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# Growth Assessment in Infants with Cow Milk Protein Allergy, Amino Acid Fed Formula versus Breast Milk Fed with Maternal Dairy Product Restriction

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## ABSTRACT

**Background:** Cow's milk protein allergy (CMPA) is an immune-mediated hypersensitivity in infants, often diagnosed through symptoms affecting multiple organ systems. Accurate diagnosis and management are crucial for infant growth and development.

**Objective:** This study aimed to compare growth outcomes, symptom improvement, and clinical signs between infants with CMPA fed amino acid-based formula (AAF) versus those exclusively breastfed with maternal cow's milk protein elimination.

**Patients and methods:** A retrospective cohort study was conducted at the Outpatient Gastroenterology Clinic, Abu Al-Rish Hospital, Cairo University, from July 2021 to July 2022. 54 infants with CMPA, diagnosed based on clinical symptoms, were divided into two equal groups: Group A (exclusive breastfeeding with maternal dietary restrictions) and group B (AAF). Data on demographics, allergy history, symptoms, and clinical assessments were collected at baseline, 3, 6, and 12 months.

**Results:** No significant differences were found between groups in demographic data ($p > 0.05$). The most common symptoms at baseline were abdominal distension (92.6%), diarrhea (74.1%), and vomiting (66.7%). After 3 months, both groups showed significant symptom improvement ($p < 0.05$), with no symptoms of diarrhea or vomiting in either group at 12 months. Growth parameters improved significantly in both groups ($p < 0.05$). The z-scores for weight-for-age, length-for-age, and weight-for-length showed significant improvements over time in both groups.

**Conclusion:** Both breastfeeding with maternal elimination diets and AAF provide effective management for CMPA. However, AAF may offer superior growth outcomes and symptom control in severe cases. Further studies are required to refine management guidelines for CMPA.

**Keywords:** Cow's milk protein allergy, Amino acid-based formula, Breastfeeding.

## INTRODUCTION

Cow's milk protein allergy (CMPA) is an immune-mediated hypersensitivity to proteins such as casein and β-lactoglobulin, distinguishing it from lactose intolerance, which involves difficulty digesting lactose. A common pediatric allergic disease, CMPA often resolves before adulthood but presents diagnostic challenges due to its varied symptoms, which depend on the immune response type, allergen sensitivity, and patient age. Accurate diagnosis and management are essential for normal growth, reducing disease burden, and ensuring effective prevention [1].

Breastfeeding is the gold standard for infant nutrition, offering unique health benefits due to its tailored composition and bioactive factors, supporting development and survival [2].The Cow's Milk-related symptom score (CoMiSS) is a tool designed to raise awareness and assist general physicians in recognizing CMPA by evaluating symptoms from multiple organ systems, including dermatological, gastrointestinal, respiratory, and general symptoms, within 5–15 minutes. It aids in symptom quantification, decision-making, and management [3].

The diagnostic gold standard for CMPA involves a 2–4 week elimination diet followed by an oral food challenge (OFC). During this period, exclusive breastfeeding is recommended for the first six months of life, with breastfeeding mothers advised to eliminate cow's milk from their diets to ensure proper infant growth and development [4].

Breastfed infants with cow's milk allergy (CMA) can continue breastfeeding if their mothers eliminate all milk products, and in some cases, other allergens like egg, soy, or seafood, from their diets. Formula-fed infants are often given free amino acid-based formula (AAF), particularly in cases of severe CMA, multiple food allergies, or conditions like eosinophilic esophagitis and food protein-induced enterocolitis syndrome, where extensively hydrolyzed formulas are not tolerated [5, 6]. While, most children outgrow CMA, some food allergies may persist into adulthood, posing risks of inadequate nutrition and growth delays in affected children [7].

This study aimed to compare growth outcomes in infants with CMA who are fed AAF versus exclusively breastfed infants whose mothers follow a dairy-free diet. Additionally, it evaluates symptom improvement, clinical signs, and laboratory parameters between infants started on amino acid formula and those managed with maternal elimination diets during exclusive breastfeeding.

## PATIENTS AND METHODS

**Study design and participants:** This retrospective cohort study was conducted in Outpatient Gastroenterology Clinic in Abu Al-Rish Hospital, Faculty of Medicine, Cairo University, involving 54 infants diagnosed with CMPA. The study was conducted in the period from July 2021 to July 2022.

**Inclusion criteria:** Infants under one year diagnosed with CMA based on symptoms across various systems.



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Dermatological symptoms include urticaria, eczema, skin rash, and itching. Respiratory symptoms include wheezing, persistent cough, shortness of breath, and cyanosis. gastrointestinal symptoms involve irritability, vomiting, diarrhea, abdominal pain, and hematemesis. Severe allergic reactions, such as facial swelling and anaphylaxis, and failure to thrive after excluding other causes.

