







# Clinical and nutritional profile of children with cow's milk protein allergy

Maísa Tirintan Jordani<sup>1</sup> , Isabela Garcia da Cunha Guimarães<sup>1</sup> , Taísa Alves Silva<sup>1</sup> , Luciene Alves<sup>1</sup> ,  
Camila Bitu Moreno Braga<sup>1</sup> , Sylvana de Araújo Barros Luz<sup>1</sup> 

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## ABSTRACT

**Objective:** this study aimed to identify the main clinical and nutritional characteristics presented by children with cow's milk protein allergy. **Method:** this was an observational, cross-sectional, quantitative and correlational study, with a convenience sample, consisting of 22 children diagnosed with allergy in different stages, aged between six months and six years, seen at the Pediatric Gastroenterology Outpatient Clinic of the Clinical Hospital of the Federal University of the Triângulo Mineiro. **Results:** eutrophy was evident in 81.8% of the children, overweight risk in 4.5%, overweight in 9.1%, and obesity in 4.5%. None of the patients presented a nutritional diagnosis of thinness. Gastrointestinal symptoms (diarrhea, vomiting, and bloody stools) were the most frequent in the evaluated patients. All patients (100%) with allergy in remission and allergy resolved showed a normal serum ferritin level, but 14.3% of the children in active allergy were below the recommended level for their age. The children had early weaning from breast milk, complementary feeding within what is indicated and the use of correct infant formulas to achieve the nutritional recommendations for age. **Conclusion:** the findings indicate that the clinical and nutritional profile of children with allergy is as expected with regard to the choice of formulas and the children's development.

**Keywords:** Allergy, Cow's milk, Nutrition, Health.

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1. Federal University of Triângulo Mineiro, Uberaba, (MG), Brazil



## INTRODUCTION

Food allergy is an adverse reaction that occurs when the immune system recognizes a food as an aggressive substance to the organism, which is then defined as an allergen<sup>1</sup>. Food allergens are defined as food components or ingredients within foods recognized by specific immune cells causing immune reactions and characteristic symptoms<sup>2</sup>. Among foods, cow's milk deserves emphasis in cases of food allergy in children, since it is usually the first food offered, and cow's milk protein allergy (CMPA) is one of the main causes of food allergy in infants and children under three years of age<sup>3</sup>.

Currently, its prevalence rate has increased by about 20% in the last ten years<sup>4</sup>. A study conducted in public nutritional services in 34 Brazilian municipalities found a 0.4% prevalence of CMPA in infants and young children<sup>5</sup>. A study by pediatric gastroenterologists pointed out an incidence of CMPA of 2.2% and a prevalence of 5.4% in children seen at the research hospital services<sup>6</sup>.

Among the factors that may be related to the occurrence of CMPA, there are intrinsic factors, such as heredity, and extrinsic factors, such as early cessation of breastfeeding, revealing that breastfeeding is an essential factor in protecting the child's health and preventing diseases such as CMPA<sup>7,8</sup>.

Among the allergens responsible for reactions resulting from CMPA, casein, alpha-lactalbumin and beta-lactoglobulin stand out<sup>9,10,11,12</sup>. The factors related to sensitization and tolerance to cow's milk protein involve genetic predisposition, infections and altered gut microbiota, age at first exposure, maternal diet, amount and frequency of allergen ingestion.<sup>3</sup> This allergy can be classified into three categories: immunoglobulin E (IgE)-mediated, non-IgE-mediated and mixed<sup>13,14</sup>. In each one of them, the symptoms manifest themselves differently, varying in skin alterations, gastrointestinal, respiratory, systemic and even cardiovascular problems, the first three being the most common.<sup>4</sup>

Most cases of CMPA are diagnosed during lactation, when breast milk is replaced by milk formulas or during the introduction of complementary feeding, being this the period of life in which rapid growth and development is observed, thus emphasizing the high relevance of the disease<sup>15,16</sup>. One of the most effective treatments to date for patients allergic to cow's milk protein is the exclusion

diet, but this elimination must be done with caution, since it can result in important side effects, such as malnutrition, deficiency of calcium, iron or other micronutrients and macronutrients, and changes in eating habits<sup>9,17,18,19</sup>. When cow's milk is excluded, it is necessary to replace it for children under six months of age or to complement it for children older than six months, which, in this case, is done with formulas based on isolated soy protein, extensively hydrolyzed proteins, or amino acids, depending on clinical criteria<sup>20,21,22</sup>.

