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ORIGINAL ARTICLE

Characteristics and Trends in the Incidence of Inflammatory Bowel Disease in Korean Children: A Single-Center Experience

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Abstract
Background Inflammatory bowel disease (IBD) is rare in Asian children and few reports on pediatric IBD have appeared.
Aims We, therefore, investigated the incidence trends and clinical characteristics of pediatric IBD in Korea.
Methods We enrolled 48 children with Crohn's disease (CD) and 14 children with ulcerative colitis (UC) from 1996 to 2007. Trends in annual enrollment and clinical characteristics were retrospectively evaluated by medical record review.
Results During the 12 years of observation, the number of new enrollments gradually increased. CD showed male predominance (33 boys, 15 girls), but more females presented with UC (4 boys, 10 girls). A relevant family history was observed in 3 (4.9%) of the 61 unrelated families. The most common presenting symptom was abdominal pain (67%) in CD and hematochezia (93%) in UC. Growth delay was observed in 10% of CD patients, but not in any of the UC patients. In CD, colonic involvement occurred in 87% of patients, ileal involvement in 87%, and both the small bowel and colon were affected in 75%. With UC, pancolitis occurred in 43% of patients, left-sided colitis in 36%, and proctitis in 21%, including all three patients with appendiceal orifice inflammation. The most frequent disease behavior was inflammatory in 85% of patients, but perianal fistula was noted in 50% of CD patients.
Conclusion This study showed that the incidence of pediatric IBD has been rapidly increasing in Korea in recent years. Relevant family history is less prevalent and phenotypic expression differs from what is seen in Western countries.

Keywords Inflammatory bowel disease · Crohn's disease · Ulcerative colitis · Child · Adolescent

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Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing disorder of unknown etiology and encompasses the two distinct disorders of Crohn's disease (CD) and ulcerative colitis (UC). The incidence of IBD is higher in the northern part of the world than in the southern, and is greater among Caucasians than in other races [1]. However, the prevalence of IBD in Asia appears to be increasing in regions previously considered to be low-incidence areas [2].

Pediatric IBD studies are important because about 25% of IBD patients are diagnosed as children, and the IBD characteristics of pediatric patients differ from those of adults [3–5]. Pediatric IBD patients in high-incidence areas

have increased in incidence in recent decades [5–9], but few Asian studies have appeared and patient numbers have been small [10–12]. A recent population-based study in Korean adults showed a rapid increase in IBD incidence [13, 14], but no recent study on Korean children has published.

Although we could not perform a population-based study in Korean children, we sought to indirectly evaluate incidence trends in pediatric IBD and the demographic and phenotypic features of Korean children with IBD by gathering our experience in a single tertiary center.

Methods

Patients

We enrolled 62 Korean children under 16 years of age, from 61 unrelated families, and managed them for IBD at the Department of Pediatrics, Asan Medical Center Children's Hospital, which is a tertiary medical center, from 1996 to 2007. There were 48 children with CD and 14 with UC. The mean follow-up duration was 42 months (range from 1 month to 12.7 years).

Methods

IBD diagnosis and the differentiation of IBD types were made according to conventional clinical, radiologic, endoscopic, and histologic criteria [15, 16]. One patient who was classified as indeterminate colitis and presenting with pancolitis and gastric erosions but did not receive colectomy was excluded in this study. Infectious enteritis or colitis were excluded by stool culture for *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Clostridium difficile*, stool tests for parasites, and tuberculosis was excluded by acid fast bacilli (AFB) staining, culture, polymerase chain reaction (PCR) of tissue samples, and chest X-ray. All patients underwent full or limited colonoscopy, and all patients with suspected CD received esophagogastroduodenoscopy at diagnosis and were studied by one or more radiographic methods (small bowel series, barium enema, abdominal computed tomography [CT], abdominal ultrasonography, magnetic resonance imaging [MRI]) to determine lesion location and behavior.

CD was classified according to the Montreal classification [17], and not the Vienna classification [18], to permit separate evaluation of perianal fistula. CD location was determined at diagnosis and behavior was classified during follow-up. The presence of any gross abnormality such as erosion, ulceration, fistula, stricture, or abscess was considered to reflect regional involvement. Perianal lesions of CD patients included skin tags, fissures, fistula, and abscesses, according to the Porto criteria [15]. UC extent was classified as pancolitis, left-sided colitis, or proctitis, according to the Montreal classification [17], and skipped lesions were also assessed. Patient body weight and height were assigned to the percentiles appropriate for the relevant age and gender, with reference to growth standards data on Korean children and adolescents [19].

