

Neonatal Presentation of Unremitting Inflammatory Bowel Disease

Sara Ebrahimi¹, MS;
Gholamreza Khademi², MD;
Seyed Ali Jafari³, MD;
Nona Zaboli Nejad⁴, MD;
Abdolreza Norouzy⁵, MD;
Bahareh Imani³, MD

¹Motahari Hospital, Jahrom University of Medical Sciences, Jahrom, Iran;

²Department of Pediatrics– PICU, Dr. Sheikh Hospital, Mashhad University of Medical Sciences, Mashhad, Iran;

³Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;

⁴Department of Pathology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;

⁵Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence:

Bahareh Imani, MD;
Department of Pediatrics, Imam Reza Hospital, Mashhad, Iran

Tel: +98 917 111 8516

Fax: +98 51 38591057

Email: ImaniBH@mums.ac.ir

Received: 08 November 2016

Revised: 24 December 2016

Accepted: 15 January 2017

What's Known

- Recent classification of inflammatory bowel disease (IBD) defined a cutoff point of 10 years in pediatric IBD as a distinct phenotype (A1a)-very-early-onset IBD. Patients diagnosed under 1 year of age are also distinct as infantile IBD.
- Infantile IBD, which has a strong relationship with gene mutation, is steadily increasing the world over.

What's New

- Our experience suggests that very-early-onset IBD has a poor prognosis and needs extensive immunosuppressive therapy earlier. An understanding of this disease will confer novel therapeutic approaches.
- Neonates with severe, chronic bloody diarrhea should be evaluated for IBD, although it is rare in the neonatal period.

Abstract

Very-early-onset inflammatory bowel disease (VEO-IBD) has a distinct phenotype and should be considered a specific entity. VEO-IBD presents with very severe clinical pictures and is frequently known by an indeterminate colitis whose clinical remission is unmanageable. This study examines the case of a neonate with VEO-IBD, not responding to medical and surgical treatment. A 7-day-old Iranian female neonate presented with severe bloody diarrhea, poor feeding, abdominal distention, and dehydration suggesting severe proctocolitis due to an allergy to the protein in cow's milk. The condition did not respond to the elimination of diet for 1 month. Infections, celiac disease, and cystic fibrosis were excluded. Immunological investigations were negative, but antineutrophil cytoplasmic antibodies were positive. Due to the neonate's persistent symptoms and failure to thrive, upper and lower endoscopies were performed, showing ulcerative colitis. At the age of 4 months, she presented with signs and symptoms of toxic colitis and acute intestinal perforation, which prompted an emergency laparotomy. Due to the necrosis of the colon, hemicolectomy and colostomy were done. The patient was resuscitated and rehabilitated and was given glucocorticoid and mesalamine. We believe that the incidence of this problem is increasing, as is shown by the rise in the number of children under 10 years old being diagnosed. These patients require more aggressive therapeutic interventions than older IBD patients to achieve complete remission because they are more likely to have extensive colonic disease.

Please cite this article as: Ebrahimi S, Khademi G, Jafari SA, Nejad NZ, Norouzy A, Imani B. Neonatal Presentation of Unremitting Inflammatory Bowel Disease. *Iran J Med Sci*. 2018;43(3):328-331.

Keywords • Infant • Inflammatory bowel diseases • Necrosis

Introduction

Inflammatory bowel disease (IBD) usually presents in young adults and adolescents; however, the North American Pediatric IBD Consortium has reasserted the onrush of IBD in the first 12 months of lifespan in 1% of patients.¹ Very-early-onset inflammatory bowel disease (VEO-IBD) has a distinct phenotype and should be considered a specific entity. The clinical manifestations of infantile-onset or VEO-IBD appear to be dissimilar to those of adult- and adolescent-onset IBD.² The described information for VEO-IBD depicts a severe clinical course of disease manifestation and elevated values of resistance to immunosuppressive intervention.² An understanding of VEO-IBD is believed to be crucial in the study of the pathophysiology of IBD in that an IBD that begins in the 1st year of life may have a

substantial correlation with genetic background. The Paris Classification *vis-à-vis* pediatric IBD separates the Montreal classification A1 (0–17 y) into A1a, 0 to 9 years of age, and A1b, 10 to 16 years of age. Children recognized less than 1 year of age are also distinct, and their condition is classified as infantile IBD.²⁻⁴

VEO-IBD comprises ulcerative colitis, Crohn's disease, and a relatively high proportion of indeterminate colitis.

The diagnosis of VEO-IBD necessitates that other causes of colitis, especially immunodeficiency and severe allergic colitis, be ruled out.^{4,5} There are no medication guidelines, and surgery might not always be a viable alternative since extensive colonic disease has a propensity to extend to the small intestine. Medication may finally be based on the detection of genetic disorders in this patient group.^{4,5}

We herein introduce a neonate with very-early-onset signs and symptoms of IBD, considered a case of VEO-IBD and a distinct phenotype. This case should be deemed a specific entity; it demonstrates the disease severity very early in life and the importance of the timely and correct management of the disease. Additionally, it shows that clinical remission is difficult to reach.