Based on these considerations, this study aimed to identify the main clinical and nutritional characteristics presented by children with CMPA in different stages, seen at the Pediatric Outpatient Clinic of the Clinical Hospital of the Federal University of Triângulo Mineiro (CH-UFTM).

## MATERIALS AND METHODS

This is an observational, cross-sectional, quantitative and correlational study. The convenience sample consisted of 22 children diagnosed with CMPA, aged six months to six years, seen at the Pediatric Gastroenterology Outpatient Clinic of the Clinical Hospital of the Federal University of Triângulo Mineiro (HC-UFTM). Participants were allocated into three groups according to the CMPA status, i.e., active allergy (n=7), resolved allergy (n=12) and allergy in remission (n=3). Patients with CMPA using enteral feeding tubes were excluded from the study.

Data collection was conducted from July 2018 to December 2018. Socioeconomic data, with the exception of family income, serum ferritin value, and the use of ferrous sulfate supplementation were collected from the medical records of the research participants. The date of the serum ferritin test results of the evaluated children was between March to October 2018. Information regarding family income, dietary history (presence and duration of exclusive breastfeeding, and age of food introduction), and clinical characteristics presented by the patients (symptoms, age of symptom onset, age of diagnosis confirmation, type and stage of allergy, type of preparation consumed for the onset of symptoms, and cow's milk substitute used) were identified by means of a semi-structured questionnaire applied to the legal guardians accompanying the children. The serum ferritin value of each patient was classified according to the reference values of the Laboratory

of Clinical Analysis of CH-UFTM for the respective age group.

To evaluate the nutritional status, the growth standards of the World Health Organization (WHO) were used, based on the analysis of the Z score of the body mass index (BMI) by age. Considering the recommended cut-off values, the children were classified as thin, eutrophic, overweight or obese<sup>23</sup>. For data analysis we used the WHOAnthro® and WHOAnthroPlus®.

To investigate food intake, we used a validated food frequency questionnaire for children aged two to five years<sup>24</sup>. The foods that are sources of heme iron, that is, foods from animal sources and of better absorption in the body, processed foods, and vegetables were selected for analysis in this study. The consumption in number of servings of each of these food groups was compared to the recommendations for each age group in childhood<sup>25</sup>. We also analyzed the frequency of consumption of foods that contain or may contain cow's milk (CM) in their composition by patients who had active, remission, or resolved allergy at the time of the interview.

STATISTICS 6.0® (StatSoft Incorporation, Tulsa, Ok, USA) and the Statistical Package for the Social Sciences (SPSS) version 17.0 software were used for all descriptive and statistical analyses, with a significance level set at 5% (p<0.05).

The study was approved by the Research Ethics Committee of the Federal University of Triângulo Mineiro (UFTM) with protocol nº 2.669.707, checking all the ethical parameters required by law.

## RESULTS

Twenty-two children participated in the study with a mean age of 2.87 ± 1.71 years, 63.6% were male and 36.4% female; 63.6% called themselves white and 36.4% brown by their respective legal guardians; 63.6% were from the city of Uberaba (MG) and 36.4% from other cities in the region. As for family income it was identified that 36.4% had an income of 1 minimum wage, 31.8% of 3 or more minimum wages, 27.3% of 2 minimum wages, and only 4.5% had an income of less than 1 minimum wage.

The mean age of onset of CMPA symptoms was 4.73±6.15 months and the mean age at diagnosis confirmation was 10.41±11.94 months.

Among the patients, 50% had the immunoglobulin E (IgE)-mediated type of allergy, 40.9% had the non-

IgE mediated type (cellular type), and only 9.1% had the mixed type (cellular and IgE mediated).

The symptoms presented by all children (100%) were due to consumption of unprocessed CM. CM derivatives, added CM in cooked or baked preparations, and processed foods containing CM caused symptoms in 54.5%, 50%, and 45.5% of patients, respectively.

As observed in Table 1, gastrointestinal symptoms were the ones that most affected the patients evaluated. Among these symptoms, the types most often mentioned by those responsible were diarrhea, vomiting, and bloody stools.

