Is Early-onset Inflammatory Bowel Disease a Primary Immune Deficiency?

Rachna Shanbhag¹, Sagar Bhattad²

ABSTRACT

Pediatric-onset IBDs (PIBDs) are a group of genetically heterogeneous diseases with variable severity. Depending on the age of onset, inflammatory bowel disease (IBD) can be classified as pediatric-onset (<17 years), early-onset (<10 years), very early-onset (<6 years), infant/toddler-onset (0–2 years), and neonatal-onset IBD (<28 days). Due to the advancement of molecular science and sequencing technologies, several monogenic defects have been identified in very early-onset IBD (VEO-IBD) over the last few decades. Inflammatory bowel disease manifesting at a very young age is more likely to be a monogenic defect. Pediatric-onset IBDs have been found to be associated with as many as 60 monogenic defects with most presenting below 6 years of age and some presenting before 1 year of age. The current article discusses early-onset IBD in detail with new concepts and a clinical and laboratory approach to these patients has been provided.

Keywords: Inflammatory bowel disease, Primary immune deficiency disease, Very early-onset IBD.

Pediatric Infectious Disease (2021): 10.5005/jp-journals-10081-1310

INTRODUCTION

The term inflammatory bowel disease (IBD) refers to chronic inflammation of the gut and encompasses a diverse group of disorders. Adult-onset IBD broadly includes two types—ulcerative colitis (UC) and Crohn's disease (CD). However, pediatric-onset IBD (PIBD) has distinct differences compared to adult-onset IBD.

PEDIATRIC-ONSET INFLAMMATORY BOWEL DISEASE

Pediatric-onset IBDs (PIBD) are a group of genetically heterogeneous diseases with variable severity. Depending on the age of onset, IBD can be classified as pediatric-onset (<17 years), early-onset (<10 years), very early-onset (<6 years), infant/toddler-onset (0–2 years), and neonatal-onset IBD (<28 days).¹ The incidence of PIBD in Asia and the Middle East varies from 0.5 to 11.4/100,000 person. This is much lower than figures in Northern/Western Europe (0.5–23/100,000) and North America (1.1–15.2/100,000).²

Inflammatory bowel disease presents in childhood in 25% of cases of which 1% present as early as in the neonatal or infantile period. According to a French study, very early-onset IBD (VEO-IBD) represents 3% of the total number of PIBDs.³

VERY EARLY-ONSET INFLAMMATORY BOWEL DISEASE

Young children presenting with IBD-like features (<6 years of age) are categorized as very early-onset inflammatory bowel disease (VEO-IBD). The incidence of VEO-IBD has been reported to be 4.37 per 100,000.⁴ Due to the advancement of molecular science and sequencing technologies, several monogenic defects have been identified in VEO-IBD over the last few decades. Many newer genetic defects are being added to this list (Table 1).

Compared to adults and PIBD, children with VEO-IBD have a more severe disease at presentation and are usually refractory to conventional immunosuppression. These children often present within the first few weeks to months of life with:

^{1,2}Division of Pediatric Immunology and Rheumatology, Department of Pediatrics, Aster CMI Hospital, Bengaluru, Karnataka, India

Corresponding Author: Sagar Bhattad, Division of Pediatric Immunology and Rheumatology, Department of Pediatrics, Aster CMI Hospital, Bengaluru, Karnataka, India, Phone: +91 9779433934, e-mail: drsagarbhattad@gmail.com

How to cite this article: Shanbhag R, Bhattad S. Is Early-onset Inflammatory Bowel Disease a Primary Immune Deficiency? *Pediatr Infect Dis* 2021;3(3):125–127.

Source of support: Nil

Conflict of interest: None

- Bloody diarrhea.
- Mucoid stools.
- Weight loss.
- Abdominal pain.
- Perianal disease—fistulas, fissures, and abscess.

The earlier the age at onset of IBD, more stronger is the possibility of a monogenic cause. It is essential to perform genetic testing in VEO-IBD as a subset of these patients may be cured with hematopoietic stem cell transplantation (HSCT).

GENETICS OF VEO-IBD

Genetic predisposition plays an important role in the development of IBD in young children.⁵ Adult-onset IBD is polygenic and

Table 1: Discovery of monogenic defects in VEO-IBD

Genetic defect	Year of discovery
IPEX	1982
IL-10 deficiency	1993
IL-10R deficiency	2010
RIPK-1	2018

IL, interleukin; IPEX, X-linked immune dysregulation, polyendocrinopathy and enteropathy; RIPK-1, receptor-interacting serine/threonine-protein kinase 1

multifactorial in origin and these diseases are caused by an interplay of genetic susceptibility, environmental factors, and intestinal microbiota. On the other hand, IBD manifesting at a very young age, is more likely to be a monogenic defect. Pediatric-onset IBDs have been found to be associated with as many as 60 monogenic defects with most presenting below 6 years of age and some presenting before 1 year of age.³ Genes associated with VEO-IBD have been tabulated in Table 2.