Statistical Analysis

Differences in proportions of patients with different clinical characteristics or outcomes were assessed using the Chi-square or Fisher's exact test. Analysis of variance (ANOVA) and the Mann–Whitney U-test were employed to compare group quantitative data. A P-value < 0.05 was considered to reflect statistical significance. All statistical analyses were performed using SPSS version 14.0.

Results

Annual Numbers of Newly Enrolled IBD Patients

Figure 1 shows the annual numbers of newly enrolled pediatric IBD patients between 1996 and 2007. These include both patients newly diagnosed at our center and patients transferred to us for treatment. Among 48 CD patients, 7 (15%) visited our center first to present their symptoms, 25 (52%) were transferred from other hospitals and diagnosed at our center, and 16 (33%) were referred to our center during treatment. Among 14 UC patients, 2 (14%) visited our center first, 5 (36%) were transferred

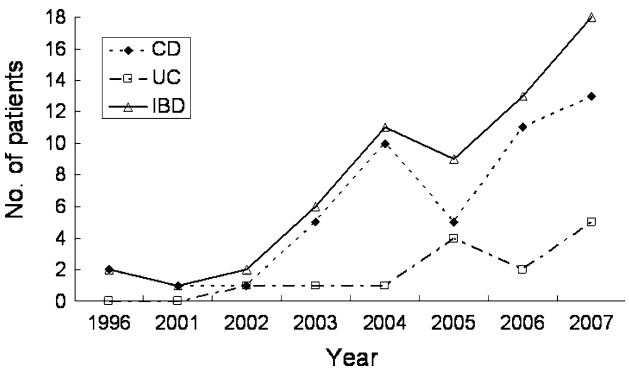

Fig. 1 Annual numbers of newly enrolled pediatric inflammatory bowel disease (IBD) patients at the Asan Medical Center. During the first 6 years of our study period, between 1996 and 2001, only four patients (6%) were diagnosed with IBD, but in the interval 2002–2007, 58 patients (94%) were so diagnosed. After the beginning of the 21st century, we noted that the numbers of children with IBD rapidly increased. There were two such children in 2002, ten in 2004, and 16 in 2006. This temporal trend of increasing patient number was more prominent for CD patients. Thus, CD was more common, and the CD:UC patient ratio was 3.4:1

from other hospitals and diagnosed at our center, and 7 (50%) were referred to our center during treatment.

During the first 6 years of the study period, between 1996 and 2001, only four patients (6%) were diagnosed with IBD, but during the later 6 years (2002–2007), 58 patients (94%) were so diagnosed. At the beginning of the 21st century, the number of children with IBD rapidly increased; there were two such children in 2002, ten in 2004, and 16 in 2006. This temporal trend of increasing patient number was observed more prominently in CD patients, with a new patient CD:UC ratio of 3.4:1.

Demographic Patient Data

The male to female gender ratio was 2.2:1 in CD patients (33 boys, 15 girls) and 1:2.5 for UC patients (4 boys, 10 girls). There was a significant male CD predominance and more females were diagnosed with UC ($P < 0.001$). For CD, the mean age of symptom onset was 11.4 years, and the average age at diagnosis was 12.0 years (range, 0.9–15.9 years). The mean duration from symptom onset to diagnosis was 7.1 months for CD patients. In UC patients, the mean age of symptom onset was 12.3 years, the average age at diagnosis 12.6 years (range, 3.8–15.6 years), and the mean duration from symptom onset to diagnosis 3.6 months. There was no significant difference between CD and UC patients in ages at onset or diagnosis, but the average duration of UC diagnostic delay was shorter than that for CD ($P < 0.05$) (Table 1).

Family History

Three (4.9%) of 61 families had histories of IBD in first-degree relatives. Two (4.3%) of 47 families with CD had family histories of CD. Two children were brothers in one family and the mother of one further child had CD. One (7.1%) of 14 children with UC had a mother with UC. There was no cross-family history of each of the diseases.

