

Gastrointestinal Milk Intolerance of Infancy

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• During a period of 30 months, cow's milk- or soy protein-induced colitis was diagnosed in 22 infants. All patients presented with hematochezia. Only three patients had substantial diarrhea. Colonoscopic evaluations demonstrated a characteristic mucosal appearance, manifested by aphthoid ulcerations with intervening, normal-appearing mucosa. Histologic findings included surface ulcerations and associated inflammation of the lamina propria and submucosa, marked by substantial eosinophilic infiltration. Both clinical symptoms and colonoscopic abnormalities rapidly resolved in all patients after the elimination of cow's milk and/or soy protein from the diet. These data indicate that hematochezia may be the predominant symptom of cow's milk protein and soy protein intolerance in many affected infants, and that colonoscopy is the most effective means of establishing a definitive diagnosis in this patient population.

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Intolerance to cow's milk and/or soy protein has been implicated in the pathogenesis of diverse symptom complexes in infancy, including colic,¹ enterocolitis,² and anaphylaxis.³ Although various testing procedures have been suggested to diagnose milk intolerance,⁴ observation of symptoms after withdrawal and rechallenge of the suspected protein remains the sole reliable diagnostic technique.⁵ To better define both the characteristics at presentation and the clinical course related to milk protein intolerance, we prospectively evaluated a group of infants with a presumptive diagnosis of cow's milk and/or soy protein intolerance.

PATIENTS AND METHODS

Over a 30-month period, 22 infants referred to the Division of Pediatric Gastroenterology and Nutrition, New York Medi-

cal College, Valhalla, were diagnosed as having milk protein intolerance. Patients ranged in age from 2 to 16 weeks (mean $\pm$ SD, 6.73 ± 4.97 weeks), and were free of associated neonatal problems. Hematochezia was present in all infants; however, substantial diarrhea (>30 g/kg/d) occurred in only three patients. At the time of presentation, 15 infants were receiving either cow's milk (11 infants) or soy protein (four infants) exclusively, and five patients were breast-fed (with soy formula supplementation in one infant). All mothers of breast-fed infants had a history of cow's milk ingestion during lactation. Two subjects were fed both cow's milk and soy protein formulas in the week before the onset of symptoms, and no infant had yet received solid food. At initial presentation, the following laboratory tests were performed: complete blood cell count, platelet count, prothrombin and partial thromboplastin time determinations, total serum protein and albumin level measurements, and quantitative IgE and IgE antibody level measurements (cow's milk, soy). Two stool cultures for *Salmonella*, *Shigella*, *Campylobacter* subspecies *jejuni*, *Clostridium difficile*, and enterohemorrhagic *Escherichia coli*, two stool samples for rotavirus culture, and three stool specimens for ova and parasite cultures were obtained in all cases. If cultures were negative, the nature and extent of colonic involvement was determined by colonoscopic examination, including multiple biopsies, using a flexible fiberoptic sigmoidoscope. All procedures were recorded on videotape for subsequent review and comparison with later studies (see below). In preparation for colonoscopy, routine formula and/or breast-feeding was discontinued four hours before the procedure, and an infant glycerine suppository was given two hours before the examination. Informed written consent was obtained from the legal guardian of each patient. This protocol had the approval of the Institutional Review Board (Committee for the Protection of Human Subjects), New York Medical College.

RESULTS

In all infants studied, the mean ($\pm$ SD) hematocrit was 0.37 ± 0.07 . Hypoproteinemia and/or clotting abnormalities were not demonstrated in any patient. Eosinophilia with a cell count greater than $0.3 \times 10^9/L$ was noted in four patients, an elevated IgE level⁷ was found in six patients, and a positive

radioallergosorbent test for cow's milk protein was determined in two infants. All stool cultures for bacterial pathogens, ova, and parasites as well as rotavirus were negative. As shown in Fig 1, the appearance of the colonic mucosa during endoscopic examination demonstrated a characteristic pattern in all patients, marked by the presence of superficial aphthoid ulcerations surrounded by an erythematous margin. The intervening mucosa appeared normal. Typical lesions were observed in the rectosigmoid colon in 19 of 22 patients, and these abnormalities were found in the descending colon (with concomitant rectal sparing) in three of 22 infants. In all patients, aphthoid ulcerations were noted in both the transverse and ascending colon during the initial examination. In addition to these observations, nonspecific colonoscopic findings (patchy erythema, loss of normal vascular pattern) were described in 12 patients. Microscopic examination of biopsy specimens obtained at ulcer margins demonstrated superficial mucosal ulceration with epithelial cell loss. Abnormalities of the surrounding lamina propria and submucosa included varying degrees of acute and chronic inflammation; however, the predominant histopathologic abnormality was an inflammatory response with marked eosinophilic infiltration (Fig 2).

After the presumptive diagnosis of protein intolerance on the basis of clinical, laboratory, and characteristic colonoscopic findings, 19 of 22 infants began receiving a protein hydrolysate formula (Nutramigen, Bristol-Myers Inc, USPNG, Evansville, Ind). In every case, rectal bleeding ceased, confirmed by an absence of blood in the stool (Hemoccult, SmithKline Diagnostics Inc, Sunnyvale, Calif), within one week of institution of therapy. Repeated colonoscopy performed two weeks after the initiation of protein hydrolysate formula feedings demonstrated normal colonic mucosa. In three breast-fed infants, breast-feeding was continued. However, each mother was placed on a cow's milk protein-free diet.

