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Review Article

Very Early-Onset Inflammatory Bowel Disease: A Challenging Field for Pediatric Gastroenterologists

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ABSTRACT

With the increasing number of children with inflammatory bowel disease (IBD), very early-onset IBD (VEO-IBD), defined as IBD that is diagnosed or that develops before 6 years of age, has become a field of innovation among pediatric gastroenterologists. Advances in genetic testing have enabled the diagnosis of IBD caused by gene mutations, also known as monogenic or Mendelian disorder-associated IBD (MD-IBD), with approximately 60 causative genes reported to date. The diagnosis of VEO-IBD requires endoscopic and histological evaluations. However, satisfactory small bowel imaging studies may not be feasible in this small population. Both genetic and immunological approaches are necessary for the diagnosis of MD-IBD, which can differ among countries according to the available resources. As a result of the use of targeted gene panels covered by the national health insurance and the nationwide research project investigating inborn errors of immunity, an efficient approach for the diagnosis of MD-IBD has been developed in Japan. Proper management of VEO-IBD by pediatric gastroenterologists constitutes a challenge. Some MD-IBDs can be curable by allogenic hematopoietic stem cell transplantation. With an understanding of the affected gene functions, targeted therapies are being developed. Social and psychological support systems for both children and their families should also be provided to improve their quality of life. Multidisciplinary team care would contribute to early diagnosis, proper therapeutic interventions, and improved quality of life in patients and their families.

Keywords: Very early-onset inflammatory bowel disease; Mendelian disorder-associated inflammatory bowel disease; Inborn errors of immunity; Treatment; Targeted gene panel

INTRODUCTION

Owing to the atypical phenotypes and clinical course, and the increasing number of children with inflammatory bowel disease (IBD) [1-8], patients who had an onset of IBD during infancy or young childhood were regarded as a unique group.

Patients with IBD can be categorized by age at diagnosis. In the Montreal classification, cases diagnosed before 17 years of age were distinguished as pediatric-onset IBD, A1 [9]. In the Paris classification, the pediatric classification created by the Porto group of the

European Society for Paediatric Gastroenterology Hepatology and Nutrition [10], A1 is further divided into A1a (diagnosed before 10 years of age) and A1b (diagnosed between 10 and 17 years of age). Among A1a cases, those diagnosed before 6 years of age are classified as very early-onset IBD (VEO-IBD) [11]. Furthermore, IBD cases with an onset by 2 years and 28 days of age were classified as infantile- and neonatal-onset IBDs, respectively [11]. Some studies define VEO-IBD as IBD with an onset before 6 years of age, probably because the duration between the onset and diagnosis of IBD varies depending on the level of suspicion and availability of medical resources.

Given their phenotypic heterogeneity and various responses to the conventional IBD treatments, differentiating VEO-IBD as Crohn's disease (CD) or ulcerative colitis (UC) posed a challenge for pediatric gastroenterologists. IBD, in general, is regarded as a polygenic disease, and a genome-wide association study revealed >230 known disease-associated genes [12]. However, some children with VEO-IBD are known to also have diseases with monogenic etiologies. Recent advances in genetic evaluation have enabled the identification of gene mutations that are responsible for some forms of IBD. Monogenic or Mendelian disorder-associated IBD (MD-IBD) is a term used to represent IBD caused by genetic mutations [11,13]. After the first report of IBD caused by the mutations of IL10RA and IL10RB by Glockers et al. [14] in 2009, approximately 60 monogenic IBDs have been reported to date [15,16]. Evaluating and managing children with VEO-IBD are a challenging field for pediatric gastroenterologists worldwide.

EPIDEMIOLOGY

The published epidemiological data for pediatric-onset IBD are mostly from Western countries [1,6,17], and detailed epidemiological data from Asia are still sparse [3,4,7]. Approximately 25% of IBD cases occur during childhood or adolescence [18], and VEO-IBD accounts for 20% of pediatric patients with IBD [7,19]. Although some studies have reported an unchanged VEO-IBD prevalence among pediatric patients over time, a Canadian study that used population-based health administrative data reported patients with VEO-IBD as the group with the most marked increase in prevalence [1,3,20].

