Cow's-Milk–free Diet as a Therapeutic Option in Childhood Chronic Constipation

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ABSTRACT

Objectives: It has been reported that a number of children with constipation respond to a diet free of cow's-milk (CM) proteins, although evidence is lacking to support an immunoglobulin E–mediated mechanism.

Patients and Methods: We performed an open-label crossover study comparing CM and rice milk in 69 children who fulfilled Rome III criteria for chronic constipation. Clinical, physical, and immunologic parameters of patients who responded (R) and who did not respond (NR) to a CM-free diet were compared.

Results: Thirty-five of the 69 children (51%) improved during the first CM-free diet phase, 8 of these did not develop constipation when CM was reintroduced, and 27 children (39%) developed constipation during the CM challenge and improved during the second CM-free diet phase (R group). Thirty-four children (49%) did not improve during the first CM-free diet phase (NR group). Bowel movements per week among R children significantly increased compared with NR children (R: 2.8–7.7 vs NR: 2.6–2.7) ($P < 0.001$). Seventy-eight percent of the children with developmental delay responded to the CM-free diet ($P = 0.007$). No significant statistical difference was found between the R and NR children in terms of fiber and milk consumption; atopic or allergic history; full-blood eosinophil count and percentage, and lymphocyte populations; immunoglobulins, immunoglobulin (Ig)G subclasses, total IgE; and serum-specific immunoglobulin E for CM proteins.

Conclusions: A clear association between CM consumption and constipation has been found in more than one third of children. However, analytical parameters do not demonstrate an immunoglobulin E-mediated immunologic mechanism.

Key Words: allergy, constipation, cow's milk

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The frequency of chronic idiopathic constipation in the pediatric population ranges from 3% to 16%, and it is 1 of the most common reasons for seeking medical advice (1). Recently, there have been no significant advances in the understanding of the mechanisms that lead to the onset of constipation or in proposing effective therapeutic approaches. It is still the case that around one third of constipated children will continue to have the problem into adulthood (2), which contradicts the extended opinion that constipation disappears before or during puberty (3). Reduced ingestion of residue-rich food (fruit and vegetables) together with excessive consumption of milk and dairy desserts have been proposed as a possible link between milk and constipation (4). More recently, it has been suggested that cow's-milk (CM) proteins could play a direct role in the genesis of constipation through an immune-mediated mechanism (5–8). The resolution of histologic and manometric abnormalities in patients on a CM-free diet further supports CM etiology (9–11). Despite these published data, few articles evaluate the influence of CM on pediatric chronic constipation, and the withdrawal of CM as a therapeutic option has had little impact in the medical community and in published guidelines for the management of these patients (12,13).

The aim of the present study was to describe the medical history and analytical parameters of children with chronic constipation and evaluate the utility of a CM-free diet as a treatment option.

PATIENTS AND METHODS

Children between 6 months and 14 years of age who were referred to our tertiary pediatric gastroenterology clinic between October 2006 and December 2007 and fulfilled the Rome III criteria for the diagnosis of pediatric chronic constipation (14,15) were evaluated for study entry. Children taking medications that can cause constipation, those with previous abdominal surgery, pilonidal sinus, or anatomic abnormalities, or with sensation of pelvic floor were excluded. Informed consent was obtained from the parents of all of the patients involved in the study, which was approved by the ethics committee of the hospital.

Sixty-nine consecutive children who fulfilled the inclusion criteria were included in the study. The parents of 2 patients remembered that their child had passed meconium after the first day of life, but in both, constipation had begun after 6 months of age. Hypothyroidism was ruled out in 7 children with cold intolerance. Abnormalities of the medullary conus and the pelvic floor were excluded in 2 children with a history of recurrent urinary tract infections and in 2 boys with urinary incontinence who had previously been continent. Nine children had developmental delay: 1 girl with Down syndrome and 8 children with nonsyndromic developmental delay, 3 of whom had associated reduced axial tone. None of them experienced autism or hypothyroidism.

Patient history items were collected and physical examinations performed following the recommendations of the 2006 Constipation Guideline Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (Tables 1 and 2).