**Exclusion criteria:** Infants with conditions mimicking CMA symptoms, such as fructose intolerance, immunologic diseases, congenital immunodeficiency disorders, other causes of chronic diarrhea, or respiratory conditions with gastrointestinal symptoms, such as cystic fibrosis.

**Grouping:** Infants were divided into 2 equal groups: Group A consisted of exclusively breastfed infants whose mothers were supported to continue breastfeeding while eliminating cow's milk protein from their diets for 2–4 weeks, supplemented with calcium and vitamin D. In severe cases, additional allergens like soy or eggs were also avoided. If no improvement occurred, other maternal foods, such as meat, were excluded. Improvement confirmed CMA, validated by reintroducing cow's milk into the diet and observing symptom recurrence. Continuous counseling on breastfeeding's importance for growth and development was emphasized, along with regular follow-ups. Group B consisted of infants fed AAF for CMA. Indications for using AAF include anaphylaxis or severe reactions, rectal bleeding causing hemodynamic instability, growth failure with or without hypoproteinemia or severe anemia, a preference to switch from breast milk to formula, or persistent symptoms despite using extensively hydrolyzed formula.

**Assessments:** All patients underwent a full history, clinical examination, and laboratory assessment. The history included details on breastfeeding (exclusive or partial and duration), artificial formula intake (age, type and amount), family history of allergies, and previous medical management (e.g., for GERD). Symptoms were assessed using the CoMiSS score. Clinical examination focused on gastrointestinal (abdominal distension, vomiting, diarrhea, constipation and rectal bleeding), respiratory (asthma, otitis media and laryngeal edema), general (activity and weight loss), cutaneous (eczema, dermatitis, urticaria and rash), and systemic symptoms (anaphylaxis). Signs included pallor, irritability, sleeplessness, excessive crying, hives, and abdominal tenderness.

The WHO recommends using the z-score or standard deviation (SD) system to grade undernutrition, with children more than 2 SD below the reference median (z-score <−2) considered undernourished, and those below 3 SD (z-score <−3) as severely undernourished (International Institute of Population Science, 1999). Moderate acute malnutrition is defined as low weight-for-height/length between −2 and −3 SD of the WHO child growth standard. Symptoms and signs were assessed at various time points (birth, 3, 6, and 12 months), with physical examination including head circumference, weight-for-age, length-for-age, and weight-for-length. Anthropometric measurements were plotted into z-scores at the first visit and repeated after 3, 6, and 12 months using Pedi tools.

Laboratory testing for all patients included a complete blood count to detect anemia, with iron therapy provided for those diagnosed with iron deficiency anemia. Additionally, a fecal occult blood test was performed using a standard laboratory technique, where a stool sample was collected and analyzed in the clinical laboratory. The result was considered positive when both the detection and quality control lines appeared in the assay.

**Ethical considerations: The study was done after being accepted by The Research Ethics Committee, Cairo University. All parents provided informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

**Data Management:** Data were analyzed using IBM© SPSS© Statistics version 24 (IBM© Corp. Released 2016, IBM© SPSS© Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp.). Categorical data were presented as numbers or proportions with valid percentages, and intergroup differences were compared using the Pearson Chi-squared test or Fisher's exact test. Quantitative variables were presented as mean and SD, with between-group differences compared using the independent-samples t-test. Repeated measures analysis of variance (ANOVA) was employed to examine the effect of time and treatment on observed changes in repeatedly measured quantitative variables, and the Tukey method was used for post-hoc pairwise comparisons. P-values $\leq$ 0.05 were considered statistically significant.

## RESULTS

There were no statistically significant differences between the studied groups in terms of demographic characteristics such as age, gender, residence, or family history of allergy. All cases were followed from the start of the study and reassessed at 3, 6, and 12 months, with no significant differences found regarding family history or types of allergy (Table 1)

**Table (1):** Demographic data and history of allergy among the studied cases of CMPA

| Variable | | Amino Acid Formula (N=27) | | Breast Feeding (N=27) | | P-value |
|---|---|---|---|---|---|---|
| **Male** | | 14 (51.9%) | | 13 (48.1%) | | 0.785 |
| **Female** | | 13 (48.1%) | | 14 (51.9%) | | |
| **Age (months)** | | 2.8 ± 0.5 | | 2.8 ± 0.5 | | 0.900 |
| **Age at presentation (months)** | | 2.5 ± 0.7 | | 2.5 ± 0.6 | | 0.706 |
| **Age at onset of symptoms** | | | | | | |
| **Since birth** | | 27 (100%) | | 26 (96.3%) | | 1.000 |
| **First 2 months of age** | | 0 (0%) | | 1 (3.7%) | | |
| **Residence** | | | | | | |
| **Urban** | | 12 (44.4%) | | 10 (37.0%) | | 0.580 |
| **Rural** | | 15 (55.6%) | | (17 63.0%) | | |
| | | **N or n/N** | **%** | **N or n/N** | **%** | |
| **Family history of allergy** | **Negative** | 21 | 77.8% | 15 | 55.6% | 0.083 |
| | **Positive** | 6 | 22.2% | 12 | 44.4% | |
| **Type of allergy** | **Allergic rhinitis** | 0/6 | 0.0% | 6/12 | 50.0% | 0.092 |
| | **Allergic sinusitis** | 1/6 | 16.7% | 1/12 | 8.3% | |
| | **Eczema** | 2/6 | 33.3% | 4/12 | 33.3% | |
| | **Bronchial asthma** | 3/6 | 50.0% | 1/12 | 8.3% | |
| **Affected family member** | **Mother** | 1/6 | 16.7% | 6/12 | 50.0% | 0.559 |
| | **Father** | 2/6 | 33.3% | 2/12 | 16.7% | |
| | **Sibling** | 3/6 | 50.0% | 3/12 | 25.0% | |
| | **Grandparent** | 0/6 | 0.0% | 1/12 | 8.3% | |

