



Current issues of pediatric inflammatory bowel disease in Korea

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Inflammatory bowel disease (IBD) is a chronic relapsing disorder of unknown etiology, which is believed to be multifactorial. Recently, the incidence of pediatric IBD has steeply increased in Korea since 2000. Poorly controlled disease activity can result in complications such as intestinal fistulae, abscess, and stricture, as well as growth retardation and delayed puberty in children. Because of a lack of confirmative tests, various diagnostic modalities must be used to diagnose IBD. Onset age, location, behavior, and activity are important in selecting treatments. Monogenic IBD must be excluded among infantile and refractory very-early-onset IBD. Early aggressive therapy using biologics has recently been proposed for peripubertal children to prevent growth failure and malnutrition.

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Introduction

Pediatric inflammatory bowel disease (IBD) was previously rare in Korea¹; therefore, most general pediatricians in Korea may have encountered a few cases of pediatric IBD during their training program. However, the incidence of IBD has risen in adults since 1990² and in children in the 2000s^{3,4}, and its incidence continues to increase without having reached a peak. The incidence of IBD has been rapidly increasing in the last 5 years. General pediatricians are expected to encounter children with IBD more frequently in the near future. To improve the understanding of pediatric IBD among Korean pediatricians, we have written this review focusing on the issues that may pertain to clinical practice in Korea.

What is IBD?

IBD is a chronic relapsing disorder of unknown etiology that encompasses the two distinct disorders of Crohn disease (CD) and ulcerative colitis (UC). In CD, inflammation can occur anywhere in the gastrointestinal tract. CD, although rarely fatal, is refractory and causes abdominal pain, diarrhea, anorexia, and weight loss (Table 1)³⁻⁵. The clinical presentations of Korean children with CD were similar that observed in Western countries⁶⁻⁸. In our study, weight loss, growth retardation, lower bone mineral density, and nutritional deficiencies were also observed⁹ (Table 2). Importantly, growth failure is one of the most important aspects in pediatric CD¹⁰. Unlike in the adult population, disease onset in children is uniquely associated with growth retardation and delayed puberty. Poor control of disease activity can result in serious complications such as intestinal fistulae,

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Table 1. Clinical presentations of Korean children with inflammatory bowel disease

Variable	CD (n=123) ³⁻⁵⁾	UC (n=54) ^{5,13)}
Male female ratio	2.1:1	1:1
Abdominal pain	95 (77)	44 (81)
Diarrhea	76 (62)	40 (74)
Hematochezia	36 (29)	50 (93)
Weight loss	68 (55)	22 (41)
Growth failure	17 (14)	1 (2)
Perianal symptoms	67 (54)	0 (0)
Extraintestinal symptoms	28 (23)	9 (17)

Values are presented as number (%).
CD, Crohn's disease; UC, ulcerative colitis.

Table 2. Distribution of the z scores of various growth parameters at diagnosis in Korean children with Crohn disease⁹⁾

Anthropometrical data	z score < -1 SD	z score < -2 SD
Height-for-age	16 (23)	3 (4)
Weight-for-height	39 (55)	20 (28)
Body mass index	35 (49)	19 (27)

Values are presented as number (%).
SD, standard deviation; BMI, body mass index.

abscess, and stricture, requiring surgery in both children and adults. The incidence of complications of IBD reported in adult Koreans is lower than that in the West; however, the rate of resection 10 years after the initial diagnosis has recently risen to 32.8%¹¹⁾. In our report, 30.0% of children with IBD required surgeries 10 years after the initial diagnosis¹²⁾. There is currently no medical cure, and the disease is considered a rare, intractable condition that persists throughout a patient's lifetime. Most children with UC in Korea present with hematochezia and diarrhea at the time of diagnosis^{5,13)}, in line with the observations in Western studies⁶⁻⁸⁾. Based on the nature of chronic relapsing IBD, early-onset IBD can greatly lower the quality of life, including an inability to work and social maladjustment, in children with IBD. Therefore, better awareness and effective measures for treating pediatric IBD are needed at a societal level.

