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CASE REPORT

Nutritional Therapy in Very Early-Onset Inflammatory Bowel Disease: A Case Report

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Abstract Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract caused by a dysregulated immune response to the fecal microbiota. Very early-onset inflammatory bowel disease (VEO-IBD) refers to a subgroup of pediatric patients with IBD diagnosed before 6 years of age. This subgroup is often characterized by increased severity, aggressive progression, strong family history of IBD, and often poor response to conventional treatments. Nutritional therapies have been utilized to treat IBD, but their role in VEO-IBD is unclear. Disease behavior in VEO-IBD is often different from disease in adolescents and adults, as it is often restricted to the colon and refractory to standard medical therapies. Up to 25% of VEO-IBD patients have an identified underlying immunodeficiency, which may impact response to therapy. While specific mutations in interleukin 10 (IL-10), the IL-10 receptor (IL-10R), and mutations in NCF2, XIAP, LRBA, and TTC7 have been identified in VEO-IBD, polymorphisms in these genes are also associated with increased risk of developing IBD in adolescence or adulthood. We describe two cases in which infants presenting with VEO-IBD achieved clinical remission using exclusive enteral nutrition, a formula-based diet which has been shown to induce remission in older children with active Crohn's disease.

Keywords Crohn's disease · Pediatric · Inflammatory bowel disease · Exclusive enteral nutrition · Nutrition

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Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract caused by a dysregulated immune response to the fecal microbiota. Very early-onset inflammatory bowel disease (VEO-IBD) refers to a subgroup of pediatric patients with IBD diagnosed before 6 years of age. This subgroup is often characterized by increased severity, aggressive progression, strong family history of IBD, and often poor response to conventional treatments [1–3]. Nutritional therapies have been utilized to treat IBD, but their role in VEO-IBD is unclear. Disease behavior in VEO-IBD is often different from disease in adolescents and adults, as it is often restricted to the colon and refractory to standard medical therapies. Up to 25% of VEO-IBD patients have an identified underlying immunodeficiency, which may impact response to therapy. While specific mutations in interleukin 10 (IL-10) [4], the IL-10 receptor (IL-10R) [5], and mutations in NCF2, XIAP, LRBA, and TTC7 have been identified in VEO-IBD, polymorphisms in these genes are also associated with increased risk of developing IBD in adolescence or adulthood [6–9]. We describe two cases in which infants presenting with VEO-IBD achieved clinical remission using exclusive enteral nutrition, a formula-based diet which has been shown to induce remission in older children with active Crohn's disease [10].

Case 1

A 10-month-old boy presented to gastroenterology clinic for a 2-month history of frequent stooling and intermittent bloody diarrhea. He was breastfeeding and eating age-appropriate foods. Mother had removed dairy, soy, and eggs from their diets without improvement. The patient

was otherwise in good health, with normal activity and without fevers. Initial laboratory values were significant for an elevated erythrocyte sedimentation rate (ESR) of 20 mm/h (normal <10 mm/h). He was started on an oral probiotic and continued on an elimination diet. At his 1-month follow-up visit, his ESR was 22 mm/h and hematocrit (Hct) had decreased to from 35 to 32%. Given continued symptoms and abnormal laboratory values, endoscopy was preformed (Table 1).

The patient had a visually normal esophagogastroduodenoscopy (EGD), but colonoscopy revealed patchy erythema from the rectum to the transverse colon. Biopsies returned showing granulomatous gastritis, duodenitis, and chronic active colitis with mild-to-moderate activity. The patient underwent immunology work-up including neutrophil oxidation burst assay which did not reveal a primary immunological disorder. He was started on EEN as primary therapy with intact cow's milk protein-based formula, Pediasure. By 2 weeks of therapy, his symptoms had improved significantly with reduced blood in his stools, but he continued to have an elevated ESR (34 mm/h) and anemia (Hct 32.3). By week 8 of therapy, he was clinically asymptomatic with normal ESR (9 mm/h), a large interval decline in fecal calprotectin, however, persistently elevated (529 mcg/g) (Table 1). After much discussion about medical therapy options, given the patient's clinical well-being, parents opted for the specific carbohydrate diet (SCD) as primary maintenance therapy with plans for close follow-up. At the time of transition to the SCD, patient was asymptomatic. With the introduction of solid foods, bloody diarrhea recurred, and therefore, EEN was restarted and sulfasalazine was initiated, and symptoms improved over the following month of EEN, but did not go into complete clinical remission. Due to concerns with dependence on formula and the beginning of food refusal, the patient was started on prednisolone and methotrexate and advanced to a normal diet. The patient entered clinical remission and was able to be weaned off of prednisolone. Dose escalation of methotrexate was required because of continued elevated sedimentation rate which normalized thereafter. He has been in clinical remission for over 18 months, with normalization of his ESR (5 mm/h) and CRP (<0.4 mg/dL).