Data are number (N) and percentage or mean ± SD, or proportion (n/N).

The most common symptoms in breast-fed infants were abdominal distension (92.6%), diarrhea (74.1%), and vomiting (66.7%), while the least common were constipation (0.0%), cough (29.6%), and runny nose (33.3%). Symptoms improved after 3 months (Table 2).

**Table (2):** Symptoms of CMPA in breast-fed infants in different follow up visits

| Variable | | 1st visit (N=27) | | After 3 months (N=27) | | After 6 months (N=27) | | After 12 months (N=17) | |
|---|---|---|---|---|---|---|---|---|---|
| | | **N or n/N** | **%** | **N or n/N** | **%** | **N or n/N** | **%** | **N or n/N** | % |
| **Activity affection** | **Negative** | 27 | 100.00% | 27 | 100.00% | 27 | 100.00% | 17/17 | 100.00% |
| | **Positive** | 0/27 | 0.00% | 0/27 | 0.00% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Abdominal distention** | **Negative** | 2 | 7.40% | 25 | 92.60% | 27 | 100.00% | 17/17 | 100.00% |
| | **Positive** | 25 | 92.60% | 2 | 7.40% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Vomiting** | **Negative** | 9 | 33.30% | 25 | 92.60% | 27 | 100.00% | 17/17 | 100.00% |
| | **Positive** | 18 | 66.70% | 2 | 7.40% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Diarrhea** | **Negative** | 7 | 25.90% | 25 | 92.60% | 27 | 100.00% | 17/17 | 100.00% |
| | **Positive** | 20 | 74.10% | 2 | 7.40% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Consistency of motions** | **Watery** | 10/20 | 50.00% | 0/19 | 0.00% | 0/18 | 0.00% | 0/17 | 0.00% |
| | **Watery to loose** | 0/20 | 0.00% | 19/19 | 100.00% | 18/18 | 100.00% | 0/17 | 0.00% |
| | **Loose** | 10/20 | 50.00% | 0/27 | 0.00% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Color of motions** | **Yellowish** | 10/20 | 60.00% | 20/20 | 100.00% | 1/20 | 5.00% | 0/17 | 0.00% |
| | **Greenish** | 8/20 | 40.00% | 0/27 | 0.00% | 2/20 | 10.00% | 0/17 | 0.00% |
| | **Brownish with digested food** | 0/27 | 0.0% | 0/27 | 0.0% | 17/20 | 85.00% | 0/17 | 0.00% |
| **Mucus in stools** | **Negative** | 22 | 81.50% | 27 | 100.00% | 27 | 100.00% | 17/17 | 100.00% |
| | **Positive** | 5 | 18.50% | 0/27 | 0.00% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Blood in stools** | **Negative** | 14 | 51.90% | 27 | 100.00% | 27 | 100.00% | 17/17 | 100.00% |
| | **Positive** | 13 | 48.10% | 0/27 | 0.00% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Bleeding per rectum** | **Negative** | 27 | 100.00% | 27 | 100.00% | 27 | 100.00% | 17/17 | 100.00% |
| | **Positive** | 0/27 | 0.00% | 0/27 | 0.00% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Color of blood in stools** | **Dark red** | 6 | 46.20% | 0/27 | 0.00% | 0/27 | 0.00% | 17/17 | 100.00% |
| | **Dark block** | 7 | 53.80% | 0/27 | 0.00% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Constipation** | **Negative** | 27 | 100.00% | 27 | 100.00% | 27 | 100.00% | 17/17 | 100.00% |
| | **Positive** | 0/27 | 0.00% | 0/27 | 0.00% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Cough** | **Negative** | 19 | 70.40% | 26 | 96.30% | 27 | 100.00% | 0/17 | 0.00% |
| | **Positive** | 8 | 29.60% | 1 | 3.70% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Runny nose** | **Negative** | 18 | 66.70% | 25 | 92.60% | 27 | 100.00% | 17/17 | 100.00% |
| | **Positive** | 9 | 33.30% | 2 | 7.40% | 0/27 | 0.00% | 0/17 | 0.00% |
| **Specific GIT medications** | **Not given** | 23 | 85.20% | 25 | 92.60% | 25 | 92.60% | 17/17 | 100.00% |
| | **Given** | 4 | 14.80% | 2 | 7.40% | 2 | 7.40% | 0/17 | 0.00% |

Data are number (N) or proportion (n/N) and valid percentage (%).

