Phenotypic Pattern of Early Versus Later-Onset Pediatric Inflammatory Bowel Disease in a Eurasian Country

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ABSTRACT

Objectives: It is not clear whether the characteristics of pediatric inflammatory bowel disease (IBD) differ between Eastern and Western countries. The aim of this study was to analyze the characteristics of PIBD in Turkey, according to the age at diagnosis.

Methods: The data of 176 children with IBD who were followed in our center were analyzed. Patients were divided into early (EO-IBD, onset at 2 to <10 years) and later-onset (LO-IBD, 10 to ≤17 years) IBD according to the age at diagnosis. Patients' data with ulcerative colitis (UC) and Crohn's disease (CD) were compared.

Results: Of 176 patients, 47 (26.7%) were diagnosed with EO-IBD. Patients with early-onset ulcerative colitis (EO-UC) had the highest rate of family history of IBD (17.6%). Pancolitis was the most common form of UC regardless of the age at onset. The rate of moderate-severe disease activity in later-onset UC (62.5%) was higher than in EO-UC (37.5%). A higher rate of extraintestinal manifestations was observed in EO-IBD patients, particularly in EO-UC (38.2%) than in LO-IBD patients. Patients with early-onset CD (EO-CD) had predominantly colonic involvement and nonstricturing, nonpenetrating disease behavior. The rate of perianal disease in patients with later-onset CD (LO-CD) (64.5%) was noticeably higher than those with EO-CD (23%).

Conclusions: Our results suggest that patients with EO-UC represented a distinct phenotype with a mild disease activity, high rate of extraintestinal symptoms, and a high proportion of family history. The analysis of our IBD cohort also demonstrated remarkably high rate of perianal disease, particularly in patients with LO-CD.

An infographic is available for this article at: *http://links.lww.com/MPG/C875*.

Key Words: early-onset, inflammatory bowel disease, pediatric, phenotype

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What Is Known

- It has been reported that disease phenotypes differ by age of onset within the pediatric inflammatory bowel disease (IBD) population.
- Conflicting results have been obtained from previous studies investigating age-related differences in different geographical areas between Western and Eastern countries.

What Is New

- Our results suggest that patients with early-onset ulcerative colitis represented a distinct phenotype with a mild disease activity, higher rate of extraintestinal symptoms, and a higher proportion of family history.
- The analysis of our IBD cohort demonstrated remarkably high rate of perianal disease, particularly in patients with later-onset Crohn's disease.

Inflammatory bowel disease (IBD) is a group of chronic inflammatory gastrointestinal disorders with increasing prevalence worldwide over the past few decades (1–3). The 3 main subtypes of this heterogeneous disease are Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified (IBD-U). It has been thought that the disease is multifactorial, and the interaction of genetic, environmental, microbial, and immunological factors play role in its etiology (4). Patients with IBD may present with a variety of gastrointestinal symptoms, depending on the subtype and location of the disease and the clinical picture may be accompanied by extraintestinal findings. Although IBD can occur at any age, up to 25% of all IBD patients are diagnosed in childhood or adolescence (5–7). Age-related differences in the course of IBD has been evaluated in pediatric and adult populations, and it has been demonstrated that pediatric IBD (PIBD) appears to have a more severe clinical course, unlike adults (8,9). It has also been reported that disease phenotypes differ by age of onset within the pediatric IBD population (10–13). Based on reported differences regarding location, rate of surgery, and rate of biologic therapy, PIBD was divided into 2 categories according to the age at onset in Paris classification: A1a (0 to <10 years) and A1b (10 to <17 years) (14).

The scientific studies regarding the epidemiology and clinical features of PIBD have mostly been conducted in Western countries including Europe, Canada, and North America. In recent years, there has been an increase in the number of publications from Eastern countries due to the increasing incidence of PIBD. There is no published data revealing the age-related characteristics of PIBD from Turkey, which acts as a bridge between the Europe and the Asia. The aim of this study was to investigate the phenotypes and the course of PIBD according to the age at onset in Turkey, a Eurasian country.

