Clinical characteristics of Iranian pediatric patients with inflammatory bowel disease

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Abstract

Background : **Inflammatory bowel disease (IBD) is a group of disorders, including Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC). Small intestine and colon are primarily affected in this group of disorders.**

Purpose : **This single center study was performed to define demographic features and clinical characteristics of Iranian pediatric patients with IBD.**

Method : **Fifty nine patients with IBD, who have been referred to Children's Medical Center Hospital during a 10-year period, were investigated in this study. The data was gathered by interviewing the patients and their families, as well as reviewing their medical records.**

Results : **Among 59 patients with IBD, 23 cases had UC and 19 cases had CD, while the remaining 17 cases had IC. Patients with UC were significantly younger at the time of diagnosis in comparison with patients with CD. The most common symptoms were abdominal pain, diarrhea, fever and growth failure. Hepatobiliary abnormalities and arthritis were common extra intestinal manifestations. The median Pediatric Crohn's Disease Activity Index was 42.5 (range 20-60), whereas the median Pediatric Ulcerative Colitis Activity Index was 40 (range 20-70). Seven of 23 UC (30.4%) had proctatis, while 16 (69.6%) had extensive colitis. In CD, 11 of 19 (57.9%) had involvement of terminal ileum and colon, while inflammation was limited to the colon in 8 cases (42.1%). The colonoscopic findings in the IC group were heterogeneous.**

Conclusion : **This study provides epidemiological data on pediatric patients with IBD, which could be useful for health care workers in prompt diagnosis and appropriate treatment of early onset IBD.** (Acta gastroenterol. belg., **2009**, 72, **230-234**).

Key words : Crohn's disease, inflammatory bowel disease, pediatrics, ulcerative colitis.

Introduction

Inflammatory bowel disease (IBD) is a group of disorders, which primarily affect the small intestine and colon. The etiology of these disorders is still unknown and is thought to be precipitated by interactions between the genetically susceptible host and the environment. IBD includes Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC). It has been estimated that 10-15 percent of patients with IBD are diagnosed at the ages below 18 years (1-4). The knowledge on the epidemiology of pediatric IBD is of particular importance, since this age group is at risk for permanent growth failure, delayed puberty, and increased risk of intestinal malignancies later in life (5-8). Moreover, children probably experience the most complete range of clinical manifestations because of the lifelong nature of the disease. Therefore, these patients require special attention (9-12).

Unfortunately, there are very limited data on childhood IBD from the developing countries. Although the exact incidence of IBD is unknown in Iran, the incidence has been shown to be increasing (13). Also, certain gene polymorphisms such as vitamin D receptor gene and multidrug resistance gene have been shown to be associated with IBD in our region (14, 15). This study was performed to define the demographic features and clinical characteristics of Iranian pediatric patients with IBD during a 10-year period.

Patients and methods

Subjects

Fifty nine patients with IBD who were < 18 years old at the time of diagnosis were investigated in this retrospective study. All the patients were referred to the Children's Medical Center Hospital, the main referral center of pediatric diseases in Tehran-Iran, during a 10-year period (1996-2006). The data were gathered by interviewing the patients and their families, as well as reviewing their medical records. For all subjects, a complete history was taken. Medical documents were reviewed ; physical examinations were performed and necessary laboratory studies were conducted. The study was approved by the regional ethics committee of Hospital. Informed consent was obtained from either patients or their parents.

Questionnaire

A four-page questionnaire was filled out for all patients. The following characteristics were investigated :

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age at presentation, gender, type of IBD, clinical presenting symptoms, extra intestinal manifestations, diagnostic time lag, and severity of disease.

The time of diagnosis was set as the date of the definitive diagnostic procedure rather than symptom onset. All data from the time of the diagnostic work-up, including the laboratory findings, serologic tests, radiologic studies, colonscopic evaluation, and histologic findings were obtained. Any surgical intervention needed at the time of diagnosis was also recorded.

Laboratory values on presentation in each patient included hemoglobin concentration, erythrocyte sedimentation rate (ESR), and serum albumin concentration.

