

Growth of infants with gastrointestinal manifestations of cow's milk protein allergy

Crescimento de lactentes com manifestações gastrointestinais de alergia à proteína do leite de vaca

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ABSTRACT

Objective

To assess linear growth and weight gain in infants with suspected cow's milk protein allergy with gastrointestinal manifestations, seen at a gastropediatrics clinic.

Methods

A retrospective cohort study conducted with demographic, clinical, anthropometric and dietary information on 84 infants first seen between 2015 and 2018 and followed-up for six months. Stature-for-age, weight-for-age, and body mass index-for-age in z-scores were evaluated according to the cut off points established by the World Health Organization in 2006. Accelerated growth or *catch-up* was considered a gain ≥ 0.67 in the z-score of the referred indices, evaluated at 3 and 6 months.

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Article based on the master's thesis of PP ASSIS, entitled "Crescimento linear e ganho de peso em lactentes com alergia à proteína do leite de vaca gastrointestinal". Universidade Federal de Pernambuco, 2021.

How to cite this article

Assis PP, Menezes JSS, Diniz AS, Antunes MMC, Cabral PC. Growth of infants with gastrointestinal manifestations of cow's milk protein allergy. Rev Nutr. 2022;35:e210075. <https://doi.org/10.1590/1678-9865202235e210075>

Results

Median age at baseline was 4.0 months and 88.1% of the infants were already in diet exclusion. Regarding the anthropometric evaluation short stature frequency was 15.5% and the underweight frequency was 8.3% and 3.6% respectively based on the weight-for-age and body mass index-for-age indices. High recovery growth was observed during the follow-up period but was not considered *catch up*. In boys, the gains in weight-for-age and body mass index-for-age were significant ($p=0.02$ and $p=0.01$ respectively) and close to the threshold that characterizes the *catch up*, 0.58 and 0.59, respectively. In girls, significant gains in stature-for-age and weight-for-age (0.38 and 0.37 respectively, $p=0.02$ for both) were observed.

Conclusion

Infants with suspected cow's milk protein allergy with gastrointestinal manifestations should have early access to specialized nutritional counseling to avoid exposure to allergenic food and control allergy symptoms, thereby avoiding malnutrition and ensuring adequate nutritional recovery.

Keywords: Cow's milk protein allergy. Growth. Infant.

RESUMO

Objetivo

Avaliar o crescimento linear e o ganho de peso de lactentes com suspeita de alergia à proteína do leite de vaca, com manifestações gastrointestinais, atendidos em um ambulatório de gastropediatria.

Métodos

Estudo de coorte retrospectivo, com informações demográficas, clínicas, antropométricas e dietéticas de 84 lactentes que iniciaram atendimento entre 2015 e 2018 e foram acompanhados durante seis meses. Foram avaliados os índices estaturalidade, peso/idade e índice de massa corporal/idade em *escore-z*, segundo os pontos de corte da Organização Mundial de Saúde de 2006. Considerou-se crescimento acelerado (ou *catch-up growth*) um ganho $\geq 0,67$ *escore-z* nos referidos índices, avaliados em três e seis meses.

Resultados

No baseline, a mediana de idade foi 4,0 meses e 88,1% dos lactentes já estavam em dieta de exclusão. A frequência de baixa estatura foi de 15,5% e a de baixo peso foi de 8,3% e de 3,6% segundo os índices peso/idade e índice de massa corporal/idade, respectivamente. Houve elevado crescimento de recuperação durante o período de acompanhamento, mas que não configurou *catch up*. Nos meninos, ganhos no peso/idade e índice de massa corporal/idade foram significantes ($p=0,02$ e $p=0,01$) e próximos do limiar que caracteriza *catch up*: 0,58 e 0,59, respectivamente. Nas meninas, foram observados ganhos significantes na estaturalidade e peso/idade, de 0,38 e 0,37 ($p=0,02$ para ambos).

