

Inflammatory bowel disease in Turkish children

Murat Cakir, Fatih Unal, Gonul Dinler, Masallah Baran, Hasan Ali Yuksekkaya, Gokhan Tumgor, Erhun Kasirga, Ayhan Gazi Kalayci, Sema Aydogdu

Trabzon, Turkey

Background: This study was undertaken to evaluate demographics, clinical manifestations, laboratory findings and outcomes of children with inflammatory bowel disease (IBD) in Turkey.

Methods: We analyzed the medical records of 127 children diagnosed with IBD (under 18 years old) between January 2004 and January 2012 in 8 pediatric gastroenterology centers.

Results: Of the 127 patients, 90 (70.9%) suffered from ulcerative colitis (UC), 29 (22.8%) from Crohn's disease (CD), and 8 (6.3%) from IBD unclassified. The mean age of the 127 patients was 11.6±4.1 years, and 11.8% of the patients were below 5 years old. Of the patients, 49.6% were male, and males were more predominant in patients with CD than in those with UC (72.4% vs. 42.2%, $P=0.008$; a male/female ratio of 2.62 in CD, $P=0.0016$). Approximately one fifth of the patients had extra-intestinal manifestations and 13.3% of the patients had associated diseases. Extraintestinal manifestations and associated diseases were more common in early onset disease [$P=0.017$, odds ratio (OR)=4.02; $P=0.03$, OR=4.1]. Of the patients, 15% had normal laboratory parameters including anemia, high platelet count, hypoalbuminemia, hypoferritinemia, and high sedimentation rate. Area under receiver operation characteristics was used to predict pancolitis in patients with UC. The values of C-reactive protein, sedimentation rate and pediatric ulcerative colitis activity were 0.61 ($P=0.06$), 0.66 ($P=0.01$) and 0.76 ($P=0.0001$), respectively. Four (4.4%) patients

with UC underwent colectomy, and finally two (1.5%, 95% confidence interval: 0-3.7%) patients died from primary disease or complications.

Conclusions: IBD is an increasing clinical entity in Turkey. Features of IBD are similar to those in other populations, but prospective multicenter studies are needed to analyze the true incidence of IBD in Turkish children.

World J Pediatr 2015;11(4):331-337

Key words: associated diseases; Crohn's disease; inflammatory bowel disease; outcome; ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is an idiopathic, lifelong, destructive chronic inflammatory condition of the gastrointestinal tract that encompasses two distinct disorders, ulcerative colitis (UC) and Crohn's disease (CD).^[1] It is thought to develop as a result of dysregulation of the immune response to normal gut flora in a genetically susceptible host.^[1]

Children with IBD may present with a range of symptoms, depending on the location, severity and chronicity of inflammation. IBD involving the colon (UC or CD) is characterized by diarrhea and rectal bleeding. In contrast, CD involving the terminal ileum and/or jejunum tends to present more subtly, with non-specific abdominal pain, weight loss and fever. Less than 30% of the patients may present with extraintestinal symptoms such as arthritis, uveitis and erythema nodosum in addition to gastrointestinal symptoms.^[1]

About 25% of the patients are diagnosed during the childhood, and the characteristics of pediatric patients differ from those of adults. The pediatric patients have more severe phenotype than the adults; there are extensive anatomic involvement in pediatric patients and rapid development of complications in untreated pediatric patients.^[2] A population based study revealed that there is a high incidence of IBD in western countries and Caucasians.^[3] Additionally, epidemiological surveys^[3-6] suggested that the incidence

Author Affiliations: Department of Pediatric Gastroenterology Hepatology and Nutrition, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey (Cakir M); Dortcelik Children Hospital, Bursa, Turkey (Unal F); 19 Mayıs University, Samsun, Turkey (Dinler G, Kalayci AG); Tepecik Education and Research Hospital, Izmir, Turkey (Baran M); Necmettin Erbakan University, Konya, Turkey (Yuksekkaya HA); Cukurova University, Adana, Turkey (Tumgor G); Celal Bayar University, Manisa, Turkey (Kasirga E); Ege University, Izmir, Turkey (Aydogdu S)

Corresponding Author: Murat Cakir, MD, Department of Pediatric Gastroenterology Hepatology and Nutrition, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey (Tel: 05326810318; Email: muratcak@hotmail.com)

doi: 10.1007/s12519-015-0042-2

©Children's Hospital, Zhejiang University School of Medicine, China and Springer-Verlag Berlin Heidelberg 2015. All rights reserved.

of pediatric-onset IBD increased gradually in western countries or regions previously considered to be low-incidence areas over the last 30 years.

