Original Article

Effect of Extensively Hydrolyzed Milk Formula on Growth and Resistance to Bronchitis and Atopic Dermatitis in Infants and Toddlers

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Abstract. *Objective:* This study aimed to evaluate the adverse effects of extensively hydrolyzed milk formula on growth in infants and toddlers.
Methods: Prospectively, 45 infants and toddlers with a positive history of cow's milk allergy confirmed by positive skin prick test and high IgE levels for either α-lactalbumin, ß-lactoglobulin, or casein and positive single-blind food challenge received extensively hydrolyzed milk formulas for 1 year. Sex-normalized percentiles of heights and weights of infants and toddlers before their enrollment in the study were compared to those at the end of the study. The contribution of breastfeeding, early use of bottle feeding and intake of adapted or special milk formulas, and history of bronchitis and atopic dermatitis on toddlers' growth were also evaluated by multivariate analysis.
Results: Similar percentiles of the children's weight and height were observed at the beginning of the study and 1 year later. According to the multivariate analysis, sex, breastfeeding, early bottle feeding, ingestion of adapted or special milk formulas, atopic dermatitis, and bronchitis were not correlated with either the children's weight or height at diagnosis of the allergy or at 1 year of follow-up ($P > .10$). Weights and heights were not different between toddlers who had atopic dermatitis or bronchitis during the study period and those who did not.
Conclusions: Growth of infants and toddlers with cow's milk allergy was not affected by the intake of extensively hydrolyzed milk for 1 year. Atopic dermatitis and bronchitis did not appear to have any deleterious effect on these children's growth.

Key words: Body measures. Food hypersensitivity. Postnatal growth.

Resumen. *Objetivo:* El objetivo del estudio fue evaluar los efectos adversos de una fórmula de leche extensamente hidrolizada sobre el crecimiento en niños de corta edad.
Métodos: Prospectivamente, 45 niños con un historial positivo de alergia a leche de vaca confirmada mediante prueba de punción cutánea positiva y niveles elevados de IgE para la α-lactoalbúmina, ß-lactoglobulina o caseína y con reto ciego - simple positivo, recibieron fórmulas de leche extensamente hidrolizada durante un año. Los percentiles normalizados por sexo de las estaturas y los pesos de los niños registrados antes de la inclusión en el estudio se compararon con los registrados al final del estudio. También se evaluó mediante análisis multifactorial la contribución de la lactancia materna, el uso temprano de lactancia artificial y la ingesta de fórmulas de leche especiales o adaptadas, así como el historial de bronquitis y dermatitis atópica en el crecimiento de los niños.
Resultados: Se observaron percentiles similares relativos al peso y la altura de los niños al inicio del estudio y al cabo de 1 año. Según el análisis multifactorial, el sexo, la lactancia materna, el uso temprano de lactancia artificial, la ingesta de fórmulas de leche especiales o adaptadas, la dermatitis atópica y la bronquitis no se relacionaron con la altura y el peso de los niños en el momento de diagnosticar la alergia o tras 1 año de seguimiento ($P > 0,10$). Los pesos y las alturas no registraron diferencias entre los niños que presentaron dermatitis atópica o bronquitis durante el período de estudio y aquellos que no.
Conclusiones: El crecimiento de los niños con alergia a la leche de vaca no se vio afectado por la ingesta de leche

extensamente hidrolizada durante 1 año. La dermatitis atópica y la bronquitis no parecieron tener ningún efecto perjudicial sobre el crecimiento de los niños.

Palabras clave: Medidas corporales. Hipersensibilidad alimentaria. Crecimiento posnatal.

Introduction

Infants are highly sensitive to environmental and dietary factors for developing food allergies, atopic dermatitis, and other allergic diseases [1, 2]. The prevalence of food allergies may range from 0.3% to 7.5% in children [3]. For children with cow's milk allergy, hydrolyzed milk formulas are the preferred treatment. Partially hydrolyzed milks are typically used for preventing food allergy whereas extensively hydrolyzed formulas are preferred for treating cow's milk allergy in children [4-6]. However, extensively hydrolyzed milk formulas may not necessarily provide the same nutrients as cow's milk or regular milk formulas and growth development may be affected [7-14].