**Table 1.** Comparison of the conjugated and isolated manifestations presented by children with CMPA, seen at the Pediatrics Outpatient Clinic of the Clinical Hospital of the Federal University of the Triângulo Mineiro, Uberaba (2018). (n=22)

Combined manifestations		Isolated manifestations	
Gastrointestinal, respiratory and skin manifestations	31.81%	Gastrointestinal manifestations	18.18%
Gastrointestinal and respiratory manifestations	27.27%	Skin Manifestations	4.54%
Gastrointestinal and skin manifestations	13.63%	Respiratory manifestations	0.0%
Respiratory and skin manifestations	4.54%		

Source: authors (2018).

The nutritional status evaluation, through the analysis of BMI Z score by age, showed eutrophy in 81.8% of the children, overweight risk in 4.5%, overweight in 9.1%, and obesity in 4.5%. None of the patients presented a nutritional diagnosis of thinness.

The serum ferritin of most children (95.5%) was normal, even though 68.18% of all children were not taking ferrous sulfate. All patients (100%) with allergy in remission and allergy resolved showed a normal serum ferritin level, but 14.3% of the children with active allergy were below the recommended level for their age.

Those patients who had gastrointestinal symptoms (90.9%) had a mean age of 3.0±1.72 years, 65.0% were male, most were eutrophic (85.0%) and all (100%) had normal serum ferritin test. On the other hand, children who had skin manifestations (54.4%) had a mean age of 2.89±1.8

years, 66.7% were male, 75.0% were eutrophic and 91.7% showed normal serum ferritin value. And patients with respiratory symptoms (63.6%) had a mean age of  $2.99 \pm 1.37$  years, 64.3% were male, 71.4% were eutrophic, and all (100%) also had normal serum ferritin.

Regarding the type of milk used, the percentages of children using amino acid-based infant formula (AA) were 31.8%, 13.6% soy-based infant formula, 27.3% extensively hydrolyzed infant formula (EHF), 4.5% rice-based infant formula, 9.1% soy milk, and 13.6% the child did not take any type of milk or was breastfeeding, with exclusion of cow's milk from the mother's diet (Table 2).

**Table 2.** Comparison between the milk used and the nutritional diagnosis, according to the BMI, of children with cow's milk protein allergy seen at the Pediatric Outpatient Clinic of the Clinical Hospital of the Federal University of Triângulo Mineiro, Uberaba (2018). (n=22)

Milk used	Nutritional diagnosis			
	Eutrophy	Risk of overweight	Overweight	Obesity
AA	33.3%	100%	0%	0%
EHF	22.2%	0%	50%	100%
Rice based	5.6%	0%	0%	0%
Soy based	16.7%	0%	0%	0%
Soy milk	5.6%	0%	50%	0%
Others	16.6%	0%	0%	0%

Source: authors (2018)

Regarding the feeding history, 63.6% of the patients' mothers offered exclusive breastfeeding (EBF), with a mean duration of  $4.79 \pm 1.88$  months (Table 3). The mean age of introduction of complementary feeding was  $6.95 \pm 4.32$  months.

**Table 3.** Comparison between the duration of EBF and the symptoms presented by children with cow's milk protein allergy seen at the Pediatrics Outpatient Clinic of the Federal University of the Triângulo Mineiro Clinical Hospital, Uberaba (2018). (n=22)

Duration of EBF	Number of children in the EBF	Type of symptoms presented
$4.42 \pm 1.73$	12	Gastrointestinal
$4.44 \pm 2.00$	9	Respiratory
$5.44 \pm 1.51$	9	Of the Skin

Source: authors (2018)

According to the evaluation of eating behavior of all research participants, through the food frequency questionnaire, it was found that the consumption of food source of heme iron was adequate, since the frequency of eating steak (63.6%), boiled meat (90.9%) and chicken (86.4%) was two to four times a week, with the exception of liver steak, in which 54.5% of children never ate and only 13.6% ate once a week. Regarding the consumption of vegetables, adequacy was also observed, because most patients ate these foods two to four times a week (60.22%), with the exception of lettuce, and different fruits at least once a day or two to four times a week (56.06%). Among all fruits mentioned in the questionnaire, only papaya and guava did not show good acceptance by children.