Data on the pediatric-onset IBD have been reported in many countries such as the USA, Great Britain, Italy, Ireland, Korea and Saudi Arabia.^[4,5,7-10] Most studies^[4,5,7-10] revealed that the incidence of IBD is increasing in childhood and the increment is more prominent in CD. The studies also found obesity related IBD, secondary IBD due to immune deficiencies or autoimmune diseases, and a high rate of colectomy in patients with UC. Because of lack of studies on pediatric-onset IBD in Turkey, we aimed to evaluate demographics, disease distribution at diagnosis, clinical manifestations, laboratory findings, and outcomes of IBD in Turkish children.

Methods

We retrospectively reviewed the medical records of children with IBD, whose symptoms appeared before 18 years of age between January 2004 and January 2012 in 8 pediatric gastroenterology centers in Turkey (Trabzon, Samsun, Bursa, Konya, Manisa, Adana and two centers in Izmir). The diagnosis of IBD was based on the typical clinical manifestations plus biochemical, endoscopic and histopathological examinations.^[11,12] All the patients underwent colonoscopic examination with or without upper endoscopy with multiple biopsies. The differentiations of diseases into CD, UC and IBD-unclassified (IC) were based on the criteria of IBD working groups of the European Society of Pediatric Gastroenterology Hepatology and Nutrition and the North American Society of Pediatric Gastroenterology Hepatology and Nutrition. Patients were labeled to have IC if there was an isolated colonic disease and histopathology was inconclusive of either CD or UC.^[11] Modified Montreal classification was used to define the location and clinical behaviors of the disease.^[12]

Demographic and clinical findings of the patients, anatomic localization of the disease, laboratory findings on admission, and outcomes of the patients were recorded.

We used the Chi-square test to compare the proportions. To compare the quantitative data we used the Mann-Whitney *U* test. A *P* value less than 0.05 was considered to reflect the statistical difference. Statistical analysis was performed using SPSS version 13.0.

Results

One hundred and twenty-seven children were diagnosed with IBD in 8 pediatric gastroenterology centers: 90

(70.9%) children with UC, 29 (22.8%) with CD, and 8 (6.3%) with IC. The annual number of new IBD patients after 2005 is shown in Fig. 1. The number of newly diagnosed patients increased after 2006, and the increase was more prominent in patients with UC.

Demographic features

Demographic features of the patients are shown in Table 1. The mean age of the patients at the time of diagnosis was 11.6±4.1 years, and 11.8% of the patients were under 5 years old. Patients with CD were younger than those with UC at the time of diagnosis (12.3±3.5 vs. 9.6±5.0 years old, *P*=0.012). The mean duration of symptoms was 7.2 months for overall, 6.2 months for UC and 8.7 months for CD. Of the patients, 49.6% were male, and CD was more common than UC in males (72.4% vs. 42.2%, *P*=0.008; a male/female ratio of 2.62 for CD, *P*=0.0016). Ten (7.8%) patients had a history of IBD in the first and second relatives. The prevalence of consanguinity was 10.2%, 10% and 6.8% in patients with IBD, UC and CD, respectively.

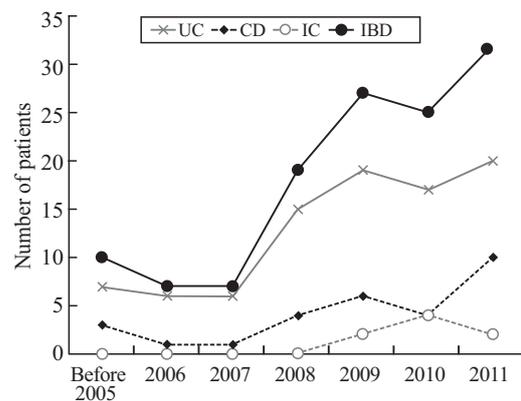


Fig. 1. Annual number of new patients with inflammatory bowel disease (IBD). UC: ulcerative colitis; CD: Crohn's disease; IC: IBD-unclassified.

Table 1. Demographic features of the patients with IBD, *n* (%)

Parameters	UC	CD	IC	Total
Number of patients	90 (70.9)	29 (22.8)	8 (6.3)	127 (100)
Age (y), mean±SD	12.3±3.5*	9.6±5.0	10.5±5.7	11.6±4.1
<5 y	6 (6.6)†	7 (24.1)	2 (25.0)	15 (11.8)
Duration of symptoms (mon), mean±SD	6.2±7.7	8.7±14.7	13.2±23.9	7.2±11.2
Male	38 (42.2)‡	21 (72.4)	4 (50.0)	63 (49.6)
Male:female	0.73	2.62§	1.00	0.98
Family history	6 (6.6)	1 (3.4)	3 (3.7)	10 (7.8)
Consanguinity	9 (10.0)	2 (6.8)	2 (25.0)	13 (10.2)

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; IC: IBD-unclassified; SD: standard deviation. *: *P*=0.012, UC group vs. CD group; †: *P*=0.015, UC group vs. CD group; ‡: *P*=0.008, UC group vs. CD group; §: *P*=0.0016, male vs. female in CD group.