PHENOTYPIC CLASSIFICATION OF VEO-IBD

Not many children with VEO-IBD present with the typical endoscopic and histological features of UC or CD. Approximately 30% of VEO-IBD cases are classified as IBD-unclassified (IBD-U). Some studies have used the term ‘UC-like’ or ‘CD-like’ to avoid labeling VEO-IBD as definite UC or CD. In a clinical report on the use of infliximab for VEO-IBD, on the basis of endoscopic findings and disease distributions, Takeuchi et al. [21] classified VEO-IBD as either the UC type (UCT: continuous colonic inflammatory lesion without definite upper gastrointestinal, small bowel, nor perianal involvement) or the non-UC type (NUCT: intestinal inflammatory lesion not consistent with UCT). According to the presence of a perianal lesion, NUCT was further divided into the NUCT with perianal disease (NUC-PD) and NUCT without perianal disease (NUC-NPD) [21]. These classifications have not been validated; however, a well-designed phenotypic classification would be useful to differentiate the diagnoses and choose the proper treatment.

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MONOGENIC OR MENDELIAN DISORDER-ASSOCIATED IBD

Monogenic or MD-IBD has been a field of innovation in VEO-IBD. To date, approximately 60 causative genes for MD-IBD have been identified, generally classified as follows: 1) epithelial barrier function defects; 2) immune dysregulation; 3) T-cell, B-cell, and complex function defects; 4) phagocyte and NADPH oxidase complex defects; 5) hyperinflammatory and autoinflammatory defects; and 6) others. The representative disorders and genes are summarized in **Table 1** [15,16,22-24].

DIAGNOSTIC APPROACH FOR VEO-IBD

After Uhlig et al. [11] introduced the first comprehensive approach for differentiating MD-IBD from VEO-IBD, several reviews and position papers have been published [15,16,25]. Although the diagnostic algorithms are practical and useful in some areas or countries, owing to the different levels of available resources, not all countries or hospitals could apply

Table 1. Mendelian disorder-associated IBDs and responsible genes

Defects	Syndrome/disorder	Gene
Epithelial barrier function defects	TTC7A deficiency	*TTC7A*
	NEMO deficiency	*IKBKG*
	ADAM17 deficiency	*ADAM17*
	Familial diarrhea	*GUCY2C*
	Kindler syndrome	*FERMT1*
	Congenital diarrhea	*SLC9A3*
	Ditrophic epidermolysis bullosa	*COL7A1*
Immune dysregulation	IPEX	*FOXP3*
	IPEX-like	*IL2RA*, *STAT1*, *MALT1*
	IL-10 signaling defects	*IL10RA*, *IL10RB*, *IL10*
	NOD2 signaling defects	*TRIM22*
T-cell, B-cell, and complex function defects	LRBA deficiency	*LRBA*
	CTLA4 deficiency	*CTLA4*
	IL-21 deficiency	*IL-21*
	Wiskott-Aldrich syndrome	*WAS*
	Bruton's agammaglobulinemia	*BTK*
	Hoyeraal-Hreidarsson syndrome	*DKC1*, *RTEL1*
	Loyes-Dietz syndrome	*TGFBR1*, *TGFBR2*
	PI3K activation syndrome	*PIK3R1*, *PIK3CD*
	SCID	*ZAP70*, *IL2RG*, *ADA*, *CD3-γ*, *LIG4*, *RAG2*
	Omenn syndrome	*DCLREIX*, *DCLRIC*
	ICOS deficiency	*ICOS*
	Caspase-8 deficiency	*CASP8*
Phagocyte and NADPH oxidase complex defects	Chronic granulomatous disease	*CYBB*, *CYAA*, *NCF1*, *NCF2*, *NCF4*, *LACC1*
	Congenital neutropenia	*G6PC3*
	Glycogen storage disease 1b	*SLC37A4*
	Leukocyte adhesion deficiency 1	*ITGB2*
Hyperinflammatory and autoinflammatory defects	X-linked lymphoproliferative syndrome 2	*XIAP*
	Hermansky-Pudlak syndrome	*HPS1*, *HPS4*, *HPS6*
	Familial Mediterranean fever	*MEFV*
	A20 haploinsufficiency	*TNFAIP3*
	Mevalonate kinase deficiency	*MVK*
	Phospholipase Cγ2 defects	*PLCG2*
	Familial hemophagocytic lymphohistiocytosis type 5	*STXBP2*
	Chronic enteropathy associated with SLCO2A1 (CEAS)	*SLCO2AI*
Others	MASP deficiency	*MASP2*
	Trichohepatoenteric syndrome	*SKIV2L*, *TTC37*
	CHAPLE syndrome	*CD55*

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them. The diagnostic algorithm should be modified by each country according to their own clinical and research resources.

Esophagogastroduodenoscopy and total colonoscopy with ileal intubation should be performed in all children suspected as having IBD, and appropriate mucosal biopsy should not be omitted [26]. Feasible small bowel imaging studies should also be pursued to understand the disease location and behavior in all patients with VEO-IBD [27]. Exclusion of enteric infection, eosinophilic gastrointestinal disorders, and non-inflammatory causes of diarrhea are mandatory for the diagnosis. Celiac disease is rare in East Asia, but it is an important differential diagnosis in many parts of the world.