The most common symptoms in AAF infants were abdominal distension (92.6%), diarrhea, and vomiting (81.5%), while the least common were constipation (0.0%), cough (7.4%), and runny nose (25.9%). Symptoms improved after 3 months (Table 3).

**Table (3):** Symptoms of CMPA in amino acid fed formula infants in different follow up visits

| Variable | | 1st visit (N=27) | | After 3 months (N=27) | | After 6 months (N=27) | | After 12 months (N=15) | |
|---|---|---|---|---|---|---|---|---|---|
| | | N or n/N | % | N or n/N | % | N or n/N | % | n/N | % |
| **Activity affection** | **Negative** | 27 | 100.00% | 27 | 100.00% | 27 | 100.00% | 15/15 | 100.00% |
| | **Positive** | 0/27 | 0.00% | 0/27 | 0.00% | 0/27 | 0.00% | 0/15 | 0.00% |
| **Abdominal distention** | **Negative** | 2 | 7.40% | 25 | 92.60% | 27 | 100.00% | 15/15 | 100.00% |
| | **Positive** | 25 | 92.60% | 2 | 7.40% | 0/27 | 0.00% | 0/15 | 0.00% |
| **Vomiting** | **Negative** | 5 | 18.50% | 21 | 77.60% | 26 | 96.30% | 15/15 | 100.00% |
| | **Positive** | 22 | 81.50% | 6 | 22.20% | 1 | 3.70% | 0/15 | 0.00% |
| **Diarrhea** | **Negative** | 5 | 18.50% | 25 | 92.60% | 25 | 92.60% | 15/15 | 100.00% |
| | **Positive** | 22 | 81.50% | 2 | 7.40% | 2 | 7.40% | 0/15 | 0.00% |
| **Consistency of motions** | **Watery** | 12/22 | 54.50% | 1/22 | 4.50% | 2/22 | 9.10% | 0/15 | 0.00% |
| | **Watery to loose** | 1/22 | 4.50% | 21/22 | 95.50% | 20/22 | 90.90% | 0/15 | 0.00% |
| | **Loose** | 12/22 | 40.90% | 0/27 | 0.00% | 0/27 | 0.00% | 0/15 | 0.00% |
| **Color of motions** | **Yellowish** | 16/22 | 72.70% | 22/22 | 100.00% | 3/22 | 13.60% | 0/15 | 0.00% |
| | **Greenish** | 1/22 | 27.30% | 0/27 | 0.00% | 1/22 | 4.50% | 0/15 | 0.00% |
| | **Brownish with digested food** | 0/27 | 0.00% | 0/27 | 0.00% | 18/22 | 81.80% | 0/15 | 0.00% |
| **Mucus in stools** | **Negative** | 17 | 63.00% | 27 | 100.00% | 27 | 100.00% | 15/15 | 100.00% |
| | **Positive** | 10 | 37.00% | 0/27 | 0.00% | 0/27 | 0.00% | 0/15 | 0.00% |
| **Blood in stools** | **Negative** | 13 | 48.10% | 27 | 100.00% | 27 | 100.00% | 15/15 | 100.00% |
| | **Positive** | 14 | 51.90% | 0/27 | 0.00% | 0/27 | 0.00% | 0/15 | 0.00% |
| **Bleeding per rectum** | **Negative** | 26 | 96.30% | 27 | 100.00% | 27 | 100.00% | 15/15 | 100.00% |
| | **Positive** | 1 | 3.70% | 0/27 | 0.00% | 0/27 | 0.00% | 0/15 | 0.00% |
| **Color of blood in stools** | **Dark red** | 3 | 21.40% | 0/27 | 0.00% | 0/27 | 0.00% | 0/15 | 0.00% |
| | **Dark block** | 11 | 78.60% | 0/27 | 0.00% | 0/27 | 0.00% | 0/15 | 0.00% |
| **Constipation** | **Negative** | 27 | 100.00% | 27 | 100.00% | 27 | 100.00% | 15/15 | 100.00% |
| | **Positive** | 0/27 | 0.00% | 0/27 | 0.00% | 0/27 | 0.00% | 0/15 | 0.00% |
| **Cough** | **Negative** | 25 | 92.60% | 26 | 96.30% | 26 | 96.30% | 15/15 | 100.00% |
| | **Positive** | 2 | 7.40% | 1 | 3.70% | 1 | 3.70% | 0/15 | 0.00% |
| **Runny nose** | **Negative** | 20 | 74.10% | 27 | 100.00% | 27 | 100.00% | 15/15 | 100.00% |
| | **Positive** | 7 | 25.90% | 0/27 | 0.00% | 0/27 | 0.00% | 0/15 | 0.00% |
| **Specific GIT medications** | **Not given** | 24 | 88.90% | 24 | 88.90% | 24 | 88.90% | 14/15 | 93.30% |
| | **Given** | 3 | 11.10% | 3 | 11.10% | 0/27 | 11.10% | 1 | 6.70% |

Data are number (N) or proportion (n/N) and valid percentage (%)

There were no statistically significant differences between the studied groups regarding symptoms at time of presentation (Table 4).