The consistency of stools was evaluated using a semiquantitative scale of 5 points, based on a simplified version of the Bristol

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TABLE 1. History in pediatric patients with constipation

- Age
- Sex
- Chief symptom
- Constipation history
  - Frequency and consistency of stools
  - Pain or bleeding with passing stools
  - Abdominal pain
  - Waxing and waning of symptoms
  - Age of onset
  - Toilet training
  - Fecal soiling
  - Withholding behavior
  - Change in appetite
  - Nausea or vomiting
  - Weight loss
  - Perianal fissures, dermatitis, abscess, or fistula
  - Current treatment
    - Current diet (24-hour recall history)
    - Current medications (for all medical problems)
      - Oral, enema, suppository, herbal
  - Previous treatment
    - Diet
    - Medications
      - Oral, enema, suppository, herbal
    - Previous successful treatments
    - Behavioral treatment
    - Results of previous tests
    - Estimate of parent/patient adherence
- Family history
  - Significant illnesses
  - Gastrointestinal (constipation, Hirschsprung disease)
  - Other
  - Thyroid, parathyroid, cystic fibrosis, celiac disease
- Medical history
  - Gestational age
  - Time of passage of meconium
  - Condition at birth
  - Acute injury or disease
  - Hospital admissions
  - Immunizations
  - Allergies
  - Surgeries
  - Delayed growth and development
  - Sensitivity to cold
  - Coarse hair
  - Dry skin
  - Recurrent urinary tract infections
  - Daytime urinary incontinence
  - Other
- Developmental history
  - Normal, delayed
  - School performance
- Psychosocial history
  - Psychosocial disruption of child or family
  - Interaction with peers
  - Temperament
  - Toilet habits at school

TABLE 2. Physical examination of children with constipation

- General appearance
- Vital signs
  - Temperature
  - Pulse
  - Respiratory rate
  - Blood pressure
  - Growth parameters
- Head, ears, eyes, nose, throat
- Neck
- Cardiovascular
- Lungs and chest
- Abdomen
  - Distension
  - Palpable liver and spleen
  - Fecal mass
- Anal inspection
  - Position
  - Stool present around anus or on clothes
  - Perianal erythema
  - Skin tags
  - Anal fissures
- Rectal examination
  - Anal wink
  - Anal tone
  - Fecal mass
  - Presence of stool
  - Consistency of stool
  - Other masses
  - Explosive stool on withdrawal of finger
  - Occult blood in stool
- Back and spine examination
  - Dimple
  - Tuft of hair
- Neurological examination
  - Tone
  - Strength
  - Cremasteric reflex
  - Deep tendon reflexes

Stool Scale (16) (1: very hard lumpy stools; 2: hard or very large stools; 3: normal stools; 4: soft-mushy stools; 5: liquid stools).

Study Design and Protocol

At the time of the first visit, all of the children were consuming CM and/or dairy products. No dietetic or behavioral recommendations were given during the length of the study. Parents whose children were taking laxative treatments before entering the study were instructed to continue or stop the treatment, according to the parents' own criteria and the evolution or resolution of constipation. The study was organized in 4 phases (Fig. 1). Diet was not modified during the first week of the study (phase I). After this, parents were instructed to withdraw CM from the diet for 3 weeks (phase II). In children younger than 2 years of age, CM was replaced by a hydrolyzed CM-protein formula. Children older than 2 years

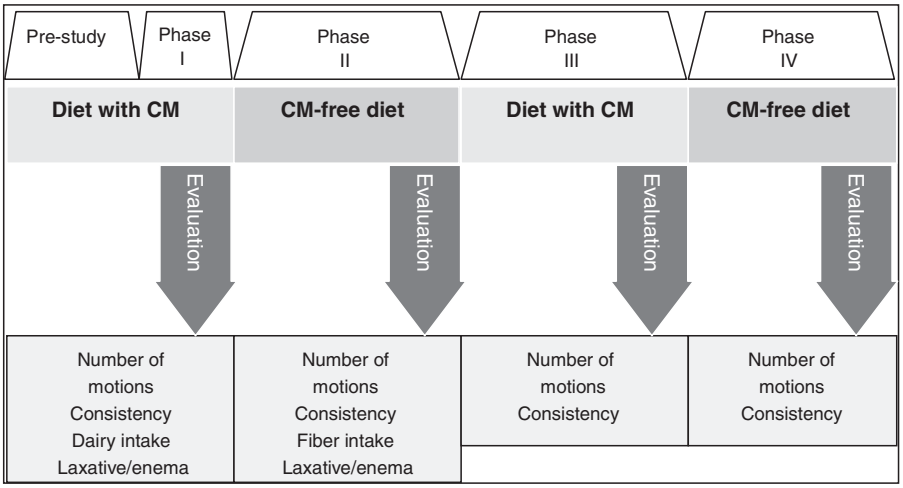

FIGURE 1. Study design. CM = cow's milk.

