

INTOLERANCE OF COW'S MILK AND CHRONIC CONSTIPATION IN CHILDREN

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ABSTRACT

Background Chronic diarrhea is the most common gastrointestinal symptom of intolerance of cow's milk among children. On the basis of a prior open study, we hypothesized that intolerance of cow's milk can also cause severe perianal lesions with pain on defecation and consequent constipation in young children.

Methods We performed a double-blind, crossover study comparing cow's milk with soy milk in 65 children (age range, 11 to 72 months) with chronic constipation (defined as having one bowel movement every 3 to 15 days). All had been referred to a pediatric gastroenterology clinic and had previously been treated with laxatives without success; 49 had anal fissures and perianal erythema or edema. After 15 days of observation, the patients received cow's milk or soy milk for 2 weeks. After a one-week washout period, the feedings were reversed. A response was defined as eight or more bowel movements during a treatment period.

Results Forty-four of the 65 children (68 percent) had a response while receiving soy milk. Anal fissures and pain with defecation resolved. None of the children who received cow's milk had a response. In all 44 children with a response, the response was confirmed with a double-blind challenge with cow's milk. Children with a response had a higher frequency of coexistent rhinitis, dermatitis, or bronchospasm than those with no response (11 of 44 children vs. 1 of 21, $P=0.05$); they were also more likely to have anal fissures and erythema or edema at base line (40 of 44 vs. 9 of 21, $P<0.001$), evidence of inflammation of the rectal mucosa on biopsy (26 of 44 vs. 5 of 21, $P=0.008$), and signs of hypersensitivity, such as specific IgE antibodies to cow's-milk antigens (31 of 44 vs. 4 of 21, $P<0.001$).

Conclusions In young children, chronic constipation can be a manifestation of intolerance of cow's milk. (N Engl J Med 1998;339:1100-4.)

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THE causes, prognosis, and treatment of chronic idiopathic constipation in children under the age of six years are still debated.¹⁻⁴ The two main hypotheses about its causation are that it is psychogenic^{5,6} and that it results from disturbances in intestinal motility.^{1,7-9} However, numerous studies have shown that psychological problems are more often the consequence than the cause of constipation.^{3,4,10-12} The role of alterations in motility still needs to be clarified.¹³

In an open study of children with chronic constipation, we recently demonstrated that constipation may be a symptom of intolerance of cow's milk.¹⁴ We hypothesized that intolerance of cow's milk can cause severe perianal lesions with pain on defecation and consequent constipation and that, in such cases, a diet free of cow's milk can rapidly resolve both the constipation and related disorders. We now report the results of a double-blind, crossover study comparing the effects of cow's milk and soy milk in children with chronic constipation.

METHODS**Patients**

All 118 consecutive patients under six years of age with chronic constipation who were referred by family pediatricians to our pediatric gastroenterology clinic between June 1994 and May 1996 were evaluated for study entry. We defined chronic constipation as chronic fecal retention (one bowel movement every 3 to 15 days), often associated with abdominal symptoms (abdominal pain, painful defecation, and so forth). The exclusion criteria were anatomical causes of constipation (Hirschsprung's disease, 1 case; spinal disease, 2 cases), constipation due to another disorder (hypothyroidism, 2 cases; psychomotor retardation, 4 cases), prior anal surgery (2 cases), use of medications that can cause constipation (chlorpromazine, 1 case), and referral for reasons other than chronic constipation (41 cases). Sixty-five children were enrolled (29 boys and 36 girls; age range, 11 to 72 months; mean, 34.6). They were all being fed full-fat cow's milk, dairy products, or commercial formulas derived from cow's milk. Previous treatment with laxatives (mainly lactulose and mineral oil) had been unsuccessful in all 65 patients.

When the patient was first seen, a detailed chart was compiled containing the results of the physical examination and case-history information such as the frequency and duration of breast-feeding during the first months of life, acceptance of formula at weaning, personal and family history of atopic disease, and especially the presence or absence of soiling, abdominal pain, anal fissure, and perianal erythema or edema.

Informed consent was obtained from the parents of all the patients involved in the study, which was approved by the ethics committee of the University Hospital of Palermo.

