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Presumed Allergic Proctocolitis Resolves with Probiotic Monotherapy: A Report of 4 Cases

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Literature Search F
Funds Collection G

BDEF 1,2 Victoria J. Martin
DEG 2,3,4 Wayne G. Shreffler
ABDE 1,4 Qian Yuan

1 Department of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital, Boston, MA, U.S.A.
2 Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Boston, MA, U.S.A.
3 Department of Pediatric Allergy and Immunology, Massachusetts General Hospital for Children, Boston, MA, U.S.A.
4 Food Allergy Center, Boston, MA, U.S.A.

Corresponding Author: Qian Yuan, e-mail: qyuan@mgh.harvard.edu
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Case series
Patients: —
Final Diagnosis: Allergic proctocolitis
Symptoms: Hematochezia • fussiness
Medication: —
Clinical Procedure: —
Specialty: Pediatrics and Neonatology

Objective: Unusual clinical course

Background: The prevalence of allergic diseases has been dramatically rising in the United States and other developed nations over recent decades. Growing evidence suggests a partial role for the microbiome in the development of these allergic diseases. Food protein-induced allergic proctocolitis (AP) (also referred to as cow's milk protein intolerance or allergy) is among the earliest and most common food allergic diseases of infancy, yet its pathophysiology is not well understood. The currently accepted clinical practice is to restrict the diet until 12 months of age.

Case Reports: We present 4 cases of clinically diagnosed AP whose symptoms quickly and completely resolved with probiotic *Lactobacillus rhamnosus* GG (LGG) monotherapy. All 4 infants avoided any dietary restrictions. The range of time from probiotic initiation to symptom resolution was 7–28 days.

Conclusions: These cases suggest an important role for the infant intestinal microbiome in the development of gastrointestinal mucosal food allergies such as AP. Prospective investigation of the intestinal microbiome in infants with AP may further our understanding of this disease's pathogenesis. The potential use of probiotic monotherapy in the treatment of AP also warrants further investigation.

MeSH Keywords: Allergy and Immunology • Breast Feeding • Microbiota • Milk Hypersensitivity • Probiotics • Proctocolitis

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/898490

Background

The prevalence of allergic diseases has been dramatically rising in the United States and other developed nations in recent decades [1,2]. Food protein-induced allergic proctocolitis (AP) is among the earliest and most common food allergic diseases of infancy, yet its pathophysiology is not well understood. AP typically presents in early infancy with mucous and blood in the stool (either hematochezia or guaiac-positive stools) and non-specific symptoms of fussiness, difficulty feeding, and gastroesophageal reflux. Symptoms typically resolve with dietary antigen restriction, and cow's milk is the most common trigger. Symptoms suggestive of AP afflict upwards of 10–15% of infants, though only 2–3% are diagnosed with challenge-proven cow's milk protein allergy [3,4]. Current guidelines for the treatment of suspected AP recommend maternal dietary restriction of the most common allergenic proteins in breastfed infants (cow's milk and soy) or a trial of extensively hydrolyzed formula in formula-fed infants [5,6]. Recent hypotheses to explain the rise in immune-related diseases have suggested that the Western lifestyle sets the stage for allergic and autoimmune diseases by altering our exposure to microbes, causing perturbations in the colonization of the intestinal mucosa and affecting mucosal immune system development [7,8]. There is evidence that adjunctive therapy with probiotic *Lactobacillus rhamnosus* GG (LGG) may hasten symptom resolution from AP when combined with hydrolyzed formula [9,10]. There are no reports of probiotic monotherapy in these infants.

With the now ubiquitous marketing and parental awareness of probiotics, we have observed a trend toward increasing use of probiotics during infancy, including as an 'intervention' by parents and primary care providers for a diverse range of GI symptoms. Over the past few years, we have noted that the symptoms of some infants with AP resolve quite quickly while taking probiotics, even in the absence of typical elimination of milk or other major allergens in several infants. We describe 4 such cases of clinically diagnosed AP whose symptoms resolved entirely with LGG monotherapy, without any need for dietary food antigen elimination.

Case Reports

Patient A is a term female conceived via *in-vitro* fertilization and born via C-section for post-dates pregnancy and an unfavorable cervix. She had no post-natal exposure to antibiotics and was exclusively breastfed (with an unrestricted maternal diet). She presented at 3 months of age to her pediatrician with a 1-week history of persistent grossly bloody guaiac-positive stools. Her parents described streaks and flecks of blood in her stool. There was no evidence of anal fissures, intestinal infection, or other obvious causes of rectal bleeding. A clinical diagnosis of allergic proctocolitis was made. Her family was resistant to dietary modification, and she was started empirically on LGG. Her bloody stools completely resolved over the following 10 days, and she was guaiac-negative after 2 weeks on LGG. Her mother continued breastfeeding throughout infancy while eating an unrestricted diet. At her well-child visits at 4, 6, and 9 months of age, the infant remained on LGG and had guaiac-negative stools. She tolerated standard introduction of solid foods, including those containing dairy products. She had no recurrence of any symptoms of AP.

Patient B is a term female born via emergency C-section without other complications of pregnancy or delivery, who was exclusively breastfed with an unrestricted maternal diet. She presented to her pediatrician at 1 month of age with fussiness, gassiness, increased spitting up, and mucous-like guaiac-positive stools in the absence of anal fissures or indication of infection. She was otherwise well. A clinical diagnosis of allergic proctocolitis was made, and she was started empirically on LGG without any dietary modifications. Her mother continued exclusive breastfeeding without any changes to her diet. Patient B's symptoms resolved. She was asymptomatic and guaiac-negative at her subsequent 2-month well-child visit, and remained asymptomatic at her 4-month visit. She had no recurrence of any symptoms of AP.