Evidence of an interrelationship between bronchial function and nutrition has been previously described. Nutritional depletion was found to be an independent risk factor for increasing hospitalization and mortality rates in adult patients with chronic obstructive pulmonary disease [15]. Malnutrition was also found to be a risk factor for severe bronchiolitis among Indian children [16]. Similarly, the growth of children with atopic dermatitis may be altered [17].

This study was performed in infants and toddlers with the following aims: a) to evaluate the adverse effects of extensively hydrolyzed milk formula on growth, and b) to assess resistance to bronchitis and atopic dermatitis.

Material and Methods

Study Design

This was an open, single-arm prospective cohort study of infants and toddlers with cow's milk allergy treated with extensively hydrolyzed milk formula for 1 year. The study was approved by the Institutional Review Board of the Hospital Universitario Materno-Infantil "12 de Octubre" in Madrid, Spain. We identified 150 potentially eligible patients with cow's milk allergy receiving medical care in the hospital's department of pneumology and allergy.

Patients

Before enrolling a patient in the study, we obtained personal history, duration of breastfeeding, early bottle feeding, a clear description of positive or negative history of atopic dermatitis or bronchitis, and whether the subjects were receiving a milk-based infant formula or any extensively hydrolyzed cow's or soy milk formula.

The patients also underwent the following pre-inclusion examinations:

– Skin prick test for α-lactalbumin, ß-lactoglobulin, and casein (ALK Abellò, Hørsholm, Denmark). Briefly, the test consisted of placing a drop (50 µL) of food glycerin extract, a drop of histamine as the positive control, and a drop of glycerin as the negative control on a child's forearm skin surface. The skin was pricked at a 90º angle through the test drops. Skin response was evaluated according to Bock and May criteria [18]. Presence of wheal and erythema was evaluated 15 to 20 minutes after the allergen challenge. An indurate wheal at least 3 mm in diameter was considered a positive test for food hypersensitivity.

– Plasma levels of IgE for α-lactalbumin, ß-lactoglobulin, casein or milk (CAP System FEIA; Pharmacia & Upjohn Diagnostics, Uppsala, Sweden).

– Single-blind food challenge: a single blind challenge was performed as previously described with fresh pasteurized cow's milk containing 3.5% fat in successive doses (0.1, 0.3, 1.0, 3.0, 10, 30, and 100 mL) the time interval between each dose was 30 minutes. Testing was halted if clinical symptoms were observed or the highest dose was reached. The children were observed for up 48 hours after the challenge. The food challenge was scored as positive if objective clinical reactions were observed such as urticaria, angioedema, wheezing, vomiting, diarrhea, abdominal pain or exacerbation of eczema. An increase in the score of atopic dermatitis of the European Task Force on Atopic Dermatitis of at least 10 points was used for defining exacerbation [18].

Parents were instructed on how to administer the extensively hydrolyzed milk formula according to the infants or toddlers' ages and weights. They were also provided with instructions on what to do if the child had skin lesions suggestive of atopic dermatitis or wheezing suggestive of bronchitis.

The participants received a diet plan from nutritionists and were followed for 1 year, during which they were periodically contacted by phone to verify their health status. Episodes of bronchitis or atopic dermatitis were clinically verified and recorded for the purpose of this study. At the end of the study period, participants underwent a complete clinical evaluation.

The infants or toddlers were included if they had a positive history of cow's milk allergy as reported by their parents in addition to having a positive skin prick test, high levels of IgE for α-lactalbumin, ß-lactoglobulin and casein, and a positive oral challenge to cow's milk.

Table 1. Effect of Extensively Hydrolyzed Milk Formulas on Children's Weight and Height

	At Baseline	At 1 Year of Follow-Up	95% CI for the Differences*
Age, months	6 (1.0 to 27)	15 (5 to 39)	NA
Weight, kg	7.8 ± 2.1	10.5 ± 2.4	– 3.1 to – 2.3
Weight in percentiles	32.8 ± 27.6	34.4 ± 23.0	– 6.5 to 3.1
Height, cm	68.6 ± 9.1	79.2 ± 8.4	– 11.8 to – 9.1
Height in percentiles	48.7 ± 33.2	47.4 ± 31.1	– 5.2 to 8.1

* CI indicates confidence interval; NA, not applicable. Weight and height differences were statistically significant between the evaluation periods *(P < .001)*. Data shown are means ± SD, or medians (range).

