Clinical Features of Ulcerative Colitis and Crohn's Disease in Turkey

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Abstract

Background and Aims: This study is aimed at determining the clinical and socio-demographic characteristics of Turkish patients with inflammatory bowel disease who have been treated in a tertiary referral center. **Patients and Methods**: The study was conducted between 1993 and 2007 at Ankara Yuksek Ihtisas Hospital, Inflammatory Bowel Disease Clinics. The clinical and epidemiologic data from this clinic were gathered and analysed. **Results:** During the study period, 702 patients were identified as having inflammatory bowel disease; among these, 507 with ulcerative colitis (72.2%) and 195 with Crohn's disease (27.8%). The mean age at diagnosis was 46.2 years in ulcerative colitis and 40 years in Crohn's disease ($p<0.001$). The male to female ratio was 1.2 for ulcerative colitis and 1.6 for Crohn's disease ($p=0.12$). Of the patients who were primarily diagnosed with ulcerative colitis 16.8 % had their diagnoses changed to Crohn's disease after the follow-up period. **Conclusions:** Peak age of onset for both Crohn's disease and ulcerative colitis were similar to other countries. A slight male predominance of Crohn's disease and ulcerative colitis were found for Turkish patients. Though it takes longer to diagnose, Crohn's disease may have a milder course in Turkish patients.

Key words

Crohn's disease – ulcerative colitis – epidemiology.

Introduction

Inflammatory bowel disease (IBD) denotes a group of diseases, triggered and sustained by a variety of factors (i.e. genetic and environmental) that share similar clinical manifestations and which primarily affect the small intestine and colon [1].

The two most common entities of IBD, ulcerative colitis (UC) and Crohn's disease (CD), are more common in developed countries than in developing ones, though this gap seems to be closing [1]. They have a bimodal distribution with a peak in 20s or 30s and a second peak later in life. The occurrence of IBD has been extensively analyzed with respect to its demographical, socio-economic, occupational, and geographic distribution, to shed light on its etiology [1, 2].

The incidence of CD and UC appears to have stabilized in most European and American regions whereas the incidence continues to rise in regions where IBD has been less common [2].

Even with this stabilization and with a prevalence of 1 million patients in the US alone, to which are added 30,000 new cases per year, the IBD remains a prominent health burden. This incidence is evenly divided between UC and CD, with a slight gender gap (i.e. UC is slightly more common in males and vice versa for CD). Both diseases also tend to occur in the higher socio-economic strata.

Although former subgroup analyses by racial and ethnic subgroups have indicated that higher rates of IBD occur in people of Caucasian and Ashkenazic Jewish origin than in individuals from other backgrounds, the distribution of IBD among ethnic and racial groups is currently viewed as dynamic [1]. Consequently, reported incidence and prevalence rates vary widely, in part owing to differences in the criteria used for diagnosis.

Unfortunately, there have been only a few rigorous studies on IBD in Turkey [3-6]. This may be attributed to the lack of cooperation between research centers. Also, as far as could be discerned, those mostly focused on populations from Western Anatolia. However, because Turkey is a wide geographic country of different ethnicities, studying the epidemiological aspects of an infrequent disease requires sampling from a wider area, which most of the studies are lacking. Despite these limitations, previous studies are helpful for providing data on IBD incidence and prevalence.

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Consequently, the objective was to define the demographic features and clinical characteristics in a relatively large group of patients from a diverse background with IBD who had been referred to our department which was located in a tertiary referral centre during a 14 year period. Because our center receives patients from all over Turkey from diverse backgrounds, it was assumed that these data may provide a more erudite insight into the possible causes of IBD and, in part, could explain the differences between the IBD profile in Turkey in comparison with other countries, both in the East and in the West.

Material and Methods

Study design

The study was conducted between 1993 and 2007 at Ankara. Throughout this period 702 patients with IBD were referred to or diagnosed in our clinic. All patients were followed up for at least one year. The study center is renowned for focusing on gastrointestinal disorders in Ankara which is one of the largest urban centers in Turkey with a population of around 7 million and receiving patients from all over Turkey.

A questionnaire was designed to gather initial data regarding the demographic and clinical features, extra-intestinal manifestations, duration of disease, history of inflammatory bowel disease in relatives, surgical interventions, and other socio-demographic and clinical variables deemed to be relevant in the light of literature in UC and CD patients. These data were gathered either by a face-to-face interview, or retrieved from the medical files of the patients.