Clinical presentation and physical findings

Clinical presentations and physical findings of the patients are shown in Table 2. Abdominal pain (77.9%), rectal bleeding (73.2%) and diarrhea (68.5%) were the most common symptoms. Rectal bleeding and diarrhea were more common in patients with UC than in those with CD ($P=0.0005$ and $P=0.011$, respectively). Malnutrition (weight $<3\%$) and short stature were seen in 20.4% and 13.3% of the patients, respectively. Six patients (6.6%) with UC were obese.

Approximately one fifth of the patients had extra-intestinal manifestations on admission. In the patients with UC, 14.4% had joint involvement, 7.7% had hepatobiliary abnormalities (abnormal liver enzymes in 6 patients and sclerosing cholangitis in 1), 1.1% had uveitis, and 1.1% had erythema nodosum. Two (6.8%) patients with CD had abnormal liver enzymes, one (3.4%) had uveitis, one had erythema nodosum, and one had joint involvement.

Six (4.7%) patients had familial mediterranean fever (FMF), four (3.1%) patients had kidney stones, and three (2.3%) patients had hypogammaglobulinemia associated with IBD.

Anatomic locations

Among the 90 patients with UC, 41% had pancolitis,

14% had extensive pancolitis (hepatic flexure distally), 34% had left-sided pancolitis, and 11% had proctitis. Isolated ileal involvement occurred in 14% of the patients with CD, colonic diseases in 34%, and ileocolonic involvement in 49%. Isolated upper gastrointestinal disease was seen in only one (3%) patient. The anatomic location of the disease was more diffuse (diffuse extension for UC: pancolitis or extensive colitis; for CD: ileocolonic involvement) with the increasing age both in patients with CD and those with UC (Fig. 2).

Clinical behaviors of CD

Twenty-four (82.7%) patients with CD had inflammatory diseases, two (6.9%) had structuring disease, and three (10.4%) had penetrating disease. Intestinal fistula was found in three (10.4%) patients. Perianal findings including skin tag, abscess and severe fissures were found in five (17.2%) patients.

Clinical characteristics of early-onset IBD (under 5 years old)

Fifteen (11.8%) patients had early-onset IBD. These patients were compared with others (Table 3). As

Table 2. Clinical presentation, physical findings and extra-intestinal manifestations of the patients, n (%)

Parameters	UC ($n=90$)	CD ($n=29$)	Total IBD ($n=127$)
Rectal bleeding	76 (84.4)*	13 (44.8)	93 (73.2)
Diarrhea	68 (75.5)†	14 (48.2)	87 (68.5)
Abdominal pain	69 (76.6)	25 (86.2)	99 (77.9)
Weight loss	36 (40.0)	11 (37.9)	47 (37.0)
Fatigue	19 (21.1)	5 (17.2)	25 (19.6)
Fever	18 (20.0)	7 (24.1)	26 (20.4)
Anorexia	19 (21.1)	7 (24.1)	27 (21.2)
Perianal symptoms	2 (2.2)	2 (6.8)	4 (3.1)
Weight $<3\%$	17 (18.8)	7 (24.1)	26 (20.4)
Height $<3\%$	10 (11.1)	6 (20.6)	17 (13.3)
Obesity	6 (6.6)	None	6 (4.7)
Protein-losing enteropathy	None	1 (3.4)	2 (1.5)
Extra-intestinal manifestations	22 (24.4)	5 (17.2)	27 (21.2)
Joint involvement	13 (14.4)	1 (3.4)	14 (11.0)
Uveitis	1 (1.1)	1 (3.4)	2 (1.5)
Liver involvement	7 (7.7)	2 (6.8)	9 (7.0)
Erythema nodosum	1 (1.1)	1 (3.4)	2 (1.5)
Associated diseases	10 (11.1)	5 (17.2)	17 (13.3)
FMF	2 (2.2)	2 (6.8)	6 (4.7)
Celiac disease	1 (1.1)	None	1 (0.7)
Autoimmune hepatitis	1 (1.1)	None	1 (0.7)
IgA nephropathy	None	1 (3.4)	1 (0.7)
Type 1 diabetes	1 (1.1)	None	1 (0.7)
Hypogammaglobulinemia	None	2 (6.8)	3 (2.3)
Mental retardation	1 (1.1)	None	1 (0.7)
Kidney stones	4 (4.4)	None	4 (3.1)

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; FMF: familial mediterranean fever; IgA: immunoglobulin A. *: $P=0.0005$, UC group vs. CD group; †: $P=0.011$, UC group vs. CD group.