How does IBD develop?

Understanding of the pathogenesis of IBD is essential for identifying several key points at which intestinal inflammation can be modulated and expanding our treatment options for IBD. The pathogenesis of the disease involves the complex interactions between genetic factors¹⁴⁾, environmental factors^{15,16)} such as commensal intestinal bacteria, and immunological factors¹⁷⁾. The discordance of IBD among monozygotic twins¹⁸⁾ and the increased incidence of IBD among immigrants to high-

prevalence countries indicate an important role of environmental factors in the development of IBD. These factors may cause disruptions in the intestinal microbiota (dysbiosis) and modify the relationships between the human intestinal microbiota and mucosal immune system. The enormous success of tumor necrotic factor- α blockade in IBD treatment, which opened a new era of investigation for the pathogenesis of IBD, suggests that IBD is an autoinflammatory disease of the intestine.

In addition, more than 100 genetic loci, of which variants may alter normal mucosal immunity in the gastrointestinal tract, were uncovered by genome-wide association studies (GWASs) in Western populations¹⁹⁻²¹⁾. Recently, a Korean GWAS also identified an extensive overlap of genetic risks with those of Western populations²²⁾. GWASs of pediatric IBD are rare, and only two pediatric GWASs have been conducted, with the studies noting several new loci^{23,24)}. However, those loci were replicated in large-scale GWAS meta-analyses in adult populations²¹⁾. Interestingly, despite an extensive overlap of genetic risk with Western populations, nucleotide-binding oligomerization domain (*NOD2/CARD15*) and autophagy-related 16-like 1 (*ATG16L1*) have not been associated with IBD in the Korean population, indicating ethnic heterogeneity²²⁾. In addition, we uncovered three new susceptibility loci (*ATG16L2*, *DUSP5*, and *TBC1D1*) in a GWAS of Korean adults and children with IBD. Our other study on pediatric genetics did not find any association with *NOD2* mutation²⁵⁾. Variations of *TNFSF15*, which was demonstrated to have a weak association with IBD in Western populations, was found to greatly contribute to IBD susceptibility in both adults and children in Korea²⁶⁾. This further supports the existence of ethnic differences in the genetics of IBD between populations.

Is the incidence of IBD increasing in Korean adults and children?

The global incidence of pediatric CD is not known²⁷⁾. The annual incidence of pediatric CD in Europe and North America is 0.2–8.5 cases per 100,000 people, and that of UC is 0.5–4.3 cases per 100,000 people. Approximately 25%–30% of all cases of CD and 20% of all cases of UC occur in subjects less than 18 years old²⁸⁾. Approximately two decades ago, IBD was considered a rare disease among Korean adults. However, the incidence of IBD started to rise rapidly after the 1990s. A study examining the frequency of IBD in Korean adults illustrated that the prevalence of IBD was 0.05 cases per 100,000 adults in the Gangdong and Songpa districts of Seoul before 1990²⁾, whereas it increased to 1.34 cases per 100,000 adults after 2000. This steep upward trend in the Korean population is reported to be ongoing. This population-based study did not include a national sample; however, it clearly revealed that the incidence of IBD is on the

rise in Korean adults. The onset of IBD is reported to be extremely rare in Korean children¹; however, recent single-center studies confirmed that the number of pediatric patients newly diagnosed with CD has increased since 2000^{3,4}. A population-based study in children is essential to accurately determine whether the incidence of IBD is rising continuously in Korea.

Does the clinical manifestation of IBD in Korean patients differ from that in the West?

In our study, most patients with CD (74%) presented with both small bowel and colonic involvement, whereas isolated ileal (13%) and colonic (13%) disease was rare³, as also reported in the Western study of Sawczenko and Sandhu⁷, which found that most patients (84%) had both ileal and colonic involvement and that the dual presentation was more common than observed in a previous report²⁹. These authors considered that isolated colonic disease was more common in the younger children of our study, as noted in a Western report³⁰.

