Allergic Constipation: Association with Infantile Milk Allergy

Jon A. Vanderhoof, Deborah Perry, Terri L. Hanner and Rosemary J. Young

CLIN PEDIATR 2001 40: 399
DOI: 10.1177/000992280104000707

Allergic Constipation: Association with Infantile Milk Allergy

Jon A. Vanderhoof, MD
Deborah Perry, MD
Terri L. Hanner, RN
Rosemary J. Young, MS, RN

Introduction

Constipation has recently been described as a manifestation of cows' milk protein allergy.[1-3] We identified 12 children with severe constipation (3 or fewer stools per week) who have responded dramatically to restriction of cows' milk protein (Table 1). It appeared to us that many of these children also had symptoms suggestive of cows' milk protein intolerance during infancy. Mean age of those evaluated was 58¼ months and 7 of the 12 were males. It was our intent to more clearly evaluate this group to see if there were any indicators of cows' milk intolerance during infancy. Historical recollection of the primary caregivers was used to identify apparent gastrointestinal symptoms in infancy for which the parents sought medical intervention.

Patients and Methods

The most representative case was a 5-year-old child who developed chronic constipation at age 2. Currently, anorexia and poor growth were also evident. On physical examination, his abdomen was abnormally distended, but nontympanic. He had easily palpable suprapubic and left lower quadrant masses with a fecal impaction noted upon digital rectal examination. Large doses of lubricant laxatives were required to initiate and continue daily stooling but were less than successful over the subsequent weeks. Rectal biopsy demonstrated the presence of normal submucosal ganglia and focal clusters of eosinophils (>10 per high-power field [HPF]) in the lamina propria. A duodenal biopsy, performed to exclude small-bowel disease, revealed increased eosinophils. Skin patch tests for IgE-mediated cows' milk allergy were negative and a serum IgE level was normal. This child's constipation and distention totally resolved on a strict cow-milk-protein–free diet. His mother refused a cows' milk protein challenge as the child, for the first time, was doing well.

The remaining patients presented similarly, but many in a less dramatic fashion. Eight of the 12 children had significant irritability as infants, 4 had diarrhea, and 5 of 12 had intermittent constipation during the first year of life. Three of the 12 had significant chronic emesis, 1 had poor growth, and these children were hospitalized during their first year for evaluation of these symptoms. Some were recommended by their physicians (5 of the 12) to try soy or hypoallergenic formulas for their gastrointestinal symptoms. Most were thought to outgrow the problem.

Over half of the parents in our series recalled irritability in infancy. This was often accompanied by multiple formula changes and attempts at treatment of colic. While nearly half had a history of constipation, some had significant episodes of diarrhea during the first year of life. Although treatment for milk protein allergy was not formally con-

Clin Pediatr. 2001;40:399-402

University of Nebraska Medical Center, Creighton University, Children's Hospital, Omaha, NE.

Reprint requests and correspondence to: Jon A. Vanderhoof, MD, Department of Pediatrics, 985160 NE Medical Center, Omaha, NE 68198-5160.

Table 1

FEATURES OF 12 CHILDREN WITH SEVERE CONSTIPATION

Age Onset (mo)	S/S (<1 yr of age)*	S/S (>1 yr of age)	Therapy Prior to Milk-Free Diet	Therapy Following Milk-Free Diet
(36)	Irritability; vomiting	Painful defecation	Castor oil	None
(60)	Irritability; constipation	Daily soiling, abdominal distention, poor growth	45 ml (MO/MOM)	15 mL daily MO/MOM
(15)	Irritability; diarrhea	Poor growth	Lactose free formula, glycerin suppositories	None
(60)	Irritability; poor growth	Poor growth; abdominal distention; daily soiling	Senna laxative	None
(84)	Irritability; vomiting	Painful defecation; abdominal pain	Phenolphthalein laxative	None
(36)	Diarrhea; ileus	Poor growth, abdominal distention	MOM 30 mL b.i.d. & Cisapride 3 mg q.i.d. daily	15 mL MOM every 2–3 days
(54)	Irritability; diarrhea	Anal fissure; painful defecation; poor growth	MOM 15 mL daily; Cisapride 4.5 mg t.i.d.; Sulfasalazine 150 mg t.i.d. daily	None
(72)	Irritability; vomiting	Daily soiling; abdominal pain	15 mL MOM daily	None
(42)	Diarrhea	Abdominal pain; distention; painful defecation	7 mL MOM daily	None
(84)	Irritability; constipation	Painful defecation	45 mL MO/MOM daily	10 ml MO/MOM daily
(132)	Constipation	Daily soiling; painful defecation	30 mL MO/MOM daily & Cisapride, 10 mg t.i.d.	None
(24)	Constipation	Painful defecation	60 mL MO/MOM daily	15 mL MO/MOM daily