In Japan, as of 2018, the targeted panel sequence for 20 MD-IBD genes (IBD panel) was approved to be tested under the Japanese national healthcare insurance. This IBD panel is practically a part of the inborn errors of immunity (IEI) panel, which covers up to 400 genes responsible for monogenic primary immune deficiencies (PIDs) and autoinflammatory diseases. For patients in which the IBD panel fails to detect the responsible genes but IEI is still suspected, 400 genes related to IEI can be evaluated as part of the national research project. If both IBD and IEI panels fail to reveal the responsible genes or variants, the current algorithm for VEO-IBD or suspected MD-BD cases in Japan recommends performing whole-exome sequencing or whole-genome sequencing. Functional testing for novel candidate genes or variants is another challenge for evaluating physicians and researchers.

ENDOSCOPIC AND HISTOLOGICAL FINDINGS

Confirmation of chronic intestinal inflammation is of utmost importance for the diagnosis of IBD, and endoscopic and histological evaluations should be performed in the first step. Endoscopies have been performed widely, even in infants. They are informative and has a satisfactory safety profile [28]. Some unique endoscopic findings have been reported for some monogenic IBDs, such as the leopard sign in chronic granulomatous disease (CGD) [29]. Regarding the histological findings of VEO-IBD, compared with older age at onset of IBD, apoptosis, severe chronic architectural changes, small intestinal villous blunting, and eosinophilic infiltration were more frequently found [30]. Accumulation of characteristic endoscopic and histological findings for each MD-IBD cases would lead to a prompt diagnosis of the disorder.

For small bowel imaging, although magnetic resonance enterography (MRE) or wireless capsule endoscopy (WCE) was recommended in the revised Porto criteria, their problem with feasibility in small children led to the use of small bowel ultrasonography as the first-line tool for investigating VEO-IBD [26,27]. MRE is challenging to perform for most patients with VEO-IBD. They usually require conscious sedation or general anesthesia for a prolonged period, and the use of polyethylene glycol or other fluids to achieve better imaging of the small bowel would expose young children to the risk of aspiration. WCE is also challenging for patients with VEO-IBD because they are unable to swallow capsules, and the relatively narrow diameter of the intestinal tract and bowel inflammation exposes them to the risk of capsule retention. In this context, the development of the dissolvable capsule and endoscope delivery device has constituted a major innovation. Confirmation of patency using a dissolvable capsule and placement of the capsule in the stomach or duodenum using an endoscope delivery device has made small bowel evaluation by

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capsule endoscopy a part of the integrated assessment of patients with VEO-IBD in the Japanese pediatric IBD community [31]. Children as light as 7.9 kg have undergone WCE [32]. Balloon-assisted enteroscopy (BAE) is another device used to evaluate the small bowel condition of patients with VEO-IBD. The number of children who have undergone this procedure is still limited; however, a prospective study from a Japanese group revealed its feasibility in children, including those with VEO-IBD [33,34]. Retrograde BAE was performed in children weighing as low as 10.9 kg and as young as 1.6 years old.

The role of ultrasonography in the evaluation of small intestinal lesions has become more critical owing to the availability, safety, and reasonable reliability of the procedure to detect inflammatory lesions, especially if performed by experts. Contrast-enhanced computed tomography is an alternative modality; however, the role of barium studies for small bowel follow-through is becoming less prominent owing to the risk of high radiation exposure and limited obtainable information [27].

Fig. 1 shows the algorithm proposed by the Japanese VEO-IBD research group. Proper use of the IBD panel and selection of cases that require further investigation is key, and the accumulation of both clinical and genetic information is crucial to identify novel candidate genes or variants. The Rare Disease Data Registry of Japan is a national project in which both clinical and genetic information are registered in the same platform. Accumulation of similar phenotypic cases together with genetic information could facilitate the detection of novel candidate genes or variants.

Collaboration among pediatric gastroenterologists, immunologists, geneticists, and bioinformaticians is key for the prompt diagnosis of MD-IBD or detection of candidate genes.

