

Identical intestinal permeability changes in children with different clinical manifestations of cow's milk allergy

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To determine the relationship between clinical symptoms of cow's milk allergy (CMA) and intestinal permeability, 51 children (mean age, 13 months) were studied during a diagnostic milk provocation test. Intestinal permeability was assessed by orally administered lactulose (4 gm) and mannitol (0.8 gm) immediately before (day 0) the milk challenge and 3 days later (day 3). Twenty-four patients evinced cutaneous symptoms and 27, gastrointestinal symptoms. The mean (95% confidence interval) urinary lactulose/mannitol recovery ratios before the milk challenge were, in both groups of patients, comparable to the level of that of control patients, 0.02 (0.01 and 0.03). A rise in lactulose/mannitol excretion ratios followed cow's milk administration by day 3 in patients with skin symptoms, 0.06 (0.03 and 0.13), as well as in patients with gastrointestinal symptoms, 0.08 (0.04, 0.17). These levels were significantly different from the control level, $p = 0.003$, and the prechallenge level, $p = 0.01$. This difference was caused by a concomitant increase in urinary recovery of lactulose and a decrease of mannitol. These results indicate that the intestinal barrier is equally altered in patients with different clinical manifestations of CMA and further suggest that enhancement of mucous membrane permeability is not a primary defect in the pathogenesis of CMA but rather a secondary phenomenon, possibly caused by a hypersensitivity reaction in the intestinal mucosa. (J ALLERGY CLIN IMMUNOL 1991;88:737-42.)

Key words: Allergy, infant, intestinal absorption, milk, permeability

The GI tract is a major host barrier to foreign Ag entry. This is accomplished by a network of several immunologic protective factors in the intestinal mucosa, including intraepithelial lymphocytes, the secretory IgA system, and other immunoglobulins, and nonimmunologic factors consisting of gastric barrier, mucosal coat, and microvillous membrane.¹ Evidence from recent clinical studies indicate that increased intestinal permeability and macromolecular absorption may be associated with various clinical situations, such as celiac disease, cystic fibrosis, Crohn's disease, acute and chronic diarrhea, and malnutrition.² Such reduced mucosal barrier function in combination with overstimulation of otherwise normal immune responses by excess contact with Ags may also underlie the pathogenesis of CMA.

Abbreviations used

CMA:	Cow's milk allergy
Ag:	Antigen
GI:	Gastrointestinal
ANOVA:	Analysis of variance

Patients with CMA commonly demonstrate symptoms from the gut, skin, or respiratory tract.³ The mechanisms involved in the generation of preferentially intestinal or extraintestinal abnormalities are unknown, but these subgroups of patients have been clearly identified by different reaction onset times, serum anticow's milk antibody levels, and in vitro cellular immune responses.^{3,4} Recent studies from this research unit have also demonstrated that the quality and extent of intestinal immune response varies in patients with CMA manifesting either GI or extra-GI symptoms.⁵ All patients with CMA, however, demonstrated a small and inconsistent local immune response specifically directed against cow's milk protein Ags, indicating defective immune exclusion at the mucosal level.

Based on these findings, intestinal permeability

From the Department of Clinical Sciences, University of Tampere, Tampere, Finland.

Received for publication Oct. 31, 1990.

Revised June 4, 1991.

Accepted for publication June 6, 1991.

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1/1/31507

changes were studied during a diagnostic milk provocation test in children with urticarial or eczematous skin eruptions or GI symptoms caused by CMA to establish whether modifications in the gut barrier function equally affect different clinical manifestations of CMA and whether these defects are primary or secondary phenomena in the pathogenesis of CMA.

PATIENTS AND METHODS

Patients

Fifty-one children (mean age, 13 months; range, 2 to 34 months) who had had a previous clinical history of adverse reactions to cow's milk were enrolled in the study group. Thirty-one patients were reported to have suffered from cutaneous symptoms (eczema, urticaria, angioedema, and vesicles), twenty-four had demonstrated GI symptoms (diarrhea, vomiting, and pain), one had suffered from bronchitis, and one patient had failed to thrive. These symptoms had disappeared after elimination of cow's milk from the diet and recurred after its reintroduction.