As for the consumption of processed foods included in the questionnaire, such as cookies with and without filling, breakfast cereal, instant noodles, fruit yogurt, Danoninho®, fermented milk, chocolate milk, snacks, soft drinks and artificial juice, it was considered to be in accordance with what is recommended for this age, since most children (65.15%) had never consumed these types of food. Table 4 shows the frequency of consumption of foods that contain or may contain CM by the three groups evaluated.

## DISCUSSION

It is important to highlight some limitations of the study, such as the small sample size and the absence of patients from appointments. The outpatient clinic sees few patients with CMPA and they missed many appointments, which made data collection impossible.

The research revealed a higher percentage of male children, similarly to the research published by Paulista Pediatrics Journal, showing a 58.4% percentage of boys with CMPA<sup>26</sup>.

The study identified that most of the participants (63.6%) were not exclusively breastfed until six months of age; and they started receiving complementary feeding from that age on. Similar results were identified in a study conducted in a children's outpatient clinic in Salvador, where only 7.5% of children evaluated were on EBF until six months of age.<sup>27</sup> In this study it was possible to observe a mean of 4.8 months in relation to the time of exclusive breastfeeding in the studied population.

**Table 4.** Frequency of consumption of foods that contain or may contain CM in their composition by patients with active, remitting or resolved allergies, Uberaba (2018). (n=22)

	Active allergy (n=7)	Frequency of consumption	Allergy in remission (n=3)	Frequency of consumption	Allergy Resolved (n=12)	Frequency of consumption
Filled cookies	14.3%	1 to 3 times/month	33.3%	2 to 4 times/week	8.3%	1 time/week
Unfilled Cookies	28.6%	1 or more times/day	66.6%	At least 2 to 4 times/week	83.3%	At least 2 to 4 times/week
Breakfast Cereal	14.3%	< 1 time/month	33.3%	1 to 3 times/month	0%	-
Yogurt/Danoninho® yogurt	28.6%	1 to 3 times/month	0%	-	50.0%	1 to 4 times/week
Fermented milk	14.3%	1 to 3 times/month	0%	-	16.7%	2 to 4 times/week
Milk chocolate	0%	-	0%	-	16.7%	1 to 3 times/month
Chocolate	28.6%	At least 1 to 3 times/month	33.3%	1 to 3 times/month	33.4%	1 to 4 times/week
Margarine/Butter	57.2%	At least 2 to 4 times/week	100%	At least 1 to 3 times/month	41.6%	At least 2 to 4 times/week
Cheese	14.3%	1 to 3 times/month	33.3%	Once/week	16.6%	2 to 4 times/week
Curd	0%	-	33.3%	1 time/week	16.6%	2 to 4 times/week
Cakes	42.85%	At least 1 to 3 times/month	100%	At least 1 to 3 times/month	58.3%	1 to 4 times/week

Source: authors (2018)

These data contradict the recommendations of the Food Guide for Brazilian Children Under Two Years of Age (2019)<sup>28</sup> on exclusive breastfeeding until the age of six months, however, the average of the introduction of food is within the recommended age range for starting complementary feeding. Still on breastfeeding, according to the Brazilian Consensus on Food Allergy (2018)<sup>22</sup>, it is considered a protective factor in the development of food allergies and should be advocated.

Regarding the nutritional status evaluation, it was observed that most of the sample presented adequacy to the parameters assessed, which corroborates the hypothesis that the replacement diet is being correctly performed or that the formula has met the nutritional needs of children. The study of Brito et al.<sup>29</sup>, conducted with children aged 0 to 5 years diagnosed with CMPA, indicated similar results: almost 90% of the participants had appropriate BMI for age. In another case-control study, when comparing the groups, the children with CMPA showed lower body weight and shorter length per height<sup>30</sup>. Another research evaluated only children with CMPA and verified, by the

BMI for age, that 12.9% of the children presented thinness or marked thinness, 67.8% eutrophy, 15.2% risk for overweight and 4.1% overweight or obesity<sup>26</sup>. However, in this study none of the patients presented a nutritional diagnosis of thinness, reinforcing that the use of formulas and the diet were in accordance with the needs of each patient. The results also indicated that part of the participants were at risk of overweight (4.5%) and overweight and obesity (13.6%). No studies were found that related CMPA and overweight and obesity, nor a possible relationship of these with the use of infant formulas by patients with CMPA. However, in the sample studied, it was found that very early on, children started to receive inadequate foods, such as processed sweets, stuffed cookies, instant noodles, among others; such practices can lead to increased risks of developing chronic diseases such as obesity, although the data of the present study show that the consumption of this type of food is low.

