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

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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). 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).

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.

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

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

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VEE 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. 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:

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

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 |
Is Early-onset IBD: A PID?

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)].

**Pathogenesis of VEO-IBD**

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

**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 XIAP mutation               |
| Male child, intractable diarrhea, eczematous/psoriasiform dermatitis, polyendocrinopathy | IPEX                          | Genetic testing for FOXP3 mutation              |
| Chronic diarrhea, organomegaly, lymphadenopathy, autoimmunity                | IPEX-like (LRBA deficiency)   | Genetic test                                    |
| Severe infections, neutrophilic leukocytosis, thrombocytosis,                | CGD                           | NBT/DHR, genetic test                           |
| hypergammaglobulinemia, bloody diarrhea                                       |                               |                                                 |
| Male child, eczema, recurrent infections, thrombocytopenia with small platelets, bloody diarrhea | WAS                           | Genetic test                                    |
| Recurrent infections/non-healing ulcers, chronic diarrhea, persistent         | LAD                           | CD18/CD11 expression flow cytometry, genetic test |
| neutrophilic leukocytosis                                                    |                               |                                                 |

*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.

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.

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