PATHOGENESIS OF VEO-IBD

The human gut is constantly exposed to antigens from the environment and the diet, and it harbors various commensal bacteria. IL-10, an anti-inflammatory cytokine, plays an important role in maintaining gut immune homeostasis. T regulatory cells (Tregs) are a major source of IL-10 and play a crucial role in preventing unwarranted gut inflammation (Fig. 1). Hence, defects in Tregs and IL-10 pathway present with autoimmune enteropathy, causing VEO-IBD.^{6,7} While gut inflammation is the predominant manifestation of some PIDs (e.g., IL-10 deficiency), IBD-like disease can be an important associated manifestation in other PIDs [e.g., chronic granulomatous disease (CGD)].

EVALUATION OF A CHILD WITH VEO-IBD

The aim of evaluating children with VEO-IBD is to identify those patients who will benefit from non-conventional therapies and to identify those at risk of non-GI complications. Evaluation includes a detailed history, including family history, physical examination,

Table 2: Monogenic causes of VEO-IBD

Genetic defects	Disease
<i>IL10</i> and <i>IL10RA</i> , <i>IL10RB</i>	IL-10 signaling defect causing VEO-IBD
<i>FOXP3</i>	IPEX
<i>IL2RA</i>	IPEX-like
<i>ADAM17</i>	ADAM17 deficiency
<i>IKBKG</i> (encoding NEMO)	X-linked ectodermal immunodeficiency
<i>CYBB</i> , <i>CYBA</i> , <i>NCF1</i> , <i>NCF2</i> , <i>NCF4</i>	CGD
<i>G6PC3</i>	Congenital neutropenia
<i>ITGB2</i>	LAD type I
<i>SLC37A4</i>	Glycogen storage disease type Ib
<i>XIAP</i>	XLP type II
<i>CTLA4</i> , <i>LRBA</i>	Polyautoimmunity and combined immune deficiency
<i>ICOS</i>	CVID
<i>BTK</i>	Agammaglobulinemia
<i>CD40</i> , <i>CD40L</i>	Hyper IgM syndrome
<i>ZAP70</i> , <i>IL2RG</i> , <i>ADA</i> , <i>RAG 1/2</i>	SCID
<i>WASP</i>	Wiskott–Aldrich syndrome
<i>STAT3</i>	Hyper IgE syndrome (autosomal dominant)
<i>MHCII</i>	Bare lymphocyte syndrome
<i>TTC7A</i>	Multiple intestinal atresia with combined immune deficiency

IL, interleukin; IPEX, X-linked immune dysregulation, polyendocrinopathy, and enteropathy; CGD, chronic granulomatous disease; LAD, leukocyte adhesion defect; XLP, X-linked lymphoproliferative syndrome; CVID, common variable immunodeficiency; SCID, severe combined immunodeficiency

endoscopic and histopathology evaluation, and genetic testing. A detailed history must include the age of onset, history of severe infections, skin involvement, and associated autoimmunity to arrive at a differential diagnosis. Family history contributes to the diagnosis if there is a history of IBD in family members and can also suggest autosomal recessive (AR), autosomal dominant (AD), or X-linked pattern (Table 3).

In the next section, we shall discuss a few cases and highlight how can one evaluate a child presenting with VEO-IBD.

Case 1

A 2-year-old boy born to a third-degree consanguineously married couple, presented with repeated episodes of bloody diarrhea from 6 months of age. He would strain while passing stools and had tenesmus. At 1 year of age, he developed a perianal abscess which was drained and treated with antibiotics. There was no history of pneumonia, recurrent ear, or skin infections. He had significant failure to thrive. He was evaluated by the pediatric gastroenterologist and upper and lower GI endoscopies were performed.

Upper GI endoscopy: Normal.

Lower GI endoscopy: Multiple ulcers were noted in the colonic mucosa.

Colonic biopsy: Cryptitis and crypt abscess suggestive of IBD.

ON FURTHER EVALUATION

- Complete blood counts (CBC) did not show any thrombocytopenia (Wiskott–Aldrich syndrome was unlikely).
- HIV card test: negative.
- Serum immunoglobulin was elevated.
- Nitroblue tetrazolium test (NBT) and dihydrorhodamine dye (DHR) tests: normal (CGD was excluded).