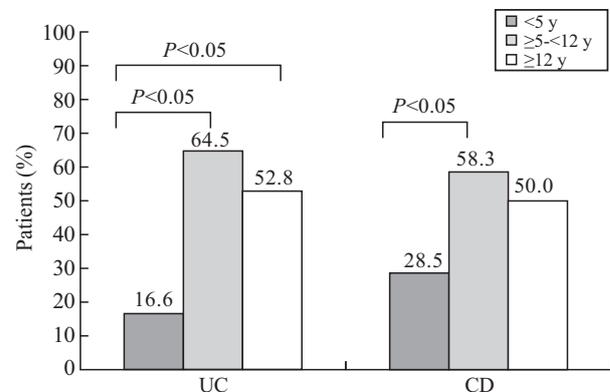


Fig. 2. Frequency of diffuse extension of the disease according to age groups. UC: ulcerative colitis; CD: Crohn's disease.

Table 3. Comparison of early-onset patients with others, n (%)

Parameters	Early-onset ($n=15$)	Others ($n=112$)
Types of IBD		
UC	6 (40.0)	84 (75.0)
CD	7 (46.6)	22 (19.6)
IC	2 (13.4)	6 (5.3)
Male	8 (53.3)	55 (49.1)
Male:female ratio	1.10	0.96
Family history	3 (20.0)	7 (6.2)
Consanguinity	3 (20.0)	10 (8.9)
Extraintestinal manifestations	7 (46.6)*	20 (17.8)
Associated diseases	5 (33.3)†	12 (12.5)

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; IC: IBD-unclassified. *: $P=0.017$, early-onset vs. others; †: $P=0.03$ early-onset vs. others.

mentioned above, early-onset disease was common in patients with CD. Family history and consanguinity were common in patients with early-onset disease but were not statistically significant. Extraintestinal manifestations and associated diseases were also common in patients with early-onset disease ($P=0.017$, odds ratio: 4.02 and $P=0.03$, odds ratio: 4.1, respectively)

Laboratory findings

Laboratory findings of the patients are shown in Table 4. No significant difference was found between the patients with UC and those with CD in hemoglobin levels, sedimentation rate, C-reactive protein (CRP) levels and frequency of anemia, leucocytosis ($>12 \times 10^9/L$), high platelets ($>450 \times 10^9/L$), hypoalbuminemia (<3.5 g/L), hypocalcaemia (<8 mg/dL), high alanin aminotransferase (>40 U/L) levels, hypoferritinemia, and vitamin B12 deficiency (<126 pg/mL). Folic acid deficiency (<3.1 ng/mL) was more common in the patients with CD than those with UC (1.6% vs. 17.3%, $P=0.006$).

Five parameters (anemia, high platelet count, hypoalbuminemia, hypoferritinemia and high sedimentation rate) were abnormal in five (5.5%) patients with UC and two (6.9%) patients with CD. All five parameters were normal in 14 (15.5%) patients with UC, three (10.3%) patients with CD, and 19 (15%) patients with IBD (Fig. 3).

Disease activity

Disease activity was assessed by pediatric ulcerative colitis activity index (PUCAI) for UC and pediatric Crohn's disease activity index (PCDAI) for CD. Mean \pm SD PUCAI score was 41.5 ± 17.4 , and 13

(14.4%) of the 90 patients with UC had PUCAI over 65 suggesting severe disease. The 29 patients with CD had a PCDAI score of 24.2 ± 7.6 , and 10 (34.4%) of them had a PCDAI score ≥ 30 .

Laboratory parameters and PUCAI for predicting extension of UC

The correlation of acute phase reactants including CRP, sedimentation rate, and PUCAI with disease extension was analyzed. The sedimentation rate, CRP and PUCAI were positively correlated with disease extension in the patients with UC ($P=0.0001$, $r=0.39$; $P=0.008$, $r=0.28$; and $P=0.0001$, $r=0.51$, respectively). Area under receiver operation characteristics for predicting the pancolitis for CRP, sedimentation rate and PUCAI was 0.61 ($P=0.06$), 0.66 ($P=0.01$) and 0.76 ($P=0.0001$), respectively (Fig. 4). The sensitivity and specificity of CRP >3.6 mg/dL, sedimentation rate >30 mm/hour and

