 and p = 0.013, respectively). The estimated marginal mean values according to feeding groups, 95% CI, were −17 (−0.36 to 0.02) for soy, 0.16 (−0.03 to 0.35) for CHy, 0.18 (−0.02 to 0.38) for Rhy, and −0.09 (−0.29 to 0.09) for BF, respectively.

Discussion

To date, only one prospective randomized trial with a statistical design adequately powered has evaluated growth by comparing the effects of special formulas (soy and casein-hydrolyzed based, respectively) in infants affected by CMA through 48 months of age (10). The study also considered some nutritional parameters, and, as both nutritional status and growth were within reference values in the two groups. The authors concluded that the selection of a formula can largely be based on the infant's tolerance to the formula. The mean starting ages for the two formulas were in any case more advanced than in the present study, whose aim was to look at the changes of growth parameters in four groups of infants with CMA differing for the type of milk consumed in the 6- to 12-month period, i.e., during the progressive, controlled introduction of solids. To prevent possible misinterpretations of data connected to the well-known differences between breastfed and formula-fed infants, we included in the study only infants who were fully breastfed for the first four completed months of life, i.e., those with CMA who switched to a formula in the 4- to 6-month period (randomized groups) and those with CMA who were kept breastfed up to 12 months (reference, non-randomized group).

Our data confirm that at 6 months of life infants with CMA present with lower values of growth parameters, as shown for infants with AD (11). Moreover, Seppo et al. have shown in their randomized trial negative *z*-scores values, as far as both length at 6–12 months, and WL at 6–36 months, respectively (10). Causes of impaired growth in infants affected by CMA are still unclear. An impaired ability to utilize nutrients, possibly caused by an allergy-induced inflammation of the gut mucosa (22), together with increased nutritional demands, particularly in cases of AD, considering the high metabolic requirements of the skin turn-over (23) and the high energy expenditure due to agitation (24), represent plausible explanations. Growth rates in the first months of life may have later effects. Both early weight restriction (12) coupled with later growth acceleration (25) could have a negative impact on future health.

In this study, during the complementary feeding period, when solids are introduced according to the individual allergic response, all CMA groups showed positive values of LA *z*-score progression, while only infants fed a hydrolyzed product (derived from rice or casein) showed a trend of positive WA *z*-score gain. Even if the intake of other foods, specifically solids, besides formulas, could have affected the rates of growth, as shown by the trend toward lower WA and WL *z*-scores found in infants with the minor degrees

of dietary compliance, no major differences have been found among the different feeding regimens on the basis of the interviews on infants' compliance. At the same time, also the amount of formula ingested in the 3 days before the visit was similar in the three artificially fed groups. Therefore, our data suggest that hydrolyzed proteins could have a qualitative advantage on a nutritional standpoint compared with complete protein sources (such as soy formulas or human milk).

The lower rates of growth in breastfed infants are consistent with present knowledge. While the nutritional efficiency of human milk proteins is higher than any other source, the protein content of human milk is lower than standard infant formulas (around 1 g/dl; 26). Moreover, as human milk proteins include several immune factors, the true supply of 'nutritional' proteins through human milk is even lower (26, 27). The limited protein supply in healthy, breastfed infants has been indeed associated with the decreased growth rates in the 6- to 12-month period when compared with formula-fed counterparts (28, 29). The switch from human milk to a special formula, with a parallel increase of energy intake, has been associated with growth improvement in allergic infants (30). This observation has raised some questions on the opportunity to maintain breast feeding, in selected cases with CMA and poor growth (31), putting on the balance all the other potential benefits of prolonged breast feeding (32).

The apparent major nutritional efficiency of high-degree hydrolysates, as from the present study, is worthing further investigations to better define the origins of the nutritional impairment in allergic infants, and to develop individually tailored products and diets. As all formulas used in this study have comparable levels of protein and energy, within recommended safe limits (27), increments observed in the groups fed hydrolysate products seem independent from their absolute nitrogenous supply. Accordingly, the quality and type, more than quantity, by which nitrogenous compounds are supplied to allergic infants could be relevant not just for the treatment of the specific symptoms, but also to improve growth. Even if hydrolysates could not be nutritionally advantageous in the first months of life, when breast- or formula-milk represent the only food source (33, 34), their use in the 6- to 12-month period might decrease local inflammatory responses, positively affecting the absorption of nutrients from the other solid foods, whose role, potentially affecting growth as well, should be explored in further studies. Cow's milk hydrolysates should respect a minimum protein content of 1.8 g/100 kcal, and it has recently been recommended (35) that products with a protein content < 2.25 g/100 kcal should be clinically tested, and higher contents considered for products deriving nitrogen from sources other than cow's milk. Indeed, earlier preliminary reports on growth in allergic infants followed from 4 to 6 months throughout the second year of life using the same RHy formula utilized in the present study, but with 25% less protein content (Risolac-1), did not show positive associations with growth rates (36, 37). More importantly, neither study was adequately powered on a statistical standpoint to show any hypothesis on growth differences as recommended (38).

In conclusion our data suggest that, in agreement with previous observations, CMA is a major determinant of growth rates in the first year of life. In the complementary feeding period hydrolyzed formulas may provide better short-term weight gain compared with soy formula, without significant differences in length progression. Nevertheless, taking into account that breastfed infants were not statistically different from all study groups, the clinical relevance of this weight gain is yet to be determined, as well as the possible role of complementary foods.

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