IBD criteria and classification

The diagnosis of IBD was made in accordance with the Porto diagnostic criteria (16) on the basis of clinical, endoscopic, histopathological and radiological evidence and after exclusion of infection and other recognized causes of inflammation. The diagnosis had to be of at least 6 months' duration. Stool studies were performed in all patients to exclude infectious causes of diarrheal illness. The histologic evaluation consisted of multiple biopsies taken from all segments of the gastrointestinal tract. Patients whose IBD diagnosis was not confirmed by endoscopic or histologic examination were excluded from further analysis.

CD was diagnosed when there was evidence of perianal disease (skin tags, abscess, fistula), endoscopic findings of segmental inflammatory affection (aphthoid or serpiginous ulcers, skip lesions, skipped areas, strictures, fistulas, mucosal atrophy, "cobblestoning") on colonoscopy, and/or mucosal abnormality at upper endoscopy (aphthous ulceration) with histologic findings of acute/chronic transmural inflammation of the tissue with intensive compound cell infiltration and noncaseating epithelioid granulomas.

UC was defined as endoscopic finding of hemorrhagic-ulcerative inflammation of the rectal mucosa with continuous spreading to the proximal parts of the large bowel with histological findings of diffuse mucosal inflammation with hyperemia and compound cell infiltration, with crypt distortion and possible presence of crypt abscesses. The presence of nonspecific gastritis did not rule out a diagnosis of UC.

IC was defined as colitis that could not definitively be declared as CD or UC, based on the above criteria.

Severity assessment

For all patients with CD and UC, the severity of disease was evaluated at the time of diagnosis using the Pediatric Crohn's Disease Activity Index (PCDAI) and Pediatric Ulcerative Colitis Activity Index (PUCAI), respectively (17-19). The PCDAI consisted of three general fields : 1. History, including data regarding abdominal pain, number of liquid stools and patient functioning ; 2. Physical examination parameters, including abdominal examination, perirectal disease, extraintestinal manifestations, weight, and height ; 3. Laboratory tests, consisting of hematocrit, albumin, and erythrocyte sedimentation rate. Each item can range on a three-point scale : except for hematocrit and erythrocyte sedimentation rate that are scored as 0, 2.5 or 5 points, others scored as 0, 5, 10 (17, 18). The PUCAI has recently been validated in order to assess the severity of UC in pediatric population. The index is based on six categories, including abdominal pain, rectal bleeding, stool consistency, number of stools per day, any episode of nocturnal bowel movement, and activity level. Each item can range from 0-10 with the exception of rectal bleeding and stools per day which range from 0-30 and 0-15, respectively (19). PCDAI scores can range from zero to 100, while PUCAI can range from zero to 85.

Statistical analysis

Data analysis was performed using SPSS statistical software package, version 14.0 (SPSS Inc, Chicago, IL). P-value of less than 0.05 was considered significant.

Results

Characteristics of patients

Fifty nine patients with IBD (23 cases of UC, 19 cases of CD and 17 cases of IC) were reviewed in this study. The ratio of male to female was similar in for all subtypes, which was 1.6 :1 for UC, 1.4 :1 for CD and IC. Four patients (6.77%) had a positive history of IBD in their family.

The severity of disease was evaluated for all patients with CD and UC. The median PCDAI and PUCAI values were 42.5 (range 20-60) and 40 (range 20-70), respectively. In both the UC and CD group, there was not any significant difference between the genders on severity of disease (Table 1).

Age distribution of patients

The mean age at the time of diagnosis was 8.5 years (range 1-14.5 years) for all patients. Patients with UC were significantly younger at the time of diagnosis in comparison with patients with CD and IC ($P < 0.001$). The disease mean duration from onset to diagnosis in all 59 patients was 8 months (range 4-16 months). CD patients had a longer time interval from onset of symptoms to diagnosis in comparison with UC and IC patients (mean of 12 months in CD *vs.* 7 months in UC and 9 months in IC), but these differences were not significant.