Table 1 Patient demographics and delays in inflammatory bowel disease (IBD) diagnosis

	CD ($n = 48$)	UC ($n = 14$)	*P*-value
Gender			<0.001
Male	33	4	
Female	15	10	
M:F ratio	2.2:1	1:2.5	
Age at symptom onset (years)	11.4	12.3	NS
Age at diagnosis (years)	12.0	12.6	NS
(range)	(0.9–15.9)	(3.8–15.6)	
Delay in diagnosis (months)	7.1	3.6	<0.05

Clinical Presentation

Presenting symptoms of CD were abdominal pain (67%), diarrhea (56%), perianal problems (50%), weight loss (46%), and hematochezia (17%). The classic symptom triad 'abdominal pain, diarrhea, weight loss' was noted in 37% of patients.

Presenting symptoms of UC were hematochezia (93%), diarrhea (79%), abdominal pain (71%), weight loss (43%), and anorexia (29%) (Table 2). Perianal symptoms were more frequently associated with CD than with UC ($P < 0.005$), and hematochezia was more commonly seen in UC patients than in those with CD ($P < 0.001$).

Height and Weight at Diagnosis

In CD children, 10% were below the third percentile for height and 17% were in the percentile range 3–10 for height. All children with UC had heights over percentile 10 for age and gender. A significant difference was seen between the two disease groups (Table 3).

Twenty-nine percent of CD children weighed below percentile 3 for age and gender and 8% were between percentiles 3 and 10. In UC children, 14% weighed below percentile 3 for age and gender and 7% were between percentiles 3 and 10. There was no significant difference between the two disease groups.

Table 2 Clinical presentations of patients at diagnosis

	CD ($n = 48$) *n* (%)	UC ($n = 14$) *n* (%)	*P*-value
Abdominal pain	32 (67)	10 (71)	NS
Diarrhea	27 (56)	11 (79)	NS
Rectal bleeding	8 (17)	13 (93)	<0.001
Weight loss	22 (46)	6 (43)	NS
Lethargy	4 (8)	3 (21)	NS
Anorexia	10 (21)	4 (29)	NS
Perianal symptoms	24 (50)	0 (0)	<0.005
Extraintestinal symptoms	12 (25)	2 (14)	NS

Table 3 Distribution of patient weight and height percentiles with respect to population data for the same age and gender

		CD ($n = 48$) *n* (%)	UC ($n = 14$) *n* (%)	*P*-value
Height	<3%	5 (10)	0	<0.05
	3–10%	8 (17)	0	
	≥10%	35 (73)	14 (100)	
Weight	<3%	14 (29)	2 (14)	0.10
	3–10%	4 (8)	1 (7)	
	≥10%	30 (63)	11 (79)	

Anatomical Site of Disease Activity at Diagnosis

Among 48 patients with CD, disease activity sites according to the Montreal classification were L1 in 6 (13%), L2 in 6 (13%), L3 in 36 (74%), and L4 in 21 (44%), indicating colonic involvement in 87%, ileal disease in 87%, and both small bowel and colonic lesions in 75%. Upper gastrointestinal tract involvement occurred in 44% of children. Younger patients (less than 10 years of age) showed more isolated colonic disease (L2, 45% of children) than older patients (3%) (Table 4) ($P < 0.005$).

Among 14 patients with UC, ten underwent examinations of the terminal ileum, one reached cecum with left-sided colitis, and three reached transverse colon with pancolitis and received additional barium enema to confirm the extent. The extent was pancolitis in 6 (43%), including one patient with ileal involvement, left-sided colitis in 5 (36%), including one patient with rectal sparing, and proctitis in 3 (21%), all of whom had appendiceal orifice inflammations, one of which extended into the cecum (Table 5). One of the ten patients with examinations of the terminal ileum showed ileal involvement.

CD Behavior During Follow-Up

For patients with CD, disease behaviors according to the Montreal classification [17] were inflammatory in 85%, stricturing in 2%, and penetrating in 13%. Perianal disease was noted in 75% of patients, including perianal fistula in 50%, perianal abscesses in 13% (including both abscesses and fistula in 6%), and skin tags in 21% (Table 6).