Conclusão

Demonstrou-se que lactentes com suspeita de alergia à proteína do leite de vaca, com manifestações gastrointestinais, deveriam ter acesso precoce ao aconselhamento nutricional para evitar exposição ao alimento alergênico, controlar sintomas e, assim, evitar a desnutrição ou garantir recuperação nutricional adequada.

Palavras-chave: Alergia à proteína do leite de vaca. Crescimento. Lactente.

INTRODUCTION

The proper growth of infants is extremely important for them to be able to reach their physical and mental potential in adulthood [1]. Insults to growth during infancy can lead to permanent damage [2].

Cow's Milk Protein Allergy With Gastrointestinal Manifestations (CMPA-GM) affects infants and can impair their growth. It is an allergy difficult to diagnose and cow's milk Diet Exclusion (DE) is a risk factor of growth deficit in CMPA-GM patients. On the other hand, cow milk intake is essential for both diagnosis and treatment [3].

Cow's Milk Protein Allergy With Gastrointestinal Manifestations can manifest itself in three forms: gastrointestinal enteropathy, enterocolitis syndrome and proctocolitis which, although clinically distinct, may have common manifestations. The most frequently observed clinical manifestations include diarrhea (in the three forms), vomiting (in gastrointestinal enteropathy) and blood in stools (in proctocolitis). Gastrointestinal enteropathy and enterocolitis syndrome are the most severe forms [4].

Growth studies in infants with suspected CMPA-GM have found growth deficits and later recovery, but further research is still needed [5,6]. Thus, the research aimed to describe the growth of infants with suspected CMPA-GM and the clinical and nutritional characteristics involved in this process.

METHODS

This was a retrospective cohort study, based on data from medical records of infants admitted to the pediatric gastroenterology service of the *Hospital das Clínicas of the Universidade Federal de Pernambuco* (UFPE), Brazil, who visited the service between 2015 and 2018.

Children under 24 months of age with suspected CMPA-GM were included in the study after evaluation by the gastropediatricians responsible for the service and kept under follow-up in three visits during six months. Patients with chronic diseases, genetic syndromes, cerebral palsy, congenital diseases and any condition that affected growth and development were excluded.

At each visit, demographic, clinical, anthropometric and dietary information was collected. Information regarding birth (gestational age and birth weight) was also collected. Infants born before thirty-seven weeks of gestation were classified as premature and when born weighing less than 2500g, they were classified as low birth weight.

During the follow-up period, the nutritional status was evaluated by the indices Stature for Age (S/A), Weight for Age (W/A) and Body Mass Index for Age (BMI/A) in z-score, considering gender, age and corrected age for premature infants. Hence, AnthroPlus software and the cutoff points of the World Health Organization for children under 5 were used [7].

Overweight (risk of overweight, overweight and obesity) was defined as $\geq +1$ z-score in the W/A and BMI/A rates. For Underweight (UW) values < -2 z-score using the same indexes were considered and for Short Stature (SS) values < -2 z-score in the S/A index.

Growth gains were evaluated by the change in z-score in the three indices, at the first visit (baseline), after three months (second visit) and after six months (third visit), considering the cutoff point of Ong et al. [8], who consider accelerated growth or *catch-up* growth a weight gain above 0.67 z-score [8].

Anthropometric data were collected following the recommendations of the Food and Nutritional Surveillance System of the Ministry of Health of Brazil [9] and statistical analyses were performed using the SPSS (Inc., Chicago, IL) version 13.0, software. Comparisons between the periods reviewed were made through the means of z-scores (S/A, W/A and BMI/A) (all presented normal distribution) with the application of ANOVA for repeated measures with Bonferroni's post hoc test. Associations were analyzed using Pearson's chi-square, linear trend chi-square and Fisher's test (5% significance level).

This study was approved by the Ethics Committee for Research in Humans at *Universidade Federal de Pernambuco* – CAAE nº 19138619.2.0000.5208.