Case Presentation

A girl (GA=37 wk and BW=1820 g [$<$ the 3rd percentile]) born from non-consanguineous parents of Iranian origin with no family history of IBD presented at the age of 7 days with feeding intolerance, severe bloody diarrhea, non-bilious vomiting, abdominal distention, anorexia, and dehydration, mimicking a serious proctocolitis owing to an allergy to the protein of cow's milk. Her condition did not respond to a 1-month elimination diet. Infections (full septic workup) and cystic fibrosis were excluded. All the cultures were negative. Stool checkup for culture and direct smear for white blood cells, pH, red blood cells, and parasites were made out. A complete blood count showed anemia (hemoglobin=9.9) and leukocytosis. Hemoglobin declined to about 2 g/dL. The erythrocyte sedimentation rate and C-reactive protein concentrations varied between about 25 and 40 mm/h and 10 and 30 mg/dL respectively, indicating inflammation.

Immunological investigations, nitroblue tetrazolium, antinuclear antibody, and anti-Saccharomyces cerevisiae antibodies were negative, but antineutrophil cytoplasmic antibodies were positive. In addition, immunoglobulins IgG, IgA, and IgM as well as quantitative T and B cell subsets by flow cytometry and nitroblue tetrazolium/oxidative burst by flow

cytometry were within the normal range.

Due to the patient's persistent symptoms and failure to thrive (Wt=2900 g at 3 months of age, $<$ the 3rd percentile), upper and lower endoscopy was performed. The macroscopic specimen revealed pancolitis, erythema, edema, fragility, and ulceration. Moreover, her histology analysis showed severe active inflammation and ulceration extending into the deep portions of the mucosa, as well as superficial muscularis propria. There was, however, no granuloma formation. Figures 1 and 2 depict the patient's histological analysis of the macroscopic and microscopic specimens, suggesting ulcerative colitis. Colonoscopy was performed; the findings demonstrated that the anus was normal, whereas there were decreased vascular markings with multiple erosions and fragility in the rectosigmoid. Biopsies were taken from the rectal mucosa, and the findings showed that there were multiple erosions and fragility in the mucosa of the descending colon. It should be noted that our colonoscopy system was not equipped with a capture system, which precluded us from providing pictures of the colonoscopy.

A diagnosis of enterocolitis/IBD was made. The condition was subsequently managed by various physicians at different health facilities. At that stage, routine clinical investigations, comprising blood counts, urinalysis, stool microscopy, and abdominal ultrasound scanning, were reported as normal. Steroids, mesalamine, and azathioprine were given to the patient.

At the age of 4 months, the patient presented

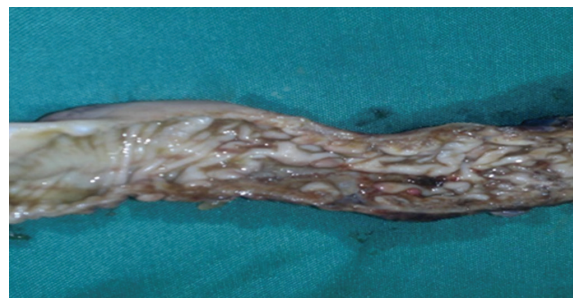


Figure 1: Histological analysis of the patient's macroscopic specimen, suggesting ulcerative colitis.

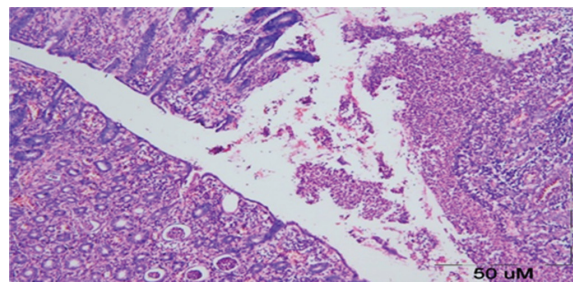


Figure 2: Histological analysis of the patient's microscopic specimen, suggesting ulcerative colitis.

with signs and symptoms of toxic colitis and acute intestinal perforation, which prompted an emergency laparotomy. Fortunately, she was in the hospital at the time and underwent a prompt emergency colectomy. Because of the extensive pediatric experience at our institution, the problem was identified and treated expeditiously. Due to the necrosis of the colon, hemicolectomy and colostomy were done. The patient was resuscitated and rehabilitated and given glucocorticoid, mesalamine, and azathioprine. However, she soon developed acute abdominal symptoms and needed readmission. After several admissions and repeated signs and symptoms of toxic colitis, a total colectomy was done. Despite these therapies, a sustained remission could not be achieved as a result of systemic inflammation.

In her last admission to the pediatric intensive care unit, she received glucocorticoid, mesalamine and azathioprine therapy in conjunction with nutritional support and total parenteral nutrition under the supervision of a nutritional specialist. The diet in similar cases is generally low in fat but high in protein. In addition, it contains easily digestible carbohydrates and is free of lactose (the EleCare formula). Increased intakes of certain nutrients such as iron, calcium, and magnesium, supplemented with fat-soluble vitamins, were also prescribed, along with additional fluids and electrolytes to replace losses due to diarrhea.