Table 4 Anatomic localization of Crohn's disease according to the Montreal classification

Montreal classification	Age (years)		Total ($n = 48$) n (%)
	≤10 ($n = 11$) n (%)	11–15 ($n = 37$) n (%)	
L1	1 (10)	5 (14)	6 (13)
L2	5 (45)[a]	1 (3)	6 (13)
L3	5 (45)	31 (83)	36 (74)
L4	4 (36)	17 (46)	21 (44)

[a] $P < 0.005$

Table 5 Anatomic localization of ulcerative colitis (UC)

Localization	Number (%) ($n = 14$)	Skipped lesion	Ileal lesion
Proctitis	3 (21%)	3[a]	0
Left-sided colitis	5 (36%)	1	0
Pancolitis	6 (43%)	0	1

[a] All three patients showed skipped appendiceal orifice inflammation, and, in one case, this extended into the surrounding cecum

Table 6 Disease behavior and perianal disease modifiers of Crohn's disease (CD), according to the Montreal classification

Behavior	n (%)
Inflammatory	41 (85)
Stricturing	1 (2)
Penetrating	6 (13)
Perianal disease modifier	36 (75)
Perianal fistula	24 (50)
Perianal abscess	6 (13)
Anal skin tag	10 (21)

Discussion

We have shown that the incidence of pediatric CD and UC has increased during the last 12 years in Korea, a country traditionally known as a low-incidence area. However, a future population-based study is required because we report only a single-center experience with newly enrolled patients. Recently, epidemiologic studies of pediatric IBD in Western countries, already known as high-incidence areas, have shown increasing prevalence rates of IBD [6–8]. Recent studies of pediatric IBD in Thailand (eight children) [11] and Taiwan (17 children) [12] also showed that pediatric IBD was increasing in those countries, but the work is difficult to interpret because both reports were single-center studies with small patient numbers. A population-based study in Korean adults also showed a rapid increase in IBD incidence [14]. Our work suggests that the incidence of pediatric IBD in Korea is increasing, in line with a global trend of rising IBD, perhaps caused by rapid changes in lifestyle and environment. The need to be aware of IBD in children, even in low-incidence areas, should be emphasized.

Recent increases in pediatric IBD in Western countries were mainly attributable to CD [5, 7, 8], and Asian children in Taiwan also showed a rise in CD [12]. In contrast to a previous study of 22 Korean children, performed in 1992, in which the CD:UC ratio was similar (1.2:1) [10], this present work in 62 children showed CD dominance (3.4:1). This change in the CD:UC incidence ratio is important in evaluating whether the increase in pediatric IBD in Korea is real or not. The ratio change supports the idea that a genuine increase in pediatric IBD has occurred in Korea, as already observed in Western countries [5, 7, 8].

Our study showed male CD predominance, as also reported in 24 Korean children with CD, where the male: female ratio was 2:1 [20]. Male predominance was also

reported in recent Western pediatric studies [4, 5, 21], a report on Korean adults [14], work on South Asian children living in Canada [22], and Asian adult studies [23, 24], whereas Western adult studies showed a slight female preponderance [25, 26]. The same result of male predominance as ours in the Korean adults suggests that age-related factors do not play a role in CD etiology in Korea, whereas the male:female ratio differences between adults and children in Western countries indicate that disease-triggering aspects, or factors predisposing to pathogenesis, may differ with age. With UC patients, our study showed a female predominance, but the Korean adult report found no gender bias [14]. In contrast to what was seen in the Korean work, Western studies have shown no gender differences in either adults or children [4, 5, 21, 25, 26]. Further study will be required, because our patient number was small.

The mean interval from symptom onset to diagnosis was 7.1 months in CD patients and 3.6 months in those with UC, notably shorter than in a previous Korean report, where the interval was 18 months [10]. As IBD incidence rises in Korea, diagnostic awareness seems to be improving. Sawczenko and Sandhu reported that the median diagnostic delay was 5 months (range, <1 month to 9 years), that rectal bleeding was associated with shorter diagnostic delay for all IBD forms, and that CD patients suffered a longer average delay than did UC patients, similar to what was seen in the present study [4].

Turning to IBD family history, 4.9% of our patients had first-degree relatives affected by IBD. Although our sample size was too small to permit definitive conclusions to be drawn, this is higher than frequencies seen in Korean adults (2.7% [14] and 1.9% [27]) and is similar to the 6.0% of children and 2.8% of adults with relevant histories reported from Japan [28]. In Western studies, the incidence of relevant family history in pediatric patients was higher (25–33%) than in our study [29, 30].