Clinical manifestations

The most common findings in all 59 patients were abdominal pain (70.7%), diarrhea (66.7%), fever (44%) and growth failure (34.6%). Presenting manifestations of CD, UC and IC are shown in Table 2. One patient with

Table 1. — **Patients' characteristics at the time of diagnosis [Median (range) or frequency (%)]**

Diagnosis	Ulcerative colitis (n = 23)	Crohn's disease (n = 19)	Indeterminate colitis (n = 17)
Age (years)	6.4 (1-13)	10.2 (5-14.5)	7.6 (3-11)
Gender			
Male	14 (60%)	11 (58%)	10 (58%)
Female	9 (40%)	8 (42%)	7 (42%)
Hemoglobin (mg/dL)	10.4 (3.5-14.5)	8.8 (7-14)	9.0 (4.5-12)
Hematocrit (%)	32.5 (23-42)	30.0 (22-40)	31.5 (21-40)
Albumin (g/dL)	4.0 (1.7-5)	3.2 (1-4.25)	4.3 (2.33-5)
AST (U/L)	34.5 (12-329)	15 (4-30)	24.5 (7-174)
ALT (U/L)	27.5 (5-85)	12 (4-27)	12.5 (6-184)
Alk phos (U/L)	414 (218-1363)	271.5 (177-1074)	307 (150-1374)
ESR mm/h	26.5 (8-119)	66 (5-110)	35 (13-90)
PUCAI	40 (20-70)	–	–
PCDAI	–	42.5 (20-60)	–
Severe	–	13 (68%)	–
Moderate	–	5 (26%)	–
Mild	–	1 (6%)	–

Table 2. — **Presenting manifestations of pediatric patients with inflammatory bowel disease**

	Ulcerative colitis (n = 23) Number (%)	Crohn's disease (n = 19) Number (%)	Indeterminate colitis (n = 17) Number (%)
Fever	11 (47.8%)	7 (36.8%)	8 (47.1%)
Abdominal pain	–	11 (57.9%)	3 (17.6%)
Diarrhea	3 (13.0%)	6 (31.6%)	14 (82.4%)
Weight loss	–	2 (10.5%)	–
Bloody stool	18 (78.3%)	–	–
Jaundice	2 (8.7%)	–	–

CD experienced recurrent oral aphthous ulcers. Among the extra-intestinal manifestations, hepatobiliary abnormalities were the most common (11.3%), followed by arthritis (9.4%). Two patients who presented with jaundice and pruritus were preliminary diagnosed as sclerosing cholingitis, in which further investigations confirmed the diagnosis of UC. One patient complicated with autoimmune hepatitis. Erythema nodosum was also detected in another patient.

Laboratory findings

Abnormal laboratory findings were common among our patients. Occult blood in stool was seen in 98.3% of cases ; in all of them the cultures for bacteria was negative. Also anemia (hematocrit less than 30%) and leukocytosis (white blood cells more than 15,000 cells/mm^3) were observed in 20 (34%) and 9 (15.5%) cases, respectively. Other laboratory data of the patients are presented in Table 1.

Colonoscopy findings

The extension of disease was evaluated by using total colonoscopy in all patients. The distribution of the disease is shown in Table 3. Perianal diseases were reported in 14 (73.6%) CD patients. In CD, 11 of 19 (57.9%) had involvement of terminal ileum and colon, while inflammation was limited to the colon in 8 cases (42.1%). The colonoscopic findings in the IC group were completely heterogeneous with multiple sites being involved. In 12 patients in which the distribution of inflammation was restricted to the colon, absolute rectal sparing was present in 5 (41.6%) patients. Colitis limited to the left colon area was seen in 4 (33.3%) and pancolitis was detected in 3 (25%) patients. Among 5 patients who had involvement of both ileum and colon, two developed small ileal ulcers without strictures or cobblestoning, while backwash ileitis was accompanied by left sided disease in one patient.

Treatment

The treatment options for each group are shown in Table 4. Medical treatment for the patients in our study includes amino-salicylates (73.6%), systemic or local corticosteroids (66.1%), and antibiotics (54.2%). Some patients benefited from multi-drug treatment. There were no significant differences in the pharmacological treatment of UC and CD. Six (10.16%) patients responded poorly to medical management and underwent surgery. Three patients with CD had resection of a stricture and one patient received surgery for perianal disease. One patient with UC, who failed to respond to intravenous steroid therapy, underwent a subtotal colectomy. One patient with IC was operated on with a total colectomy owing to pancolitis at the time of diagnosis.