were offered rice milk to replace CM. Parents were instructed not to use soy milk and soy-containing products to replace CM and dairy products because of the increased prevalence of soy allergy among CM-allergic children (17).

Children who failed to respond during phase II finished the study. Those children whose constipation resolved after 3 weeks on a CM-free diet continued onto phase III, and CM was reintroduced for the next 3 weeks. Parents were advised to provide their children with 500 mL of milk per day during phase III. Children who did not become constipated during phase III finished the study, and in those in whom constipation relapsed during phase III, CM was withdrawn for the next 3 weeks (phase IV). According to their progress during the study, children whose constipation did not resolve during phase II were classified as nonresponders (NR); those whose constipation resolved during phase II, relapsed during phase III, and resolved during phase IV were regarded as responders (R); and children whose constipation resolved during phase II but did not relapse during phase IIII were declared indeterminate responders (IR).

Constipation was considered resolved if the child fulfilled the following criteria: the occurrence of 3 or more bowel movements per week without use of laxative treatment or enemas and no discomfort, pain, or irritability during defecation.

After the end of the study, NR children resumed CM and were given dietetic advice and laxative treatment was prescribed if constipation persisted. Children classified as IR continued on CM, whereas children in the R group were initially kept on CM-free diet, and were given soy milk. Increasing amounts of CM and dairy products were progressively introduced in their diet to determine the amount of CM or dairy products they were able to tolerate. If calcium intake was considered insufficient, then calcium supplementation was prescribed.

Parents were given a notebook and asked to record the following items during the final week of each phase: phase I, depositions and consistency of each deposition, use of laxatives or enemas, and ingestion of CM, dairy products, vegetables, fruits, and cereals; phase II, depositions, consistency of each deposition, use of laxatives or enemas, and ingestion of vegetables, fruits, and cereals; phase III, depositions and consistency of each deposition; phase IV, depositions and consistency of each deposition.

A blood sample was taken from each child during phase I to measure peripheral eosinophil count and serum levels of immunoglobulin (Ig) A, IgM, IgG (and IgG subclasses), and total IgE. Specific IgE against CM proteins (β-lactoglobulin, α-lactoalbumin, and casein) (Phadebas IgE paper radioimmunosorbent test kit, Pharmacia Diagnostics, Uppsala, Sweden) and IgA class autoantibodies against tissue transglutaminase were also determined. Serum-specific IgE antibodies to CM proteins >0.35 KU was regarded as positive.

Immunologic studies included flow cytometry analysis of peripheral blood lymphocytes to determine total leukocytes (CD45), T lymphocytes (CD3), T helper lymphocytes (CD4), T cytotoxic lymphocytes (CD8), B cells (CD19), and natural killer cells (CD16) using commercially available fluorescent monoclonal antibodies (all from BD Biosciences, Erembodegen, Belgium) on a FACScan flow cytometer (BD Biosciences).

Statistical Methods

Frequencies and percentages were used to describe categorical variables, mean and standard deviations for normally distributed continuous variables and medians and interquartile ranges for the rest. Wilcoxon test for paired samples was used to analyze depositional frequency and consistency before and after withdrawal of dairy products for each group, whereas comparisons between groups both before and after withdrawal of these products were carried out using the Mann-Whitney test. The effect on the improvement of patients after CM withdrawal of constipation history, anamnesis, physical examination, and immunologic results was evaluated using χ^2 or Fisher exact tests (categorical variables) or using Student t test, or Mann-Whitney test (continuous variables). Logistic regression models were fitted with those covariates that had P values <0.1 in the univariate analyses to model the probability of improvement in both frequency and consistency as a function of those factors.