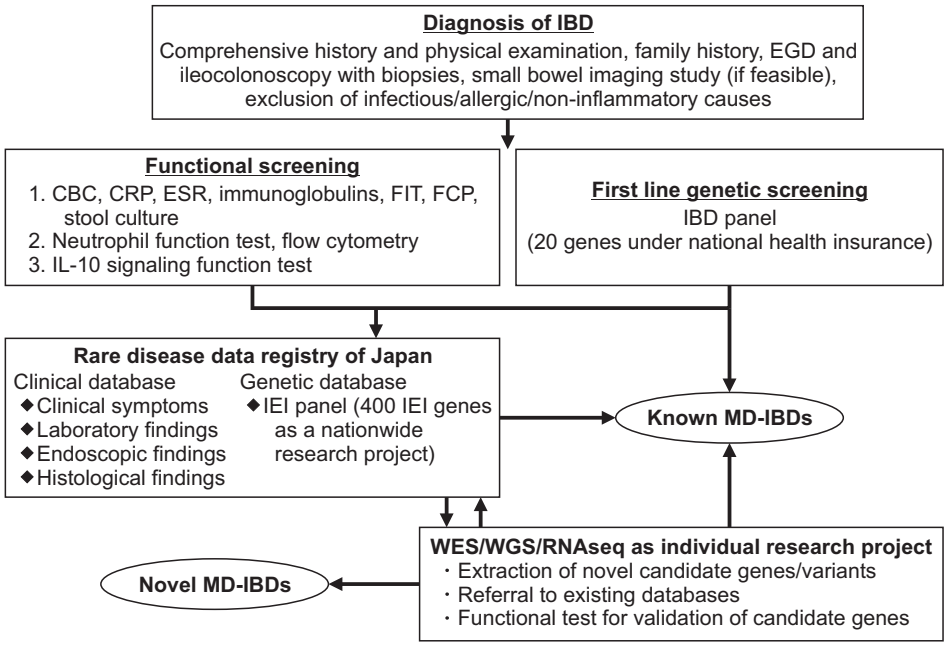

Fig. 1. A diagnostic approach for probable Mendelian disorder-associated IBD in Japan.
IBD: inflammatory bowel disease, EGD: esophagogastroduodenoscopy, CBC: complete blood counts, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, FIT: fecal immunochemical test, FCP: fecal calprotectin, IEI: inborn errors of immunity, MD-IBD: Mendelian disorder-associated IBD, WES: whole exome sequencing, WGS: whole genome sequencing, RNAseq: ribonucleic acid sequencing.

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TREATMENT

After the exclusion of PID, which could expose children to the risk of life-threatening infection, most children with VEO-IBD are treated as if they have UC or CD [35-37]. However, the lack of well-designed clinical trials and limited clinical experience make the treatment of VEO-IBD challenging.

Exclusive enteral nutrition

Exclusive enteral nutrition (EEN) is a safe and effective induction therapy for pediatric IBD [35]. Younger children, especially infants, may adapt to EEN because their desire to eat meals may not be as strong as that of older children. However, prolonged EEN could interfere with the proper development of chewing and swallowing, and could lead to an increased risk of developing eating disorders. In this particular age group, the amino acid-based elemental formula is generally used as the first-line treatment for VEO-IBD [16]. It is safe, and physicians could retain the time to differentiate PID, which could expose the child to the risk of severe infection from the use of immunosuppressive medications. Administration of live attenuated vaccines during exclusive enteral nutrition is also beneficial to minimize the future risk of serious infection with varicella or measles. Some elemental formulas are deficient of certain nutrients such as fat or selenium; thus, proper supplementation of such nutrients should always be considered by managing physicians and dieticians.

Thiopurines

Owing to the increased knowledge on the risk of hemophagocytic lymphohistiocytosis (HLH) and malignancies, the use of immunomodulators, especially thiopurines, for patients with IBD has become controversial [38]. To reach a therapeutic range, relatively increased doses of thiopurines are required for patients with VEO-IBD [39]. In East Asia, the risk of certain NUDT-15 variants as the cause of acute severe leukocytopenia and alopecia has been recently reported [40,41]. Currently, the polymorphism of the NUDT-15 genes is examined under the national health insurance to prevent severe adverse events, and the test is recommended before starting thiopurine therapy in Japan. Given the unproven effectiveness and risk of biologicals for this vulnerable population, the usefulness and risk of this orally administrated drug should further be investigated.

Infliximab

Real-world data on the use of infliximab for VEO-IBD have been reported through retrospective case series [21,42,43]. In such studies, the discontinuation rate of infliximab therapy appeared higher in patients with VEO-IBD than in those with IBD onset at an older age. A Japanese group that used infliximab in 17 patients with VEO-IBD reported it to be less effective for UCT with a relatively high rate of infusion reaction. Conversely, patients with NUCT with or without perianal disease tolerated infliximab therapy with prolonged effectiveness [21].

Only few reports have described the use of adalimumab, golimumab, ustekinumab, and vedolizumab therapies in this age group, and experience in the use of these less antigenic biologics should be accumulated.