Total serum IgE and cow's milk-specific IgE antibodies were measured with the IgE RIA and Phadebas RAST kits, respectively (Pharmacia Diagnostics, Uppsala, Sweden). Additionally, the initial examination included determination of serum IgG, IgA, and IgM.

After clinical examination, the patients received cow's milk-free diet for 4 weeks. Cow's milk was substituted by a tolerated (soy or protein hydrolysate) formula in infants younger than 1 year of age; older patients received calcium supplementation. After milk elimination, the patients were admitted for a diagnostic milk challenge.

Control patients

Thirteen children (mean age, 17 months; range, 4 to 34 months) with no signs or symptoms of CMA or other chronic illness were enrolled in the study as control subjects. Eleven patients with respiratory infections were studied during convalescence. Two additional control patients were electively admitted for examination unrelated to the GI tract. The control children ingested milk without any restrictions, the amount being the same as in the study patients on day 3 (median, 600 ml/day).

Informed consent was obtained from the children's parents, and the study was approved by the hospital's committee on ethical practice.

Milk-challenge procedure

After milk elimination of 4 weeks, the patients were free of any symptoms and signs of CMA or other illness. They were hospitalized and administered the following volumes of cow's milk *openly* to establish the diagnosis of CMA: day 1: 2, 5, and 10 ml; day 2: 20, 50, and 100 ml; day 3: normal as needed milk intake appropriate for age (median, 600 ml/day). The time interval between each dose was 2 hours. This schedule was accelerated if no reaction occurred within 12 hours. *Placebos were not used in the challenge to establish the diagnosis of CMA because placebo responses are rare in this age group.*⁶ The patients remained in the hospital until normal milk intake could be commenced

or an adverse reaction occurred, with a minimum of 4 days. For chronic tolerance, the patients were observed at 1 week and 1 month after commencing the milk challenge.

A trained nurse and the attending physician examined the patients at the time of any adverse reaction to determine the time of onset and the quality of reactions. The patients were grouped according to their main complaints and symptoms at presentation and after the milk challenge. The time of the onset of the reaction (hours) was defined as the duration from the last administered dose to the onset of symptoms.

Permeability test

Permeability tests were performed before starting the milk challenge (day 0) and 3 days later (day 3) during the challenge period after an overnight fast of at least 6 hours. A 100 ml solution containing 4 gm (11.7 mmol/L) of lactulose and 0.8 gm (4.4 mmol/L) of mannitol (227 mOsm/kg of H₂O) was administered by mouth. All urine passed during the next 5 hours was collected and measured. An aliquot was immediately frozen and kept at -20° C until analysis.

For lactulose and mannitol gas-liquid chromatography determination, a Shimadzu GC-14A gas chromatograph and a Shimadzu C-R5A integrator were used (Shimadzu Corp., Kyoto, Japan) with the CP-Sil 5 CB capillary column (Chrompack, Middelburg, The Netherlands). The sugar alcohols, lactulose, mannitol, and inositol were purchased from Sigma Chemical Co., St. Louis, Mo.

One milliliter (0.5 mmol/L) of inositol as an internal standard and 1.0 ml of Duolite MB 5113 mixed resin (BHD Chemicals, Ltd., Poole, England) as desalt were added to 1 ml of urine. The samples were shaken and centrifuged at 2000 g for 10 minutes, and the supernatant was transferred to a glass tube to dry under a stream of air at 60° C. The sugars were derivatized according to Sweely et al.⁷ and Laker and Mount⁸ by trimethylsilylation with Tri-Sil reagent (Pierce Chemical Co., Rockford, Ill.). After the addition of 200 µl of silylating reagent, the glass tube was closed and placed in an incubating oven (60° C) for 10 minutes. The derivatized sugars were separated by means of temperature programming from 180° C at 1 minute to 260° C at 30° C per minute, with the upper temperature maintained until the lactulose peak emerged. The total analysis time was 6.7 minutes. The peaks were quantitated by peak-height measurement. The total amount of lactulose or mannitol was calculated by subtracting the starting level from the 5-hour collection level, as previously described.⁹

The urinary mannitol concentration before the permeability test has been previously found to be insignificant.⁹

The urinary recovery of lactulose and mannitol is expressed as percentage of the oral dose administered.