**Table (4):** Comparison regarding symptoms at time of presentation between the studied groups

| Variable | | Amino Acid Formula (N=27) | | Breast Feeding (N=27) | | P-value† |
|---|---|---|---|---|---|---|
| | | N or n/N | % | N or n/N | % | |
| **Activity affection at presentation** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Weight loss** | **Negative** | 0 | 0.0% | 0 | 0.0% | NA |
| | **Positive** | 27 | 100.0% | 27 | 100.0% | |
| **Abdominal distention** | **Negative** | 2 | 7.4% | 2 | 7.4% | 1.000 |
| | **Positive** | 25 | 92.6% | 25 | 92.6% | |
| **Vomiting** | **Negative** | 5 | 18.5% | 9 | 33.3% | 0.214 |
| | **Positive** | 22 | 81.5% | 18 | 66.7% | |
| **Diarrhea** | **Negative** | 5 | 18.5% | 7 | 25.9% | 0.513 |
| | **Positive** | 22 | 81.5% | 20 | 74.1% | |
| **Consistency of motions** | **Watery** | 12/22 | 54.5% | 10/20 | 50.0% | 0.565 |
| | **Watery to loose** | 1/22 | 4.5% | 0/20 | 0.0% | |
| | **Loose** | 9/22 | 40.9% | 10/20 | 50.0% | |
| **Color of motions** | **Yellowish** | 16/22 | 72.7% | 12/20 | 60.0% | 0.382 |
| | **Greenish** | 6/22 | 27.3% | 8/20 | 40.0% | |
| **Mucus in stools** | **Negative** | 17 | 63.0% | 22 | 81.5% | 0.129 |
| | **Positive** | 10 | 37.0% | 5 | 18.5% | |
| **Blood in stools** | **Negative** | 13 | 48.1% | 14 | 51.9% | 0.785 |
| | **Positive** | 14 | 51.9% | 13 | 48.1% | |
| **Bleeding per rectum** | **Negative** | 26 | 96.3% | 27 | 100.0% | 1.000 |
| | **Positive** | 1 | 3.7% | 0 | 0.0% | |
| **Color of blood in stools** | **Dark red** | 3 | 21.4% | 6 | 46.2% | 0.236 |
| | **Dark block** | 11 | 78.6% | 7 | 53.8% | |
| **Constipation** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Cough** | **Negative** | 25 | 92.6% | 19 | 70.4% | 0.036 |
| | **Positive** | 2 | 7.4% | 8 | 29.6% | |
| **Runny nose** | **Negative** | 20 | 74.1% | 18 | 66.7% | 0.551 |
| | **Positive** | 7 | 25.9% | 9 | 33.3% | |
| **Specific GIT medications** | **Not given** | 24 | 88.9% | 23 | 85.2% | 1.000 |
| | **Given** | 3 | 11.1% | 4 | 14.8% | |

Data are number (N) or proportion (n/N) and valid percentage (%).

There was no statistically significant differences between the studied groups regarding symptoms at 3 months of presentation (Table 5).

**Table (5):** Comparison regarding symptoms at 3 months between the studied groups

| Variable | | Amino Acid Formula (N=27) | | Breast Feeding (N=27) | | P-value† |
|---|---|---|---|---|---|---|
| | | N or n/N | % | N or n/N | % | |
| **Activity affection** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Weight loss** | **Negative** | 1 | 3.7% | 1 | 3.7% | 1.000 |
| | **Positive** | 26 | 96.3% | 26 | 96.3 | |
| **Abdominal distention** | **Negative** | 25 | 92.6% | 25 | 92.6% | 1.000 |
| | **Positive** | 2 | 7.4% | 2 | 7.4% | |
| **Vomiting** | **Negative** | 21 | 77.6% | 25 | 92.6% | 0.250 |
| | **Positive** | 6 | 22.2% | 2 | 7.4% | |
| **Diarrhea** | **Negative** | 25 | 92.6% | 25 | 92.6% | 1.000 |
| | **Positive** | 2 | 7.4% | 2 | 7.4% | |
| **Consistency of motions** | **Loose** | 1/22 | 4.5% | 0/19 | 0.0% | 1.000 |
| | **Seedy** | 21/22 | 95.5% | 19/19 | 100.0% | |
| **Color of motions** | **Yellowish** | 22/22 | 100.0% | 20/20 | 100.0% | NA |
| **Mucus in stools** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Blood in stools** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Bleeding per rectum** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Constipation** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Cough** | **Negative** | 26 | 96.3% | 26 | 96.3% | 1.000 |
| | **Positive** | 1 | 3.7% | 1 | 3.7% | |
| **Runny nose** | **Negative** | 27 | 100.0% | 25 | 92.6% | 0.491 |
| | **Positive** | 0 | 0.0% | 2 | 7.4% | |
| **Specific GIT medications** | **Negative** | 24 | 88.9% | 25 | 92.6% | 1.000 |
| | **Positive** | 3 | 11.1% | 2 | 7.4% | |

