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# Non-IgE-Mediated Cow Milk Allergy Is Linked to Early Childhood Clusters of Commonly Seen Illnesses: A Pilot Study

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## Abstract

**Objective.** There are few established diagnostic tools to define non-IgE-mediated food hypersensitivity reactions. Cow milk protein allergy (CMPA) is a multisystem disorder affecting the gastrointestinal, skin, and lower and upper airway systems. This link is frequently missed because of subspecialty evaluation of the multisystem effects individually. The authors hypothesize that a more global evaluation based on a simple scored questionnaire will reveal this link. **Methods.** Over an 18-month period, children younger than 2 years with non-IgE-mediated CMPA were identified. A symptom questionnaire was developed and scored and also applied to a control population. The prevalence of symptoms in each group was compared and a cumulative score was determined. Symptoms evaluated included gastrointestinal, aerodigestive, lower airway, and skin symptoms. A positive response was scored 1 and a negative response scored 0. **Results.** Significant differences in prevalence rates between CMPA and control populations were noted, particularly in aerodigestive symptoms. There were marked differences in cumulative score between populations ( $P < .001$ ). The authors identified a cut-off score at which there was close to 80% sensitivity and 90% specificity for distinguishing CMPA from a control population. **Conclusion.** A global evaluation of multiple systems can be an important diagnostic tool in determining CMPA in infants.

## Keywords

cow milk allergy, infants, questionnaire

## Introduction

Over the past decade, the prevalence of food allergies has increased.<sup>1</sup> Because of the complex nature of the disease and the lack of a standardized approach to the diagnosis and management of food allergies, the National Institute of Allergy and Infectious Diseases has developed “best practice” clinical guidelines for the diagnosis and management of food allergies.<sup>2</sup>

Cow milk protein hypersensitivity is a significant health problem with potential for varying medical and nutritional complications. In children younger than 2 years, cow milk protein allergy (CMPA) is well recognized.<sup>3,4</sup> The true prevalence of CMPA has been difficult to establish, although studies have suggested prevalence rates for CMPA that vary from 2% to 12%.<sup>5–7</sup> The complexity of CMPA can be linked to an immunologic spectrum of pathogenesis ranging from

IgE-mediated, non-IgE-mediated as well as mixed immunological mechanisms. CMPA is a multisystem disorder that can present with gastrointestinal, cutaneous, and upper and lower respiratory syndromes.<sup>8–12</sup> Individually, many of these symptoms overlap with routine illnesses seen in the setting of well child visits.

Gastrointestinal manifestations of food allergies are well described. Interestingly, there have been increasing reports of refractory gastroesophageal reflux disease (GERD) in infants younger than 1 years of age<sup>13,14</sup> and a

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casual observation of increased prevalence of aerodigestive disease during the time of increased prevalence of food allergies.

Recent literature suggests that food allergy syndromes may affect not only the mucosal lining of the intestinal tract but also the deeper submucosal and muscular layers leading to dysmotility and nociceptive syndromes such as infantile colic, constipation, and vomiting.<sup>15-17</sup>

Whereas IgE-mediated and mixed reactions may be identified by skin testing, food allergen-specific serum IgE determination, elimination trials, and oral challenges, the non-IgE-mediated reactions are difficult to identify with currently available techniques. The double-blinded, placebo-controlled food challenge is considered the present gold standard for diagnosis of food allergy. This standard is difficult, expensive to perform, and may not be readily available in many clinical settings. Moreover, non-IgE-mediated food reactions depend on the quantity of exposure and may have a prolonged delay for onset of symptoms,<sup>18</sup> which may further lead to under diagnosis based on classical oral challenges. In recognizing this diagnostic difficulty, the National Institute of Allergy and Infectious Diseases guidelines for diagnosis of non-IgE-mediated food hypersensitivity reactions particularly food protein-induced enteropathy syndrome and food protein-induced enterocolitis syndrome may be based on a convincing history and absence of symptoms when the causative food is eliminated from the diet. The diagnostic dilemma in dealing with these allergy syndromes was emphasized by the inability for the expert panel to make recommendations based on a clear rationale, expert opinion, or based on existing quality of evidence.<sup>2</sup>

Early recognition and management of CMPA will reduce the need for unnecessary invasive and expensive investigations and procedures in affected infants and hence reduce the economic burden of management. The objective of this pilot study was to determine if a multisystem approach to the evaluation of patients younger than 2 years may help in the diagnosis of CMPA. A secondary objective of this study was to evaluate a multisystem questionnaire that would help diagnose non-IgE-mediated early CMPA and be easy to apply and score in a busy clinical setting. The validity of the questionnaire in determining the presence of CMPA was also studied.