RESULTS

Baseline characteristics of the 69 patients are shown in Table 3. In 35 children (51%), constipation resolved during CM-free diet in phase II. Thirty-four patients (49%) did not respond to the CM-free diet (NR group), and in 27 of 35 patients whose constipation resolved during phase II, relapse occurred when CM was reintroduced during phase III but subsequently resolved in all of them during phase IV (R group) (Fig. 2). Among the children classified as responders, constipation resolved within 1 to 5 days after initiating CM-free diet and reappeared again within 2 to 5 days

TABLE 3. Baseline characteristics of the 69 children

Sex, M/F	25/44
Age, mo	60 ± 43.2
Age at the onset of constipation, mo	16.4 ± 27.3
Constipation from birth, no.	23
Duration of constipation, mo	16.3 ± 27.3
Discomfort during defecation, no.	63
Recurrent abdominal pain, no.	35
History of hematochezia, no.	37
History of anal fissures, no.	38
Sphincter control, no.	59
Fecal incontinence at least 1 wk, no.	18 of 59
Fecal retention posturing, no.	43
Previous treatment for constipation, no.	43
Premature birth, no.	3
History of hospital admissions, no.	12
Onset of bottle feeding, mo	3.5 ± 2.9 (13 from birth)
History of atopy, no.	15
History of allergy, no.	5 (CMP: 2; mites: 3)
Celiac disease on gluten-free diet, no.	3
Cold intolerance, no.	7
Recurrent urinary tract infection, no.	2
Developmental delay, no.	9
Family history of chronic constipation, no.	38
Fecal masses in the left iliac fossa, no.	16
Hard feces in the rectum, no.	39
Anal lesions, no.	13
Social dysfunction or child abuse, no.	0
Malnutrition, no.	0

Plus/minus values are mean ± SD.
CMP = cow's-milk protein.

of reintroducing CM-containing diet. There were 8 patients who improved with CM-free diet in phase II but did not develop constipation when CM was reintroduced in phase III (IR group). In this group, constipation had improved slowly in 1 to 3 weeks during phase II. Figures 3 and 4 show the number and consistency of depositions of R and NR children in phase I and phase II of the study.

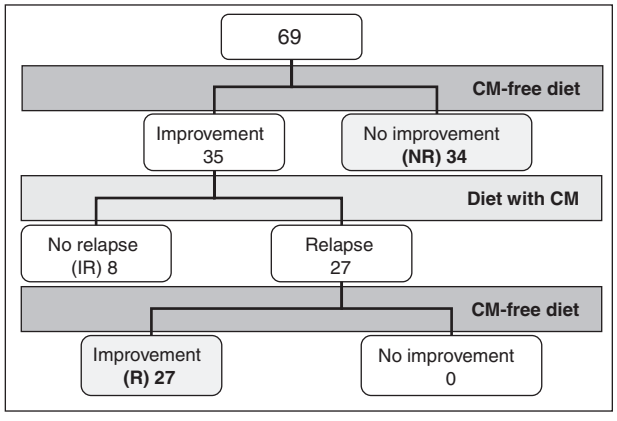

FIGURE 2. Diagram of the response to cow's-milk–free diet.

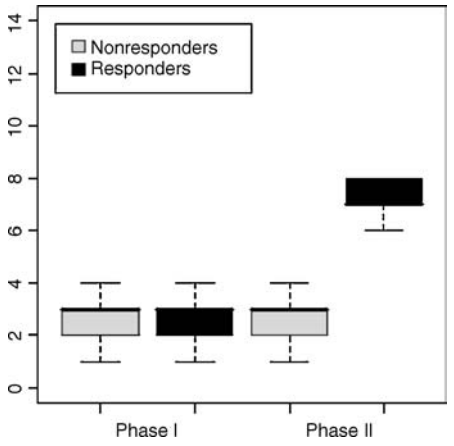

FIGURE 3. Bowel movements per week.