Case 2

A 2-month-old boy presented to gastroenterology clinic for a 1 month history of frequent loose stools, intermittent hematochezia, anemia, and elevated CRP. He had been diagnosed by his primary care provider with multiple

Table 1 Laboratory values for Patient 1 on EEN

Time from presentation	Jan 2014/0	Feb 2014	April 2014	June 2014
	Presentation	Colonoscopy	On 2 weeks EEN	On 8 weeks of EEN
Hematocrit (%)	35	32.1	32.3	34.9
ESR (mm/h)	20	22	34	9
CRP (mg/dL)	<0.8	<0.8	<0.8	<0.8
Fecal calprotectin (mg/kg)	–	1250	–	529
Albumin (g/dL)	4.5	4.2	3.8	4.3
Anthropometrics: weight/length (percentile for age)	–	–	26	25–50

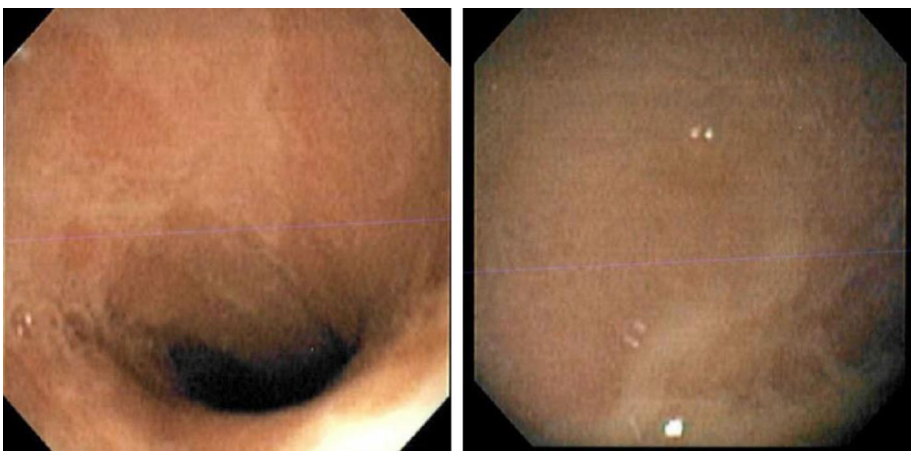
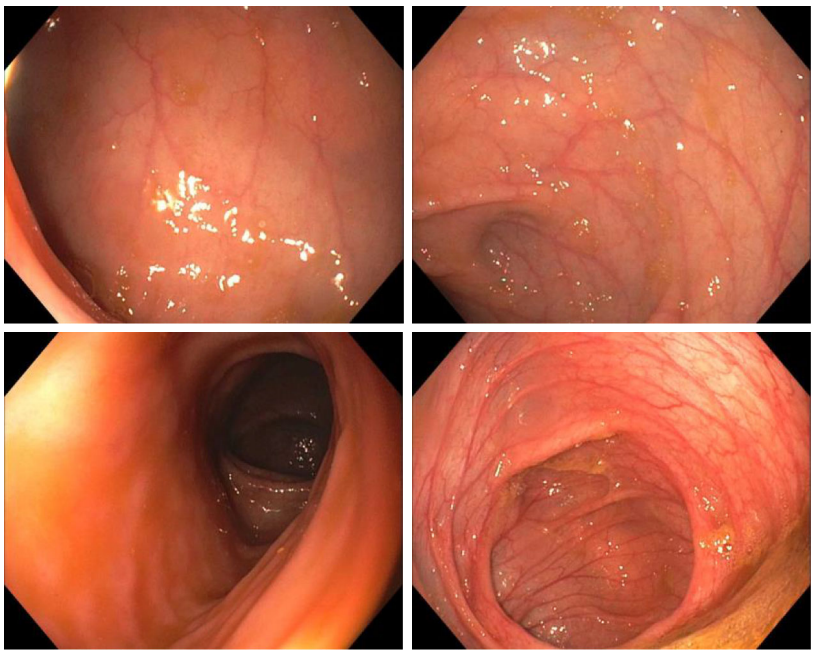


Fig. 1 Colonoscopy prior to dietary therapy September 2014

Table 2 Laboratory values for Patient 2 on EEN

Time from presentation	July 2014	October 2014	February 2015	March 2016
	Presentation	1 month on EEN, before SCD initiation	EEN plus 3 months of SCD	1 year of SCD
Hematocrit (%)	23.1	27.3	29.1	26.8
ESR(mm/h)	83	69	22	35
CRP (mg/dL)	2.6	1.1	<0.8	<0.8
Fecal calprotectin (mg/kg)	–	–	–	35
Albumin (g/dL)	3.8	3.8	4.2	4.3
Anthropometrics: weight/length (percentile)	–	25-50	90	90



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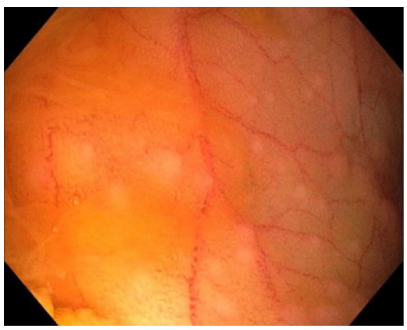