## Methods

### Study Population

Children younger than 2 years seen in the pediatric gastroenterology clinic and general pediatric clinics from

June 2008 to October 2009 were enrolled in the study. A retrospective chart review was used to identify patients with a diagnosis of CMPA. Children were included in the CMPA group if (a) a diagnosis of CMPA was given following a 2-week elimination diet that led to clinically significant improvement or resolution of gastrointestinal symptoms; (b) a history of failed management of refractory reflux, chronic diarrhea, constipation, or growth failure was noted; and (c) non-IgE-mediated disease was confirmed using food allergen-specific serum assay (ImmunoCAP, Phadia US, Portage, MI). Those CMPA patients who were identified were subsequently contacted and administered the questionnaire in a cross-sectional manner. At the same time, a group of children younger than 2 years were recruited during a routine health supervision visit. Both pediatric gastroenterology and general pediatric clinics were situated in a tertiary care center. As this study involves recall of symptoms from birth, control and CMPA groups were not age matched.

Patients who had medical conditions that may predispose to symptoms similar to CMPA allergy symptoms such as trachea-esophageal fistula, pyloric stenosis, cerebral palsy, and neurodegenerative disorders were excluded from the study.

### Symptom Selection

Symptoms for questionnaire were selected based on a preliminary retrospective review of charts of patients who were diagnosed with CMPA and responded to elimination diet. A review of literature defining intestinal and extraintestinal manifestations of CMPA was also performed.<sup>3,4,8,9,11,16,17</sup> Both chart and literature review suggests a strong family association regarding food allergies.<sup>19</sup> Questions related to family history were restricted only to first-degree relatives of the study subject. Questions defining the severity of lung disease were graded depending on the need for medical management of lung disease as this could be easily determined through chart review rather than guardian recall. The severity of seborrheic dermatitis and atopic dermatitis were similarly categorized by a need for medical management. Vomiting was graded as being less than 5 times per day or greater than 5 times per day. A frequency of 5 episodes per day was chosen as this is an easily recalled number and would represent a vomit/spitting episode occurring with a least 50% of feeds in an early infant. A formula change was defined as a change to a soy-, hydrolysate-, or amino acid-based formula. The question of sibling with formula change was not specific to the type of formula secondary to parent's difficulty remembering the formula type.

## Questionnaire Development and Testing

Each symptom was given an individual score, and an overall score was calculated from the individual scores. Individual score was given as 1 for a positive response and 0 for a negative response. Severity based on documented medical management was graded as 1 if medical management was needed and as 0 if no medical management was needed. Vomiting was scored based on frequency with 0 if there was no vomiting, 1 if vomiting was less than 5 times per day, and 2 if greater than 5 times per day. Though this scoring technique limits the degree of flexibility,<sup>20</sup> it reduces the chance of bias recall in the study population. Questionnaires were completed by health care professionals through direct interview with guardian in a clinical setting or through a phone interview after informed consent were obtained. To improve the validity of the questionnaire, the question "other symptom that responded to dairy elimination" was included. If a symptom appeared with similar prevalence in CMPA and control groups, it was removed from the final questionnaire.

This questionnaire was designed to be used during a clinical visit. Many questions incorporated into the questionnaire are part of routine history taking. Time taken to apply questionnaire by a health care professional and ease of use was assessed by study investigators. The questionnaire is given in Figure 1.

## Sensitivity and Specificity

Sensitivity and specificity of the questionnaire was determined by comparing the incidence and frequency of symptoms between the CMPA cohort and the control group of patients. The aim is to identify a composite symptom score derived from a simple questionnaire, with high sensitivity and specificity of more than 80%.

## Statistical Methods

It was projected that a minimum sample size of 40 patients with confirmed CMPA and 40 control healthy subjects will be needed for the study. This assumes that there will be at least a 30% difference in the mean composite score between patients with CMPA and controls. Differences between CMPA and control group in responses given for each questionnaire item were assessed using  $\chi^2$  test or Fisher's exact test if any comparison cell had less than 5 observations. Differences between groups for continuous variables (eg, age, total score) were assessed using the Wilcoxon rank sum test.