Mannitol is a hexitol but, for convenience, is designated as "sugar" in the present article.

Statistical analysis

To determine the statistical significance of differences between the study groups, a two-tailed independent Student's *t* test and an ANOVA with paired contrasts were applied. The repeated observations were studied with ANOVA for repeated measures and Student's paired *t* test.

TABLE I. Clinical reactions and reaction onset times after diagnostic milk challenge in patients with CMA

	Urticaria (%) (n = 17)	Eczema (%) (n = 7)	GI symptoms (%) (n = 27)	Statistical value
Clinical reaction*				
Immediate (<1 hr)	41	29	37	$X^2 = 5.11^\dagger$ $p = 0.28$
Intermediate (1-24 hr)	59	42	41	
Late (>24 hr)	0	29	22	
Dose eliciting the symptom (ml)‡	5 (0.1, 200)	100 (1.0, 200)	100 (1.0, 200)	$H = 9.73^\S$ $p = 0.008$

*Percent of patients studied.

†Chi-square test.

‡Median (range).

§Kruskal-Wallis test.

A chi-square test was applied to determine the differences in proportions. Logarithmic transformations were performed because of skewed distributions in urinary recovery of the test markers. They are presented as geometric means with 95% CI. For comparing several pairs of means, a series of 95% CI was constructed with Tukey's test.¹⁰ The test doses eliciting the symptoms were compared with the nonparametric Kruskal-Wallis test.

RESULTS

Clinical response to cow's milk challenge

The milk provocation classified the study patients into three major groups (Table I). Cutaneous symptoms were mainly acute urticarial and eczematous skin eruptions. In patients with GI symptoms, 78% had diarrhea; 44%, vomiting; and 4%, acute abdominal pain. There was, however, some overlap between the groups. Five patients with acute urticaria and four patients with eczema had GI symptoms as well. Six patients with predominance of GI symptoms also developed cutaneous symptoms. Only three patients demonstrated respiratory symptoms (bronchitis).

The patients with urticaria demonstrated immediate or intermediate reactions to low doses of cow's milk, whereas patients with eczema and GI symptoms also had delayed reactions (Table I).

Clinical characteristics of patients

The mean (SD) ages of patients with CMA with skin symptoms and GI symptoms were 13.0 (7.8) months and 12.6 (6.9) months, respectively. They were somewhat younger than the control patients, with a mean (SD) age of 17.1 (8.1) months, but the age differences (95% CI) between these patients and control patients, 4.1 (−1.8, 10.0) months and 4.5 (−1.3, 10.3) months, respectively, were statistically not significant (Tukey's test).¹⁰ The patients with CMA with skin and GI symptoms did not differ from

each other in breast feeding (4.4 and 4 months, respectively) or in the age at onset of symptoms suggestive of CMA (3.4 and 4.4 months, respectively). However, patients with urticarial or eczematous skin eruptions had observed dietary precautions for atopy more often (42%) than patients with GI symptoms (19%); $p = 0.07$.

Elevated total serum IgE and milk-specific IgE RAST values were frequently found in patients with CMA with cutaneous symptoms. The mean (95% CI) total serum IgE was 37.7 (15.2, 93.8) kU/L in patients with urticaria, 31.5 (3.2, 306.7) kU/L in patients with eczema, and 7.32 (3.3, 16.1) kU/L in patients with GI symptoms; $p = 0.02$. The proportion of patients with positive (>0.4 kU/I) milk-specific RAST were 53%, 50%, and 20%, respectively; $p = 0.07$. All patients had normal total serum IgG, IgM, and IgA levels.

Intestinal permeability changes in response to cow's milk challenge

Before milk challenge, the lactulose/mannitol recovery ratios in urine were comparable in control subjects and in patients with CMA, irrespective of clinical reaction type (Table II). The urinary recovery of mannitol was lower in patients than in control subjects, but the difference was statistically not significant ($F = 0.98$; $p = 0.38$).

A significant increase in lactulose/mannitol excretion ratios followed cow's milk administration by day 3 in patients with CMA, manifesting cutaneous and GI symptoms alike. There were no differences between patients reacting with urticarial or eczematous skin eruptions.

Urinary recovery of lactulose and mannitol on day 3 in the patients with skin and GI symptoms did not differ significantly from that of the control patients.