As far as extra-intestinal manifestations were considered, the data included any extra-intestinal disease diagnosed before, concurrent with, or after any initial contacts for IBD. We extracted the data for each of the following groups: muco-cutaneous, musculoskeletal, liver, eye, and urinary tract involvement. Specialist diagnosis was required to include such extraintestinal complications in the present study. Primary sclerosing cholangitis (PSC) was defined by the following criteria: persistently elevated serum gamma glutamyl transferase or alkaline phosphatase levels for at least 3 months, characteristic radiographic appearance of sclerosing cholangitis and/or histologic features consistent with PSC on liver biopsy and absence of conditions associated with secondary sclerosing cholangitis [7].

Standard pelvic X-rays for examination of the sacroiliac joints were performed when a patient had inflammatory back pain, asymmetric oligoarthritis, limited chest expansion or limited lumbar spinal movements. The modified New York criteria [8] were used to classify ankylosing spondylitis. Peripheral arthritis was defined as at least one episode of pain and swelling in one or several joints.

Finally, the lag time between onset of symptoms and time of diagnosis confirmation was determined.

Statistical analysis

The data were entered into a database and analysed with Statistical Package for Social Sciences for Windows™ 13.0 program (Chicago, IL., USA). Parametric and non-parametric tests were used according to the types of data and the results were interpreted within a confidence interval of 95 %. P was set at 0.05.

Results

Basic socio-demographic and clinical variables

During the study period, 702 patients were identified as having IBD; among these, 507 were diagnosed as having UC (72.2%) and 195 as CD (27.8%). The mean age at diagnosis was 46.2 years (S.D. 14.0, range 14-88 years) in UC and 40 years (S.D. 12.1, range 17-74 years) in CD patients. This age difference was significant ($p<0.001$).

The mean duration of disease was found to be 9.7 (SD 6.5) years for CD and 9.7 (SD 6.4) years for UC ($p=0.815$, Mann-Whitney U test). The average follow-up duration was 6.3 years for patients with CD (SD 4.0), and 6.9 (SD 5.2) years for UC ($p=0.432$).

The male to female ratio was 1.2 for UC and 1.6 for CD, showing a slight, though insignificant predominance of males with CD and UC ($p=0.12$). The vast majority of studied patients were resident in central Anatolia (68.0 % and 60.8 % for UC and CD patients, respectively) (Fig. 1). More than half of the IBD cases had a minimum of high-school education (Table I).

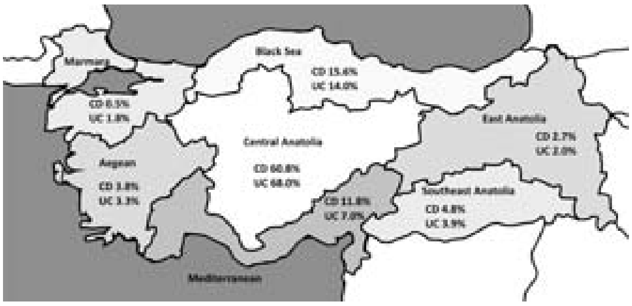

Fig 1. Geographical distribution of patients with respect to current residence.

In 8 patients (11.3%) with CD and 39 patients (19.6%) with UC ($p=0.112$), initial symptoms of the disease had been noted during pregnancy.

Clinical presentation and treatment

The predominant complaints of UC patients at presentation were hematochezia and/ or bloody diarrhea, whereas the predominant complaint for CD was abdominal pain (Table II). Diarrhea without blood was present in 97 (49.7%) patients with CD.