Statistical significance was claimed for any test result at or below the accepted type I error rate of .05.

Receiver operating characteristic (ROC) analysis was used to determine how the questionnaire distinguished between CMPA and control groups.<sup>21</sup> ROC analysis simultaneously estimates the probability of being in the CMPA group assuming the given questionnaire score indicates a positive screening test result (sensitivity) and the probability of being in the control group assuming the given questionnaire score indicates a negative screen result (specificity). Subsequent comparison of sensitivity and specificity for each observed test score allows for identification clinically relevant cutpoints.

Data analysis was conducted using Stata version 11.1 (College Station, TX). This study was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences.

## Results

Over the study period, 191 patients were considered to have a diagnosis of CMPA. A total of 101 of these patients had a follow-up visit in the gastrointestinal clinic of whom 65 were tested for food allergen-specific serum IgE. Of these, 43 were determined to be negative for allergen-specific serum IgE and responded to elimination diet. These were the 43 patients selected for the CMPA group. A total of 41 controls were recruited from the general pediatric clinic. When applied in a clinical setting, range of time spent applying the questionnaire was 3 to 6 minutes.

Demographic and questionnaire responses are summarized by group in Table 1. The most common symptom presentation in the CMPA population was vomiting within the first month of life, 32 (74%). Of these, 29 (90%) recorded frequencies of greater than 5 times per day. Of the patients presenting with vomiting, 30 (90%) had failed medical management of GERD (63% on a proton pump inhibitor, 20% on an H2 antagonist, and 10% on a prokinetic agent alone). The 2 patients who were not on antireflux therapy had resolution of vomiting with formula change. Thirty (70%) of patients in the CMPA group already had a formula change prior to their initial visit. There were 4 cases (2 from control group and 2 from CMPA group) that were adopted or in foster care and evaluation of family history were not complete. Additional symptoms and findings noted in the CMPA population were abdominal distension 7 (16%) and anemia 5 of 34 (14.7%) of those checked (Table 1).

The total questionnaire score was statistically different between the 2 groups as the CMPA group average

|                    |                                                                                               |                                                                       |             |
|--------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|-------------|
| Q01                | How often did your child vomit in the first month?                                            | No vomiting<br>Less than 5 times per day<br>More than 5 times per day | 0<br>1<br>2 |
| Q02                | Were different formulas tried?                                                                | 0 = No                                                                | 1 = Yes     |
| Q03                | Did child gag or choke regularly on feeds?                                                    | 0 = No                                                                | 1 = Yes     |
| Q04                | Was your child's doctor concerned about poor weight gain in first year?                       | 0 = No                                                                | 1 = Yes     |
| Q05                | Did you consider your child to have excessive irritability or colic?                          | 0 = No                                                                | 1 = Yes     |
| Q06                | Did your child pass large painful stools?*                                                    | 0 = No                                                                | 1 = Yes     |
| Q07                | Did your child have blood in the stools?                                                      | 0 = No                                                                | 1 = Yes     |
| Q08                | Was there always lots of mucus or "cold" in the stool?*                                       | 0 = No                                                                | 1 = Yes     |
| Q09                | Did you consider your child to have diarrhea?                                                 | 0 = No                                                                | 1 = Yes     |
| Q10                | Did your child have cradle cap or "scabs" in his/her hair?*                                   | 0 = No                                                                | 1 = Yes     |
| Q11                | Was this treated with anything?*                                                              | 0 = No                                                                | 1 = Yes     |
| Q12                | Did your child have recurrent eczema or rashes?*                                              | 0 = No                                                                | 1 = Yes     |
| Q13                | Was this treated with anything?*                                                              | 0 = No                                                                | 1 = Yes     |
| Q14                | Did your child have wheezing or persistent cough?                                             | 0 = No                                                                | 1 = Yes     |
| Q15                | Was this treated with medicines?*                                                             | 0 = No                                                                | 1 = Yes     |
| Q16                | Did your child have persistent congestion in the nose and eyes?                               | 0 = No                                                                | 1 = Yes     |
| Q17                | Was this treated with any medicines?                                                          | 0 = No                                                                | 1 = Yes     |
| Q18                | Did your child have more than 3 episodes of ear infection in the first year?                  | 0 = No                                                                | 1 = Yes     |
| Q19                | Did your child have ear tubes placed?                                                         | 0 = No                                                                | 1 = Yes     |
| Q20                | Was your child diagnosed with a swallow dysfunction ?                                         | 0 = No                                                                | 1 = Yes     |
| Q21                | Are there any siblings?*                                                                      |                                                                       |             |
| Q22                | Did siblings need a change in formula as a young infant?*                                     | 0 = No                                                                | 1 = Yes     |
| Q23                | Did any siblings have similar problems as a young infant?                                     | 0 = No                                                                | 1 = Yes     |
| Q24                | Did mom or dad have problems as infants that required a formula change or needed goat's milk? | 0 = No                                                                | 1 = Yes     |
| Q25                | Were there any other unusual problems you noted in your child?                                |                                                                       |             |
| Total Score (0-24) |                                                                                               |                                                                       |             |