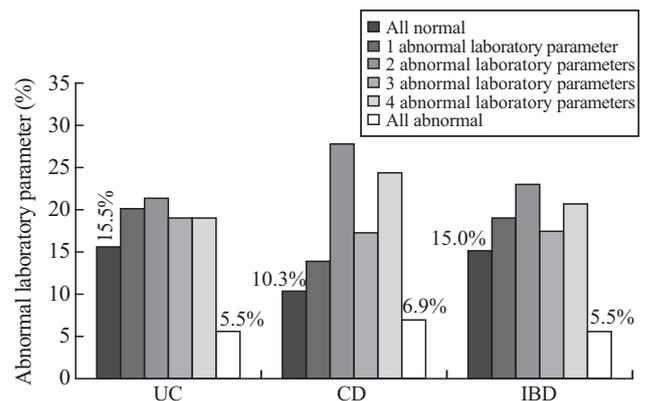


Fig. 3. Frequency of abnormal laboratory parameters. IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease.

Table 4. Laboratory findings of the patients, n (%)

Parameters	UC (n=90)	CD (n=29)	Overall (n=127)
Hemoglobin (g/dL)	10.1 \pm 2.1	10.2 \pm 2.2	10.2 \pm 2.2
Anemia	43 (47.7)	16 (55.1)	63 (49.6)
Leucocytosis	29 (32.2)	17 (58.6)	48 (37.7)
High platelets	39 (43.3)	18 (62.0)	60 (47.2)
Sedimentation rate (mm/h)	39.8 \pm 24.2	47.1 \pm 29.8	40.0 \pm 26.0
CRP (mg/L)	7.1 \pm 9.6	11.1 \pm 17.1	8.0 \pm 11.6
Hypoalbuminemia	24 (26.6)	11 (37.9)	38 (29.9)
Hypocalcemia	9 (10.0)	4 (13.7)	14 (11.0)
High ALT levels	5 (5.5)	1 (3.4)	6 (4.7)
Low ferritin	35 (38.8)	5 (17.2)	42 (33.0)
Low vitamin B12*	4/66 (6.0)	1/24 (4.1)	6/97 (6.2)
Folic acid deficiency*	1/61 (1.6) [†]	4/23 (17.3)	5/91 (5.4)
pANCA*	25/57 (43.8)	1/12 (8.3)	26/70 (37.1)
ASCA*	1/10 (10.0)	5/11 (45.4)	6/24 (25.0)

UC: ulcerative colitis; CD: Crohn's disease; CRP: C-reactive protein; ALT: alanin aminotransferase; pANCA: perinuclear anti-neutrophil cytoplasmic antibodies; ASCA: anti-saccharomyces cerevisiae antibodies. *: positive/ tested; [†]: $P=0.006$, UC group vs. CD group.

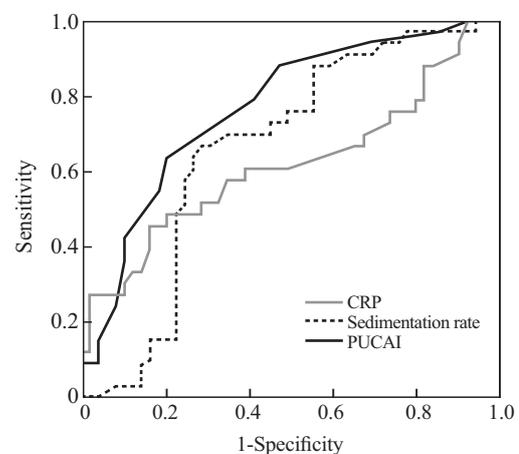


Fig. 4. ROC curve of CRP, erythrocyte sedimentation rate and PUCAI for the prediction of disease extension in UC. ROC: receiver operator characteristic; CRP: C-reactive protein; PUCAI: pediatric ulcerative colitis activity index; UC: ulcerative colitis.

PUCAI >35 for pancolitis were 60%-58%, 72%-53% and 79%-60%, respectively.

Outcomes

All of the patients received medical treatment as first line therapy with 5-aminosalicylic acid (oral or rectal), and corticosteroids (70.8%). 5-aminosalicylic acid and azathioprine were used for maintenance treatment and relapses were subsided after treatment with corticosteroids. Cyclosporine (3.9%), methotrexate (3.1%) and tumour necrosis factor- α blockers (14.9%) were also used in unresponsive patients. On the follow-up, four (4.4%) patients with UC underwent colectomy. Overall, two [1.5%, 95% confidence interval (CI): 0-3.7%] patients died from primary diseases or complications.

Discussion

In this study we investigated demographic, clinical and laboratory findings and outcomes of a large cohort of Turkish children with IBD. The cohort represented approximately one fourth of the whole pediatric patients with IBD in Turkey.