S/S = signs/symptoms; MO/MOM = combination product including mineral oil and milk of magnesia (Haley's MO®); MOM = milk of magnesia.

*Symptoms in infancy were defined by parental report of presence.

sidered in 7 of the 12 infants, multiple formula changes had been tried by all of the parents in an attempt to alleviate symptoms. In retrospect, many of these children may truly have had undiagnosed cows' milk protein allergy in infancy.

Upper and/or lower gastrointestinal endoscopy was performed in this group of patients at evaluation for constipation because of suspected allergic constipation, Hirschsprung's disease, or abdominal pain initially thought to be related to acid peptic or small-bowel disease. Biopsy results were reviewed by both a pediatric pathologist and a pediatric gastroenterologist. Ten of 12 patients underwent rectal biopsies. All results were positive for ganglion cells. Eight of the 10 rectal biopsy specimens were abnormal: one demonstrated eosinophilia with greater than 10 eosinophils per HPF in the lamina propria, eosinophils in the muscularis mucosa, and eosinophilic crypt abscess. Seven demonstrated focal eosinophilia, 4 with increased lymphoid aggregates. Two rectal biopsy results were completely normal. Painful defecation was a common presenting complaint seen in many of the older consti-

pated children in our series. Based on our findings of inflammation in many rectal biopsies in these children, allergic inflammation associated with cows' milk could have been responsible for the discomfort.

Seven of the 12 underwent small bowel biopsy; 5 had abnormal results. Mild chronic inflammation with increased eosinophilia was noted in all 5. Gastric and esophageal biopsy specimens were also obtained and were normal. Of the 5 patients who had both rectal and small-bowel biopsies, 4 had characteristic allergic eosinophilia in both the small bowel and rectal biopsy specimens. One of the 12 patients had normal small bowel and rectal biopsy results, nevertheless, responded to cow milk protein restriction.

Nine patients were purposely or inadvertently challenged with cow milk protein after 10 (±5.5) months of a strict cow-milk-protein–free diet. Seven experienced a relapse of symptoms and 2 had no return of constipation. At 22 ±2.5 months, 5 of those who previously relapsed were rechallenged along with the remaining 3 and experienced no return of symptoms. Two continue on the milk-free diet (follow-up 34 months).

Discussion

Although allergic disease has only recently been appreciated as a cause of childhood constipation, allergies to food products are thought to affect 6% to 8% of infants, most often resulting in diarrheal disease.[4] IgE-mediated reactions account for half of these allergies with the skin and gastrointestinal tract being most commonly affected. Food-related intolerances with an immunologic basis, but without evidence of IgE-mediated sensitivity, also occur. Celiac disease, allergic eosinophilic gastroenteritis, and cow milk and soy protein–induced enterocolitis are such disorders.[5]

The association between cows' milk protein and chronic constipation was first noted by Buisseret[6] and later emphasized by Chin and colleagues.[1] Cow milk protein allergy as a possible cause of childhood constipation has recently been noted by Iacono and associates,[2] who described 27 patients with a mean age of 26.6 months with chronic idiopathic constipation. Twenty-one children experienced a resolution of symptoms on a cow-milk-protein–free diet and upon rechallenge had a return of their constipation. A more recent study by Iacono and co-workers[3] involved a double-blind, 2-week crossover study in 65 children with chronic constipation comparing the consumption of cow milk with soy milk. Forty-four of the 65 children had increased stool frequency while receiving soy milk. These studies also identified that, over time, symptoms of cow milk protein intolerance may change in symptom expression, initially presenting with bloody diarrhea, however later presenting with constipation.