Patients included in the study did not have any clinical evidence or history of systemic diseases or abnormal neurological, cardiac, liver or renal function. Patients were excluded if they had been taking oral steroids, immunosuppressive agents, or antihistamines with a prolonged half life.

Statistical Analysis

The patients' weight and height were compared to local standard growth tables (Instituto de Investigación sobre Crecimiento y Desarrollo Fundación F Orbegozo, Bilbao, Spain) and were expressed in terms of the percentile for the child's age. Mean weight and height at baseline and a year later were compared with a paired Student *t* test and the 95% confidence interval (CI) for the differences was calculated. The Pearson correlation coefficient was obtained for weights and heights between the baseline and 1-year evaluations. Multivariate analysis was used to analyze whether sex, previous or current atopic dermatitis or bronchitis, breastfeeding, early bottle feeding, adapted formula and special formula were associated with the children's weight and height percentiles. After the final evaluation, patients were grouped a posteriori according to whether or not they had suffered from bronchitis or atopic dermatitis during the study period in order to analyze whether either of those conditions was related to the children's weights or heights. In every statistical analysis, a difference on a 2-tailed test was considered significant at a level of *P* less than .05.

Results

All 45 infants or toddlers who satisfied the inclusion criteria and received the extensively hydrolyzed milk formula for 1 year completed the study evaluations. None of the participants had been receiving extensively hydrolyzed milk formula before entering the study. Twenty-three were male (51.1%) and 22 were female (49.9%). As expected, at 1 year of follow-up, the patients had grown significantly as evidenced by the increased weights and heights (Table 1). Extensively hydrolyzed whey/casein formula was used by 18 (40%) children, extensively hydrolyzed casein formula by 11 (24%), extensively hydrolyzed whey formula by 6 (13.3%), soy formula by 4 (8.8%), extensively hydrolyzed soy formula by 1 (2.2%), and breastfeeding by 5 (11.1%). Percentile weights and heights at baseline were similar to those at 1 year of follow-up.

The coefficient of correlation between the children's weight at baseline and 1 year later was 0.85 (95% CI, 0.74-0.92; $P < .0001$). For height the correlation was 0.87 (95% CI, 0.76-0.92; $P < .0001$). The coefficient of correlation between weight and height was 0.93 (95% CI, 0.88-0.96; $P < .0001$) at baseline and 0.95 (95% CI, 0.92-0.97; $P < .0001$) at the 1-year follow-up examination. According to the multivariate analysis, none of the variables (positive breastfeeding, early bottle feeding, children's sex, presence of atopic dermatitis or bronchitis, intake of extensively hydrolyzed formula) explained either the children's weight or height at the beginning of the study ($P > .10$).

Atopic dermatitis was reported in 18 (40%) patients

Table 2. Effect of Atopic Dermatitis or Bronchitis on the Growth of Infants and Toddlers With Cow's Milk Allergy Fed With Extensively Hydrolyzed Milk for 1 Year

	With Disease	Without Disease	95% CI for the Differences*
Bronchitis	n = 8	n = 37	
Weight, kg	11.0 ± 2.8	10.4 ± 2.4	- 1.3 to 2.5
Height, cm	80.9 ± 9.	78.9 ± 8.2	- 4.7 to 8.7
Atopic dermatitis	n = 13	n = 32	
Weight, kg	11.2 ± 2.9	10.2 ± 2.2	- 0.6 to 2.6
Height, cm	82.1 ± 9.1	78.1 ± 8.0	- 1.5 to 9.5

* CI indicates confidence interval. Values shown for weights and heights are means ± SD. Differences were not significant *(P > .05)*.

at the beginning of the study and in 13 (28.9%) at the end, whereas bronchitis was reported in 5 (11.1%) and 8 (17.8%), respectively. However, atopic dermatitis or bronchitis did not appear to affect the children's growth after 1 year of being fed with extensively hydrolyzed milk formula (Table 2). The multivariate analysis did not show that the presence of atopic dermatitis or bronchitis during the study period or any of the factors previously analyzed correlated with children's weight or height at the end of the study period ($P > .10$). Since percentile weights and heights at the beginning were not different compared to those at the end of the study period (Table 1), we did not perform any multivariate analysis with these data.