RESULTS

Out of the 116 infants admitted to the service during the study period, 84 were kept under follow-up for suspected CMPA-GM after the gastropediatrics assessment. This follow-up took place for 6.2 ± 1.6 months

and the loss rate was 27.6%. Some variables were compared between follow-up infants and losses, with no evidence of differences between the groups assessed (Table 1).

At baseline, the infants' median age was 4.0 months (P25=3.0 and P75=7.0) and 53.6% were male. The frequencies of prematurity and low birth weight were 13.4% and 12.9%, respectively. Among the infants evaluated, 15.5% presented SS and UW was present in 8.3% and 3.6% of them considering W/A and BMI/A, respectively (Table 1).

Table 1 – Comparison of baseline demographic, clinical and anthropometric characteristics of children with gastrointestinal manifestations of allergy to cow's milk protein, in the gastropediatrics service of *Hospital das Clínicas da Universidade Federal de Pernambuco*, who were followed up and losses occurred during follow-up. Recife (PE), Brazil, 2015-2018.

Variables	Follow up n=84			Losses n=32			p*
	n	%	95% CI	n	%	95% CI	
Gender							0.724
Male	45	53.6	42.4-64.4	19	59.4	40.8-75.8	
Female	39	46.4	35.6-57.6	13	40.6	24.2-59.2	
Gestational age**							0.408
Preterm	11	13.4	7.2-23.1	07	21.9	9.9-40.4	
At term	71	86.6	76.8-92.8	25	78.1	59.5-90.0	
Birth weight**							0.257*
Underweight	08	12.9	6.1-24.4	06	19.4	8.1-38.0	
Insufficient weight	17	27.4	17.2-40.4	04	12.9	4.2-30.7	
Adequate weight	37	59.7	46.5-71.7	21	67.7	48.5-82.7	
Age (months)							0.249
≤6	61	72.6	61.6-81.5	19	59.4	40.8-75.8	
≥7	23	27.4	18.5-38.4	13	40.6	24.2-59.2	
Mean (P ₂₅ and P ₇₅)		4.0 (3.0 and 7.0)			5.0 (4.0 and 7.0)		
Stature/age							0.593 [†]
Short stature	13	15.5	8.8-25.4	05	15.6	5.9-33.5	
Adequate stature	71	84.5	74.6-91.2	27	84.4	66.4-94.1	
Weight/age							0.984 [‡]
Underweight	07	8.3	3.7-16.9	03	9.4	2.4-26.2	
Eutrophy	69	82.1	71.9-89.3	26	81.2	63.0-92.1	
Overweight	08	9.6	4.5-18.4	03	9.4	2.4-26.2	
Body Mass Index/age							0.074 [‡]
Underweight	03	3.6	0.9-10.8	00	0.0	0.0-13.3	
Eutrophy	67	79.7	69.3-87.4	24	75.0	56.2-87.9	
Overweight	14	16.7	9.7-26.7	08	25.0	12.1-43.7	

Note: *Pearson chi-square; **The number is different due to the number of respondents. 95% CI = 95% Confidence Interval; [‡]Linear trend chi-square; [†]Fisher test.

Also at baseline, only 15.5% were on exclusive breastfeeding, the others were already using some type of Hypoallergenic Formula (HF), predominantly composed of free aminoacids (48.8%). Formulas were extensively hydrolyzed (32.1%), and 33, 3.0% of the infants had already started Complementary Feeding (CF). In 88.1% of cases, the lactating mother (breastfeeding mother) was already excluding cow's milk from the infant's diet. From the beginning of DE to baseline, about two months had elapsed.

As for the clinical presentation, 51.2% of the infants were taken to the service with diarrhea, 48.8% with blood in stool, and 25.0% with vomiting. The association of vomiting and diarrhea occurred in only 13.1% of the infants a fact that drew attention. In addition, dermatological manifestations occurred in 28.6% of them and respiratory manifestations in 7.1%.