**Figure 1.** Questionnaire used to evaluate for cow milk hypersensitivity

\*Indicates questions that could be left out of final questionnaire because of no significant difference between cow milk protein allergy (CMPA) and control groups.

score was 10.7 whereas the control group average score was 3.7 (Table 1). Excluding those questionnaire items that did not differ significantly between control and CMPA population (cradle cap and its treatment, eczema and its treatment, painful defecation, mucus in stools, congestion treatment, and sibling with formula change) from the total score yielded an adjusted score that was also statistically significant between CMPA (8.7) and control (2.3; Table 1).

Examining the results of the ROC analysis (Table 2), the total scores of 2 and 10 had either absolute sensitivity or specificity, respectively. Selecting a total score of  $\geq 6$ , midway between the 2 absolutes, yields a 88% sensitivity for detecting patients with dairy hypersensitivity (38/43 CMPA patients with score  $\geq 6$ ) and a specificity of 71% (29/41 control patients with a score  $< 6$ ) with all questions included. Examining the adjusted score, a decreased sensitivity of 79% (34/43 CMPA  $\geq 6$ ) and an

**Table 1.** Symptom Frequency in Patients With Cow Milk Protein Allergy (CMPA) Compared With Control (Healthy) Population

|                                                                  | Control    | CMPA        | P                  |
|------------------------------------------------------------------|------------|-------------|--------------------|
| N                                                                | 41         | 43          |                    |
| Age (months) <sup>a</sup>                                        | 11.2 (5.1) | 7.7 (5.2)   | .001               |
| Female                                                           | 19 (46.3)  | 24 (55.8)   | .385               |
| Questionnaire items                                              |            |             |                    |
| Q01: Vomiting in first month                                     | 15 (36.6)  | 32 (74.4)   | <.001              |
| Q02: Different formulas tried                                    | 0 (0.0)    | 30 (69.8)   | <.001 <sup>b</sup> |
| Q03: Gag or choke regularly on feeds                             | 3 (7.3)    | 16 (37.2)   | .001 <sup>b</sup>  |
| Q04: Poor weight gain in first year                              | 5 (12.2)   | 20 (46.5)   | .001 <sup>b</sup>  |
| Q05: Irritability or colic                                       | 3 (7.5)    | 22 (51.2)   | <.001 <sup>b</sup> |
| Q06: Large painful stools                                        | 11 (26.8)  | 18 (41.9)   | .148               |
| Q07: Blood in the stools                                         | 2 (4.9)    | 15 (34.9)   | .001 <sup>b</sup>  |
| Q08: Mucus in the stool                                          | 2 (4.9)    | 8 (18.6)    | .089 <sup>b</sup>  |
| Q09: Diarrhea                                                    | 8 (19.5)   | 19 (44.2)   | .016               |
| Q10: Cradle cap or "scabs" in hair                               | 18 (43.9)  | 15 (34.9)   | .398               |
| Q11: Cradle cap treated <sup>c</sup>                             | 5 (27.8)   | 3 (27.3)    | Nonsignificant     |
| Q12: Recurrent eczema or rashes                                  | 10 (24.4)  | 18 (41.9)   | .090               |
| Q13: Eczema/rashes treated <sup>c</sup>                          | 6 (66.7)   | 7 (41.2)    | .411 <sup>b</sup>  |
| Q14: Wheezing or persistent cough                                | 9 (22.0)   | 20 (46.5)   | .018               |
| Q15: Wheeze/cough treated <sup>c</sup>                           | 2 (22.2)   | 14 (70.0)   | .041 <sup>b</sup>  |
| Q16: Persistent congestion in the nose and eyes                  | 8 (19.5)   | 29 (67.4)   | <.001              |
| Q17: Congestion treated <sup>c</sup>                             | 3 (42.9)   | 15 (55.6)   | .681 <sup>b</sup>  |
| Q18: More than 3 episodes of ear infection in the past year      | 1 (2.4)    | 16 (37.2)   | <.001 <sup>b</sup> |
| Q19: Ear tubes placed                                            | 0 (0.0)    | 13 (30.2)   | <.001 <sup>b</sup> |
| Q20: Swallow dysfunction                                         | 1 (2.4)    | 19 (44.2)   | <.001 <sup>b</sup> |
| Q21: Siblings                                                    | 24 (58.5)  | 24 (55.8)   | Nonsignificant     |
| Q22: Siblings with formula change as a young infant <sup>c</sup> | 6 (27.3)   | 11 (52.4)   | .092               |
| Q23: Siblings with features of CMPA <sup>c</sup>                 | 8 (36.4)   | 16 (76.2)   | .014 <sup>b</sup>  |
| Q24: Parents with formula change as an infant                    | 3 (7.5)    | 19 (46.3)   | <.001 <sup>b</sup> |
| Questionnaire total score (0-24) <sup>a</sup>                    | 3.7 (2.8)  | 10.7 (4.3)  | <.001              |
| Score of differing items only (0-15) <sup>a</sup>                | 2.3 (2.2)  | 8.7 (3.3)   | <.001              |
| Abdominal distension                                             | 0 (0.0)    | 7 (16.3)    | .012 <sup>b</sup>  |
| Anemia <sup>d</sup>                                              |            | 5/34 (14.7) |                    |