He was diagnosed to have IBD by the gastroenterologist but the early age of onset (6 months) warranted further evaluation. Genetic analysis (whole-exome sequencing) was performed by next-generation sequencing and a pathogenic mutation in the IL-10

Fig. 1: Role of Tregs and IL-10 in the pathogenesis of VEO-IBD. [Macrophages play an important role in gut inflammation. Their proinflammatory potential is kept under check by the release of anti-inflammatory cytokine (IL-10) by the Tregs. Failure of macrophages to respond to IL-10 gives rise to proinflammatory signals resulting in the development of colitis]

Table 3: Evaluation in a child with VEO-IBD

Presentation	Defect	Testing
Neonatal onset, perianal disease-fistulas, diarrhea	IL-10, IL-10R deficiency	Genetic test*
Male child, diarrhea, panenteric/perianal disease	XLP	Genetic testing for <i>XIAP</i> mutation
Male child, intractable diarrhea, eczematous/psoriasiform dermatitis, polyendocrinopathy	IPEX	Genetic test for <i>FOXP3</i> mutation
Chronic diarrhea, organomegaly, lymphadenopathy, autoimmunity	IPEX-like (LRBA deficiency)	Genetic test
Severe infections, neutrophilic leukocytosis, thrombocytosis, hypergammaglobulinemia, bloody diarrhea	CGD	NBT/DHR, genetic test
Male child, eczema, recurrent infections, thrombocytopenia with small platelets, bloody diarrhea	WAS	Genetic test
Recurrent infections/non-healing ulcers, chronic diarrhea, persistent neutrophilic leukocytosis	LAD	CD18/CD11 expression flow cytometry, genetic test

*Genetic test, exome sequencing study; IPEX, X-linked immune dysregulation, polyendocrinopathy and enteropathy; CGD, chronic granulomatous disease; WAS, Wiskott-Aldrich syndrome; LAD, leukocyte adhesion defect; NBT, Nitroblue tetrazolium test; DHR, Dihydrorhodamine dye, XLP, X-linked lymphoproliferative disease

Fig. 2: Perianal fistula—manifestation of VEO-IBD in a 9-month-old boy

receptor gene was identified and the child underwent a successful bone marrow transplant.

DIAGNOSIS: VEO-IBD DUE TO IL-10R DEFECT

Case 2

A 9-month-old boy presented with a history of repeated episodes of mucus-containing stools (10–12 episodes/day) since the age of 7 months. He would cry incessantly while passing stools. He was failing to thrive, though he had had no serious infections or hospitalizations. On examination, he was found to have perianal fistula and anal tag (Fig. 2).

On Evaluation

Complete blood counts: Hb-11 g/dL, TC-24,000/mm³, N-60%, L-32%, PC-1,023,000/mm³.

Serum immunoglobulins: hypergammaglobulinemia.

Nitroblue tetrazolium test/DHR: abnormal, suggestive of impaired oxidative burst.

Diagnosis: VEO-IBD in a child with chronic granulomatous disease.

TAKE HOME MESSAGE

- The onset of IBD below the age of 6 is called VEO-IBD and warrants detailed investigation.
- Very early-onset IBD is uncommon and accounts for 3% of PIBD.
- Very early-onset IBD is monogenic while adult-onset IBD is often polygenic.
- Very early-onset IBD must be investigated in detail including immunological and genetic evaluation.
- Hematopoietic stem cell transplantation is curable in certain forms of VEO-IBD, e.g., IL-10 and IL-10R defects.

REFERENCES

1. Stein RE, Baldassano RN. Inflammatory bowel disease. In: St Geme K, Blum S, Tusker W, et al. Nelson textbook of pediatrics. 21st ed., vol. 1, Philadelphia: Elsevier; 2020. p. 1986.
2. Šýkora J, Pomahačová R, Kreslová M, et al. Current global trends in the incidence of pediatric-onset inflammatory bowel disease. *World J Gastroenterol* 2018;24(25):2741. DOI: 10.3748/wjg.v24.i25.2741.
3. Shim JO. Recent advance in very early onset inflammatory bowel disease. *Pediatr Gastroenterol Hepatol Nutr* 2019;22(1):41–49. DOI: 10.5223/pghn.2019.22.1.41.
4. Benchimol EI, Fortinsky KJ, Gozdyra P, et al. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011;17(1):423–439. DOI: 10.1002/ibd.21349.
5. Doecke JD, Simms LA, Zhao ZZ, et al. Genetic susceptibility in IBD: overlap between ulcerative colitis and Crohn's disease. *Inflamm Bowel Dis* 2013;19(2):240–245. DOI: 10.1097/MIB.0b013e3182810041.
6. Paul G, Khare V, Gasche C. Inflamed gut mucosa: downstream of interleukin-10. *Eur J Clin Investigat* 2012;42(1):95–109. DOI: 10.1111/j.1365-2362.2011.02552.x.
7. Eastaff-Leung N, Mabarrack N, Barbour A, et al. Foxp3+ regulatory T cells, Th17 effector cells, and cytokine environment in inflammatory bowel disease. *J Clin Immunol* 2010;30(1):80–89. DOI: 10.1007/s10875-009-9345-1.