Study Design

At the first visit, the parents were asked to record the child's signs and symptoms, and all medications were stopped. Routine laboratory tests and a rectal biopsy were performed. After 15 days of observation, the patient was assigned to receive either soy milk or cow's milk for the next 2 weeks. The milk was supplied in bottles coded A or B by the hospital dispensary. Depending on the

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patient's dietary habits and age, the total amount of milk given to the patient during the two weeks ranged from 5 to 10 liters. For infants who were less than 15 months of age, the feeding bottles contained a formula based on cow's milk (Transilat, Plasmon, Milan, Italy) or a formula based on soy (Plasmonsoy, Plasmon). For children who were 15 months or older, the bottle contained commercially available whole cow's milk or soy milk. After a one-week washout period, during which the diet was unrestricted, as was the intake of soy or cow's milk and its derivatives, the patients were then switched to the other type of milk for another two weeks. The purpose of the washout period was to cancel the influence of the psychological aspect of the previous treatment period. The order of treatment was randomly assigned by a computer-generated method with the individual patient as the unit of randomization. The researchers were unaware of the order of treatment.

Children with eight or more bowel movements during a treatment period were considered to have had a response. At the end of the two treatment periods, the protocols were evaluated and the code was broken. All children were followed up for a mean of 10 months (range, 3 to 20).

Laboratory Tests

At base line, total serum IgE (with the Phadebas IgE paper radioimmunosorbent test kit, Pharmacia Diagnostics, Uppsala, Sweden) and the erythrocyte sedimentation rate were measured; a circulating eosinophil count and white-cell and red-cell counts were performed, as were the following tests: protein C reaction test, milk-specific IgE antibody assay (Phadebas radioallergosorbent test kit), and skin tests with whole cow's milk, lactalbumin, casein, and β -lactalbumin (Lofarma Diagnostic, Milan, Italy).

The following results were considered elevated or abnormal: total IgE above 60 kallikrein units per liter (the mean value +2 SD recorded in age-matched healthy children by our laboratory); more than 400 eosinophils per cubic millimeter; for milk-specific IgE antibodies, a score of more than 1 (i.e., >4 sorbent units per milliliter); for skin tests, any wheal whose diameter exceeded that of the control and was more than one fourth the diameter of the wheal induced by histamine.

Clinical Assessment

At base line and at the end of the two study periods, the children were examined by a researcher who was unaware of the laboratory test results and the histologic findings. During the study periods, the parents recorded the number of bowel movements, as well as the appearance of the stools and the child's degree of difficulty in passing them according to a previously validated scoring system¹⁴ in which a score of 1 indicated mushy or liquid stool, a score of 2 soft feces and no pain on passing stools, and a score of 3 hard feces and difficulty and pain on passing stools.

To ensure that the children did not receive any other kind of milk or milk-containing foods during the study periods, the parents were given a list of the most common milk-containing foods to be avoided. During the study periods, they were asked to record the amount and type of food their child had eaten each day. At the end of the study, we analyzed these diaries to evaluate adherence to the diet and the quantity of milk consumed. The parents were able to contact us whenever necessary, and frequent telephone contacts helped to ensure adherence to the diet.

Challenge Procedure

After the two study periods, the children with a response to the cow's-milk-free diet were given the soy-milk diet for another month and then underwent a double-blind challenge with cow's milk. All the challenges were performed in the hospital, as previously described.¹⁴⁻¹⁶ During the challenge, the child was randomly assigned to receive cow's milk or a placebo containing soy milk. The challenge was performed with an initial quantity of 5 ml, and the equivalent of a full feeding (the amount of milk the children

customarily received at a meal) was given over a three-hour period. If no clinical reaction was observed within 12 hours after the beginning of the challenge, the patient was discharged and the challenge was continued at home, with bottles coded A or B by the hospital dispensary. During the two-week challenge period, the parents recorded any clinical symptoms, and the patients were reexamined in the hospital for any adverse reaction and at the end of the challenge periods. The challenge was stopped when a clinical reaction occurred — in particular, when there were no bowel movements for 72 hours and the patient had abdominal pain, perianal lesions, or both.

Rectal Biopsy and Histologic Analysis

Rectal biopsies were performed in all subjects on the first visit. Twenty patients with a response to the cow's-milk-free diet were selected at random to undergo a second rectal biopsy before the challenge with cow's milk, one month after beginning the cow's-milk-free diet. Biopsy specimens were obtained with Watson's pediatric capsule 4 to 6 cm from the anus. Mucosal specimens were fixed in 10 percent neutral buffered formalin, embedded in paraffin wax, and stained with hematoxylin and eosin, Schiff's periodic acid, and Masson's trichrome. The specimens were evaluated for the following histologic features: abnormal crypt architecture, defined according to Surawicz's criteria¹⁷; mixed inflammation (with eosinophils and lymphocytes) of the lamina propria; lymphoid follicles; depletion of goblet-cell mucin; and edema.