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METHODS

The prospectively recorded medical data of 197 patients who were followed up in our tertiary center and diagnosed with IBD before the age of 18 were revised. Patients diagnosed younger than 2 years of age or with a defined monogenic defect or those with unclassified IBD were excluded from the analysis. Demographic, clinic, endoscopic, histopathologic data of the remaining 176 patients were compiled. A positive family history was accepted as the presence of IBD in family members with first-degree consanguinity. All patients enrolled to the study had been diagnosed according to Porto criteria (15). Patients were categorized into two groups according to the age at diagnosis: Early-onset IBD (EO-IBD) was defined as IBD diagnosed between 2 and 10 years of age, and later-onset IBD (LO-IBD) was defined as IBD diagnosed between 10 and 17 years of age. The disease phenotype (location or extent, behavior, perianal involvement) was assessed according to the Paris classification (14). Disease activity was scored by the Pediatric Crohn's Disease Activity Index (PCDAI) for patients with CD, and the Pediatric Ulcerative Colitis Activity Index (PUCAI) for patients with UC (16,17). Anthropometric data [Body mass index (BMI), weight for age (WFA), height for age (HFA) z scores] were used to assess growth status. We also evaluated the extraintestinal manifestations (EIM) related to the systems or organs other than the gastrointestinal system (dermatological or mucosal, skeletal, hepatic-pancreatic-biliary, ophthalmologic) at the time of admission. Furthermore, we compared the characteristics of EO-IBD and LO-IBD between patients with CD and UC.

Statistical analyses were performed using SPSS software version 22. Values for continuous variables were given as mean ± standard deviation while categorical variables were provided as percentages. Normality of distribution was ascertained by the Kolmogorov–Smirnov test and the Shapiro–Wilk test. Continuous data were compared using Student t test or the Wilcoxon rank sum tests depending on normality of distribution. Categorical variables were compared by Chi-square or Fisher exact tests. P values of <0.05 were considered statistically significant.

The study was approved by local Ethics Committee of Marmara University School of Medicine.

RESULTS

Of 197 patients, 14 (7.1%) were diagnosed as IBD under the age of 2. A defined genetic defect was detected in 10 of 14 of infant patients. Excluding the infantile IBD group, a genetic defect was further detected in 6 more patients. The data of the remaining 176 patients with UC or CD were analyzed for the study.

In our study group the age at diagnosis was median 13 years (mean 11.8 ± 3.9, range 15 years), and 26.7% (47/176) of our patients were diagnosed between the ages of 2–10 years (EO-IBD). Most of the patients in EO-IBD group were UC (72.3%). However, the frequency of UC in LO-IBD group was 51% and the difference was statistically significant ($P = 0.01$) (Table 1).

Among patients with EO-IBD, the mean age at diagnosis was significantly higher in patients with CD than in those with UC [mean 7.7 ± 1.6 years (median 8 years, range 6 years) vs mean 6 ± 2.4 years (median 6 years, range 7 years)] ($P = 0.01$). On the other hand, the mean age at diagnosis was comparable between CD and UC patients in the LO-IBD group [mean 13.9 ± 2.1 years (median 14 years, range 7 years) vs mean 13.5 ± 2.3 years (median 14 years, range 7 years)] ($P = 0.3$).

The male-to-female ratio EO-IBD and LO-IBD group of patients were 0.96 and 0.82, and the gender distribution between the groups was comparable ($P > 0.05$). However, male predominance among CD patients (61.6% vs 55.6%) and female predominance among UC patients (55.9% vs 65.2%) was observed in both EO-IBD and LO-IBD populations (Table 1).

Overall 17.9% of the study group had consanguinity between the parents. The rate of consanguinity in patients with LO-IBD group (19.2%) was higher than the EO-IBD group (11.9%); however, the difference was not statistically significant (Table 1). In this cohort, 9% of patients had family history of IBD, with a higher incidence in EO-IBD group of patients (14.8%) compared to the LO-IBD group (5.4%), and the difference was statistically significant ($P < 0.05$). Patients with EO-UC had the highest rate of family history of IBD (17.6%) (Table 1).

