

Original Article

INFLAMMATORY BOWEL DISEASE IN IRAN: A REVIEW OF 448 CASES

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Background – Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases of unknown etiology. Inflammatory bowel disease (IBD) was believed to be infrequent in Iran; however, unofficial reports have confessed the continuing rise in IBD. Here, we present our experience with 448 patients with IBD referred during a 10-year period, 1992 – 2002.

Methods – Demographic and clinical features, extraintestinal manifestations, extension of disease, and complications of 401 patients with UC and 47 with CD were assessed retrospectively. The diagnosis was based on Lennard Jones criteria. The exact course of physicians' visits of 250 patients with IBD was asked through a face-to-face interview. Finally, the lag time between onset of the disease and time of definite diagnosis was determined.

Results – The mean (\pm SD) age at diagnosis was 30.5 ± 11.8 years. Male to female ratio was 0.8:1.0 for UC and 1.3:1.0 for CD. Eighty-three percent of CD and 84.5% of UC patients were nonsmokers. Patients with UC chiefly presented with rectorrhagia (41.9%) or bloody diarrhea (31%), whereas those with CD complained of abdominal pain (47.5%) or diarrhea (27.5%). Of the patients, 14.1% had noted IBD in their family. Among UC patients, proctosigmoid was revealed to be affected in 51.9%. However, left-sided colitis and pancolitis were reported in 30% and 18.1%, respectively. Colorectal cancer was diagnosed in 2 patients (0.4%). The mean lag time between the onset of symptoms and definite diagnosis was 13.9 and 17.7 months for UC and CD patients, respectively. A total of 32.4% of patients with IBD had at least one of the five major extraintestinal manifestations.

Conclusion – The demographic and clinical features of IBD are more or less the same as other developing countries. It seems as if gradual adoption of a western lifestyle may be associated with continuing rise in IBD. Higher prevalence of infectious disease and common disorders such as hemorrhoid, and lack of attention to the increased incidence of IBD in Iran are possible reasons for delayed diagnosis of IBD.

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Keywords: Crohn's disease • epidemiology • Iran • ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) encompasses a group of diseases triggered and perpetuated by a variety of diverse genetic, environmental, and immunologic factors that share similar clinical manifestations and

primarily affect the small intestine and colon. The two most common entities of IBD, ulcerative colitis (UC) and Crohn's disease (CD) are more common in developed countries than developing countries. They are frequently diagnosed in patients in their 20s or 30s; however, there is a second peak later in life. The occurrence of IBD has been extensively analyzed with respect to its demographic, socioeconomic, occupational, and geographical distribution, to shed light on its unknown etiology.¹

The incidence of CD and UC appears to have stabilized in most European and American locales, whereas the incidence continues to rise in regions

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where IBD has been less common.² Reported incidence and prevalence rates vary widely, in part, owing to differences in the criteria used for diagnosis.

Unfortunately, there have been few old studies on IBD in Iran.³⁻⁶ This is largely attributed to the lack of a national registry system as well as the traditional beliefs on rarity of IBD in Iran. On the other hand, since Iran is a geographically wide country of different ethnicities, studying the epidemiological aspects of an infrequent disease requires great financial support which most of research centers are lacking. Despite these limitations, previous studies which mostly report a series of IBD patients registered in private gastroenterology (GE) clinics are available in local journals. They are helpful in viewing a probable increase in IBD incidence and prevalence.

We aimed to define the demographic features and clinical characteristics in a relatively large group of patients with IBD who had been referred to our department during a 10-year period. Meanwhile, we attempted to determine the extraintestinal manifestations, familial aggregation, and the exact course of physicians' visits among these patients. These data may provide insight into the possible causes of IBD and, in part, could explain the differences between the IBD profile in Iran in comparison with other countries.

We hope our study could pave the way for further epidemiological studies to determine the incidence and prevalence of IBD in Iran.

Patients and Methods

Between 1992 and 2002, 448 patients with IBD were referred to or diagnosed in two university hospitals and two private GE clinics. These centers are well-known GE centers in Tehran (capital of Iran) which welcome individuals with GE problems from all around the country. The diagnosis of IBD was verified on the basis of well-established clinical, endoscopic, radiological, histological, and surgical criteria as described by Lennard Jones.¹

A questionnaire was designed to gather initial data regarding the demographic and clinical features, extraintestinal manifestations, extension of disease, presence of inflammatory bowel disease in relatives, surgical interventions, and the exact course of physicians' visit in 401 UC and 47 CD patients. These data were gathered either by telephone or face-to-face interview, or retrieved from the medical files of the patients.