Morphometric studies were performed with a Leica interactive image analyzer (model Q500 MC, Leica, Heerbrugg, Switzerland). The following features were assessed: maximal length of surface epithelial cells, the numbers of intraepithelial lymphocytes and eosinophils, and the number of eosinophils in the lamina propria. For the measurement of cellular length, 200 cells per specimen were randomly selected. We counted the numbers of intraepithelial lymphocytes and eosinophils in cross sections of 50 crypts randomly selected from each slide and the numbers of lymphocytes and eosinophils per 100 deep-crypt epithelial cells. The quantitative assessment of eosinophils in the lamina propria was expressed as a percentage of eosinophils per 1000 lamina propria cells per section (five sections per biopsy were examined). The pathologist examining the biopsy specimens was unaware of the subjects' laboratory test results and the clinical response to the diet.

Statistical Analysis

Frequency analysis was performed with Fisher's exact test. The Wilcoxon rank-sum test was used to compare the number of bowel movements per day and the qualitative fecal scores. Student's t-test (for parametric analysis) or the Mann-Whitney U test (for nonparametric analysis) was used to compare the morphometric data on the rectal mucosa. All P values were two-tailed, and P values of less than 0.05 were considered to indicate statistical significance.¹⁸

RESULTS

The base-line characteristics of the 65 patients are shown in Table 1. During the first study period, 33 patients received cow's milk and 32 soy milk; 21 of the children who received soy milk and none of the children who received cow's milk had a response ($P < 0.001$). During the second study period, 32 children received cow's milk and 33 soy milk; 23 of the children who received soy milk and none of the children who received cow's milk had a response ($P < 0.001$). Table 2 shows the number of bowel movements and the qualitative fecal scores during the two study periods. The number of bowel movements significantly increased and the fecal score sig-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 65 PATIENTS.*

CHARACTERISTIC	VALUE
Age (mo)	34.6±17.1
Sex (M/F)	29/36
Breast-feeding at birth (no.)	35
Refused food at weaning (no.)	3
Duration of illness (mo)	8.7±3.5
Previous treatment with laxative (no.)	65
Family history of intolerance of cow's milk (no.)	26
Personal history of intolerance of cow's milk (no.)	16
Concomitant symptoms of intolerance of cow's milk (bronchospasm, dermatitis, or rhinitis) (no.)	12
Soiling or encopresis (no.)	4
Abdominal pain (no.)	27
Anal fissure and perianal erythema or edema (no.)	49
Patients with abnormal test results (no.)	
Eosinophil count	16
Serum IgE level	10
Skin tests with milk antigens	11
Specific IgE antibodies to milk antigens	20

*Plus-minus values are means ±SD.

TABLE 2. NUMBER OF BOWEL MOVEMENTS AND QUALITATIVE FECAL SCORES DURING EACH STUDY PERIOD FOR THE 65 PATIENTS.

VARIABLE	OBSERVATION PERIOD	COW'S MILK*	SOY MILK	P VALUE†
No. of bowel movements				
Median	4	4	10	<0.001
25th to 75th percentile	3-5	3-5	4-12	<0.001
Qualitative fecal score‡				
1	0	0	2	<0.001
2	0	0	42	<0.001
3	65	65	21	<0.001

*Six patients were withdrawn from the study during the cow's-milk study period (on days 9 to 12) because of the reappearance of constipation and other related disorders; for these patients, the number of bowel movements per period was prorated.

†The Wilcoxon rank-sum test was used.

‡A score of 1 indicates mushy or liquid stools, a score of 2 soft feces and no pain on passing stools, and a score of 3 hard stools and difficulty and pain on passing stools.

nificantly improved when the patients were receiving the soy diet.

Forty-four of the 65 patients (68 percent) had a response to the soy-milk diet. During this period, all those with a response had at least one bowel movement daily after two to six days, soft feces, and no

discomfort on defecation, and erythema and perianal edema completely resolved. Six patients did not complete the protocol. All six had had a response to the soy diet during the first study period, but 9 to 12 days after starting the cow's-milk diet, they again began to have constipation and were withdrawn from the study. These six were included in the intention-to-treat analysis.