Data are number (N) or proportion (n/N) and valid percentage (%)

There was no statistically significant differences between the studied groups regarding symptoms at 6 months of presentation (Table 6).

**Table (6):** Comparison regarding symptoms at 6 months between the studied groups

| Variable | | Amino Acid Formula (N=27) | | Breast Feeding (N=27) | | P-value† |
|---|---|---|---|---|---|---|
| | | N or n/N | % | N or n/N | % | |
| **Activity affection** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Weight loss** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Abdominal distention** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Vomiting** | **Negative** | 26 | 96.3% | 27 | 100.0% | 1.000 |
| | **Positive** | 1 | 3.7% | 0 | 0.0% | |
| **Diarrhea** | **Negative** | 25 | 92.6% | 27 | 100.0% | 0.491 |
| | **Positive** | 2 | 7.4% | 0 | 0.0% | |
| **Consistency of motions** | **Semisolid** | 2/22 | 9.1% | 0/18 | 0.0% | 0.492 |
| | **Seedy** | 20/22 | 90.9% | 18/18 | 100.0% | |
| **Color of motions** | **Yellowish** | 3/22 | 13.6% | 1/20 | 5.0% | 0.699 |
| | **Brownish** | 1/22 | 4.5% | 2/20 | 10.0% | |
| | **Brownish with digested food** | 18/22 | 81.8% | 17/20 | 85.0% | |
| **Mucus in stools** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Blood in stools** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Bleeding per rectum** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Constipation** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Cough** | **Negative** | 26 | 96.3% | 27 | 100.0% | 1.000 |
| | **Positive** | 1 | 3.7% | 0 | 0.0% | |
| **Runny nose** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Specific medications** | **Negative** | 24 | 88.9% | 25 | 92.6% | 1.000 |
| | **Positive** | 3 | 11.1% | 2 | 7.4% | |

Data are number (N) or proportion (n/N) and valid percentage (%)

There was no statistically significant differences between the studied groups regarding signs at 3 months of presentation (Table 7).

**Table (7):** Comparison regarding signs at 3 months between the studied groups

| Variable | | Amino Acid Formula (N=27) | | Breast Feeding (N=27) | | P-value |
|---|---|---|---|---|---|---|
| | | N | % | N | % | |
| **Pallor** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Irritability** | **Negative** | 23 | 85.2% | 23 | 85.2% | 1.000† |
| | **Positive** | 4 | 14.8% | 4 | 14.8% | |
| **Hives** | **Negative** | 21 | 77.8% | 24 | 88.9% | 0.467† |
| | **Positive** | 6 | 22.2% | 3 | 11.1% | |
| **Eczema** | **Negative** | 26 | 96.3% | 26 | 96.3% | 1.000† |
| | **Positive** | 1 | 3.7% | 1 | 3.7% | |
| **Rhinitis** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Asthma** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Abdominal tenderness** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Abdominal mass** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |
| **Guarding** | **Negative** | 27 | 100.0% | 27 | 100.0% | NA |
| | **Positive** | 0 | 0.0% | 0 | 0.0% | |

Data are number (N) and valid percentage (%)

There were no statistically significant differences between the studied groups regarding anthropometric parameters at different follow-up visits when compared with z-scores. Supine length remained affected after 1 year of age, requiring further follow-up, investigations, and management. All cases were classified as having moderate acute malnutrition (low weight for height/length −2 to ≥−3 standard deviations of the median WHO child growth standard) (Figure 1A, 1B & 1C).