Regarding the location of disease in Korean adults with CD, 66.7%–75.7% of patients had CD in both the small intestine and colon, 10.8%–25.9% exhibited disease in the small intestine, and 7.4%–13.5% displayed disease in the colon, in line with the findings in the pediatric population². The relatively higher rate of CD in the small intestine and colon as well as the markedly low rate of colonic CD indicates that ethnical differences exist in terms of disease location in adult patients with CD. Moreover, the rate of anal fistula was higher in Korean adults than in Western populations. A study on Korean adults reported that anal fistula was the initial symptom in 15.8% of patients, and the accumulative incidence of anal fistula over 10 years was 49.7%, which is markedly higher than the rates of 13%–38% reported in the West^{11,31}. Our study³ also found a higher incidence (50%) of perianal fistula than noted in Western children, including rates of 8% in the work of Kugathasan et al.⁶ and 15% in the study by Palder et al.³².

Infantile and very-early-onset IBD

According to the Paris classification for pediatric IBD, IBD in subjects less than 10 years old is classified as very-early-onset (VEO) IBD³³. VEO IBD often involves isolated colitis³⁴. The prevalence of anti-*Saccharomyces cerevisiae* antibody (ASCA) and anti-CBir1 increases and decreases, respectively, until the age of 10 years³³. As VEO IBD has more severe phenotypes and a greater family history, the disease has been postulated to have highly penetrant mutations of Mendelian-like disease. A case of infantile IBD with an IL10R mutation was the first case of a

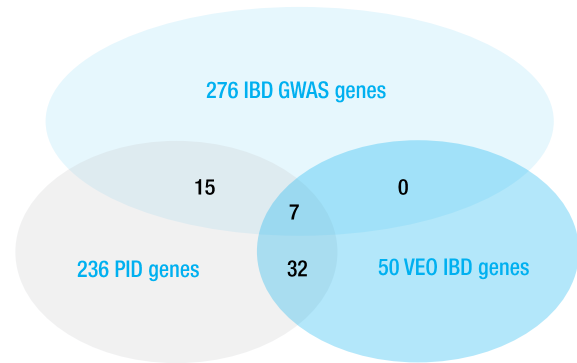


Fig. 1. Overlap among the genes of primary immunodeficiency (PID), very-early-onset (VEO) intestinal bowel disease (IBD)^{19,20,24,38,39}, IBD GWAS, inflammatory bowel disease genome-wide association study.

Mendelian form of monogenic IBD³⁵. A recent Korean study also illustrated that as many as 50% of subjects with infantile IBD carried IL10RA mutations³⁶.

Recently, two reviewers identified approximately 50 genes associated with monogenic IBD^{37,38}. Interestingly, three-fourths of these genes are known to be associated with primary immunodeficiency³⁹, for which treatments have not been established with the exceptions of hematopoietic stem cell transplantation and repeated immunoglobulin infusion (Fig. 1). In addition, the diagnosis of these heterogeneous diseases is also challenging because of the limits of conventional evaluations for immunodeficiency in clinical practice. Therefore, whole-exome sequencing (WES) is recommended to diagnose monogenic IBD to avoid a “diagnostic odyssey”^{37,38}. A case of infantile IBD featuring an XIAP mutation was the first example of the application of WES for diagnosing monogenic IBD⁴⁰. However, interpreting variants of unknown significance in WES remains challenging.

Diagnosis and classification of IBD

No single unique test or surrogate markers that can diagnose IBD alone exist; therefore, the diagnosis of IBD can be made according to the portfolio for suspected patients through history taking, physical examination, and laboratory, radiologic, endoscopic, and histologic criteria^{41,42}. Detailed diagnostic guidelines were devised for adult Korean patients with IBD^{43,44}. Those for pediatric Korean patients have not been created, although they should become available in the near future. First, history taking, physical examination, and laboratory tests for anemia and inflammatory markers should be performed. Then, infectious enteritis or colitis should be excluded. In addition, Korea is an endemic area of tuberculosis; therefore, tuberculosis should be excluded cautiously in children with IBD.