Recent epidemiological studies^[3,5,13] revealed that the incidence of pediatric-onset IBD (CD in particular) is increasing, especially in Canada and USA. A similar increase has been noted in European countries such as Scotland, Wales, Ireland and England.^[3] In our study it was impossible to analyze the incidence rate in our population, because pediatric gastroenterology centers vary in their regions. But the increase of new pediatric patients with IBD (UC in particular) is prominent in our cohort. The reason for the increasing incidence is uncertain but it may be due to lifestyle changes and the rising incidence of obesity.^[3] Additionally, low vitamin D level has been recognized to be associated with increased prevalence of autoimmune diseases such as IBD, diabetes mellitus and rheumatoid arthritis in recent studies. Vitamin D receptor and ligand deficiency are associated with severe IBD in animal models.^[14] The increased incidence of IBD may be associated with the increased prevalence of IBD among the adolescents because of the lack of sunlight exposure or cultural factors. We did not assess the vitamin D level in our patients, it was shown that vitamin D deficiency is prevalent among the adolescents in Turkey.^[15]

Contrary to pediatric data, patients with UC were more than those with CD (70.9% vs. 22.8%) in our study. CD was more common than UC in children in the USA, United Kingdom, Scotland, Wales and Sweden.^[5,8,16-18] Our results were similar to those found in the Italian pediatric-IBD database and adult-IBD database.^[4]

The mean age of the patients at the time of diagnosis with IBD was 11.6 years which was younger than that in other studies.^[5,7,18] This may be related to increased awareness of symptoms of IBD. The short duration of symptoms (7.2 months) in contrast to other studies support the awareness of symptoms of IBD. We found that the percentage of males was significantly higher than that of females in patients with CD, and the percentage of males was higher in patients with CD than in those with UC. These findings were in sharp contrast with some previous studies,^[5,7,19] but consistent with recent studies from the UK, Canada and USA. The result indicated that gender-related factors may play a role in the pathogenesis of CD. Positive family history is the most important factor for the development of IBD especially in the early-age. We found that 7.8% of the patients had a positive family history of IBD and 10.2% had parental consanguinity. These findings were lower than those of the previous studies.^[4,5,20,21]

Most of our patients had classic symptoms of IBD such as abdominal pain, diarrhea and rectal bleeding on admission, which were similar to those reported previously. Bloody diarrhea was more common in patients with UC than in those with CD. Obesity was seen in 6.6% of the patients in our study. The prevalence of overweight/obesity was 23.6% in children with IBD in the USA and obesity was associated with severe diseases.^[22] Approximately, one fifth of our patients had extra-intestinal manifestations on admission. Joints were the frequently affected sites especially in patients with UC. The extra-intestinal manifestations were less in our patients than in American children, but similar to those in Korean children.^[5,9]

IBD was associated with other diseases in 13.3% of our patients. The association of FMF with IBD was reported previously. Mediterranean fever gene (*MEFV*) mutation was detected approximately in 20% of the Turkish children with IBD.^[23] In an adult study, *MEFV* mutation was found in 25% of the patients with IBD, which was higher than that in the healthy controls.^[24,25] Sometimes, patients with FMF presented with bloody diarrhea, weight loss or other symptoms of IBD.^[26] Our patients who were treated with colchicine presented with symptoms of IBD. Autoimmune diseases such as type 1 diabetes mellitus, celiac diseases and autoimmune hepatitis were found in one of our patients. IBD was also associated with other auto-immune diseases such as rheumatoid arthritis, systemic lupus and type 1 diabetes mellitus, and there was an increased risk of immune mediated condition in children with IBD.^[27]

Early-onset IBD is seen in patients with IBD below 6 years old in terms of genetic and environmental factors. Approximately 15% of the patients were diagnosed

before 6 years old and 6% before 3 years old.^[28] Colon diseases and positive family history were the predominant characteristics of patients with early-onset IBD.^[28] In our study 11.8% of the patients were younger than 5 years old. Family history and consanguinity were more common in early-onset IBD patients, but they were not statistically significant. Extraintestinal manifestations and associated diseases were commonly seen in patients with early-onset diseases.

The diagnosis of IBD is dependent on the macroscopic and microscopic findings of endoscopy. Laboratory evaluation is especially important in patients presenting with mild symptoms excluding bloody diarrhea. Hemoglobin levels, platelet counts, acute phase reactants including CRP, sedimentation rate, albumin level and ferritin level are the frequently used laboratory parameters. We found that approximately 50% of the patients had anemia and high platelet count. Of the patients, 30%-33% had decreased ferritin and albumin levels, respectively. Additionally, 6.2% of the patients had vitamin B12 deficiency. Folic acid deficiency was found in 5.4% of the patients, and was more common in patients with CD than in those with UC (1.6% vs. 17.3%, $P=0.006$). However, the laboratory parameters may be normal in some patients. In our study, 15% of the patients had normal laboratory parameters including hemoglobin levels, platelet count, albumin and ferritin levels, and sedimentation rate. Therefore, normal laboratory levels should not dissuade the pediatric gastroenterologist or pediatrician for considering the diagnosis of IBD. Similar to our study, Mack et al^[29] studied the usefulness of hemoglobin level, platelet count, albumin level and erythrocyte sedimentation rate for the diagnosis of IBD in children, and they found normal levels in 21% of the patients with mild CD and 54% of the patients with mild UC.

