

CLINICAL NOTES

Allergic colitis in monozygotic preterm twins

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Abstract

Allergic colitis (AC) typically develops in the first weeks or months of life and is characterized by the presence of red blood in the stools of healthy breastfed or formula fed infants. In this paper, we describe a case of rectal bleeding in monozygotic preterm twins that was resolved with the introduction of a cow's milk protein-free diet (CMPFD). The occurrence of this disorder in monozygotic twins raises the question as to whether the underlying abnormality in the immune regulation, which leads to poor acquisition of tolerance to cow's milk proteins, might be inherited or environmentally acquired. The case also highlights the use of the probiotic *Lactobacillus GG* (LGG) in the treatment of allergic colitis.

Keywords: Allergic Colitis, preterm twins, *Lactobacillus GG*

Introduction

Rectal bleeding in infants is an alarming symptom and requires additional investigation. Although it is a benign and self-limiting disorder in most cases,⁽¹⁾ it represents the primary symptom in 0.3% of all children admitted through the emergency room.^(1,2) Rectal bleeding in full term and preterm babies is a common presenting symptom in many serious diseases such as necrotizing enterocolitis, Hirschprung's disease, and hemorrhagic disease. Milder causes, in otherwise asymptomatic babies, are anal fissure, swallowing blood syndrome, infectious colitis and allergic proctocolitis.^(1,3)

Allergic colitis (AC) typically develops in the first weeks or months of life and is characterized by the presence of red blood in the stools of otherwise healthy breastfed or formula fed infants. The bleeding can range from spotting to hemorrhage and often increases until the causal agent is removed from the diet. While, in most cases, there is no failure to thrive,⁽⁴⁾ and while many foods have been associated with allergic colitis, cow's milk proteins are implicated in almost all cases of allergic colitis in this population.^(5,6) Because most laboratory tests, skin prick tests, and specific IgE titers are negative in most infants, after excluding other possible diagnoses, the diagnosis of allergic colitis is typically based on clinical history and the patient's response to the elimination of the offending

antigen from the diet. In these children, oral provocation test should be executed to confirm the diagnosis.⁽⁴⁾ The elimination diet in these infants is usually only temporary, since the proctocolitis is generally benign and self-limiting, and the infant is often able to tolerate a normal diet by the end of first year.⁽⁷⁾ In this paper, we describe two cases of rectal bleeding in monozygotic preterm twins that resolved with a cow's milk protein free diet (CMPFD) using an extensively hydrolyzed formula supplemented with the probiotic *Lactobacillus GG* (LGG).

Case report

S.P., a monozygotic male twin, was born preterm at 31 weeks of gestation. At one month of age (35 weeks of corrected age), he was admitted to the neonatal intensive care unit for vomiting, and stools streaked with blood and mucus with a possible diagnosis of volvulus or necrotizing enterocolitis. At admission, the baby appeared toxic; the abdomen was slightly distended without rebound or tenderness of the abdominal wall or signs of peritonitis. Some excoriated lesions were visible in the perianal region. The abdominal X-ray showed no signs of intestinal distention, air fluid levels, or intramural air. Hematologic studies showed increased inflammatory markers (CRP 77 mg/dl, WBC 12.8×10^3 cell/mmc) and a

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(Received 21 June 2012; revised 20 September 2012; accepted 24 September 2012)

marked reduction in hemoglobin. A blood transfusion was performed and antibiotics, including with Ampicillin/Sulbactam and Amikacin were started.

Despite a rapid improvement in the patient's clinical condition following the initiation of antibiotic-therapy, blood and mucus in the stool were still present after 1 week of treatment. Testing for eosinophils in the stool was positive and fecal calprotectin was also increased (414.5 µg/g/stool). As the infant had been fed cow-milk based infant formula since early infancy, it was suspected that the symptoms might be due to an intolerance to cow's milk protein. As such, his formula was replaced with CMPFD, an extensively hydrolyzed casein and probiotic infant formula (Nutramigen LGG; Mead Johnson Nutritionals, Evansville, Indiana). In this formula, the LGG concentration was 2.5×10^7 to 5×10^8 colony forming units (CFU/g) and providing a minimum of LGG, 1.46×10^7 CFU/100 ml).