All patients should undergo a full colonoscopy with ileal

intubation and mucosal biopsy for histology and culture. We perform esophagogastroduodenoscopy at the time of diagnosis, in addition to radiographic methods such as small bowel series, barium enema, abdominal computed tomography (CT), ultrasonography, and magnetic resonance enterography (MRE) to determine the lesion location and behavior. In the pediatric population, MRE is preferred to CT, as it involves no radiation exposure and it is useful for dynamic studies. MRE is particularly useful in assessing the small intestine; however, we perform capsule endoscopy when MRE alone is not sufficient to confirm lesions confined to the small intestinal mucosa.

The initial evaluation of disease behavior and locations as well as disease activity is important, as it can affect the treatment regimen or selection of medical therapies. We classify the disease status according to the Paris Classification³³. Disease location and behavior such as inflammatory, fistulizing, and stricturing are determined at diagnosis and during follow-up. The presence of any macroscopic abnormality, such as mucosal ulceration, fistula, stricture, or abscess, was considered to indicate regional involvement. The perianal lesions of patients with IBD also include skin tags, fissures, fistulas, and abscesses. In addition, disease activity should be assessed at the time of diagnosis according to the Pediatric Crohn's Disease Activity Index (PCDAI) for CD, which is based on symptoms (30%), physical examination (30%), laboratory parameters (20%), and growth data (20%)⁴⁵. PCDAI scores range from 0 to 100, and they are categorized as follows: no disease activity (<10), mild disease activity (11–30), and moderate to severe disease activity (≥ 30)⁴⁶. The Pediatric Ulcerative Disease Activity Index (PUCAI) for UC should be also assessed⁴⁷. PUCAI scores range from 0 to 85, and they are categorized as follows: no disease activity (<10), mild disease activity (11–34), moderate disease activity (35–64), and severe disease activity (≥ 65). In addition to these diagnostic tools, bone densitometry and an evaluation of nutritional status are also needed.

What is the goal in the treatment of IBD?

In the past, because of the lack of treatment options, the goal of treating IBD was symptom relief to improve quality of life. In children, an additional goal was to prevent growth retardation⁴⁸. However, the recent introduction and aggressive use of biologics has improved patient responses. At present, the primary goal of treatment goes beyond clinical remission to mucosal healing on endoscopy⁴⁹. The endoscopic severity is recognized as the most accurate predictor of forthcoming surgery. It is well known that there is a discrepancy and poor correlation between clinical severity and endoscopic severity⁵⁰. Mucosal healing may not be predicted by CDAI or PCDAI. According to the current

understanding of the disease, mucosal damage is accumulated regardless of the clinical disease activity to inflict permanent gastrointestinal damage with a stricturing or penetrating disease⁵¹. Studies in children disclosed similar results. During a mean follow-up period of 36 months, 20% of patients progressed to a stricturing and penetrating disease⁵².

Step-up therapy has been the mainstay of the treatment algorithm, in which the primary treatment was determined according to the disease activity and behavior to be gradually strengthened when there was no response. Recently, top-down therapy has been considered more effective in patients with at least disease moderate activity^{53,54}. However, more scientific evidence is needed to support the use of universal top-down therapy in children. To compensate for the shortcomings of both strategies, targeted early aggressive therapy has recently been proposed. This is a more individualized approach to treating IBD. Siegel et al.⁵⁴ reported that the early use of biologics in high-risk pediatric patients could reduce complications by more than 75%. However, Dubinsky et al.⁵⁵ argued that early aggressive therapy should be conducted in certain patient populations after assessing clinical, immunological, and genetic risk factors. Pediatric patients with poor early responses who enter puberty can experience potential growth retardation before displaying a response to therapy. Top-down therapy may be more beneficial in those patients to minimize the peripubertal accumulation of intestinal damage and avoid underdevelopment from inadequate therapy.