We analyzed the correlation of acute phase reactants and PUCAI with the extension of colitis in patients with UC. We found that PUCAI was superior to CRP and erythrocyte sedimentation rate for the prediction of extension of colitis in patients with UC. PUCAI >35 had a higher sensitivity and specificity for pancolitis. PUCAI was developed for the noninvasive assessment of disease activity in patients with UC, and it was shown that it may be used for the prediction of steroid response.^[30,31] Recently, a strong correlation was found between PUCAI and the likelihood of undergoing surgical procedure.^[32] CRP and erythrocyte sedimentation rate were used in the diagnosis of UC, but the results were different. Turner et al^[33] found that CRP is better than erythrocyte sedimentation rate in predicting the activity and extension of the disease and is more closely correlated with endoscopic appearance.

The rate of colectomy was lower in our study than

in other studies. The rate of colectomy decreased with the use of novel immunomodulators in the past years.^[34] In our patients the mortality rate was 1.5% (95% CI: 0-3.7%). Peneau et al^[35] analyzed the mortality rate in children with IBD in France and found that the mortality rate was 0.84%, which was not different from the rate of the general population.

In conclusion, this is the first report about the demographic findings, clinical manifestations, and outcomes of children with IBD in Turkey. IBD is an increasing disease in Turkey. The data of this study showed similar features as shown in other studies, but further prospective multicenter studies are needed to detect the exact incidence of IBD in children in this country.

Funding: None.

Ethical approval: Our study was retrospective and made based on the file records examination. Informed consent was obtained from participants (parents) to participate in the study.

Competing interest: None.

Contributors: Cakir M wrote the main body of the article under the supervision of all authors. All authors contributed to the intellectual content and approved the final version.

References

- 1 Shanahan F. Inflammatory bowel disease: immunodiagnostics, immunotherapeutics, and ecotherapeutics. *Gastroenterology* 2001;120:622-635.
- 2 Hait E, Bousvaros A, Grand R. Pediatric inflammatory bowel disease: what children can teach adults. *Inflamm Bowel Dis* 2005;11:519-527.
- 3 Henderson P, Wilson DC. The rising incidence of paediatric-onset inflammatory bowel disease. *Arch Dis Child* 2012;97:585-586.
- 4 Castro M, Papadatou B, Baldassare M, Balli F, Barabino A, Barbera C, et al. Inflammatory bowel disease in children and adolescents in Italy: data from the pediatric national IBD register (1996-2003). *Inflamm Bowel Dis* 2008;14:1246-1252.
- 5 Kugathasan S, Judd RH, Hoffmann RG, Heikenen J, Telega G, Khan F, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr* 2003;143:525-531.
- 6 Al-Qabandi WA, Buhamrah EK, Hamadi KA, Al-Osaimi SA, Al-Ruwayeh AA, Madda J. Inflammatory bowel disease in children, an evolving problem in Kuwait. *Saudi Saudi J Gastroenterol* 2011;17:323-327.
- 7 Sawczenko A, Sandhu BK, Logan RF, Jenkins H, Taylor CJ, Mian S, et al. Prospective survey of childhood inflammatory bowel disease in the British Isles. *Lancet* 2001;357:1093-1094.
- 8 Hope B, Shahdarpuri R, Dunne C, Broderick AM, Grant T, Hamzawi M, et al. Rapid rise in incidence of Irish paediatric inflammatory bowel disease. *Arch Dis Child* 2012;97:590-594.
- 9 Kim BJ, Song SM, Kim KM, Lee YJ, Rhee KW, Jang JY, et al. Characteristics and trends in the incidence of inflammatory bowel disease in Korean children: a single-center experience.