While S.P. was still in the hospital, his twin brother, N.P., was also hospitalized in the same department for stools streaked with blood. Fecal detection of eosinophils and assay of fecal calprotectin (228 µg/g/stool) were positive. N.P.'s diet was also replaced with Nutramigen LGG. After few days, rectal bleeding ceased in both infants. They were discharged, and continued the same formula (Nutramigen LGG) at home.

One month later, the two babies were reevaluated, and their parents reported no further episodes of rectal bleeding. In both infants, skin prick tests and patch tests for cow's milk protein were negative as were tests for calprotectin and stool eosinophils. At that moment they were submitted to an oral challenge with cow's milk proteins and after 4 days of receiving cow-milk-based formula they presented with an urticarial skin reaction and blood and mucus in the stools. Immediately, cow's milk formula was discontinued and Nutramigen LGG was resumed. Six months after discharge, cow's milk protein challenge was again carried out in both twins, this time with negative results.

The twins were started on a regular diet including cow's milk without suffering any further allergic reaction.

Discussion

Several studies have been conducted to investigate the cause of rectal bleeding in term and preterm infants. Cow's milk allergy has been considered the most common cause of bloody stools in infants.⁽¹⁻⁸⁾ Allergic proctocolitis was first described by Rubin in 1940 and is characterized by inflammatory alteration of the colon and the rectum, secondary to an immune reaction triggered by ingestion of food protein.⁽⁴⁻¹⁰⁾ Both allergic colitis and food protein-induced enterocolitis result from a cell-mediated reaction to food.⁽⁴⁾ Maayan-Metzenger, in his study conducted on 147 infants with isolated rectal bleeding, found a significant difference in the type of feeding between the control and study groups. Breast feeding was significantly more common in the former

than the latter group (83.1% vs. 52.6%, respectively, $p < 0.0001$).⁽³⁾ Allergic proctocolitis occurs not only in formula fed infants, but also in exclusively breast fed infants.⁽⁹⁾ In our literature review, we found only one case of proctocolitis described in twins: two term Japanese girls (in our case the twins were preterm) born by cesarean section (as in our case) that assumed formula feeding at birth.⁽¹⁰⁾ In this case report, symptomatology (blood in the stool) appeared in both newborns on day 4 of life, while in our case the symptoms appeared at 1 month of life and were not contemporaneous among the twins. Similar to our findings, the authors reported a CRP increase, yet, in their study cow's milk allergy was diagnosed on the basis of high serum specific milk IgE antibodies, which is an unusual finding at that age, as the results of cow's milk CAP-RAST and skin prick tests are not always positive. In our case the diagnosis was based on clinical symptoms, FC high values and positivity of eosinophyls in stools. The occurrence of this disorder in monozygotic twins raises the question as to whether an underlying abnormality in immune regulation, which leads to poor acquisition of tolerance, might be inherited or otherwise environmentally transmitted. Certainly, allergy is more common in siblings than in the general population and cow's milk protein allergy associated with protracted diarrhea of infancy has also been reported in siblings.⁽¹¹⁾ Another possibility, however, is that a certain type of microbiota might render an individual at higher risk for cow's milk allergy⁽¹²⁾ and this could also explain why the disorder may be more common in siblings, especially twins. We know that the gastrointestinal microbiota are transferred largely through the gastrointestinal tract and subsequently the vagina of the mother to the infant during the birthing process, at least initially.^(13,14)

Studies have shown that certain probiotics can transiently colonize infants when administered to the mother.⁽¹⁵⁾ In our study, it is possible that the mother could have transferred microbiota, which might have made both twins more susceptible to allergic colitis. However, at the moment, there is not much literature regarding newborns twin microbiota.^(16,17) No single laboratory test is either sensitive or specific enough to be diagnostic of allergic colitis, but the finding of either peripheral eosinophilia or eosinophils in stool is often considered suggestive of AC. Diagnosis of AC can be established by the response to elimination of cow's milk allergens and standardized challenge.^(18,19) In our cases, the elimination of the cow's milk protein diet resulted in the resolution of the rectal bleeding, normalization of hemoglobin, and the absence of eosinophils in the stool samples.