None of the patients with EO-CD in this cohort had isolated ileal involvement except one. There were no differences regarding isolated colonic, ileocolonic or upper gastrointestinal involvements between the patients with early- and later-onset CD. Of 63 patients with later-onset CD, 13 (20.6%) patients exhibited stricturing and/or penetrating behavior at the time of diagnosis. On the other hand, nearly all patients with early-onset CD had nonstricturing, nonpenetrating disease behavior except for one.

More than half of Crohn patients (57.3%) had perianal disease in our cohort. The frequency of perianal involvement in patients with later-onset CD (64.5%) was noticeably higher than those with early-onset CD (23%), and the difference between patients with later-onset and early-onset CD was statistically significant (Fig. 1). Granuloma at diagnosis was observed in 46.1% of the patients EO-CD and 42.3% of the patients with LO-CD, and these figures were comparable (Table 2).

Pancolitis was the most common form of UC regardless of the age at onset (40% in early-onset UC vs 40.8% in later-onset UC). Proctitis was found in 12.1% of patients with LO-UC while only one patient with EO-UC had proctitis (Fig. 2).

Most patients with early- or later-onset CD had moderate-to-severe disease activity (61.5% vs 72.4%), and the difference in disease activities between early- and later-onset CD was not significant. However, the rate of moderate/severe disease activity in later-onset UC (62.5%) was higher than in early-onset UC (37.5%) ($P < 0.05$) (Table 2).

In this study group, 14% of the patients were underweight (WFA z score < −2). The rates of wasting (BMI z score < −2) and stunting (HFA z score < −2) were 17.2% and 4.5%, respectively. There were no differences in mean WFA, HFA, and BMI z scores

TABLE 1. Characteristics and comparison of patients with early- and later-onset IBD.

Characteristics	EO-IBD N = 47 AND (26.7%)	LO-IBD N = 129 AND (73.3%)	P
UC/CD (%)	72.3/27.7	51.2/48.8	0.01
Male/female (ratio)	0.96	0.82	0.64
Family history (%)	14.8	5.4	0.04
Consanguinity (%)	11.9	19.2	0.23
Extraintestinal manifestation (%)	36.1	11.6	0.001
BMI Z score (mean ± SD)	−0.81 ± 1.8	−0.7 ± 1.3	0.9
HFA Z score (mean ± SD)	−0.17 ± 1.31	−0.36 ± 1.0	0.34
WFA Z score (mean ± SD)	−0.53 ± 1.81	−0.69 ± 1.15	0.54
BMI Z score < −2 (%)	17	16.8	0.91
HFA Z score < −2 (%)	7.6	3.3	0.25
WFA Z score < −2 (%)	15.3	13.5	0.77

BMI = body mass index, HFA = height for age, SD = standard deviation, WFA = weight for age.

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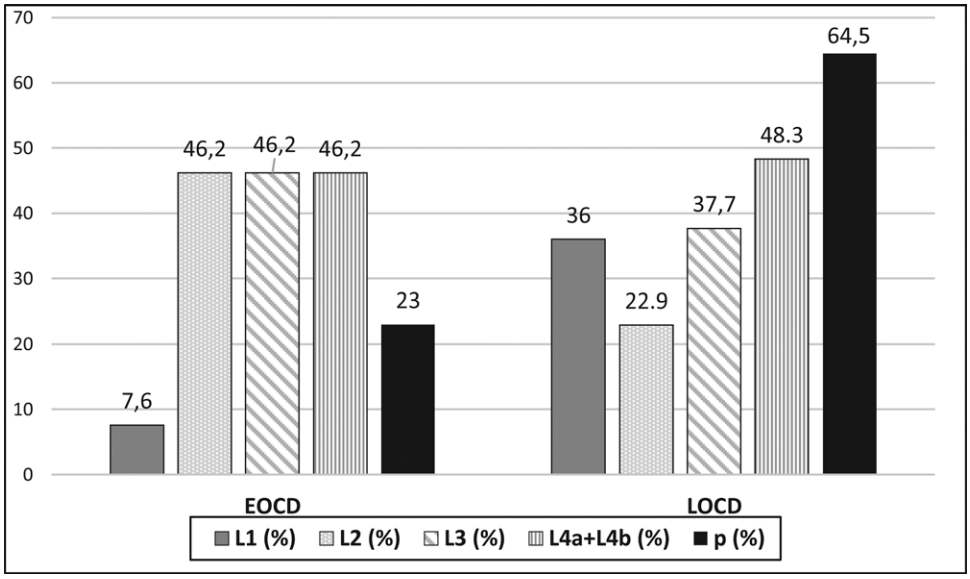

FIGURE 1. The distribution of the patients according to the involved segment of the gastrointestinal tract in early- and later-onset Crohn's disease.

between EO-IBD and LO-IBD. WFA, HFA, and BMI z scores were also comparable across the age categories within both UC and CD groups (Tables 1 and 2).