All 44 children with a response to the cow's-milk-free diet underwent a double-blind, placebo-controlled challenge with cow's milk in the hospital after a further month on the diet. None of those who received the placebo (soy milk) had a clinical reaction. No patient who received cow's milk had an acute reaction, but in all patients constipation associated with hard stools and discomfort on defecation reappeared after 5 to 10 days of the diet. The cow's-milk-free diet was therefore recommenced, with a consequent normalization of bowel movements in all patients. Thus, 44 of the 65 patients were given a diagnosis of constipation related to intolerance of cow's milk.

The severity of constipation in children with a response and in those without a response was similar at base line. However, anal fissures with erythema or edema were more common among those with a response (40 of 44 patients vs. 9 of 21, $P<0.001$). Anal lesions tended to disappear within the first seven days after the initiation of the soy-milk diet and reappeared three to six days after the reintroduction of cow's milk, often before the reappearance of constipation. Furthermore, at diagnosis, symptoms of suspected intolerance of cow's milk were more common in children with a response (11 of 44 patients vs. 1 of 21, $P=0.05$): recurrent bronchospasm in 4 patients, rhinitis in 4, and dermatitis in 3.

At entry into the study, there was a trend toward a higher frequency of positive skin tests among the patients with a response (10 of 44 vs. 1 of 21, $P=0.07$) and a higher frequency of specific IgE antibodies to cow's milk antigens (18 of 44 vs. 2 of 21, $P=0.009$). At entry, 31 of the children with a response had positive results for one or more of the immunologic tests, as compared with 4 of the children with no response ($P<0.001$). During the follow-up, after four to eight months, there was a normalization or a significant reduction in serum immunologic values (data not shown) in the children with a response.

None of the patients had alterations in liver and kidney function or in indicators of metabolism or inflammation (white-cell count or erythrocyte sedimentation rate and protein C reaction) during the study.

Table 3 shows the histologic findings of the rectal biopsies. The length of surface epithelial cells was significantly shorter in the children with a response than in those with no response, giving a cuboidal as-

TABLE 3. HISTOLOGIC AND MORPHOMETRIC FINDINGS ACCORDING TO THE RESPONSE TO A COW'S-MILK-FREE DIET.

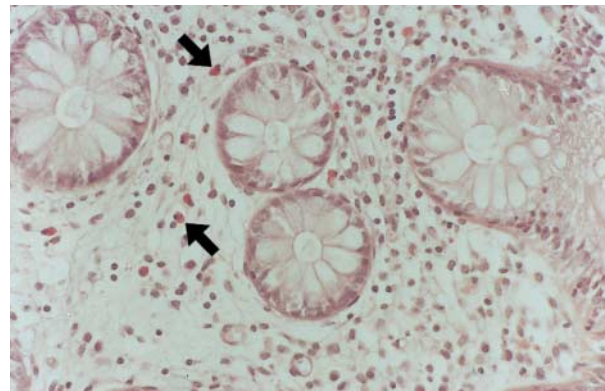
VARIABLE	RESPONSE (N=44)	NO RESPONSE (N=21)	P VALUE
Histologic analysis (no.)			
Abnormal crypt architecture	13	2	0.06
Depletion of goblet-cell mucin	3	0	0.32
Inflammation	15	2	0.03
Lymphoid nodules	15	3	0.08
Interstitial edema	4	0	0.26
Morphometric evaluation*			
Length of surface epithelial cells (μm)	40.4 \pm 6.2	51.3 \pm 8.1	0.001
Intraepithelial lymphocytes (per 100 deep-crypt cells)	3.4 \pm 0.8	3.1 \pm 0.6	0.21
Intraepithelial eosinophils (per 100 deep-crypt cells)	3.0 \pm 1.8	0.8 \pm 0.3	0.001
Eosinophils in the lamina propria (% of total cells)	7.15 \pm 4.31	4.21 \pm 2.31	0.009

*Plus-minus values are means \pm SD.