The presence of an inflammatory process in the gut is suggested, in our case, by the elevation of calprotectin in stool samples. Calprotectin is a calcium and zinc protein that accounts for 60% of the cytosol proteins in neutrophils and is elevated in the presence of on-going inflammation.⁽²⁰⁾ There is an age-dependent variation in fecal calprotectin,^(21,22) where upper references for newborns are higher than those in children.^(23,24) In a previous work

our group demonstrated that fecal calprotectin is significantly higher in infants suspected of having AC than in a comparison group of healthy infants.⁽²⁵⁾

In our current case report, after diagnosing allergic colitis, we eliminated cow's milk protein and supplemented the diet CMPFD with probiotics, in particular LGG. There is, in fact, more and more evidence regarding the ability of this particular probiotic to modulate the immune system and to influence the course of allergic diseases. It is likely that LGG hastened the recovery of these infants. Indeed, in a previous study, our group found more rapid resolution of allergic colitis when LGG was added to an extensively hydrolyzed formula.⁽²⁵⁾

The mechanism for this is open to speculation. LGG significantly down regulates the expression of the high-affinity IgE receptor subtype α (FCER1A) and HRH4 (HRH4) genes after 24-h stimulation.⁽²⁶⁾ FCER1 plays a key role in mediating the allergy-related IgE-dependent activation and degranulation of mast cells⁽²⁷⁾ as demonstrated in FCER1-deficient mice that fail to show allergic reactions after sensitization.⁽²⁸⁾ By suppressing the expression of *FCER1* and *HRH4* genes, LGG could attenuate mast-cell activation and release of allergy-related mediators. Additionally, the gene that encodes expression of the member of the mitogen-activated protein kinase (MAPK) family (MAPK12) and that participates in the signaling events that lead to the production of Th2 type cytokines IL-3, IL-4, IL-5 and IL-13 and in the generation of eicosanoids,⁽²⁷⁾ was also down regulated in LGG-stimulated mast cells. These findings suggest that LGG has an inhibitory effect on mast-cell genes that are involved in the IgE signaling cascade, beyond inhibition of IgE receptor gene expression.⁽²⁶⁾ It was also shown that LGG is able to modulate not only the immune response, but also reduce the epithelial damage induced by cytokines. Recently, in fact, a 40-kDa protein (p40) present in LGG culture supernatant has been identified and found responsible for preventing cytokine-induced intestinal epithelial cell apoptosis by activating antiapoptotic PI3K/Akt (EGFR dependent-pathway) signaling and for protecting intestinal barrier function from hydrogen peroxide-induced insults.^(29–31) Other reported effects of LGG-derived soluble factors include promotion of cytoprotection pathways in intestinal epithelial cells⁽³²⁾ and inhibition of cytokine production in macrophages.⁽³³⁾ It is noteworthy that our twins gained oral tolerance and could assume cow's milk proteins before the Japanese twins (6 months vs. 15 months): this could be related to the presence of LGG in hydrolyzed formula, as recently demonstrated.⁽³⁴⁾

Our cases provide further evidence for the familial association of non-IgE cow milk allergy. Whether this is related to an inherited immunologic trait, maternal transmission of GI microbiota, or another yet undefined environmental variable remains unknown. It also highlights the benefits of LGG in the treatment of this disorder.

Declaration of interest

The authors reported no conflict of interest.

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