Hematopoietic stem cell transplantation

Some MD-IBDs have been reported to be curable by allogeneic hematopoietic stem cell transplantation (allo-HSCT). IL-10 receptor signaling defects; immunodysregulation,

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polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome; and severe forms of CGD and X-linked inhibitor of apoptosis (XIAP) deficiency are well-known MD-IBDs that benefit from allo-HSCT. However, allo-HSCT carries significant risks such as life-threatening infection, graft-versus-host disease, and toxicity from the medications used for conditioning. Therefore, the risks and benefits of allo-HSCT over the conventional treatments for IBD and patients' immunological conditions should always be carefully discussed among patients, caregivers, and medical teams. Allo-HSCT for PID requires expertise for conditioning and posttransplantation management. The superiority of a reduced-intensity conditioning regimen for PID has been reported [44-46]. For XIAP deficiency, HLH is a common posttransplant complication that could negatively affect prognosis, and early control of HLH using dexamethasone palmitate and etoposide could improve the outcome [44].

Targeted therapies

Identification of genes associated with IBD leads to an understanding of its pathogenesis, which could in turn lead to more targeted interventions. Infliximab is contraindicated for the treatment of refractory CGD associated with enterocolitis, as it led to a lethal outcome in 2 of 5 patients [47]. Instead, thalidomide or anti-IL-1 therapy such as anakinra or canakinumab has been successfully used [48-50]. Anti-IL-1 therapy has also been effective in the context of IL-10 signaling defects and mevalonate kinase deficiency, and it can be used as a bridge to allo-HSCT for sick children with IL-10 signaling defects [51,52]. For CTLA4 and LRBA deficiencies, abatacept, a CTLA4 agonist, has been used successfully [53].

With the known risk of allo-HSCT, further investigation and collaborative efforts should be undertaken to search for and develop more targeted therapies for MD-IBDs.

Immunizations

Providing age-appropriate vaccinations should be the foremost consideration of pediatricians for this vulnerable population. Live attenuated vaccines such as those for measles, rubella, varicella, mumps, and BCG should be administered before the start of immunosuppressive medication in non-immunocompromised children. Inactivated vaccines have better safety profiles. The child's immunization schedule should always be determined in a way that ensures appropriate protection from infectious diseases [54].

For children receiving prolonged immunosuppressive treatments for their underlying disorders, evaluation of the efficacy and safety of live attenuated vaccines has been reported with encouraging results [55]. Safety issues concerning live attenuated vaccines for patients receiving biologics should also be investigated.

Surgery

Some studies have reported higher surgical rates in children with VEO-IBD, especially those with infantile IBD [56,57]. However, the Canadian cohort of patients with VEO-IBD showed a low frequency of surgical interventions in the younger group than in the older pediatric group [2]. Recent innovations in medical treatment may have decreased the need for surgery; however, the risk and benefit of surgical interventions such as ileostomy placement for patients with refractory colitis or perianal disease should always be considered.

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SUPPORT FOR PATIENTS AND FAMILY

The diagnosis and treatment of VEO-IBD are an innovative field; thus, more efficient diagnostic algorithms and therapeutic options will likely be proposed in the future. Meanwhile, support for children with IBD and their families is still under consideration. Proper genetic counseling for the parents of children with MD-IBD is mandatory. Furthermore, psychological and emotional family supports, especially for those requiring prolonged hospitalization or home-care devices such as home parenteral nutrition, should not be ignored. A multidisciplinary team approach, including nurses, dieticians, clinical psychologists, child-life specialists, and medical social workers, would be beneficial for an integrated care pathway.

SOCIAL CHALLENGE

Various medications have been approved for use in adults with UC or CD. Although most patients with VEO-IBD receive some of these medications to control disease activity, most of the medications have not been approved for use in children, especially those with VEO-IBD. Furthermore, owing to the small number of patients, developing medicines for certain MD-IBDs is challenging.

Nevertheless, this vulnerable group of children requires prompt diagnosis and management for the improvement of their future well-being and quality of life. Establishment of diagnostic criteria for each monogenic IBD and their respective treatment guidelines as a global effort may improve the quality of care provided for patients with VEO-IBD.

CONCLUSION

The advances in the field of VEO-IBD have given rise to a new era of increased understanding of the pathophysiology of the disease and emergence of targeted treatments. Prompt diagnosis with a well-designed diagnostic algorithm and development of proper treatments for individual patients' conditions will remain a challenge for the next decade. A study in a different ethnic group with various genetic backgrounds and collaborative efforts beyond the national level would facilitate efforts to overcome these challenges.

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