The incidence of EIM at the time of admission was 18.2% in our study group. The most frequent extraintestinal manifestations were related to skin or mucosa [aphthous stomatitis (5.1%), erythema nodosum (2.3%), pyoderma gangrenosum (0.6%)] and followed by joints [axial and/or peripheral arthritis (5.7%)]. The frequency of pancreatitis and primary sclerosing cholangitis were 2.8% and 1.1%, respectively. Uveitis was detected in only 1 patient with CD (0.6%). A higher rate of EIM was observed in patients with EO-UC than in patients with LO-UC, and the difference between these 2 groups was statistically significant ($P < 0.05$). However, the frequency of EIMs was comparable between patients with early- and later-onset CD (Table 2).

DISCUSSION

The term "pediatric IBD" is recognized to represent a unique phenotype, not just a specific age group. Not only the clinical

TABLE 2 Characteristics and comparison of patients with early- and later-onset Crohn's disease and ulcerative colitis.

	CD			UC		
Characteristics	EO-CD	LO-CD	*P*	EO-UC	LO-UC	*P*
Age at diagnosis (years), mean ± SD (median)	**7.7 ± 1.2 (8)**	13.9 ± 2.1 (14)		6 ± 2.4 (6)	13.5 ± 2.3 (14)	
Male/female (%)	61.6/38.4	55.6/44.4	0.69	44.1/55.9	34.8/65.2	0.36
Family history (%)	7.6	6.3	0.85	17.6	4.5	**0.03**
consanguinity (%)	25	23	0.89	6.6	17.2	0.17
PCDAI (moderate to severe) (%)PUCAI (moderate + severe) (%)	61.5	72.4	0.43	37.5	62.5	**0.04**
BMI Z score (mean ± SD)	−0.50 ± 1.95	−0.91 ± 1.37	0.38	−0.94 ± 1.88	−0.62 ± 1.28	0.36
HFA Z score (mean ± SD)	−0.34 ± 0.99	−0.45 ± 0.92	0.69	−0.09 ± 1.44	−0.26 ± 1.08	0.55
WFA Z score (mean ± SD)	−0.36 ± 1.55	−0.82 ± 1.14	0.23	−0.61 ± 1.94	−0.54 ± 15	0.83
BMI Z score < −2 (%)	16.6	21.3	0.99	18.5	12.2	0.44
HFA Z score< −2 (%)	8.3	3.2	0.42	7.4	3.5	0.59
WFA Z score < −2 (%)	25	14.7	0.4	11.1	12.2	0.99
Extraintestinal manifestation (%)	30.7	15.8	0.2	38.2	7.5	**0.001**
Perianal disease (%)	23	64.5	**0.006**	–	–	
Granuloma (%)	46.1	42.3	0.8	–	–	
B1 behavior (%)	92	75	0.17	–	–	
B2 and/or B3 behavior (%)	7.6	20.6	0.17	–	–	

BMI = body mass index, CD = Crohn's disease, HFA = height for age, SD = standard deviation, UC = ulcerative colitis, WFA = weight for age.