There were no significant differences between respondent and nonrespondent children during study phase I (diet with CM) in terms of bowel movements per week (2.85 ± 1.85 vs 2.66 ± 1.21), stool consistency (1.4 ± 0.84 vs 1.4 ± 0.6), and use of laxatives and enemas (26% vs 38%). Among nonrespondent children, there were no significant differences between study phase I (diet with CM) and phase II (CM-free diet) in terms of bowel movements per week (2.66 ± 1.21 vs 2.74 ± 1.28), stool consistency (1.4 ± 0.6 vs 1.68 ± 0.78), and use of laxatives or enemas (38% vs 32%). However, children from the respondent group had significantly ($P < 0.001$) more bowel movements per week and more consistent stool, and did not use laxatives in CM-free diet (phase II) compared with phase I (2.85 ± 1.85 vs 7.7 ± 2.85, 1.4 ± 0.84 vs 3 ± 0, and 26% vs 0%, respectively). These differences were also significant between respondent and nonrespondent children during study phase II ($P < 0.001$). Milk and dairy product consumption during phase I (diet with CM) was higher in the respondent group (4132 ± 945 mL/week) than in the nonrespondent group (3671 ± 976 mL/week), but the difference was not significant ($P = 0.148$). There were no

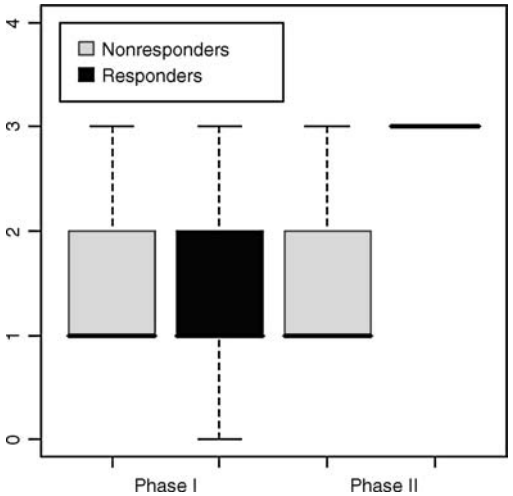

FIGURE 4. Stool consistency (1: very hard lumpy stools; 2: hard or very large stools; 3: normal stools; 4: soft-mushy stools).

TABLE 4. Clinical history and physical examination

	R group	NR group	*P*
Sex (male), %	38	33	0.791
Gestational age at birth, wk	39 (± 1.5)	39 (± 1.3)	0.981
Meconium elimination delay, %	4	0	0.443
Hospital admission as neonate, %	19	9	0.447
Age at which bottle feeding started, mo	3.6 (± 2.4)	3.3 (± 2.3)	0.792
Sphincter control, mo	27 (± 7)	25 (±7)	0.374
Atopy history, %	19	21	0.635
Allergic history, %	4	12	0.371
Celiac disease (on gluten-free diet)	2	1	0.595
Cold intolerance, %	11	12	1
Recurrent UTI, %	4	3	0.579
Urinary incontinence, %	0	10	0.499
Recurrent abdominal pain, %	50	50	1
Developmental delay, %	26	6	0.007*
Family history of constipation, %	63	38	0.055*
Age at 1st visit, mo	52 (± 40)	60 (± 40)	0.74
Age at constipation onset, mo	15 (± 20)	17 (± 34)	0.436
Defecation discomfort, %	100	91	0.248
Hematochezia or anal lesions, %	56	56	1
Fecal soiling or encopresis, %	35	33	0.903
Retentive posturing, %	69	70	1
Fecal masses in left iliac fossa, %	35	20	0.46
Hard feces in rectum, %	41	45	0.815
Anal lesions, %	11	24	0.644

Plus/minus values are mean ± SD.
NR = nonrespondent group; R = respondent group; UTI = urinary tract infection.
* *P* value after multivariate analysis.

differences regarding average fiber consumption between respondent and nonrespondent groups during CM-free diet phase II (47 ± 32 vs 46 ± 38 g). No statistically significant differences were found in constipation history, medical history, or physical examination between respondent and nonrespondent groups (Table 4). Forty-eight percent of the respondent children versus 25% of the nonrespondent children had first-degree relatives with constipation history ($P = 0.081$). Seventy-eight percent of the children with developmental delay responded to CM-free diet versus 33% of the children without developmental delay improved during CM-free diet in phase II ($P = 0.065$).

After multivariate analysis of variables with statistical significance $P < 0.1$, only developmental delay showed statistical significance ($P = 0.007$), and although not significant, there was a trend suggesting the implication of familial history of constipation ($P = 0.055$).

No differences were found between respondent and nonrespondent groups in terms of eosinophil count, humoral immunity, cellular immunity, CM protein–specific IgE, and antitissue transglutaminase IgA (Table 5).