The patient was discharged with a weight of 4500 g at 5 months of age. She was readmitted several times after that due to severe malnutrition, failure to thrive, poor wound healing, and sepsis.

Unfortunately she died at home, probably due to sepsis and dehydration, at 7 months of age. There was no follow-up, and an autopsy was not performed. It is deserving of note that a written consent regarding reporting this case was taken from her parents.

Discussion

We introduced a neonate presenting with signs and symptoms of IBD at 7 days of age, which is considered a case of VEO-IBD. This case illustrates the disease severity in a patient presenting very early in life and the importance of the timely and appropriate management of the disease. What the case also demonstrates is how difficult it is to achieve clinical remission.

We believe that the incidence of this problem will rise, hence the ever-increasing importance of realizing the differences between these very young patients and older ones. Patients with VEO-IBD require strong-growing therapeutic

medication to accomplish complete remission, parenteral nutrition, early administration of steroids and immunosuppressant, more surgical medication, and more attention paid to relapses.⁵

The ratio of infantile IBD to whole IBD patients in studies conducted by Ruemmele et al.⁴ and Walker-Smith et al.⁶ was 1% to 2%. In one study, in comparison to the adults, the pediatric group showed a significantly low frequency of chronic active disease. Additionally, microscopic skip areas and relative rectal sparing were more frequent among the pediatric patients. Two of the 70 pediatric patients showed completely normal rectal biopsies at initial presentation, in contrast to none of the adult patients. The authors, accordingly, concluded that the absence of the features of chronicity, mild active disease, and microscopic skip areas at initial presentation in the pediatric patients did not exclude the possibility of ulcerative colitis.⁵

Our patient showed rectosigmoid involvement with severe active inflammation. Ulceration extending into the deep portions of the mucosa, superficial muscularis propria, lack of granuloma formation, and absence of ileal involvement suggested ulcerative colitis.

Only a few reports have analyzed the onset and outcome of IBD in different pediatric age groups, with 3 series dealing specifically with children younger than 5 years of age.^{7,8}

Based on our information, our case is the youngest patient with IBD. VEO-IBD in the infancy period is genetically and phenotypically a dissimilar disease entity from adult-onset or older child-onset IBD. It has a strong connection with the IL-10 receptor gene. Unfortunately, we did not have access to gene analysis for our patient, which is the limitation of our study.

VEO-IBD has a distinct phenotype and should be regarded as a specific entity. It encompasses ulcerative colitis, Crohn's disease, and a relatively high proportion of indeterminate colitis. VEO-IBD presents with a very severe manifestation and a guarded prognosis with life-threatening signs and symptoms. It needs aggressive therapeutic interventions.

The important factor is likely a genetic predisposition to develop IBD in early infancy.

Conclusion

These children most likely will have extensive colonic disease. Early diagnosis and medication algorithms are demanded for this ever-increasing patient population to ascertain optimum medical care for long-term outcomes such as growth and development. Very young children and infants

with IBD most likely have a genetic predisposition that can be identified using current available genetic investigations.

Acknowledgement

Special thanks are due to the management and staff of Sheykh Hospital of Mashhad University of Medical Sciences for all their cooperation.

Conflict of Interest: None declared.

References

1. Helbling R, Nyddeger A, Angelini F, Gete AVS, Hofer M. P03-024—Early onset IBD treated by tocilizumab. *Pediatric Rheumatology*. 2013;11:A222. doi: 10.1186/1546-0096-11-S1-A222.
2. Shim JO, Seo JK. Very early-onset inflammatory bowel disease (IBD) in infancy is a different disease entity from adult-onset IBD; one form of interleukin-10 receptor mutations. *J Hum Genet*. 2014;59:337-41. doi: 10.1038/jhg.2014.32. PubMed PMID: 24785691.
3. Traa MX, Orkin BA, Flores A, Popowich DA. Toxic colitis in a 10 year old girl with Crohn's disease. *J Pediatr Surg Case Rep*. 2013;1:284-7. doi: 10.1016/j.epsc.2013.08.003.
4. Ruemmele FM, El Khoury MG, Talbotec C, Mauraige C, Mougenot JF, Schmitz J, et al. Characteristics of inflammatory bowel disease with onset during the first year of life. *J Pediatr Gastroenterol Nutr*. 2006;43:603-9. PubMed PMID: 17130735.
5. Odze RD. A contemporary and critical appraisal of 'indeterminate colitis'. *Mod Pathol*. 2015;28 Suppl 1:S30-46. doi: 10.1038/modpathol.2014.131. PubMed PMID: 25560598.
6. Walker-Smith JA, Lebenthal E, Branski D. *Pediatric and Inflammatory Bowel Disease: Perspective and Consequences*. Monday: Karger Medical and Scientific Publishers; 2009. p. 67–75.
7. Odze R. Diagnostic problems and advances in inflammatory bowel disease. *Mod Pathol*. 2003;16:347-58. doi: 10.1097/01.MP.0000064746.82024.D1. PubMed PMID: 12692200.
8. Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis*. 2011;17:1314-21. doi: 10.1002/ibd.21493. PubMed PMID: 21560194.