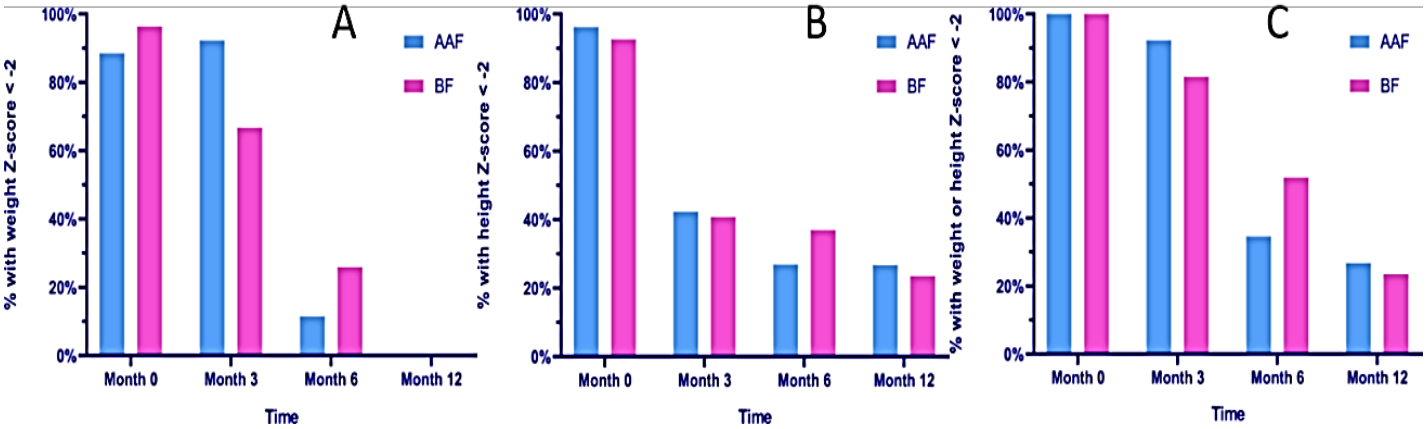


**Figure (1):** Percentage of patients with (A) low body weight, (B) low length, (C) impaired growth among the studied groups.

Repeated measures analysis of variance (ANOVA) showed a statistically significant effect of time on body weight and body weight z-scores, with no significant time-group interaction. The between-group differences were not statistically significant for either body weight (p = 0.638) or body weight z-score (p = 0.368) (Figure 2A & 2B).

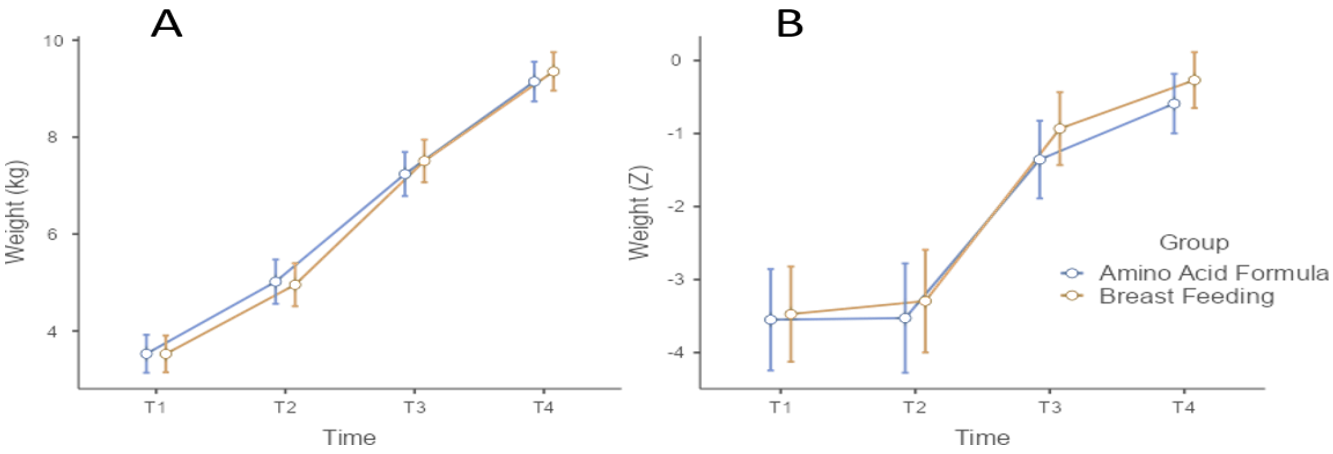


**Figure (2):** Change in (A) body weight, (B) body weight Z-score in both groups in the follow up visits.

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## DISCUSSION

CMA is one of the most common food allergies, peaking during childhood, with food challenge prevalence estimated in the range between 0.5 and 3% in Europe, with a decreased rate from northern to southern [8]. CMPA is an immune-mediated hypersensitivity in infants, often diagnosed through symptoms affecting multiple organ systems. Accurate diagnosis and management are crucial for infant growth and development [1, 2].

This study aimed to detect difference in growth in infants with CMA who kept exclusively breast fed whose mothers are on dairy product restricted diet and infants fed on amino acid formula and to assess improvement of symptoms and signs between using amino acid formula from the start and elimination diet in exclusively breastfed infants in different visits.