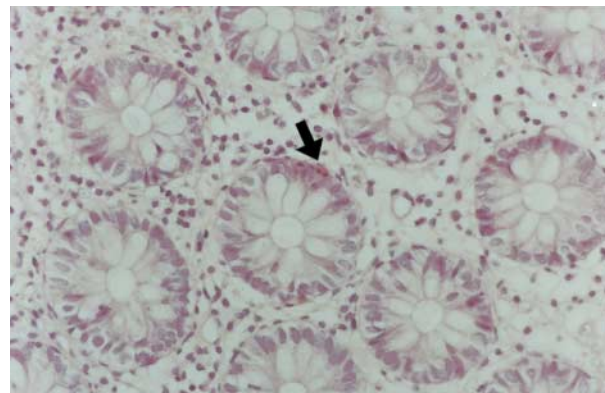
pect to the surface epithelium. Furthermore, inflammation was more frequent in the children with a response; the inflammation was characterized by infiltration by lymphocytes, but the most relevant finding was the infiltration of the lamina propria by eosinophils and the presence of intraepithelial eosinophils in the crypts (Fig. 1). We found inflammatory changes in 26 of the 44 children with a response and in 5 of the 21 children with no response ($P=0.008$). One or more histologic alterations were found in the rectal mucosa in all 44 children with a response and in 12 of the children with no response ($P<0.001$). A random sample of 20 children with a response underwent a second rectal biopsy immediately before they underwent the challenge (one month after they began the cow's-milk-free diet). The histologic findings were normal in 8 patients and considerably improved in the other 12 patients (reduced inflammation, disappearance of lymphoid nodules, reduction in the cuboidal aspect of the surface epithelium, and increased mucin in the glandular cells).

The mean (\pm SD) daily consumption was 450 \pm 120 ml of soy milk and 470 \pm 135 ml of cow's milk. Analysis of the main constituents of the diet (proteins, carbohydrates, and fibers) did not show any qualitative or quantitative variations during the study period (data not shown).

During the follow-up, none of the children with a response had constipation; cow's milk was reintroduced into the diets of 15 children after 8 to 12 months of the cow's-milk-free diet, and in all cases constipation returned within 5 to 10 days. The children with no response to the soy-milk diet were treated with high doses of laxatives, with a subsequent improvement in stool frequency. In all cases,



A



B

Figure 1. Rectal Mucosa in a Patient with Constipation Related to Intolerance of Cow's Milk at Base Line, Showing Infiltration of the Mucosa by Eosinophils.

The arrows indicate the diffuse infiltration of eosinophils into the lamina propria (Panel A) and the presence of intraepithelial eosinophils (Panel B) (hematoxylin and eosin, $\times 275$).

however, the symptoms returned once treatment with laxatives was stopped.

DISCUSSION

Although chronic diarrhea is the most common gastrointestinal symptom of intolerance of cow's milk in children, our current results confirm our earlier observation that chronic constipation can also occur.¹⁴ We found a relation between the intake of cow's milk and constipation in about two thirds of the patients studied. However, it is possible that the children noticed the difference in taste between cow's milk and soy milk. Thus, we cannot totally rule out psychological factors, which are frequently suggested as the cause of chronic constipation.^{5,6} On the other hand, we did not find any evidence of a psychological aversion to cow's milk, such as a refusal of the formula or prolongation of breast-feeding in infants being weaned onto formula containing cow's milk. Furthermore, the results of the double-

blind challenge with cow's milk confirmed that constipation was a symptom of intolerance of cow's milk in most of our patients.

We may have overestimated the frequency of intolerance of cow's milk as a cause of constipation. Our gastroenterology center has experience in the treatment of food allergies, and the pediatricians who referred patients to our clinic may thus have preselected our patients. Furthermore, all the patients had been previously treated unsuccessfully with laxatives; thus, the high frequency of constipation related to intolerance of cow's milk in our study may have been due in part to our inclusion of patients with no response to laxatives. On the basis of these considerations, we must emphasize the highly selected nature of our group of patients.

Immunologic tests showed hypersensitivity in nearly three quarters of the children with constipation related to intolerance of cow's milk, with the most common mechanisms being IgE-mediated; thus, hypersensitivity increases the probability that constipation will be a manifestation of food intolerance. Although the rectal biopsy did not show any specific mucosal alterations, signs of inflammation were much more frequent in the children with a response. The infiltration of eosinophils is the main characteristic of patients with intolerance of cow's milk, but as has been reported previously,^{19,20} we often observed a mixture of lymphocytes, eosinophils, and monocytes.

Our data suggest that the concomitant presence of other manifestations of intolerance of cow's milk (bronchospasm, dermatitis, and rhinitis) increases the probability that constipation will be found to be a symptom of intolerance of cow's milk. However, as others have reported, constipation may be the only presenting symptom.^{21,22} Furthermore, clinical examination of the children in our study showed a very high frequency of severe anal fissures. Because these lesions reappeared after the reintroduction of cow's milk and before the onset of constipation, we hypothesize that they are one of the mechanisms causing constipation. Pain on defecation can cause retention of feces in the rectum, with consequent dehydration and hardening of the stools, thus aggravating constipation.

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