Currently, clinical, serological, and genetic risk factors are being extensively studied to facilitate patient selection. Previously known clinical risk factors of surgical resection of the small intestine and complications include extensive involvement of the small intestine, perianal fistula, young age at diagnosis, and the use of steroids⁵⁶. The presence of antibodies to three bacterial antigens (ASCA, anti-OmpC, and anti-CBir1) has also been reported to be associated with prognosis⁵². Studies in Western populations reported an association between variations in *NOD2/CARD15* with prognosis²⁰; however, this association was not supported in Korean studies^{25,57}. Henckaerts et al.⁵⁸ reported over 30 genes associated with susceptibility to IBD. We also found in our study that *TNFSF15* was associated with clinical manifestations²⁶. Detailed reviews of the management of IBD were described previously^{48,59}. Doctors need to be aware of the rapid changes in the understanding of the pathogenesis and the rapid development and introduction of newer drugs. For example, for anti-tumor necrosis factor- α , as the U.S. Food and Drug Administration (FDA) continues to monitor the safety of this drugs, doctors should pay attention to the results that they are providing (www.fda.gov/cder/drug/early_comm/TNF_blockers.htm).

Growth and nutrition in pediatric CD

Growth failure is one of the most important aspects of pediatric CD¹⁰. The decrease in height velocity usually occurs before the onset of gastrointestinal symptoms. One-fourth of patients with CD and growth retardation may not achieve their full adult height potential. Therefore, interventions should be initiated before the completion of puberty. First, the disease should be controlled. Second, we must optimize nutrition and minimize corticosteroid use⁶⁰. Interventions are effective if performed in prepubertal patients or in the early stages of puberty. The prevalence of growth retardation at the time of diagnosis in Korean children is approximately 5%, which is less than that reported in a Western report⁹. Severe weight loss and low body mass index were observed in approximately one-third of patients. One-fifth of children already have osteoporosis at the time of diagnosis. In addition, altered nutrition markers for macronutrients as well as micronutrients were highly prevalent at time of diagnosis of CD in Korean children (Table 3).

Conclusions

Understanding the unique features of pediatric IBD is important for its diagnosis and management. First, some clues to the pathogenesis of the disease can be uncovered when we understand the reasons of the current change in the incidence or prevalence between different regions and ethnic backgrounds. Second, we must consider different management strategy when pediatric patients have different characteristics compared to adults.

Poorly controlled disease activity can result in inevitable surgery and growth retardation in children with IBD. Various

diagnostic methods in the diagnosis and treatment of IBD have been used to evaluate the locations, behavior, and activity of the disease. Monogenic IBD must be excluded among patients with infantile and refractory VEO IBD. Recently, early aggressive therapy using biologics has recently been proposed for children with IBD who are at great risk of growth failure and malnutrition. A population-based study is needed to accurately estimate the incidence of pediatric IBD in Korea.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Table 3. Prevalence of subnormal serum levels of various biochemical markers at diagnosis in Korean children with Crohn disease⁹

Biochemical marker	No. (%) (n=71)
Hemoglobin (g/dL)*	44/71 (62)
Albumin (<3.5 g/dL)	43/70 (61)
Iron (<50 µg/dL)	49/64 (77)
Transferrin saturation (<16%)	46/64 (72)
Ferritin (<100 µg/L)	45/65 (69)
Calcium (<8.8 mg/dL)	24/68 (35)
Magnesium (<1.8 mg/dL)	6/61 (10)
Folate (<5 ng/mL)	25/63 (40)
Vitamin B12 (<211 pg/mL)	1/62 (2)
Zinc (<70 µg/dL)	26/51 (51)

*Hemoglobin levels used to define anemia: children 6 months to 5 years, 11.0 g/dL; children 5-11 years, 11.5 g/dL; children 12-13 years, 12.0 g/dL; men, 13.0 g/dL; nonpregnant woman, 12.0 g/dL.

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