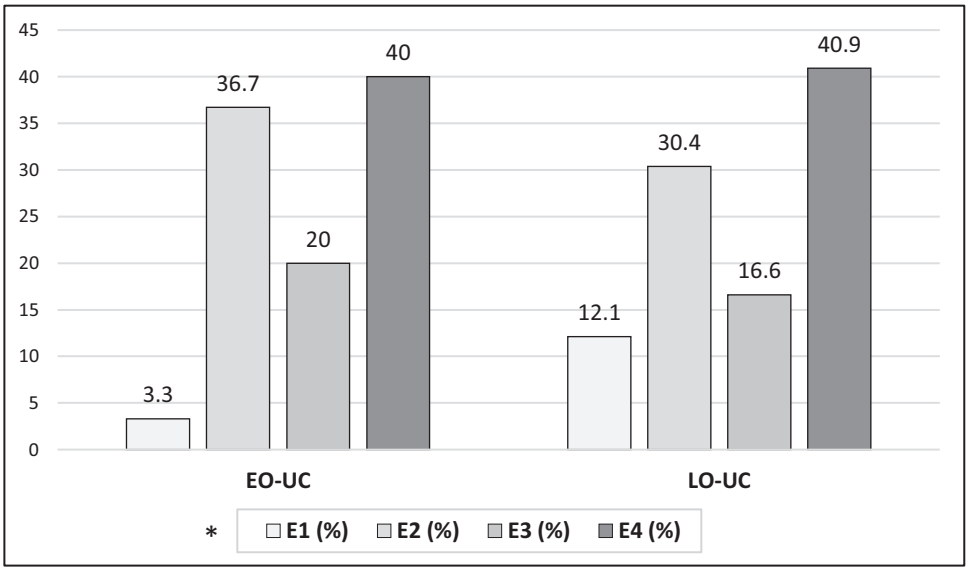

FIGURE 2. The distribution of the patients according to the extent of the disease in early- and late-onset ulcerative colitis.

features but also the course of pediatric IBD differ according to age groups. Some reports have suggested that patients diagnosed younger than 6 years of age have a distinct disease phenotype, and differ epidemiologically (10–13). Thus, the term "very early-onset IBD," referring to pediatric IBD that occurs before age of 6, is widely used today. However, our study is based on the Paris classification, in which, pediatric IBD is divided into two groups according to disease onset: before 10 years of age (A1a) and after 10 years of age (A1b) (14).

In a subset of IBD patients typically diagnosed before 2 years of age, monogenic defects that cause innate immune errors have been increasingly identified (18). These immune errors are inherited according to Mendelian traits, which are distinct from the polygenic trait accepted in IBD pathogenesis. These monogenic immune disorders clinically mimic IBD phenotype. It is controversial whether infants with monogenic defects can be classified as having IBD. Therefore, very young patients presented with IBD phenotype were not included in this study.

The prevalence of EO-IBD in our cohort was 26.7%, consistent with previous reports (19,20). Most of the patients in EO-IBD group were UC, while the rate of UC and CD in the LO-IBD group was almost equal. Similarly, it has been reported in a few cohort studies from the Middle East and Japan that the incidence of UC is higher in EO-IBD patients (21,22). In contrast, previous studies from Western countries have reported that patients with the EO-IBD, particularly those with onset <6 years of age, were more likely to have CD (23–26).

In this study cohort, there was male predominance in patients with CD, as previously reported (27–29). While the predominance of female gender among our UC patients was remarkable. However, there was no significant gender difference between the EO-IBD and LO-IBD groups.

The overall incidence of family history in this cohort was not as high as previously reported, but a higher incidence of IBD within the family was documented in the EO-IBD group, which was consistent with published data (30,31). This supports a stronger genetic influence on the pathogenesis of EO-IBD. An obviously higher rate of positive family history found in this cohort of patients with EO-UC, and it was similar to the figures previously reported (12,21,32,33).

The segments of gastrointestinal tract affected by IBD also differed in patients with early- or later-onset IBD. Isolated colonic disease is a well-recognized feature of early-onset CD. Our patients with EO-CD had predominant colonic involvement, whereas those with LO-CD more likely had ileocolonic disease that was compatible with previous reports (25,27,33–35). Almost half of the patients with both early- and later-onset CD had upper gastrointestinal involvement besides colon and/or ileum. The prevalence of upper gastrointestinal and/or small intestinal involvement has scarcely been published in early-onset CD (6,32,35). This can be attributed to the lack of routine gastroscopy particularly in those presenting with colonic manifestations in early childhood. Our study was conducted at a tertiary care center in a university hospital where upper GI endoscopy is a routine procedure in all patients with suspected IBD regardless of age. The higher prevalence of upper GI involvement in our study than in previously published data can be explained by the practice of the Porto criteria to all patients with suspected IBD.