Surgical interventions due to disease were more common in CD with 100 patients requiring surgery (51.8 %). Contrarily, only 10.4 % of patients with UC underwent surgery (n=52). Approximately 25% of patients with CD had undergone an appendectomy (n=48, 25.8 %) whereas 3.3 % of patients with UC had undergone this procedure (n=15, $p<0.001$). Interestingly, only 9 of the patients with CD had

Table I. Socio-demographic characteristics of patients with Crohn's Disease (CD) and Ulcerative Colitis (UC)

Variable		CD (n, %)	UC (n, %)	Statistical Test*
Gender	Male	120 (61.5)	279 (55.0)	P=0.12
	Female	75 (38.5)	228 (45.0)	
Current residence	Central Anatolia	113 (60.8)	310 (68.0)	P=0.889
	Black Sea	29 (15.6)	64 (14.0)	
	Mediterranean	22 (11.8)	32 (7.0)	
	South East Anatolia	9 (4.8)	18 (3.9)	
	Aegean	7 (3.8)	15 (3.3)	
	East Anatolia	5 (2.7)	9 (2.0)	
	Marmara	1 (0.5)	8 (1.8)	
Region of origin	Central Anatolia	76 (50.0)	186 (52.8)	P=0.889
	Black Sea	33 (21.7)	79 (22.4)	
	Mediterranean	18 (11.8)	35 (9.9)	
	South East Anatolia	12 (7.9)	22 (6.3)	
	Aegean	9 (5.9)	14 (4.0)	
	East Anatolia	3 (2.0)	12 (3.4)	
	Marmara	1 (0.7)	4 (1.1)	
Education	None	6 (5.5)	10 (3.9)	P=0.889
	Primary	25 (22.9)	75 (29.5)	
	Secondary	17 (15.6)	32 (12.6)	
	High School	33 (30.3)	63 (24.8)	
	University	28 (25.7)	74 (29.1)	
Smoking status	Current smoker	77 (42.1)	61 (13.3)	<0.001
	Never	64 (35.0)	254 (55.5)	
	Smokes when ill	24 (13.1)	35 (7.6)	
	Does not smoke during illness	18 (9.8)	108 (23.6)	
Oral contraceptive use	Never	58 (84.1)	166 (83.4)	P=0.773
	Past	10 (14.5)	27 (13.6)	
	Current	1 (1.4)	6 (3.0)	
NSAID use	Never	49 (49.0 %)	96 (44.2 %)	P=0.334
	Past	18 (18.0 %)	42 (19.4 %)	
	Current	33 (33.0 %)	79 (36.4 %)	
Measles history	Infection	45 (75.0 %))	103 (78.0 %)	P=0.643
	Vaccination	8 (15.4 %)	10 (9.2 %)	P=0.242

* Chi Square and Mantel-Haenszel Tests

had a tonsillectomy (4.8 %), whereas 2.6 % of the patients with UC received this procedure (n=12, p=0.148). 41 of the patients (21.8 %) with CD were diagnosed on occasion compared to 3 of those with UC (0.6 %). The operations performed for patients with UC were: ileal pouch with ileo-anal anastomosis (n=46), primary suture due to perforation during colonoscopy (n=3), subtotal colectomy (n=3). Two of the patients who had undergone subtotal colectomy had a preoperative diagnosis of colon cancer, and the other patient was operated for stenosis in the sigmoid colon. The surgery specimens revealed UC in all of these patients. When patients receiving chemo-therapy were evaluated, it was found that 68.0 % of the patients with CD had received steroid therapy, whereas this rate was found to be 39.0 % in patients with UC. Among patients with CD who are in remission, 38% were receiving mesalamine or sulfasalazine alone, 28% were receiving azathiopurine alone, 27% were receiving a combination of azathioprine and mesalamine or sulfasalazine and 2% were receiving methotrexate. Five percent of these patients were not receiving any medication for CD. Ninety-six percent of patients with UC who are in remission were receiving oral and/or topical mesalazine or sulfasalazine and 4% were receiving immunosuppressive therapy.

Family history, extent of disease and complications

In the UC group, there were 27 patients (5.9%) with first- and second-degree relatives affected by IBD. Regarding CD

Table II. Predominant complaints of patients with ulcerative colitis and Crohn's disease

Complaint	Crohn's Disease (n, %)	Ulcerative Colitis (n, %)
Abdominal pain	158 (81.4)	70 (14.0)
Weight loss	57 (29.7)	30 (6.0)
Bloody diarrhea and/ or hematochesia	34 (17.7)	456 (91.2)
Fever	14 (7.3)	11 (2.2)

patients, family history of IBD was positive for 10 patients (5.4 %, p=0.819).