DISCUSSION

To determine whether children with chronic constipation could benefit from a CM-free diet, we applied a 4-phase CM withdrawal and reintroduction protocol to 69 children with the condition who fulfilled our inclusion criteria. Thirty-nine percent of the children studied responded to a CM-free diet, supporting the hypothesis that CM plays a significant role in many children with constipation. Interestingly, although it has been suggested that constipation among children with developmental delay may be secondary to their condition, our study shows that 78% of the children in this subgroup also responded to a CM-free diet. Despite this association, the demonstration of a causal relation between CM and constipation would require a double-blind crossover placebo-controlled trial. A previous study trial using chocolate flavor in CM, soy milk, and rice milk was unsuccessful in masking the taste of the formulas, and therefore the ideal trial could not be conducted.

It has been proposed that the link between constipation and CM ingestion is the result of children consuming an excess of dairy products and having a low residue diet because they eat fewer vegetables and, especially, fewer fruits (18). However, in the present study, dairy and fiber consumption was similar in children who improved and in those who did not respond after a CM-free diet, suggesting that dairy products and fiber intake are not predictors of response to CM-free diet.

Iacono et al (7,8) and Daher et al (19) reported a high prevalence of positive serum-specific IgE antibodies and skin prick test for CM protein among constipated children who responded to a CM-free diet. Shah et al (20) found a high prevalence of personal and familial history of atopy and food allergy. We have observed that a similar percentage of R and NR children displayed a history of atopy or allergy, and no differences were found between R and NR children regarding eosinophil count, total IgE, or CMP-specific serum-specific IgE antibodies.

Moreover, our study shows that total immunoglobulins, IgG subclasses, and lymphocyte populations were similar in both groups, in contrast to previous reports suggesting that children experiencing non-IgE-mediated food allergies may present a pattern of minor immunodeficiency consisting of increased IgG1,

TABLE 5. Immunologic results

	R group	NR group	*P*
Eosinophil, $\times 10^{12}$/L	210 ± 109	307 ± 254	0.103
CD3+, %	68.2 ± 5.7	67 ± 5.7	0.640
CD4+, %	36.8 ± 8.8	38.9 ± 4.2	0.456
CD8+, %	23.4 ± 6	23.1 ± 5.7	0.930
CD19+, %	15.2 ± 9.2	17.5 ± 4.2	0.672
NK cells, %	9.7 ± 5.5	9.9 ± 5.9	0.971
IgG, mg/dL	943 ± 160	940 ± 219	0.989
IgA, mg/dL	95 ± 60	81 ± 54	0.465
IgE, KU/L	13 ± 11	92 ± 190	0.055
IgM, mg/dL	119 ± 68	116 ± 43	0.850
IgG1, g/L	7.07 ± 1.02	7.21 ± 1.4	0.886
IgG2, g/L	1.41 ± 0.57	1.16 ± 0.72	0.338
IgG3, g/L	0.36 ± 0.1	0.4 ± 0.17	0.529
IgG4, g/L	0.25 ± 0.29	0.42 ± 0.63	0.359
CMP-specific IgE + serum-specific IgE antibodies >0.35 KU, %	25	22	1
Anti-tTG IgA +	0	0	1

Plus/minus values are mean ± SD.

Anti-tTG = antitissue transglutaminase; CMP = cow's milk protein; Ig = immunoglobulin; NK = natural killer; NR = nonrespondent group; R = respondent group.

decreased IgG2/G4, and low-normal IgA levels, together with increased percentages of CD4 and CD19 and decreased CD8 and natural killer lymphocytes (21). In our study, we did not find a recognizable pattern of immune deviation in children with CM-sensitive constipation.

However, a clear cause and effect link between CM ingestion and chronic constipation has been observed in more than one third of children participating in our study. The fact that constipation resolved and relapsed in 1 to 5 days of CM withdrawal and reintroduction in respondent children suggests the intervention of late allergy reactors. Indeed, if it were proven that constipation is a form of food allergy presentation, it should be classified as a delayed symptom. Most delayed allergic reactions are not IgE mediated, and therefore IgE-mediated immunologic parameters should not be expected (22). Our results seem to discard an IgE-mediated mechanism, but we have not obtained any conclusive information regarding other possible immune mechanisms of constipation in our CM-sensitive children.

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