Patient C is a term female born via normal spontaneous vaginal delivery without complications of pregnancy or delivery. She was exclusively breastfed. Her mother is a vegetarian, but consumed normal amounts of cow's milk protein and did not restrict any major allergens. At 1 month of age, she presented to her pediatrician with fussiness and increased spitting up. At 2 months of age, she had increased frequency of stools but they were not yet guaiac tested. Two weeks later, she was noted to have flecks of gross blood in her stool, and was persistently guaiac-positive at her next visit at 3 months of age. There were no anal fissures or indication of infectious or other causes. She was clinically diagnosed with AP and started on LGG. Seventeen days later, she was seen in follow-up. Her fussiness and grossly bloody stools had resolved, and her stool was guaiac-negative in the office. Her mother remained on a dairy-containing diet. At 9 months of age, she remained asymptomatic, had tolerated the introduction of yogurt, and remained guaiac-negative. She is now 2 years old and drinks whole cow's milk. She had no recurrence of any symptoms of AP.

Patient D is a term male born via repeat C-section without complications of pregnancy or delivery. He was exclusively breastfed from birth with an unrestricted maternal diet. His stool was tested at his 1-month well-child visit for symptoms of intermittent fussiness, spitting up, and a sibling with a history of allergic proctocolitis. He was guaiac-positive and there were no anal fissures or indication of infectious or other causes. Over

Table 1. Four cases of presumed allergic proctocolitis resolution with LGG monotherapy.

Case	Gender	Delivery mode	Age (days) at diagnosis	Time (days) to symptom resolution*
A	Female	C-section	95	13
B	Female	C-section	31	7
C	Female	Vaginal Delivery	94	17
D	Male	C-section	30	28
			Mean=62.5	Mean=16.3

* From initiation of LGG to guaiac negative stools.

the next week, he remained persistently guaiac-positive. At 32 days of age, he was clinically diagnosed with AP and started on LGG, while his mother continued breastfeeding with an unrestricted maternal diet. At his 2-month well-child visit, his symptoms had resolved and his stools were guaiac-negative. He tolerated standard introduction of unrestricted solid foods at 4 months of age and remained asymptomatic and guaiac-negative at his 6-month well-child visit.

In these 4 cases, complete symptom resolution (including transitioning from persistently guaiac-positive to guaiac-negative stools) occurred in a mean of 16.3 days with a range of 7–28 days, as shown in Table 1. All 4 infants were able to tolerate cow's milk protein in their maternal breast milk, avoiding dietary restriction or hydrolyzed formula, and they each subsequently tolerated the standard introduction of solid foods. The dose of LGG used in these cases was between 2.5 and 5 billion colony-forming units (CFU) per day.

Discussion

The prevalence of allergic diseases is on the rise, and some have hypothesized that this may be driven by changes in our microbiome [8]. Food protein-induced allergic proctocolitis (AP) is among the earliest and most common food allergic diseases of infancy, yet its pathophysiology is not well understood. AP is diagnosed clinically in infants with persistently guaiac-positive or grossly bloody stools in the absence of other causes. Current guidelines recommend treatment with dietary restriction for 2 to 4 weeks, followed by an open challenge under medical supervision [5]. In clinical practice, though, AP is typically treated empirically with dietary restriction until 12 months of age. There is some evidence that the addition of a probiotic (LGG) improves outcomes [9,10]. Probiotic monotherapy in AP has not been reported. To the best of our knowledge, this is the first case report of infants with AP resolving on probiotic monotherapy.

Recent evidence from our group [11] and others [12] suggests that allergic proctocolitis is associated with the diagnosis of other allergic intestinal diseases, specifically eosinophilic esophagitis, later in childhood. Other risk factors for the development of eosinophilic esophagitis included cesarean section and antibiotic use early in life, suggesting a possible shared pathophysiology related to the intestinal microbiome [11,12]. We hypothesize that insults to the normal development of the infant intestinal microbiome result in dysbiosis in early infancy and confer risk for the development of allergic proctocolitis and perhaps other gastrointestinal food allergic diseases throughout childhood.

Conclusions

Some have suggested that current clinical practice of presumptive diagnosis of AP without histopathology leads to significant over-diagnosis of AP [13]. But clinically, sigmoidoscopy or colonoscopy is rarely performed in infants with only rectal bleeding because of its invasiveness (unless there are symptoms indicative of other possible etiologies, such as poor growth, excessively irritability, or profuse bleeding). Furthermore, there is growing evidence that there may be negative (allergic) consequences to strict avoidance of dietary antigens during infancy [14]. Therefore, evaluation of interventions that may mitigate the need for dietary restriction in infancy is timely and important. We cannot say that the infants reported here achieved resolution with LGG sooner than they would have without LGG and, indeed, well-designed studies assessing the natural history of AP are lacking. Careful prospective investigation of the infant intestinal microbiome and its role in gastrointestinal food allergic diseases may reveal novel pathophysiology in this disease. Randomized clinical trials investigating the management of food-induced allergic proctocolitis are needed. This series of cases also suggests that the use of probiotics as monotherapy in the treatment of food-induced allergic proctocolitis warrants further study.

Statement

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