Figure 1 shows the evolution of anthropometric indices in the sample. In the S/A z-score, there was a stature increase from the first to the second visit, demonstrating an acceleration of growth. From the second visit, stature started to increase at a normal pace. But the *catch-up* of linear growth has not been established.

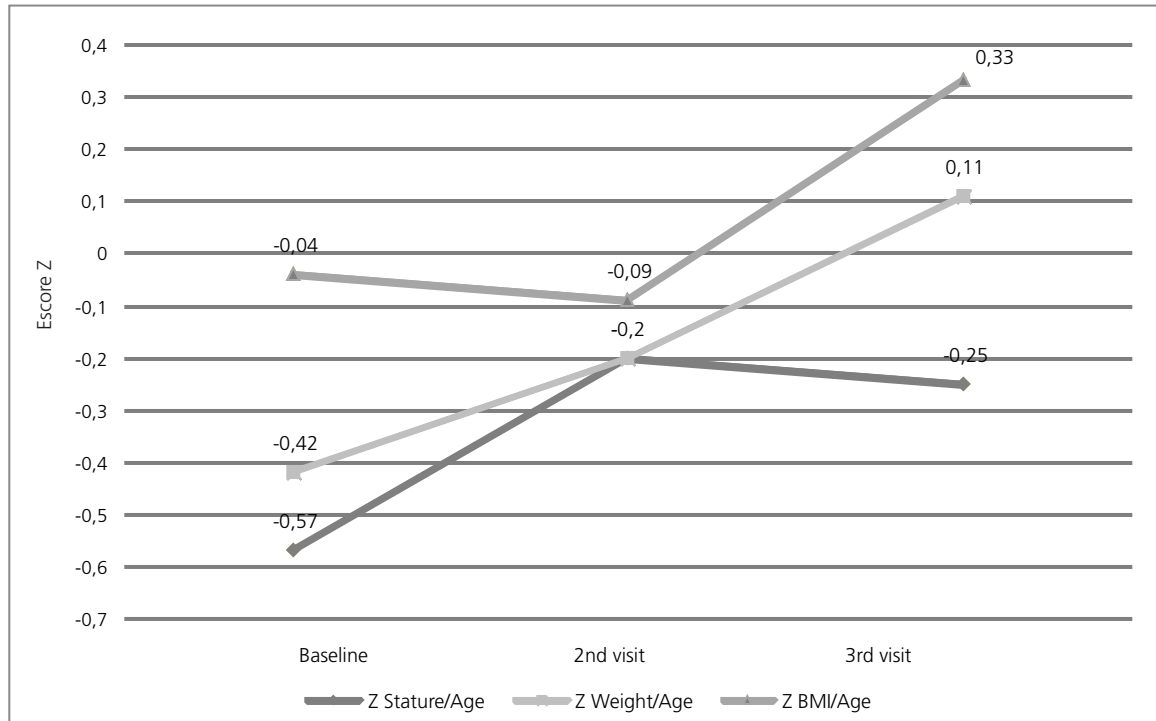


Figure 1 – Description of the Z-scores of the stature/age, weight/age and BMI/Age indices of infants (n=84) with gastrointestinal manifestations of allergy to cow’s milk protein, in the gastropediatrics service of the *Hospital das Clínicas da Universidade Federal de Pernambuco. Recife (PE), Brazil, 2015-2018.*

Table 2 – Evolution of Z-score of anthropometric indices during the follow-up period, according to gender of infants (N=84) with gastrointestinal manifestations of allergy to cow’s milk protein, in the gastropediatrics service of *Hospital das Clínicas da Universidade Federal de Pernambuco. Recife (PE), Brazil, 2015-2018.*