TABLE II. Urinary recovery of test markers in patients with CMA before (day 0) and during milk challenge (day 3) and in control subjects

	Before cow's milk challenge (day 0)	During cow's milk challenge (day 3)	Paired Student's <i>t</i> test	
			<i>t</i>	<i>p</i>
Patients with skin symptoms (N = 24)				
Lactulose/mannitol ratio	0.02(0.01, 0.03)	0.06(0.03, 0.13)	2.76	0.01
Mannitol (%)	2.77(1.38, 5.56)	2.29(1.05, 5.01)	0.15	0.88
Lactulose (%)	0.05(0.02, 0.11)	0.14(0.06, 0.29)	1.69	0.11
Patients with GI symptoms (N = 27)				
Lactulose/mannitol ratio	0.02(0.01, 0.03)	0.08(0.04, 0.17)	2.88	0.01
Mannitol (%)	1.87(0.97, 3.62)	1.27(0.62, 2.60)	0.43	0.68
Lactulose (%)	0.03(0.01, 0.06)	0.09(0.03, 0.23)	2.92	0.01
Control subjects (N = 13)				
Lactulose/mannitol ratio	0.01(0.01, 0.02)			
Mannitol (%)	3.54(2.52, 4.96)			
Lactulose (%)	0.05(0.03, 0.08)			

Means (95% CI).

By contrast, the urinary recovery ratios of these two probes were significantly elevated from the control level ($F = 6.68$; $p = 0.003$). Hence, the modifications in intestinal sugar permeability were found to be the result of a concomitant increase in urinary recovery of lactulose and a decrease in urinary recovery of mannitol.

According to ANOVA for repeated measures, there was a significant increase in lactulose/mannitol recovery ratio during provocation ($F = 15.91$; $p = 0.0005$). However, the interaction term between groups and periods was statistically not significant ($F = 0.09$; $p = 0.77$), indicating that the increase was identical for these groups of patients.

DISCUSSION

The results of the present study are consistent with previous findings that an abnormally high intestinal permeability is associated with GI allergy¹¹ and further extend these conclusions to patients with CMA presenting cutaneous symptoms.

The permeability of intestinal mucosa to potentially antigenic macromolecules has been the subject of several studies yielding conflicting results.¹² Indications of compromised intestinal permeability have been demonstrated in patients with atopic dermatitis with or without food allergy,¹³ but also results in contrast to these have been demonstrated.¹⁴ There is further controversy as to whether such defects are primary or secondary to the development of CMA. Factors increasing intestinal permeability and macromolecular absorp-

tion, for example, prematurity,¹⁵ malnutrition,¹⁶ and acute gastroenteritis,¹⁷ are considered important contributory factors in the pathogenesis of CMA.

The present study does not support the notion that modifications of mucous membrane permeability are primary abnormalities, being present before clinical symptoms have developed. A rise in intestinal permeability was found to follow the appearance of symptoms. Although there should be caution in interpreting the results of open food challenges, the present study indicates that, for CMA, active mechanisms rather than a leaky gut are responsible for the development of a clinical disease.

In previous studies the permeability tests have been performed at an early stage during the challenges; either the test markers were administered at the same time as the first doses of cow's milk or immediately after.^{18, 19} It cannot be excluded that, in patients with GI symptoms and eczema, the reactions are delayed at the gut mucosal level and that these have remained undiscovered by early testing. In the same way, if the provocation and the intestinal permeability tests are performed after a very short elimination period, a positive permeability test would rather indicate prolonged intestinal dysfunction and not a primary defect of mucous membrane permeability.

An alternative explanation for contradictory results might be the, as yet, unestablished practice of assessing GI permeability.^{2, 12} Only minor morphologic abnormalities of the small intestinal mucosa have been demonstrated in children with eczema caused by food

allergy,²⁰ and in patients with GI allergy, normal histology has not excluded increased endocytosis.^{21, 22} This finding reinforces the possibility that intestinal permeability changes are not gross histopathologic alterations of small intestinal mucosa. In addition, it has previously been demonstrated by this research unit that, although sugar permeability and macromolecular absorption vary in the same way, these appear to be distinct processes, and therefore, increased sugar permeability does not necessarily mean enhanced macromolecular absorption.²³