<sup>a</sup>Scores reported as mean (standard deviation); otherwise n (%) reported.

<sup>b</sup>Fisher's exact test used; otherwise  $\chi^2$  test used (Wilcoxon rank sum for continuous variables).

<sup>c</sup>Responses only scored if preceding response was positive.

<sup>d</sup>n = 34 patients who had hemoglobin levels checked in first 2 years.

increased specificity of 93% (38/41 control <6) were observed. Combining the 2 absolutes and the midpoint into an index of the total score yielded an ROC curve with an area under the curve of 0.89, indicating that these cutpoints are able to discriminate between CMPA and control groups (Figure 2).

## Discussion

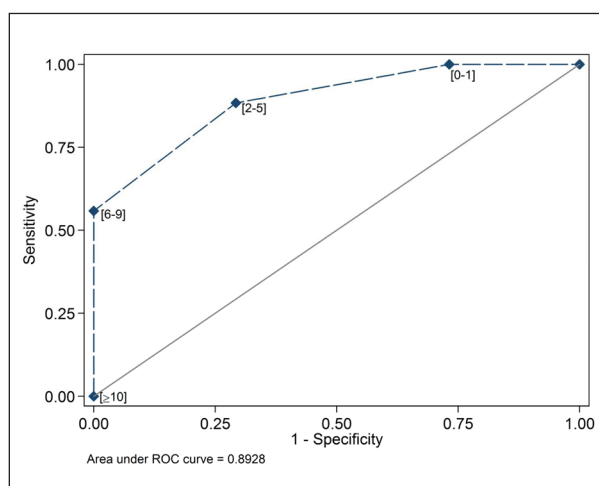
This study supports the hypothesis that non-IgE-mediated CMPA can result in multisystem involvement with overlap of symptoms involving the gastrointestinal,

aerodigestive, skin, and respiratory systems. The study also suggests that there exist a set of symptoms that occur in infants younger than 2 years when viewed cumulatively can be used as a useful diagnostic tool to identify CMPA patients. This study also suggests that the questionnaire used had very good sensitivity and specificity to distinguish infants with CMPA from infants with routine isolated childhood illnesses. The study reveals that an overall score  $\geq 6$  is suggestive of CMPA. Supplemental information obtained regarding symptoms as implied by the open-ended "other symptoms" in the questionnaire or by review of medical