In this study, CMPA was diagnosed in equal proportions of males and females, with most cases identified before three months of age, which is consistent with previous research by **Høst *et al.*** [9], and **Yimyaem *et al.*** [10] who reported that CMPA typically presents within the first six months of life. Early symptom onset has been documented shortly after introducing cow's milk protein, with rare cases presenting beyond 12 months [11]. Additional studies by **Arancibia *et al.*** [12] who reported a median age of symptom onset at 20 days and confirmation by 113 days. CMPA often involves multiple organ systems, primarily the gastrointestinal tract and skin, and can be associated with diverse extra-intestinal manifestations such as fatigue, joint pain, poor sleep, and other systemic symptoms [13].

Unchangeable risk factors, such as male sex, ethnicity (higher prevalence in Asian and Black children), and family history of atopy, are well-established in food allergies [14]. In our study, a slightly higher prevalence of CMPA was observed in infants from rural areas, which contrasts with findings by **Shao *et al.*** [15] where CMPA was more prevalent in urban areas. This urban-rural disparity in CMPA prevalence has been attributed to higher rates of Cesarean sections in urban populations, which are linked to changes in the neonatal microbiota, favoring a Th2 response and increasing the risk of atopy and other chronic conditions [16].

In this study, a higher prevalence of family history of atopy was observed in the breastfed group compared to the amino acid-fed group, although the difference was not statistically significant. Family history of atopy, including allergies related to food, skin, respiratory, or medications, is a recognized risk factor for CMPA and is critical in the diagnostic process. These findings are consistent with **Korol *et al.*** [17], who reported a family history of atopy in a significant proportion of CMPA children, with rates ranging from 41% to 91% depending on the degree of familial relation.

In this study, a positive family history of eczema was equally prevalent in both groups, while bronchial asthma was more common in the amino acid-fed group, although the difference was not statistically significant. These findings align with previous research by **Fuertes *et al.*** [18] indicating that a family history of allergic disorders, particularly eczema or asthma, significantly increases the risk of allergy in infants. Infants with a family history of atopy tend to present more frequently with digestive, skin, and respiratory symptoms, as well as sleep disorders. Notably, skin conditions like atopic dermatitis and eczema were more common in infants with a positive family history of atopy [19].

In this study, the most common symptoms in infants with CMA included abdominal distension,

diarrhea, vomiting, and malnutrition, with all cases showing malnutrition at diagnosis, which improved over time. These findings are consistent with those of a Chinese study by **Yang *el al.*** [20] who also reported gastrointestinal symptoms, particularly diarrhea, as the most frequent manifestation in infants under six months, with malnutrition more commonly observed in formula-fed infants. The study highlighted that artificial feeding may contribute to more severe CMPA and malnutrition compared to breastfeeding.

Growth assessment in the current study demonstrated that all growth parameters were initially affected at diagnosis, with significant improvement over time in both breastfed and amino acid formula-fed groups, ultimately showing no statistical difference between them after six months. These findings align with **Chebar *et al.*** [21] who observed growth impairments in infants on elimination diets but noted improvements following dietary adjustments. Also, our findings align with **Tuokkola *et al.*** [22] who reported slower growth in children on milk elimination diets without catch-up growth by age five.

In this study, supine length z-scores improved after 12 months of treatment, which aligns with previous studies indicating slower growth improvement in CMPA cases. An earlier study by **Noimark *et al.*** [23] reported no significant catch-up growth in length by 24 months in infants with CMPA, suggesting the need for continued growth monitoring in these patients throughout childhood. Similarly, a Japanese study by **Mukaida *et al.*** [24] found that children with persistent allergies, particularly to cow's milk, experienced prolonged growth delays, with reduced height-for-age z-scores lasting up to 10 years.

In this study, infants with CMPA showed improvement in stool symptoms, including gross and occult blood, after 3 months of treatment with an elimination diet or amino acid formula. Mucous in the stool was observed in both groups, with no significant difference in improvement between them. These findings align with those from a cohort study by **Martin *et al.*** [25] on infants diagnosed with food protein-induced allergic proctocolitis (FPIAP), where 78% had either gross blood or mucous in their stool as presenting symptoms, all of which improved with treatment. Additionally, a study by **Borschel *et al.*** [26] on infants with food protein-induced proctocolitis found that stool occult blood became negative after 42 days of introducing an AAF.

## LIMITATIONS

Despite our notable findings, our study has some limitations as this study has relatively small sample size, which may limit the generalizability of the findings. Additionally, the study design did not include a long-term follow-up beyond 12 months, which would be valuable in assessing the sustained effects of treatment on growth and symptom resolution in CMPA. Another limitation is the lack of a standardized method for assessing the severity of symptoms, which could lead to variability in the interpretation of clinical outcomes.

## CONCLUSION

CMPA was diagnosed at a slightly earlier age in the AAF group. Growth parameters, particularly weight and length, were affected at diagnosis, with moderate acute malnutrition in all cases. Common symptoms included abdominal distension and diarrhea, with vomiting more prevalent in the amino acid fed group. Growth improved after 6 months of management, although taste issues with amino acid formula reduced compliance. Occult blood in stool was common at presentation but resolved by the 6-month follow-up.

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