Consistent with published data, inflammatory disease behsavior was the most common phenotype in patients with both early- and later-onset CD (7,35,36). The prevalence of perianal disease in our cohort was remarkably high, and similarly, high prevalence of perianal disease has been reported particularly from Eastern countries (32,36–40). Patients with late-onset CD had strikingly high prevalence of perianal disease and furthermore, nearly one fifth of this group had penetrating/structuring disease behavior as well. Given the disease behavior and high rate of perianal disease, LO-CD seems more likely to exhibit an aggressive phenotype that includes strictures, fistulas, and/or abscesses.

In this cohort, pancolitis was the most common endoscopic feature in both early- and later-onset UC, as previously published (21,25,27,32). Isolated proctitis, resembling adult UC was observed in 12.1% of patients with LO-UC, supporting the age-related phenotype association.

Most of the patients with UC and CD patients in this IBD cohort had moderate-to-severe disease activity at diagnosis. It has previously been reported that patients particularly with EO-CD had higher disease activity (26,36,38). But, the rate of moderate/severe disease activity at diagnosis were compatible between early- and later-onset CD groups in our study. On the other hand, in the UC group, patients with later-onset disease had much more severe disease activity compared to EO-UC, and this difference was remarkable.

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It has been known that impairment in linear growth is an important finding in pediatric IBD, particularly in CD. However, the mean HFA z scores were comparable between EO-IBD and LO-IBD groups and across the age categories within both UC and CD. The rate of stunting indicating moderate or severe chronic malnutrition was also similar between the groups, indicating the absence of linear growth retardation in patients with CD in our cohort.

Previously, the frequency of extraintestinal manifestations (EIMs) in pediatric IBD patients has been reported at quite different rates. The diversity of definitions for EIM seems to be one of the main reasons, the other being the misclassification of some adverse reactions such as hepatitis, pancreatitis as EIM. In the pediatric IBD population, EIM occurs before the diagnosis in up to 30% of cases, while at least one EIM is reported to have developed in 20% of patients with IBD within 5 years of diagnosis. In this study, the high rate of EIMs we detected in EO-IBD, particularly in EO-UC, emerged as a phenotypic trait specific to this group. A similar high incidence of EIMs associated with EO-UC was reported previously in a study reported from Japan (38).

Herein, we described the phenotype of pediatric IBD in a quite comprehensive cohort from a tertiary referral center in a university hospital. Compared with the previously published multicenter reports, the relatively small sample size may be considered as a limitation; however, we believe that the homogeneity in clinical practice and meticulous work-up strengthens our data in this single-center study. The EO-IBD phenotype in our cohort confirmed well-known traits despite some conflicts with previously published data from different geographical areas. The EO-IBD group in our cohort consisted predominantly of patients with UC. EO-UC in this group demonstrated a phenotype with a higher rate of family history, extraintestinal manifestations and a milder disease activity compared to later-onset UC. The most striking phenotype of the patients with CD was significantly higher frequency of perianal CD, which is consistent with the data reported from Eastern countries (30,32,37,41). Our results supported that the phenotypic expression of pediatric IBD differed according to the age at disease onset. This heterogeneity suggests that the approach to patients should be age dependent.

It is noteworthy that conflicting results have been obtained from previous studies investigating age-related differences in different geographical areas between Western or Eastern countries. This may be due to discrepancies in the age groups selected, differences in facilities and clinical practices of different centers rather than the absence of distinct phenotypes. Thus, comprehensive studies in homogeneously defined age groups would be more informative for the description of age dependent phenotypes of pediatric IBD.

CONCLUSIONS

The phenotypes of both ulcerative colitis and Crohn's disease differ by age of onset in pediatric population. Our results suggest that patients with early-onset ulcerative colitis represented a distinct phenotype with a mild disease activity, higher rate of extraintestinal symptoms, and a higher proportion of family history. Analysis of our IBD cohort also revealed a relatively high rate of perianal disease in later-onset Crohn's patients.

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