Variables*	Baseline X±SD (95% CI)**	2º visit (3 months) X±SD (95% CI)	3º Visit (6 months) X±SD (95% CI)
Boys (n=45)			
Z score for stature/age	-0.44±1.18 (-0.80 a -0.09) ^a	-0.28±1.43 (-0.71 a 0.15) ^a MD=0.27	-0.17±1.38 (-0.58 a 0.25) ^a
Z score for weight/age	-0.42±1.14 (-0.77 a -0.08) ^a	-0.32±1.49 (-0.77 a 0.13) ^a MD=0.58	0.16±1.06 (-0.16 a 0.47) ^b
Z score for BMI/age	-0.24±1.23 (-0.61 a 0.13) ^a	-0.19±1.80 (-0.74 a 0.35) ^{a,b} MD=0.59	0.35±1.09 (0.02 a 0.68) ^b
Girls (n=39)			
Z score for stature/age	-0.70±1.44 (-1.17 a -0.24) ^a	-0.51±2.07 (-1.18 a 0.16) ^{a,b} MD=0.38	-0.32±1.05 (-0.67 a 0.02) ^b
Z score for weight/age	-0.26±1.04 (-0.60 a -0.07) ^a	-0.07±1.04 (-0.40 a 0.27) ^{a,b} MD=0.37	0.11±1.04 (-0.23 a 0.44) ^b
Z score for BMI/age	0.21±0.95 (-0.10 a 0.52) ^a	0.20±1.17 (-0.18 a 0.58) ^a	0.41±0.99 (0.09 a 0.74) ^a

Note: *ANOVA for repeated measures with Bonferroni’s post hoc test; **Mean+Standard Deviation (95% Confidence Interval). ^{a,b}Different letters show significant differences at the 5% level. MD: Mean Difference (3rd visit – Baseline).

Assessing the evolution of the z-score of the indices according to gender (Table 2), it was observed that, in boys, the gain in S/A was not statistically significant. However, W/A and BMI/A showed significant gains ($p=0.02$ and $p=0.01$) and close to the threshold that characterizes *catch up*, 0.58 and 0.59, respectively. As for girls, there was a significant gain in S/A and W/A, 0.38 and 0.37 with $p=0.02$ for both indexes.

At the end of the follow-up period, the percentage of SS diminished 7.1% and that of UW 2.4% according to the W/A ratio. However, there was an increase in the percentage of OW, which rose 20.3% by W/A and 29.8% by BMI/A.

DISCUSSION

It was evidenced that a high percentage of infants were taken to the service with SS and UW, with frequencies similar to those in other studies in infants with suspected CMPA-GM [5, 6] and much higher than what is expected in infants from a healthy population, which is 2.3% [9]. During the six months of follow-up, there was growth recovery, but it was not intense enough to configure a *catch up* growth.

It is noteworthy that the frequency of SS was much higher than that of UW, which shows the chronic character of the deficit, as the S/A ratio shows the cumulative effect of a pathological process on the growth of an infant. Furthermore, with the short stature, the UW adjusts to the SS masking the real nutritional status by the BMI/A index. This is observed considering the small percentage of UW by this index, which was close to the 2.3% control threshold at baseline.

Among the risk factors for the adequate growth of patients with CMPA, cow's milk DE plays an important role [3], especially when breastfeeding is not possible, as milk formulas provide the infant with essential nutrients [10]. As noted, in this population, breastfeeding was infrequent. The data did not allow us to assess the adequacy of consumption of HFs, but as they are expensive, the nutritional status can be affected by overdilution [11] until the admission to the service where families benefit from the offer of the formula.

In children under six months of age, the nutritional risk increases, as CF has not yet started [12]. In this study, the infants were less than six months old at baseline and one third of them had already started CF. Data available do not allow assessing CF's quality, but we may think that this occurred in order to reduce costs with HF. In this context, the time spent under DE is also important [3] and the two months that elapsed from the beginning of DE to baseline may have been enough to promote the nutritional damage found.