The extension of disease activity was evaluated by using endoscopy, biopsy and ultrasonography. Of 507 UC patients, 161 (31.7 %) had proctitis (inflammation up to 15 cm from the anus), 150 (29.6 %) had left-sided colitis (inflammation up to the splenic flexure), and 196 (38.7 %) had pancolitis and extensive colitis. Among the CD patients, maximal location of disease prior to first surgery was terminal ileum in 47 (24.1%), colonic in 41 (21.0%), ileocolonic in 105 (53.9%) and upper gastrointestinal only in 2 (1%) patients. Disease behavior was nonstricturing, nonpenetrating (inflammatory) in 98 (50.3%), stricturing in 61(31.3%), internal penetrating in 36 (18.4%), perianal penetrating disease in 25 (12.8%) patients according to the Montreal classification [9].

As for complications, the most common extraintestinal complication in patients with UC was found to be PSC, whereas this was acute arthropathy for patients with CD. Acute local complications were commonly found in patients with CD and the commonest of those was intestinal obstruction (Table III).

Diagnostic and prognostic variables

The mean lag time between the onset of complaints and confirmation of diagnosis was 12.3 (SD 20.9) and 19.2 (SD 38.8) months for UC and CD, respectively (p=0.002). On average, both patients with UC and CD had 1.7 relapses during the follow up though SD differed (1.6 for UC and 1.8 for CD). Also, 32 (16.4 %) of the patients who were primarily diagnosed with UC had their diagnoses changed to CD after the follow-up period, whereas the initial rate of misdiagnosis was 0.4 % for the CD group (n=2). Finally, 3 of the patients with UC (0.6 %) developed colorectal cancer during the study period.

Table III. Complications in patients with Crohn's Disease (CD) and Ulcerative Colitis (UC)

		CDn (%)	UCn (%)
Extraintestinal	Acute arthropathy	17 (8.9)	15 (3.0)
	Sacroileitis	8 (4.2)	6 (1.2)
	Ankylosing spondylitis	7 (3.6)	5 (1.0)
	Ocular problems	5 (2.6)	6 (1.2)
	Erythema nodosum	6 (3.1)	1 (0.2)
	Pyoderma gangrenosum	0 (0.0)	0 (0.0)
	PSC	8 (4.2)	17 (3.4)
Acute local	Intestinal obstruction	73 (38.0)	0 (0.0)
	Internal fistulae	33 (17.1)	0 (0.0)
	Toxic megacolon	1 (0.5)	3 (0.6)
	Perforation (colon for UC)	22 (11.5)	6 (1.2)
	Abscess	25 (13.0)	0 (0.0)

Discussion

Ulcerative colitis and Crohn's disease are chronic inflammatory bowel diseases for which the pathogenesis still remains to be clearly defined. Knowledge of differing incidences and prevalence rates, as well as clinical features of IBD in different geographic areas and ethnic groups, may provide insight into the possible risk factors and mechanisms that contribute to the occurrence of IBD.

The exact incidence and prevalence of IBD in Turkey is still not known. A preliminary study conducted on clinical populations from the Trakya region of Turkey reported that the overall prevalence of UC was 4.9 per 100,000: 2.18 per 100,000 in rural areas and 5.87 per 100,000 in urban ones. Also, as in other Mediterranean countries, both the incidence and the prevalence of UC were low [4]. According to the scant epidemiological information we have, it may be assumed that the prevalence of IBD in Turkey is roughly equal to those in developed countries. This may be possibly related to industrialization and the uniform life-style it brings. Also, other changes in living environment and diagnostic modalities may contribute. Countries, lying further east of Turkey seem to be following the same trend as illustrated by a study from Iran [10].

The present study identified several important pieces of demographic information. First, the peak age of onset for both CD and UC were similar to other Western and Asian countries as well as those reported in a previous study from Turkey and that those with UC are significantly older [1, 3, 10].

Second, a slight male predominance of CD was in accordance with regions with low incidence rates, whereas, unlike other studies, we found a slight male predominance in UC. Our results also did not concur with those reported by Ulker et al [3]. That study reported a male-to-female ratio of 1.2/1 for UC and, 1/1.3 for CD. This difference may be due to sampling biases and epidemiologic studies on non-selected populations may provide healthier figures.