**Table 2.** Sensitivity and Specificity of Observed Total Scores and Classification Percentage of Cow Milk Protein Allergy (CMPA)

| Score           | Sensitivity (%) | Specificity (%) | Classified (%) |
|-----------------|-----------------|-----------------|----------------|
| 0               | 100.00          | 0.00            | 51.19          |
| 1               | 100.00          | 19.51           | 60.71          |
| 2 <sup>a</sup>  | 100.00          | 26.83           | 64.29          |
| 3               | 97.67           | 39.02           | 69.05          |
| 4               | 93.02           | 51.22           | 72.62          |
| 5               | 90.70           | 63.41           | 77.38          |
| 6 <sup>a</sup>  | 88.37           | 70.73           | 79.76          |
| 7               | 79.07           | 78.05           | 78.57          |
| 8               | 74.42           | 87.80           | 80.95          |
| 9               | 72.09           | 95.12           | 83.33          |
| 10 <sup>a</sup> | 67.44           | 100.00          | 83.33          |
| 11              | 55.81           | 100.00          | 77.38          |
| 12              | 44.19           | 100.00          | 71.43          |
| 13              | 30.23           | 100.00          | 64.29          |
| 14              | 23.26           | 100.00          | 60.71          |
| 15              | 20.93           | 100.00          | 59.52          |
| 16              | 16.28           | 100.00          | 57.14          |
| 17              | 6.98            | 100.00          | 52.38          |
| 18              | 4.65            | 100.00          | 51.19          |
| 20              | 2.33            | 100.00          | 50.00          |
| 21+             | 0.00            | 100.00          | 48.81          |

<sup>a</sup>Cutpoints for increasing likelihood of CMPA diagnosis.

**Figure 2.** Receiver operator characteristic (ROC) curve for selected cutpoints classifying likelihood of cow milk protein allergy (CMPA)

records suggest that abdominal distension may be a pertinent symptom in patients with CMPA. There were

interesting observations noted during this study. Upper and lower airway pathology such as congestion, recurrent otitis media, swallow dysfunction, gagging/choking with feeds, and wheezing/persistent cough were strongly associated with CMPA.

A thorough and careful history with a subsequent elimination trial of the suspected food for at least 2 weeks with resulting improvements in symptoms are necessary for the diagnosis of CMPA. This is particularly so when the allergy pathway involves a non-IgE-mediated or mixed non-IgE/IgE-mediated reaction. Double-blind placebo-controlled food challenge is should be considered the gold standard for the diagnosis of food allergies in older children and adults; however, a standardized approach to such studies accounting for a possible prolonged time interval before the return of symptoms must be determined in future studies as symptoms may take days to be expressed.

Failure of standard management practices for common childhood illness of the gastrointestinal, aerodigestive, skin, and respiratory symptoms should question the underlying cause of the illness. The study population was recruited from a gastrointestinal specialty clinic in which the most common presentation was early onset persistent vomiting (74%). The underlying cause for GERD refractory to medical management has come under scrutiny. Recent data suggest that the use of proton pump inhibitors, which are effective in reducing the noxious consequence of acid refluxate, has resulted in only questionable reduction in GERD-associated behavior whereas adult studies question the association between GERD and its extraesophageal manifestation suggesting the presence of other inflammatory contributors to disease.<sup>22-24</sup> It must also be noted that although many infants are diagnosed with lactose intolerance, because of the prominent gastrointestinal symptoms with CMPA, congenital lactase deficiency is extremely rare<sup>25,26</sup> and could not account for the multitude of symptoms noted in these patients. Aerodigestive symptoms, particularly persistent upper airway congestion, were also quite common (67%). Recent otolaryngology literature has also explored the role of allergies as the underlying cause of multiple aerodigestive disease.<sup>27,28</sup>

## Limitations

This study can only be considered a pilot study as it was performed in a cohort whom CMPA was diagnosed and had positive response to elimination with respect to their gastrointestinal manifestations. Future clinical studies confirming the validity of the questionnaire in patients not previously diagnosed with CMPA

will be needed. Another limitation of this study is the dependence on the caregivers' recall of symptoms that may approach up to 2 years if symptoms presented in early infancy.

Placement of an infant on an elimination diet is not without risk, particularly for both macronutrient and micronutrient malnutrition. In this study, all patients placed on dairy protein elimination diets were counseled by a nutritionist to ensure that a healthy nutritionally appropriate diet was maintained. This should be considered a standard practice in any infant being placed on an elimination trial.

## Conclusion

In conclusion, this pilot study suggests that a global evaluation of multiple systems with a simple scored questionnaire can be an important diagnostic tool in determining CMPA in infants. Early diagnosis may be helpful in restricting unnecessary investigation, medical therapy, and surgical therapy. This study also suggests that there is a strong association between upper and lower airway disease and CMPA, which will need further evaluation in future studies.

## Declaration of Conflicting Interests

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