- Dig Dis Sci 2010;55:1989-1995.
- 10 El Mouzan MI, Al Mofarreh MA, Assiri AM, Hamid YH, Al Jebreen AM, Azzam NA. Presenting features of childhood-onset inflammatory bowel disease in the central region of Saudi Arabia. *Saudi Med J* 2012;33:423-428.
 - 11 Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:340-361.
 - 12 Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011;17:1314-1321.
 - 13 Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011;17:423-439.
 - 14 Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. *Exp Biol Med (Maywood)* 2004;229:1136-1142.
 - 15 Karagüzel G, Dilber B, Çan G, Ökten A, Değer O, Holick MF. Seasonal vitamin D status of healthy schoolchildren and predictors of low vitamin D status. *J Pediatr Gastroenterol Nutr* 2014;58:654-660.
 - 16 Barton JR, Gillon S, Ferguson A. Incidence of inflammatory bowel disease in Scottish children between 1968 and 1983; marginal fall in ulcerative colitis, three-fold rise in Crohn's disease. *Gut* 1989;30:618-622.
 - 17 Cosgrove M, Al-Atia RF, Jenkins HR. The epidemiology of paediatric inflammatory bowel disease. *Arch Dis Child* 1996;74:460-461.
 - 18 Lindberg E, Lindquist B, Holmquist L, Hildebrand H. Inflammatory bowel disease in children and adolescents in Sweden, 1984-1995. *J Pediatr Gastroenterol Nutr* 2000;30:259-264.
 - 19 Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. *Am J Epidemiol* 1999;149:916-924.
 - 20 El Mouzan M, Al-Mofarreh M, Assiri A, Hamid Y, Saeed A. Consanguinity and inflammatory bowel diseases: is there a relation? *J Pediatr Gastroenterol Nutr* 2013;56:182-185.
 - 21 Weinstein TA, Levine M, Pettei MJ, Gold DM, Kessler BH, Levine JJ. Age and family history at presentation of pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2003;37:609-613.
 - 22 Long MD, Crandall WV, Leibowitz IH, Duffy L, del Rosario F, Kim SC, et al. Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2011;17:2162-2168.
 - 23 Uslu N, Yüce A, Demir H, Saltik-Temizel IN, Usta Y, Yilmaz E, et al. The association of inflammatory bowel disease and Mediterranean fever gene (MEFV) mutations in Turkish children. *Dig Dis Sci* 2010;55:3488-3494.
 - 24 Akyuz F, Besisik F, Ustek D, Ekmekçi C, Uyar A, Pinarbasi B, et al. Association of the MEFV gene variations with inflammatory bowel disease in Turkey. *J Clin Gastroenterol* 2013;47:e23-e27.
 - 25 Sari S, Egritas O, Dalgic B. The familial Mediterranean fever (MEFV) gene may be a modifier factor of inflammatory bowel disease in infancy. *Eur J Pediatr* 2008;167:391-393.
 - 26 Beşer OF, Kasapçopur O, Cokuğraş FC, Kutlu T, Arsoy N, Erkan T. Association of inflammatory bowel disease with familial Mediterranean fever in Turkish children. *J Pediatr Gastroenterol Nutr* 2013;56:498-502.
 - 27 Kappelman MD, Galanko JA, Porter CQ, Sandler RS. Association of paediatric inflammatory bowel disease with other immune-mediated diseases. *Arch Dis Child* 2011;96:1042-1046.
 - 28 Heyman MB, Kirschner BS, Gold BD, Ferry G, Baldassano R, Cohen SA, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr* 2005;146:35-40.
 - 29 Mack DR, Langton C, Markowitz J, LeLeiko N, Griffiths A, Bousvaros A, et al. Laboratory values for children with newly diagnosed inflammatory bowel disease. *Pediatrics* 2007;119:1113-1119.
 - 30 Cakir M, Ozgenc F, Yusekkaya HA, Ecevit CO, Yagci RV. Steroid response in moderate to severe pediatric ulcerative colitis: a single center's experience. *World J Pediatr* 2011;7:50-53.
 - 31 Turner D, Mack D, Leleiko N, Walters TD, Uusoue K, Leach ST, et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. *Gastroenterology* 2010;138:2282-2291.
 - 32 Gray FL, Turner CG, Zurakowski D, Bousvaros A, Linden BC, Shamberger RC, et al. Predictive value of the Pediatric Ulcerative Colitis Activity Index in the surgical management of ulcerative colitis. *J Pediatr Surg* 2013;48:1540-1545.
 - 33 Turner D, Mack DR, Hyams J, LeLeiko N, Otley A, Markowitz J, et al. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or both? A systematic evaluation in pediatric ulcerative colitis. *J Crohns Colitis* 2011;5:423-429.
 - 34 Rungoe C, Langholz E, Andersson M, Basit S, Nielsen NM, Wohlfahrt J, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. *Gut* 2014;63:1607-1616.
 - 35 Peneau A, Savoye G, Turck D, Dauchet L, Fumery M, Salleron J, et al. Mortality and cancer in pediatric-onset inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2013;108:1647-1653.

Received December 24, 2013

Accepted after revision May 28, 2014