Review Article

Very early-onset inflammatory bowel disease: a review of literature

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Abstract

Very early-onset inflammatory bowel disease: is a subtype of inflammatory bowel disease (IBD) and is defined by its onset in children younger than 6 years of age. The etiology includes the interplay of various factors such as genetic predisposition, environmental factors, gut microbiota and strong family history. The clinical presentation can present with both gastrointestinal symptoms such as bloody and/or mucus-containing diarrhea, recurrent vomiting, peri annal symptoms like fistulas, abscesses and perinatal skin tags and also present as extra-intestinal symptoms likeintermittent fevers, arthritis, folliculitis, uveitis etc.In this article we discuss about various treatment methods used in VEO-IBD including medical therapy, surgical therapy, hematopoietic stem cell transplantation and nutritional approach.

In this systematic review, we have tried to summarized the current knowledge about VEO IBD.

Key words : VEO- IBD, bloody diarrhea, hematopoietic stem cell transplantation, monogenic disorders

Introduction

Inflammatory bowel disease (IBD) is agroup of disorders that is associated with inflammation of the gastrointestinal tract due to dysregulated immune response to environmental trigger.

Usually, IBD presents as a bimodal presentation in the age group 15- 35 and 55- 70 years. [1]

IBD consists of 2 diseases ulcerative colitis which involves inflammation localized to the colon region and Crohn’s disease which involves the inflammation in any site ranging from the buccal cavity to the anus.[1]

Very early-onset inflammatory bowel disease (VEO-IBD) is defined as the presentation of IBD symptoms in children less than 6 years of age. It is a subtype of Inflammatory Bowel Disease (IBD). [15][20].

VEO-IBD makes up-to 3% -15% of IBD diagnosed in patients of pediatric age group. [2]although rare, there has been increase in incidence recently.

Etiology

VEO-IBD is phenotypically heterogenous disease due to which patients can present with a wide range of symptoms, ranging from mild disease to extensive involvement of the colon presenting more aggressive than older-onset IBD. The severity also depends on the interplay of aggressive phenotype, early onset of the disease and strong family history.

It is believed that VEO-IBD and primary immunodeficiency is closely linked due to the presence of interlinked genes that is responsible for the disease presentation. Hence considering VEO-IBD as a monogenic disease.

The VEO-IBD has shown an increase in number from 1.3 to 2.1 per 100,000 children from 1994 to 2009, which in turn resulted in the mean annual increase of 7.4%. This in turn indicates the presence of environmental factors that contribute to the disease formation.[4]

The onset of the VEO-IBD in the early ages, along with the gut microbiota development that takes place in the first 3 years seems to play a role in the disease development. Although this factor and role in development of the disease is understudied. [2]

Immunology

Genome wide association studies (GWAS) has suggested a strong association between major histocompatibility complex (MHC) haplotypes and IBD.

GWAS has further identified 163 genetic loci comprising of 300 candidate genes that is thought to beassociated with IBD and it stated that only a small portion was involved in the hereditary nature of IBD.However, VEO-IBD mostly presents with an underlying genetic condition, up-to 50 genetic variants have been found and are collectively termed as monogenic IBD.[10]

Additionally, the studies also suggests that the genes involved in VEO-IBD primarily has immunological function and barrier function of the gastrointestinal tract, and later presents as VEO-IBD due to disordered functioning of the immune system.[3] [4][10]

Additional underlying immunodeficiencies or genetic disorders have been identified in VEO-IBD patients as mentioned in the below table:

Table 1. Identification of genetic disorders

Epithelial barrier function defects:	Dystrophic Epidermolysis Bullosa, ADAM17 deficiency, Familial diarrhea
Phagocyte defects:	Chronic Granulomatous Disease, Glycogen Storage Disease 1b, Leukocyte Adhesion Defect, Congenital Neutropenia
Autoimmune disorders:	ALPS, Familial HLH, XIAP
Immune dysregulation:	IL10RA, IPEX (FOXP3)
T-cell/B-cell defects: IgE,	Common Variable Immunodeficiency , Hyper IgE, Hyper IgM syndrome, Wiskott-Aldrich syndrome, PI3CKD mutation

·ALPS: autoimmune lymphoproliferative syndrome; XIAP: X-linked inhibitor of apoptosis

·IPEX : Immune Dysfunction Polyendocrinopathy X linked

Pathology

Diagnostic features are similar to those in adults, including active inflammation (neutrophilic cryptitis and crypt abscesses) and chronic mucosal changes (crypt

branching, crypt dropout, increased lymphoplasmacytic mucosal inflammation causing crypt liftoff). [6]

Small bowel architectural changes may be more difficult to appreciate, but severe duodenal villous atrophy and cellular metaplasias (Paneth cell in left colon, pyloric in terminal ileum and colon) are reliable features of chronic inflammation. In rare cases, chronic mucosal alterations may be encountered with relatively mild inflammation.