The mechanism by which cow milk protein allergy causes constipation is not completely understood. Most reactions to dietary proteins in infancy have a pattern of delayed onset, in contrast to the IgE-mediated reactions, which tend to be more immediate. Immaturity of the intestinal immune system may be a factor as the incidence of food protein intolerance decreases with age. The gastrointestinal tract is uniquely adapted to prevent luminal antigens from crossing the epithelium and to control the systemic immune response to foreign proteins.

It is thought that eosinophils may be directly responsible for much of the tissue injury in this disease.[7] When exposed to milk protein antigen, the sensitized infant develops inflammatory cells, particularly eosinophils that infiltrate into the mucosa, resulting in destruction of epithelial cells, which causes diarrhea and rectal bleeding. Eosinophils also bind IgA, which may be a factor in gut inflammation.

Winter and associates[8] demonstrated that a moderate number of eosinophils (>6/HPF) in the lamina propria of a rectal biopsy specimen was highly suggestive of food protein–related allergy. They also determined that the number of eosinophils in the lamina propria does not correlate with the peripheral eosinophil count. The presence of eosinophils in the muscularis mucosa has been identified as a marker for colonic allergic injury, similar to previously recognized associations between eosinophils in the muscularis mucosa of the gastric antrum and allergic gastroenteritis.

Removal of milk protein from the diet ameliorated the constipation in our group of patients. Treatment required strict removal of all milk protein from the diet. Label reading for ingredients was key as foods not obviously categorized as dairy products such as many processed snack foods, lunchmeats, and breads to name a few, often have large amounts of milk protein. Parents were instructed regarding the removal of all cows' milk proteins including casein, whey, and lactalbumin. Soy or rice milks were used as substitutions for beverages or use on cereals. Dairy-free soy and tofu cheese, ice cream, and yogurt could

be used. Parents were given instructions on methods to increase nondairy sources of dietary protein and calcium while on cow milk protein restriction.

It has been our experience that without strict adherence to the diet, a less than complete response is seen. Many children in our series required concomitant use of stool softening initially, which was slowly reduced as the symptoms resolved. Children who were subsequently challenged with milk protein purposely or inadvertently experienced rapid relapse of constipation. We, therefore, recommend strict removal of all cow milk protein for a minimum of 6 to 12 months. This number was chosen arbitrarily as it was thought that this period would allow for correction of immunologic factors involved in the allergic process.

Cow milk protein intolerance is a poorly recognized cause of constipation in children. This review is limited by its retrospective nature, but has heightened our awareness to a subgroup of children with constipation who have a history of cow milk protein intolerance in infancy. History of such symptoms during infancy should alert the clinician to a possible allergic cause of the constipation. Histologic features typical of cow milk protein allergy in small intestinal and rectal biopsy specimens may be useful in establishing the diagnosis. Further studies of a prospective nature are needed to determine the true incidence. Placebo-controlled trials, although difficult, may ultimately be required to fully understand the extent of this disorder.

REFERENCES

1. Chin KC, Tarlow MJ, Allfree AJ. Allergy to cow milk presenting as chronic constipation. *Br Med J Clin Res Ed.* 1983;287:1593.
2. Iacono G, Carroccio A, Cavataio G, et al. Chronic constipation as a symptom of cow milk allergy. *J Pediatr.* 1995;126:34-39.
3. Iacono G, Cavataio F, Montalto G, et al. Intolerance of cow milk and chronic constipation in children. *N Engl J Med.* 1998;339:1100-1104.
4. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food-protein-induced enterocolitis syndrome. *J Pediatr.* 1998;133:214-219.
5. Gryboski JD. Gastrointestinal milk-related disorders. *Pract Gastroenterol.* 1982;6:7-12.
6. Buisseret PD. Common manifestations of cow milk allergy in children. *Lancet.* 1978;1:304-305.
7. Odze RD, Wershil BK, Leichtner AM, et al. Allergic colitis in infants. *J Pediatr.* 1995;126:163-170.
8. Winter HS, Antonioli DA, Fukagawa N, et al. Allergy related proctocolitis in infants: diagnostic usefulness of rectal biopsy. *Mod Pathol.* 1990;3:5-10.