In the group, almost 50% of the infants were taken to the service with only blood in stools, a manifestation that characterizes proctocolitis, the mildest form of the disease and which is classically not associated with growth alterations. Meanwhile, only 13.1% had the most severe form of CMPA-GM (associated diarrhea and vomiting) which is the form with the greatest impact on nutritional status [4]. Still, the infants in the study had impaired growth at the start of treatment and accelerated recovery after the follow-up period. This is worrying, because when health and nutrition conditions are favorable again, the affected infants grow rapidly in order to return to their normal growth channel [13]. Thus, *catch-up* growth ensues, which can influence the development of non-communicable chronic diseases (NCDs) by developmental plasticity [14].

The evolution of the z-scores revealed a significant linear growth in the first three months of follow-up and, even if *catch up* was not technically configured, this occurrence can cause damage to health in the long term, especially among infants whose growth acceleration was significant and close to the threshold that defines the *catch-up*, as they may enter the risk group for NCD in the future. Other follow-up studies of infants with CMPA also found a similar occurrence [6,15].

The SS and the increase in OW that was evidenced at the end of the follow-up period may be a reflection of the recovery process, as in infants in this condition weight gain is earlier than in linear growth and, generally, infants only return to their normal growth channels between the first and second year of life, after the disease is controlled [13]. That is, they may not continue with this nutritional presentation at the end of the recovery period.

Another important aspect is that the infants in this study were predominantly formula-fed and thus gained weight faster than when on exclusive or predominant breastfeeding [16]. Thus, formula-fed infants recuperating their growth are likely to experience faster regrowth than if they were breastfed. This fact enhances the importance of breastfeeding, which is already well documented in the literature, being also beneficial for the development of the microbiome and the infant's immune and metabolic systems, enabling an appropriate inflammatory response [17].

Thus, also for infants with suspected CMPA-GM, breastfeeding associated with cow's milk exclusion in the lactating woman's diet is ideal. This will promote a slower recovery, reducing long-term *catch-up* effects. Policies to encourage breastfeeding can be differentially favorable to the health of this population.

In the service where the study took place, it was not always possible to apply the oral challenge test, which is the "gold standard" for the diagnosis of CMPA, due to operational difficulties such as those already described in the literature [3]. Hence, this study included infants with suspected CMPA-GM after evaluation by experienced gastropediatricians.

As a limitation, we can mention the absence of a control group, which would allow a comparison between allergic and non-allergic infants, subject to the same conditioning factors as the study population, which occurred due to the use of secondary data. In addition, this type of data collection does not allow verifying the standardization of assessment techniques and instruments, but the team is trained and experienced in clinical and nutritional assessment and the service has the infrastructure ad hoc. The inclusion of premature infants could be another limitation due to the growth of recovery inherent to this condition. However, all the 11 (13.4%) infants included were late preterm, with a gestational age between 34 completed weeks and 36 weeks and 6 days, and all were evaluated using the corrected age for preterm infants. Thus, prematurity would not be a confounding variable in the study.

Despite the methodological limitations, this study shows that the growth of infants suspected of CMPA-GM deserves scientific research attention, as deficits seem to be more associated with DE and the clinical presentation itself, phenomena that occur before the diagnosis is confirmed, which may take some time or fail to materialize.

CONCLUSION

The results of this research reveal that infants with suspected CMPA-GM have impaired growth, but after being entered into a follow-up program, they regain growth significantly. These findings demonstrate that this population's guardians should receive specialized nutritional counseling early, to avoid infants' unwanted exposure to allergenic food and in order to control symptoms and, thus, avoid malnutrition or ensure adequate nutritional recovery.

CONTRIBUTORS

PC CABRAL, MMC ANTUNES and PP ASSIS participated in the study conception and design and writing of the article. AS DINIZ and JSS MENEZES participated in the data review and interpretation. All authors contributed to the final review of the work.

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Received: April 14, 2021

Final version: November 3, 2021

Approved: December 15, 2021