Some histologic features are identified to be diagnostic and distinct for patients with VEO-IBD such as increased incidence of crypt apoptosis, severe mucosal architectural changes, mucosal eosinophils, and small bowel villous blunting as compared to older onset pediatric IBD. [6]

In patients with monogenic disorders causing VEO-IBD, making the diagnosis will be hard for the pathologist due to overlapping pathological findings.[10] [3] [4]

However, certain characteristic findings were present in the diagnostic endoscopic biopsies in primary immunodeficiency patients with VEO-IBD such as increased frequency of apoptosis, moderate to severe chronic architectural changes, small intestinal villous blunting often in the absence of inflammation, and eosinophils in the crypts, lamina propria, and surface epithelium seen on biopsies. [14]

Clinical features

VEO-IBD patients can present with both intestinal symptoms such as bloody and/or mucus-containing diarrhea, recurrent vomiting, perianal skin tags, fistulas as well as extra-intestinal manifestations such as intermittent fevers, arthritis, arthralgias, folliculitis and uveitis.

The above-mentioned symptoms that last for more than 2 weeks despite exclusive amino-acid based diet should raise suspicion of VEO-IBD.[2]

In infants less than 12 months, presenting with bloody stools, we should exclude cows milk protein intolerance, allergic colitis and infection should be considered initially before diagnosingVEO-IBD.[2]

Monogenic etiology of VEO-IBD is linked with primary immunodeficiency, hence should always be considered in VEO-IBD patient through a thorough immune workup.

Primary immune deficiencies should be strongly considered and evaluated in patients with ≥4 new ear infections per year; ≥2 severe sinus infections in a year; ≥2 months of antibiotic treatment with little effect; ≥2 pneumonias per year; insufficient weight gain or growth delay; recurrent deep skin or organ abscesses. [2]

Differential diagnosis

VEO IBD presents with symptoms similar to many other diseases including [2] [12] :

- Gastroenteritis - shigella, salmonella,yersinia , E.Coli
- Celiac disease
- Food allergies
- Cows milk protein intolerance
- Congenital intestinal transport defects such as specific carbohydrate malabsorption (eg, glucose-galactose malabsorption)
- Disorders of amino acid and peptide assimilation (eg, enterokinase synthesis deficiency)
- Disorders of fat assimilation (eg, abetalipoproteinemia)
- Disorders of mineral and electrolyte absorption and secretion (eg, congenital chloride diarrhea and congenital sodium diarrhea)

Investigations

It is vital to rule out the common differentials before diagnosing a patient with VEO-IBD. The investigation can be carried out by stool studies and lab tests. Although serologic markers such as auto-antibodies and antibodies against microbial antigens do help in IBD, it plays a limited role in diagnosing VEO-IBD.[8]

The order of investigations needed to be carried out are mentioned in the table below[2] -

	1st Tier Tests	2nd Tier Considerations
Bloodwork	CBC and differential Comprehensive Metabolic Panel (CMP) ESR CRP *Consider celiac screen and thyroid function tests depending on presentation*	Immunoglobulin classes (IgA, IgG, IgM, IgE) *Must use age-specific norms, especially in infants* Lymphocyte subsets by flow cytometry Antibody to vaccines—Vaccination *history must be obtained to evaluate this* Allergen testing for older children DHR testing TREC/TCR repertoire TB testing HIV serology
Stool studies	Occult blood *ShigellaSalmonellaYersiniaEnterohemorrhagic and Enteropathogenic E. coliCampylobacterC. difficile* (if >12 months) Calprotectin or quantitative lactoferrin	*Giardia Cryptococcus*

Treatment

Although some studies do include patients with VEO-IBD, there is no randomized control studies done specially on VEO-IBD patients for specific therapeutic management. Hence, all medication mentioned this article reflect the data collected from older children and adult-onset IBD. [12]

Furthermore, we also discuss other various therapeutic ways to manage VEO-IBD, including surgery, allogenic hematopoietic stem cell transportation (HSCT), nutrition and complementary medicine. [2] [9]

Medical therapy

Studies suggests that for VEO-IBD patients less than 1 year of age, is refractory tothe standard therapeutic treatment used in IBDwhich includes 5-ASA, Immunomodulators (Azathioprine, methotrexate), and anti-TNF antibodies.