Patients diagnosed with CMPA are instructed to ingest substitutes that contain high protein content and allow for good development. According to the study by Solé et al.<sup>11</sup>, before industrialized

formulas with hydrolyzed proteins or based on amino acids, other mammalian milks were used; proving to be inadequate due to the appearance of other adverse clinical manifestations after its ingestion. The participants in this study do not use other mammalian milks, but AA formulas, EHF, soy-based infant formula, rice formula, soy milk, and others, or did not take any type of milk or were breastfeeding. The study conducted in a Health Care Unit in Belém found that the most commonly provided formulas are amino acid-based formula (47.1%) and extensively hydrolyzed protein-based formula (42.9%)<sup>31</sup>. Brito et al.<sup>29</sup> also observed the highest consumption of these two types of infant formulas to replace the CM. Vandenplas's research, on the other hand<sup>32</sup>, evidenced the use of extensively hydrolyzed protein-based formula as the first choice, rice-based formula and soy-based formula as second choice options, and the use of amino acid formulas only for more severe cases. Infant formulas are nutritionally safe and their cost may vary, with some being more expensive, such as AA, and others being cheaper; in addition to the issue of palatability<sup>33</sup>. These factors, according to the literature, along with the indications of professionals, guide parents when choosing and how to administer them.

The complementary feeding described by the participants proved to be adequate, since most patients consume adequate amounts of vegetables and food sources of heme iron. According to Alves et al.<sup>34</sup>, The complementary feeding of children with CMPA should follow the same principles that are recommended for healthy children, with no need to restrict foods with allergenic proteins, such as egg and fish. According to the recommendations of the Ministry of Health, it is important to have a varied consumption of foods within the same group<sup>35</sup>. However, we observed the presence of food products that contain or may contain CM in the dietary routine of some children who were in the active allergy phase, which contradicts the main recommendation for the treatment of CMPA, which is the exclusion of CM and derivatives from the diet<sup>22</sup>.

In principle, in food allergy, iron deficiency can occur due to fecal losses or malabsorption secondary to injury of the small intestine or systemic inflammation. Although not a diagnostic test for allergy, such as CMPA, the CBC helps in the detection of complications associated with it, such as anemia. In this study, we analyzed the results of the serum ferritin value and

the use of ferrous sulfate supplementation of the study participants. In general, serum ferritin was normal, and most were not taking ferrous sulfate. However, 14.3% of the children with active allergy had a serum ferritin value below that indicated for their age. For these cases, we emphasize the importance of further investigations and guidance on diet and use of ferrous sulfate, for example.

In cases of treatment of CMPA, the nutritionist and the pediatrician should be aware of the age ranges that this pathology can affect and keep up to date with the therapies and diagnoses, providing the needs of these infants according to individual daily recommendations. In addition, parents and caregivers should be taught to read and interpret food product labels, as erroneous interventions may cause persistent worsening. The data found in this study indicate that the caregivers follow the professionals' guidelines, since no cases of manifestations of CMPA symptoms due to an inadequate replacement diet were observed.<sup>36</sup>

Only health professionals can recommend infant formulas for children with special dietary needs, such as children with CMPA, as well as how to prepare them and the quantities to be offered individually. They can also advise on whether micronutrient supplementation is required.<sup>28</sup>

## CONCLUSION

It is concluded that children with CMPA present, as a manifestation of the disease, predominantly gastrointestinal symptoms. Their nutritional status is adequate and they do not present iron deficiency anemia. As for the feeding pattern, the replacement of the CM is done mainly by infant formulas AA and EHF, there is varied and adequate consumption of vegetables and red meat, low consumption of processed foods, and concordant start period of complementary feeding, but early weaning of breast milk.

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Corresponding Author:  
Maísa Tirintan Jordani  
maisajordani@hotmail.com

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