Third, with respect to smoking, it is reported that nonsmokers have a higher risk of developing UC. In contrast, smoking appears to be a factor causing CD to worsen [11]. Ulker et al reported that 30.8 % of their patients with UC had a history of smoking and that 16.0 % of them were still smoking (3). They reported that in a minority of their patients (2.2%) the relation between quitting smoking and the onset of the disease was clear (within 15 days - 6 months). They also found that the disease started at a later age in the patients with UC who were smokers (39.8 compared to 31.8) [3]. According to that study, the ratio of CD patients with a history of smoking was 35.1 %. Of these, 30.7 % were still smokers and 4.3 % were ex-smokers [3]. Our data are in accordance with those findings. Though both our data and those of Ulker's support the theory of smoking in UC patients, it is hard to draw any firm conclusions regarding CD because the sample sizes are quite small.

The cumulative number of CD-related surgery is comparable to other reports from Western and Asian countries [10]. Despite a longer time between the onset of symptoms and diagnosis confirmation as compared with other studies, the need for surgery seems not to differ markedly. Though Ulker's study did not report figures for surgery in IBD, we may infer that our results may point to a milder course of CD among the Turkish population. However, drawing a precise conclusion requires studies with larger sample sizes and a longer follow-up period. To decide whether a previous history of appendectomy and tonsillectomy had any impact on the development of IBD among the patient population, a case-control study may be necessary.

The presence of a family history for IBD in our study was found to be lower than that reported from western countries and Iran whereas it was higher than that reported previously from Turkey [1, 3, 10]. Ulker et al. reported a family history of IBD in 1.6 % of their patients with UC whereas they did not report corresponding figures for CD [3]. This difference may be due to sampling. Familial occurrence of IBD may reflect the background prevalence rates. Because previous epidemiological studies conducted on Turkish population did not quote figures for familial aggregation of IBD, our results should be deemed preliminary and be supported with further investigations.

There are many factors that make the comparison of the disease extent between different studies less reliable. These include differences in diagnostic modalities, definition of disease extent, performing a true total colonoscopy, and completeness of case ascertainment. However, previous studies have shown no definite difference between Asian and Western countries regarding the extent of disease and our results seem to support those reports [1].

We have found that 10.0 % of UC and 39.6 % of CD patients may have one of the five major extra-intestinal diseases studied in this report. This is far greater than the 6.1% rate reported in Chinese UC patients [12] and 6.2% rate reported by Bernstein et al. However, in the latter study, those with peripheral arthritis have been deliberately excluded [13]. Our data are comparable to those found in the Iranian, Indian, Korean and Western populations [10,11,14-16]. Additionally, the prevalence of PSC in UC patients was similar to those in past reports [1,2]. Only 3 of our patients developed colorectal cancer throughout the study (0.6 %) and these rates are similar to those reported for Asian populations but lower than for Western ones [1,10].

Also, the high prevalence of measles infections and immunizations seems to be significant; this brings to mind reports about the relationship of past measles infection and CD [1]. However, the high prevalence of measles infection in our country and the lack of a control group prevents us from making further comments on the etiological role of this infection.

Another significant result of this study is the relatively higher prevalence of misdiagnosis and longer times of untreated disease for CD. According to our results 16.4 % of the patients who were primarily diagnosed with UC had their diagnoses changed to CD after the follow-up period, whereas the corresponding rate was 0.4 % for the CD group. The mean time between the onset of symptoms and the time of diagnosis was 12.3 months for UC and 19.2 months for CD. There may be several explanations for this fact. First, the rather non-specific initial symptoms of IBD might be underrated both by the patients and by the physicians in the field. Secondly, higher prevalence of infectious diseases and common disorders such as hemorrhoids may have resulted in misdiagnosis of the disease. Thirdly, the negative attitudes of patients towards endoscopic procedures might also have resulted in a delay in the diagnosis.

The main limitations of our study are its cross-sectional design and not addressing people's socio-economic status. However, we think the relatively large study population consisting of people from diverse backgrounds more than made up for these shortcomings.

Conclusions

The peak age of onset for both CD and UC was similar in Turkey to other Western and Asian countries. A slight male predominance of CD and UC was found for Turkish patients.

Our data support the theory of smoking in UC patients; however, it is hard to draw any firm conclusions regarding CD because the sample size is quite small.

It takes longer to diagnose CD than UC. This might be related to the patients' and physicians' attitude toward the symptoms of CD.

Conflicts of interest

None to declare. The authors have no financial affiliations to disclose.

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