Those who had the 'classic symptom triad' (abdominal pain, diarrhea, and weight loss) comprised 37% of CD patients, and the most prevalent symptom was abdominal pain (67%). This result was similar to that of Sawczenko and Sandhu [4], who showed that only 25% of CS patients presented with the 'classic triad' and 72% with abdominal pain. In contrast to our results and those of Sawczenko and Sandhu [4], Spray et al. [21] reported that most CD children presented with the classical triad. Most children with UC presented with hematochezia and diarrhea in our study; this was similar to what was seen in Western studies [4, 5, 21].

An earlier study in Korean children showed a high incidence of growth retardation (58% in CD patients, 20% in UC), defined as membership of growth percentiles below 3, and may reflect the longer interval of 18 months between symptom onset and IBD diagnosis [10]. In our study, the proportion of growth-retarded patients (10%) was smaller, possibly due to more effective diagnosis. Compared with the report of Sawczenko and Sandhu [4], where symptom duration before diagnosis was close to that of our study, the proportions of children with height or weight below percentile 3 were similar to our results. This suggests that early IBD recognition can minimize growth failure.

In our study, most CD patients (74%) presented with both small bowel and colonic involvement, whereas isolated ileal (13%) and colonic (13%) disease were rare, as also reported in the Western study of Sawczenko and Sandhu [4], who found that most patients (84%) had both ileal and colonic involvement and that the dual presentation was more common than in a previous report [31]. These authors considered that isolated colon or small bowel disease diagnoses had decreased because of improvements in modern investigation protocols. We studied all patients using relatively modern approaches, which might detect a higher proportion of patients with both ileal and colonic involvement than was possible in a previous Korean pediatric study, where 7 of 12 patients (58%) had dual presentations [10]. Isolated colonic disease was more common in the younger children of our study, as in a Western report [32].

Turning to UC location, most children in Western studies had pancolitis [4, 5, 33], but in adults, UC was mainly confined to the rectum and left-sided colon [34, 35]. Our pancolitis frequency of 43% is lower than that seen in Western pediatric UC patients [4, 5], where the proportions were about 90%, but similar to the frequencies seen in Western [34, 35] and Korean adult studies [13], and to that of an earlier Korean pediatric report [10]. Another important result is that one-third of our patients showed skipped lesions. One patient had rectal sparing, and a further three patients showed skipped appendiceal orifice inflammation (AOI), which was reported to be common in adults [36]. However, this condition is rarely seen in children. Several explanations are possible. Prior to treatment, it is difficult to obtain a clear image of the cecum in pediatric patients. Also, UC was previously thought to be always continuous from the rectum and, therefore, the insertion of an endoscope in the oral direction was discontinued in many cases when a normal region appeared. Finally, colonoscopy is difficult in children. Even in our study, 4 of 14 children did not undergo complete colonoscopies. These findings suggest that it is necessary to conduct entire colonoscopies, including terminal ileal examinations. However, Byeon et al. [37] reported that, in patients with distal UC, AOI had no prognostic implications in terms of remission relapse or proximal disease extension. Further study using full colonoscopic examinations with ileal intubation will be needed to confirm the clinical significance of AOI in pediatric UC patients.

To assess disease behavior, we applied the Montreal classification rather than Vienna classification to separately evaluate perianal fistula, because our patients showed a high incidence of fistulation. Our patients were similar to those in the study of Kugathasan et al. [5], who reported that 90% of patients had inflammatory disease. However, we did not consider a perianal fistula to be a penetrating condition and our study showed a higher incidence (50%) of perianal fistula than that observed in Western children (8% in the work of Kugathasan et al. [5] and 15% in the study of Palder et al. [38]).

We consider that the incidence of pediatric IBD has been rapidly increasing in Korea in recent years, even though this is not a population-based study. This work has also shown that pediatric IBD in Korea differs from that in the West, with clinical features including a lower incidence of relevant family history, a higher frequency of perianal fistula in CD children, and a lower incidence of pancolitis in UC patients. However, a further prospective population-based study will be needed to evaluate the incidence and phenotypes of pediatric IBD in Korea.

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