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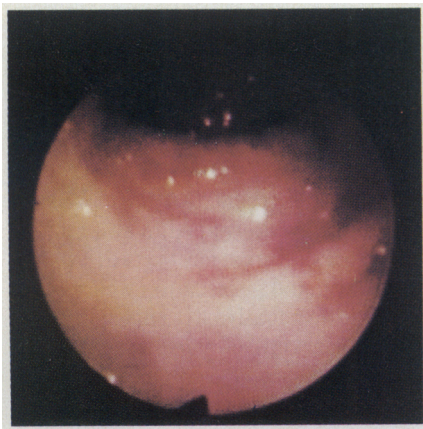


Fig 1.—Typical colonoscopic appearance in infant with suspected cow's milk protein intolerance. Note presence of aphthoid ulcerations with normal-appearing surrounding mucosa.

Within two weeks, symptoms ceased in these infants. Two months after symptom resolution, 17 formula-fed infants were rechallenged with cow's milk or soy protein-based formula. In all cases, a recrudescence of the presenting clinical findings was heralded by the reappearance of blood in the stools. Repeated colonoscopies, limited to the descending colon, demonstrated characteristic mucosal abnormalities in all infants. In every case, symptom resolution and blood-free stools were rapidly achieved after reinstitution of the protein hydrolysate formula feedings.

COMMENT

The clinical findings in this group of infants establish the importance of biopsy-proved colitis in milk and/or soy protein intolerance. These data indicate that in affected infants presenting with hematochezia, aphthoid ulceration of the colonic mucosa may be a characteristic finding. Furthermore, in contrast with several earlier studies,⁸⁻¹⁰ substantial diarrhea did not appear to be a major finding in our patient population. Criteria for establishing the diagnosis of milk protein intolerance remain somewhat controversial. Previously, both serologic and skin testing were shown to be of questionable value,¹¹ since abnormal results may fail to discriminate between protein allergy and atopy induced by other antigens.¹² The technique developed by Goldman et al,⁵ which involves elimination and rechallenge with the suspected offending protein on three separate occasions, has

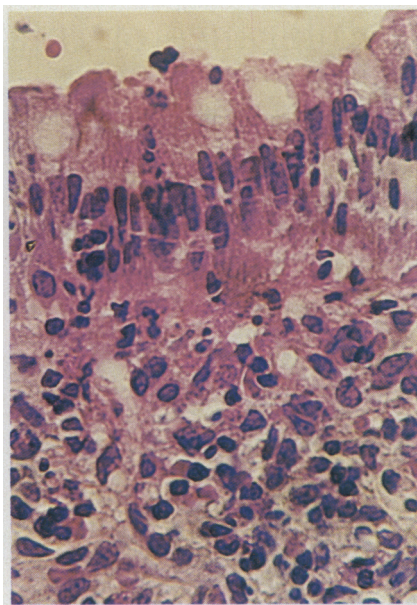


Fig 2.—Histologic section of colonic mucosa shows hyperplastic surface epithelium with inflammatory cell infiltrate and lamina propria with numerous eosinophils (hematoxylin-eosin, original magnification $\times 400$).

been the most widely accepted method of establishing a diagnosis of food intolerance. The present results suggest that early colonoscopy in infants presenting with hematochezia without an obvious cause (eg, anal fissures, infection) is the most efficacious means of identifying a protein intolerant population. Although the appearance of the colonic mucosa seen in our patients, including histologic findings (mucosal ulceration, eosinophilic infiltration), may be similar in other disease states (eg, inflammatory bowel disease, Behçet's syndrome),¹³ rapid resolution and reappearance of colonic abnormalities after withdrawal and rechallenge with the appropriate protein clearly establish a clinical diagnosis of protein intolerance. Of note is the fact that all infants tolerated colonoscopic evaluations without difficulty, and intravenous and/or intramuscular sedation were not required. In addition, minimal preparation, consisting of cessation of feedings four hours before the procedure and an infant glycerine suppository given two hours before colonoscopy, was sufficient to allow for adequate inspection of the colonic mucosa without interference from fecal material.

In the present study, infants who were breast-fed before clinical presentation experienced symptom resolution

after withdrawal of cow's milk protein from the maternal diet, while the infants continued to breast-feed. These findings contrast somewhat with results in a similar group of infants, who experienced a highly variable response to maternal protein restriction under the same clinical conditions.¹⁴ Thus, further evaluation of symptomatic, breast-fed infants will be required to establish a conclusive diagnosis of cow's milk protein intolerance in this group.

The results reported herein indicate that hematochezia may be a frequent clinical finding in infants presenting with milk protein intolerance. Obviously, since this study did not evaluate the total population of milk-intolerant infants, additional investigation will be required to determine the overall importance of these findings in patients who are allergic to protein. Nevertheless, the observation of characteristic colonic mucosal lesions in suspected cases may confirm the diagnosis of protein intolerance.

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