Discussion

In this study, the intake of extensively hydrolyzed milk formula by infants and toddlers with cow's milk allergy during a 1-year period did not appear to adversely affect the children's growth despite the high rate of atopic dermatitis or bronchitis among them. In contrast, Henriksen et al [8] showed that 50% of children who were on a diet free of cow's milk had lower intake of lipids and total energy resulting in heights below the 10th percentile. Due to the lower amount and number of nutrients found in extensively hydrolyzed milk formulas in comparison with cow's milk or regular infant formulas [12], it may be hypothesized that children's growth may be affected even with short periods of exposure to such formulas [13]. We were unable to document whether the toddlers received supplemental foods or nutritional supplements in addition to the diet plan established by the nutritionists, and therefore cannot rule out the possibility that the absence of deleterious effects on children's growth after 1 year of drinking extensively hydrolyzed cow's milk formulas was influenced by the provision of additional sources of nutrients by the children's parents.

In a cohort of children with a mean age of 7 months who had atopic dermatitis and cow's milk allergy, low serum albumin was present in 6% of the patients, 24% had abnormal urea concentration, and 8% had low deicosahexaenoic acid levels in serum phospholipids and their growth was delayed in comparison to healthy age-matched children [10]. The delay in infants' growth was more pronounced in the subgroup of patients with early onset of the disease. A recent study showed that more children with cow's milk allergy or multiple food allergies consumed dietary calcium in amounts lower than recommended compared with children without cow's milk allergy or with a single food allergy [19]. The risk of having less than the recommended daily intake of calcium and vitamin D in children with food allergy was lower if children received nutritional counseling or consumed a cow's milk-free infant formula or calcium-fortified soy beverage [19]. Seppo and colleagues [20] found no growth delay in infants fed with extensively hydrolyzed whey formulas, although most of the children received calcium and vitamin D supplements. In our study, whey/casein and casein formulas were used more frequently for feeding the children and we observed no differences in their percentiles for weight and height at 1 year of follow-up.

In children with food allergies, malnutrition may result from a variety of factors including a reduction of nutrient intake because of the allergic status of the children. Differences in the flavor of cow's milk and other milk formulas may favor a lower milk intake, contributing to the malnutrition of allergic children. However, if a proper mixture of amino acids is provided to children with cow's milk allergy for supplementing the milk formula, patients may grow similarly to healthy children [3-5]. Recommended intakes of protein and energy for normal healthy individuals based on the 1989 recommended daily allowances for an infant from 0 to 0.5 months are 2.2 g/kg per day and 108 kcal/kg per day, respectively; for an infant from 0.5 to 1 year the recommendations are 1.6 g/kg per day and 98 kcal/kg per day, respectively; and for a child from 1 to 3 years old they are 1.2 g/kg per day and 102 kcal/kg per day [21]. In the present study, we failed to clarify whether the children received a proper protein and caloric supply from foods other than cow's milk products to help them maintain weight and height at similar percentiles to those recorded at the beginning of the study.

Protein hydrolysate formulas appear to have excessive amounts of amino acids in comparison with regular infant formulas, as reflected by findings of high concentrations of serum urea nitrogen and plasma amino acids [22]. Greater nitrogen loss has also been reported in individuals who received L-amino-acids as their source of protein in comparison to those who received whole protein [22]. In children with food allergy, intake of complete and/or complementary proteins in addition to sufficient calories should be assured in order to provide essential amino acids in adequate amounts, and a reduced and more balanced amino acid content of hydrolysate formulas may be beneficial.

A growth delay has been demonstrated in children with bronchitis or atopic disease [17], although growth impairment has been found to be temporary [23]. We observed no adverse effect at 1 year of follow-up in toddlers who had either atopic dermatitis or bronchitis during the follow-up period.

We were unable to include an age-matched control population of normal individuals on non-hydrolyzed milk formulas. However, the toddlers' weight and height were age-adjusted to percentiles according to local growth tables. By this procedure, the children's growth was normalized, facilitating pre- and postintervention comparisons, in which we observed no statistically significant differences. However, a study with a larger sample size and including a control group would help to clarify long-term the effects of extensively hydrolyzed milks on children's growth.

In conclusion, this study found that the weight and height of toddlers with cow's milk allergy receiving extensively hydrolyzed milk formulas for approximately

1 year was not adversely affected even in infants and toddlers with bronchitis or atopic dermatitis as comorbidities. Because of the limitations of the study, future confirmation is needed before a lack of adverse effect of these formulas can be ruled out in this age.

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