The patients in the present study have also been investigated for their local immune responses to cow's milk challenge.⁵ Patients who reacted with urticarial or eczematous skin eruptions or GI symptoms were demonstrated to have separate local immunologic features. These conclusions are in accordance with previous work on systemic humoral and cell-mediated immune responses.^{3, 4} It was somewhat surprising to learn that the intestinal permeability was affected in the same way in these patient groups, although some support for these findings can be gained from previous experimental studies.^{21, 24-26} Direct studies in animal models and indirect studies in humans indicate that morphologic and functional alterations are associated with different hypersensitivity reactions. Among the mucosal changes described in immediate hypersensitivity reactions are edema, enterocyte shedding, and disruption of the basement membrane, whereas delayed, cell-mediated immune reactions lead to villus atrophy and crypt hyperplasia. In these reaction types, in vitro experimental studies have proved enhanced transport of macromolecules, indicating disruption of the mucosal barrier.^{21, 26} No quantitative or qualitative comparisons of intestinal permeability between these reaction types can be made, however, on the basis of these studies.

Taken together, the results of the present study suggest that patients with CMA are not a homogeneous group. A common factor for these patients is, however, an increase in intestinal permeability in response to cow's milk Ags. Enhanced absorption of macromolecules at the time of reduced mucosal barrier function could induce a further increase in nonspecific intestinal permeability to multiple Ags, thereby broadening the sensitivity. Increased intestinal permeability could hence underly the development of multiple food allergies.

I thank Pekka Sillanauke, PhD, and Timo Koivula, MD, for collaboration, and Pekka Laippala, PhD, for statistical consultation. Special thanks are due to Erika Isolauri, MD, for her active work throughout the experiment and her invaluable comments in editing this article.

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Cromolyn versus triamcinolone acetonide for youngsters with moderate asthma

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Although both cromolyn (C) and inhaled corticosteroids are anti-inflammatory therapies for childhood asthma, there are few controlled comparisons of these medications for asthma therapy in children. None were conducted in the United States, and none specifically study triamcinolone acetonide (T) versus C. This 12-week evaluation followed 31 youths, aged 8 to 18 years, with moderate asthma who were assigned to receive C or T according to a prerandomized and blinded code. Patients were instructed to take two inhalations from the study metered-dose inhaler (active T or placebo) and to inhale the contents of one study-provided ampule (C, 20 mg, or placebo) from a compressor-driven home nebulizer three times per day. Patients also used albuterol, two inhalations from a metered-dose inhaler, three times a day (before study medication) and, additionally, if needed. Patients maintained a daily diary, recording extra medication use, adverse experiences, peak flow rates morning and night, and asthma symptom scores. Laboratory assessment of pulmonary function was done at 1, 4, 8, and 12 weeks. Cosyntropin challenge and methacholine bronchoprovocation challenge were performed at the beginning and end of the study. C and T provided similar, adequate asthma control. Symptoms of wheezing, cough, and chest tightness decreased, and daily peak expiratory flow rate increased with both regimens compared to during a 2-week baseline when patients received medication only as needed. There was no significant change in methacholine sensitivity and no change in endocrine function, as measured with fasting plasma control before and after administration of cosyntropin. Although there were significant intragroup differences in the T- but not C-treated groups, there were no discernible significant differences between C and T at these dosages. (J ALLERGY CLIN IMMUNOL 1991;88:742-8.)

Key words: Cromolyn, inhaled steroids, triamcinolone, childhood asthma

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Supported by A.S.T.H.M.A., Inc., Seattle, Wash., and Rorer Central Research, Horsham, Pa.

Received for publication Jan. 10, 1991.

Revised May 29, 1991.

Accepted for publication May 31, 1991.

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1/1/31509

Histology of lung biopsy sections from patients with asthma¹ as well as bronchoalveolar lavage cell differentials from these patients attest to the importance of inflammation of the airways in the pathogenesis of asthma.^{2,3} With this insight, clinicians are now focusing pharmacologic intervention on drugs with apparent anti-inflammatory activity.^{4,5} Studies on airway hyperresponsiveness indicate that both aerosolized corticosteroids and C are capable of decreasing hyperresponsiveness, presumably because of their anti-