Table 3. — **Distribution of inflammation recorded on colonoscopy of patients with inflammatory bowel disease**

Diagnosis	Distribution of inflammation		Other findings	
Ulcerative colitis (n = 23)	*Proctitis* 7 (30.4%)	*Extensive colitis* 16 (69.6%)	*Cryptitis or crypt abscess* 19 (82.6%)	
Crohn's disease (n = 19)	*Terminal ileum and colon* 11 (57.9%)	*Limited to the colon* 8 (42.1%)	*Granuloma* 2 (10.5%)	*Cryptitis or crypt abscess* 1 (5.3%)
Indeterminate colitis (n = 17)	*Terminal ileum and colon* 5 (29.4%)	*Limited to the colon* 12 (70.6%)	*Cryptitis or crypt abscess* 12 (70.6%)	

Table 4. — **Treatment options for patients with inflammatory bowel disease**

Treatment	Pharmacotherapy			Surgery
	Amino-salicylates	Corticosteroids	Antibiotics	
Ulcerative colitis (n = 23)	19 (82.6%)	17 (73.9%)	12 (52.1%)	1 (4.3%)
Crohn's disease (n = 19)	11 (57.8%)	12 (63.1%)	9 (47.3%)	3 (15.7%)
Indeterminate colitis (n = 17)	12 (70.5%)	10 (58.8%)	11 (64.7%)	2 (11.7%)

Discussion

Understanding on the clinical manifestations of IBD in different geographic areas can provide thorough insight into the possible risk factors and mechanisms that contribute to the occurrence of IBD. Epidemiological data from developing countries on childhood IBD are scanty, compared with Western countries. The present study is the first report from pediatric patients with IBD in Iran, in which there are some differences in characteristics of children with IBD from those in the Western countries.

In the previous studies on pediatric-onset IBD, there is no consistency in gender predominance for children. Our findings indicate a male predominance for UC, CD and IC, which is in agreement with some previous studies (21-24). However, no such difference has been found in other studies (25-28).

Studies have shown a relatively long interval between the start of symptoms and the diagnosis of IBD in children (29, 30). However, because of the retrospective nature of most studies, it is difficult to determine the duration of disease before the diagnosis is made. In our study, the average interval between onset of symptoms and diagnosis was 7 months for UC, 12 months for Crohn's disease and 9 months for IC. The reason for this delay could be partly because of the insidious onset of the disease and the wide range of differential diagnoses, which results in the difficulty to a specific diagnosis considering nonspecific symptoms.

Abdominal pain, diarrhea and weight loss were previously considered to be the "classic triad" of CD. A study performed during the period of 1980-1989 revealed that nearly 80% of CD children presented with the triad of abdominal pain, diarrhea and weight loss (31). However, over the last two decades the clinical presentations of childhood CD have been shown to be changed. In a survey of childhood IBD carried out in the British Isles during 1998-1999, only 25% of patients presented with this classic triad (32). However, nearly all of our CD patients presented with such classic triad.

IC has been defined in different studies as a disease, in which features of both UC and CD coexist, or alternatively, a disease in which a definite diagnosis of UC or CD cannot be made according to current criteria (33, 34). A wide range of IC has been reported in pediatric IBD (3% to 23%) (35-39). It is unclear whether the reason for this difference is due to variability in definition of IC or because of incorrect disease classification. In our study, about 30% of patients were classified as IC which is a relatively high rate in compare to other studies. However, IC might represent an evolving form of IBD that presents before definitive disease phenotype.

It has been shown that there are some differences in the nature of UC in children, compared to adults. The anatomic distribution of UC is limited to the left colon in approximately 36% of adult patients (39). However, a number of previous studies in children and adolescence report a higher proportion of UC with extensive disease (40-42). The extension of disease in our population of patients was rather similar to previous studies, in which pancolitis was observed in 70% of patients. This underscores the importance of a full colonoscopy in establishing the extent of the disease in children (16).

In summary, our study provides epidemiologic data regarding the characteristics of a group of pediatric patients with IBD in a tertiary center in Iran. Constructing a population-based registry in our region could be suggested in order to provide better epidemiologic data on these diseases. We hope that our clinical and epidemiological experience forms a basis for future studies of the pathogenetic factors in IBD among children.

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