Turner et al report shows VEO-IBD(ulcerative colitis) patients who received somemetronidazole, amoxicillin, doxycycline +/- vancomycin showed promising results. [2]

If there was an underlying monogenetic cause, identifying the genetic etiology will help in providing a much more focused and successful therapeuticintervention with minimal harmful side effects for the patient.

For example, abatacept—a CTLA4-IgG1 fusion drug—and hydroxychloroquine can be given to patients with CTLA4 and LRBA defect and deficiency respectively.

Studies also suggest the use of anakinra, an IL-1 receptor antagonist, we can use it in patients with IL-10 signaling defects, as they will be too ill to undergo transplant or some who cannot wait for too long for their matched donors.[2]

Blocking IL-1 has also been shown to be effective in patients with mevalonate kinase deficiency (MVK).

As we know more about the diseases, the modalities of interventions can also be altered for a focused and successful management.

Surgery therapy

The requirement of surgical intervention in a patient with VEO-IBD is inconclusive

Benchimol et al reported less need for surgical intervention among a Canadian cohort of VEO-IBD as compared with that of older-onset,and Al-Hussaini et al reported no significant difference in surgical interventions in a Saudi Arabian VEO-IBD cohort. [2]

In turn, Kammermeier et al reports an increased need for surgical intervention in infantile Crohn's-like disease.[2]

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is a curative technique for several monogenic causes of VEO-IBD, including Chronic granulomatous disease (CGD), IPEX syndrome, and IL-10 receptor signaling defects.

Certain other conditions we use HSCT include- life-threatening infection, failure of engraftment, graft versus host disease, and acute and long-term toxicity from medications used for conditioning, including infertility, and secondary malignancy.

However, certain things should be strictly followed and kept in mind for the procedure-

- Risks and benefits must be carefully weighed. For instance, VEO-IBD is life-threatening in patients with IL-10 signaling defects, and HSCT can be life-saving.

- However, VEO-IBD in CGD can be more disregarded, as the disadvantage outweigh the benefits in this case.

- The timing can also be important, such as in IPEX syndrome, where the treatment of the organ will provide survival rate after transplantation

Nutritional Approaches

For children with VEO- Crohns, the infants small intestine might be affected and they might be in exclusive enteral feed, in this case we can start induction therapy, which can done orally or through a nasogastric tube.[2]

However no such reports are there for ulcerative colitis.

Health Maintenance

Health maintenance aims at optimizing the childrens' health throughout their developmental age to prevent any predisposition to VEO-IBD. Even optimizing health while being diagnosed with VEO-IBD, as starting early provides a better quality of life.

Certain ways to achieve this is by-

- Regular optimal vitamin D and calcium intake along with regular weight-bearing exercise can be crucial for bone health in IBD, especially in patients with poor nutrition and frequent steroid use.

- Children with VEO-IBD using immunomodulators or biological are at a slightly higher risk of acquiringskin cancer. Hence it is advised to use sunblock with at least SPF 50 especially in infants less than 6 months of age. [2]
- The children should also be assessed annually by an ophthalmologist for possible ocular manifestations of VEO-IBD, such as uveitis and episcleritis, and possible cataract formation that can occur from regular steroid use.[2]

- It is also vital that these children stay up-to-date with their vaccinations. [2]

Prognosis

However, a study states that the prognosis of VEO-IBD patients is worser than pediatric IBD patients. As they follow a much more severe disease course with poorer response to steroids and requires surgical intervention much more than in pediatric-IBD. [13]

Due to the rarity of the disease there are few studies and randomized control trials done on VEO-IBD. However the current advancing technologiesare giving us hope to a promising identification system such as early genetic diagnosis and successful therapeutic techniques involving cytokines and genes, microRNA, microbial signature etc. can give us an insight on early detection and early care using multidisciplinary approach, hence giving us a child with better prognosis and a better quality of life with minimal impairment.[9]

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