Fig. 2 Colonoscopy after dietary therapy August 2016

episodes of gastroenteritis and milk protein allergy. On presentation, he was noted to have an ESR of 83 mm/h and CRP of 2.6 mg/dL (normal <0.8 mg/dL), anemia (Hct 23.1%), and mild hypoalbuminemia (3.8 g/dL). The patient underwent endoscopy. EGD was visually normal, while the colon revealed erythematous, friable mucosa with shallow

ulcers, and exudate in the descending and transverse colon (Fig. 1). Biopsies revealed mild active inflammation with chronic architectural changes in the rectum and sigmoid colon. The descending colon demonstrated moderate to severely active inflammation with ulceration, and the transverse colon demonstrated focal mild active inflammation. At the time of colonoscopy, the patient was found to have worsening anemia with Hct of 20.1% and therefore admitted to the hospital for transfusion. He was started on EEN with an amino acid-based hypoallergenic infant formula (Elecare Infant).One month later, he was clinically asymptomatic, however, had persistently elevated ESR (69 mm/h) and anemia (Hct 27.3). After two months of EEN therapy, and after much discussion with the family about therapy options, solid foods from the SCD were introduced per parental preference. By four months of therapy (partial enteral nutrition and SCD foods), he continued to be in clinical remission and by 22 months of age was transitioned off of EEN and exclusively onto the SCD. Further work-up revealed no known immunodeficiency. His CRP had normalized; however, he continued to have persistent elevation in ESR (35 mm/h) and macrocytic anemia (hematocrit 26.8%, MCV 97.1) (Table 2). His anemia was further worked up and determined to be from a mutation known to cause Diamond–Blackfan Anemia and continues to follow with hematology. Clinically, he remained asymptomatic with normal CRP but mild elevation in ESR. Therefore, given persistent elevation of inflammatory markers despite clinical quiescence, he underwent repeat colonoscopy 23 months after diagnosis. He was found to have a visually normal colon with only mild chronic colitis without activity on microscopic examination (Fig. 2). The continued elevation in sedimentation rate was felt to be related to ongoing anemia associated with Diamond–Blackfan (Table 3).

Table 3 Differential diagnosis for VEO-IBD

Infections including bacterial, parasitic, and viral
Allergic colitis
Eosinophilic colitis
Hemolytic uremic syndrome
Primary immunodeficiency including
Severe combined immune deficiency
Combined variable immunodeficiency
Chromic granulomatous disease
Wiskott–Aldrich syndrome
Immune dysregulation, polyendocrinopathy, enteropathy, x-linked (IPEX)
NEMO
Glycogen storage disease 1b
IL10 receptor defects
Hermanksy–Pudlak syndrome
Autoimmune enteropathy
Hemophagocytic lymphohistiocytosis

Discussion

Although similar medication therapies are used in VEO-IBD as well as conventional IBD, these cases illustrate the positive impact on EEN in VEO-IBD. In older pediatric populations, EEN has been shown to induce remission in approximately 85% of newly diagnosed Crohn's patients and has the equivalent response to corticosteroids in children with Crohn's disease [11]. However, no studies have yet addressed the role of EEN in VEO-IBD population [10].

The North American Society of Gastroenterology (NASPGHAN) recommends EEN as a primary therapy for children with inflammatory Crohn's disease [11]. EEN is associated with minimal side effects as well as better mucosa healing when compared to steroids [12, 13]. Our experience in infants with VEO-IBD shows that EEN can be efficacious and well suited for this age group [12]. A major parental concern for our first child was breaking the dependency to formula and introducing foods as he got older. This may be amplified in the very young VEO-IBD population during the critical time of food introduction.

A multicenter prospective observational study evaluated the clinical presentation and therapeutic management of VEO-IBD and identified an increased administration of corticosteroid and immunomodulators in VEO-IBD patients compared to patients with similar disease activity in other age groups [14]. This important finding was thought to be related to more aggressive phenotype in this population and/or increased awareness of the importance of mucosal healing [14]. This study supports the need for safe and effective therapeutic options, such as EEN, for the VEO-IBD population. It may be the case that EEN as primary or adjunctive therapy alongside immunosuppression is superior to immunosuppression alone. Certain risk allele genotypes have been associated with efficacy of EEN in pediatric Crohn's disease, and further characterization of genetic risk in VEO-IBD may help guide the use of EEN in this population [15].

EEN as a treatment option in VEO-IBD also improves the nutritional status of our patients. While the nutritional benefits of EEN have been well studied in older children with IBD, it is equally or more important in the VEO-IBD population [16]. The use and protocols of EEN vary widely both nationally and internationally; therefore, studying the outcomes of therapy can be challenging. Given the small population of VEO-IBD and young age of presentation, it

would be ideal to create protocols and study the role of EEN as primary or adjunctive therapy in this patient population.

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