As far as extraintestinal manifestations were considered, the data included any extraintestinal disease diagnosed before, concurrent with, or after any initial contacts for IBD. We extracted the data for mucocutaneous, musculoskeletal, hepatic, ophthalmic, and urinary tract involvements. Diagnosis had to be made by a specialist in order to be included in our study analysis.

Among 448 patients with IBD, 250 had attended face-to-face interviews. Of these, 164 UC and 22 CD patients could remember their exact

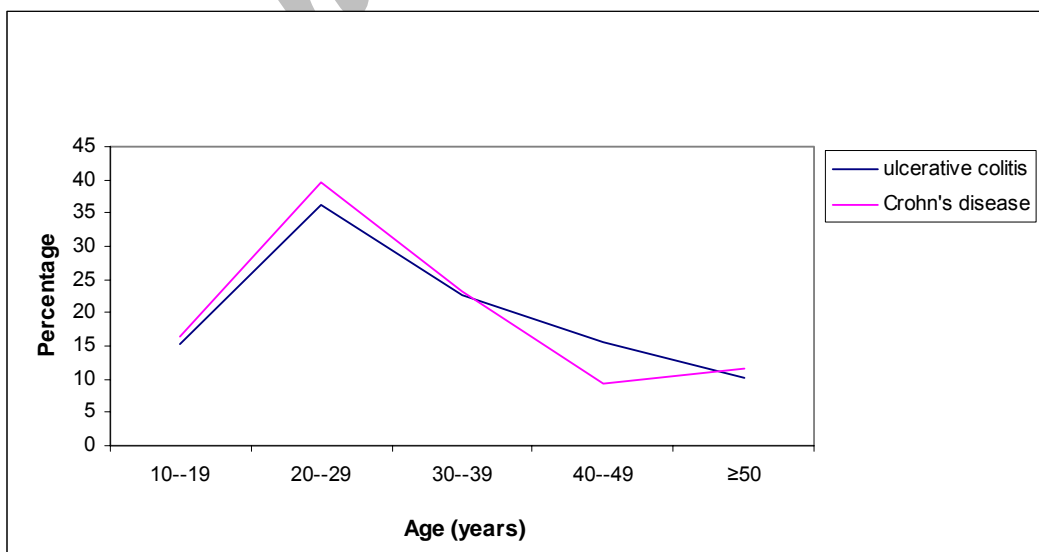


Figure 1. Ulcerative colitis and Crohn's disease: age-specific frequency rates by inflammatory bowel disease type.

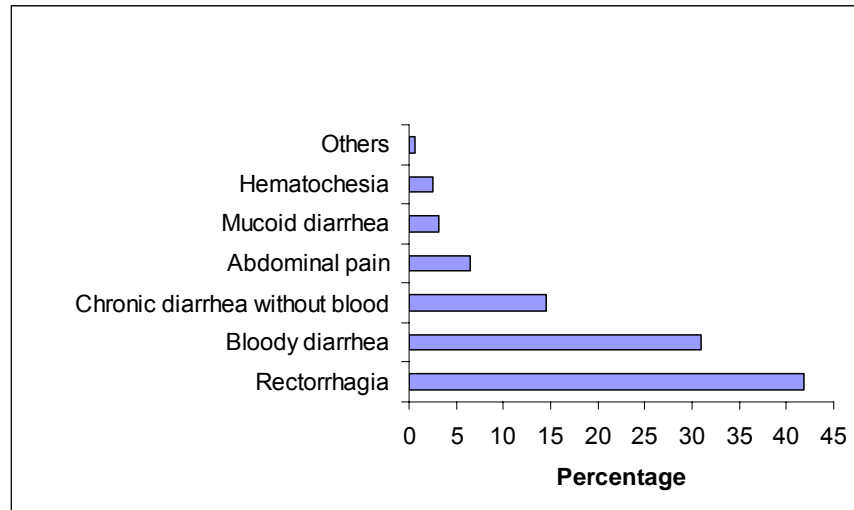


Figure 2. The predominant chief complaints of ulcerative colitis patients.

course of disease thoroughly. This included their medical visits from the beginning of their symptoms till definite diagnosis. Finally, the lag time between the onset of symptoms and the time of definite diagnosis was determined.

Ethical consideration

Having our goals explained, the patients were asked to participate in an interview. The patients could interrupt their cooperation whenever they desired.

Results

During the study period (1992 – 2002), 448

patients were identified to have IBD; among these, 401 were diagnosed as UC and 47 as CD patients. The mean age at diagnosis was 31.9 years (range: 14 to 83 years) in UC and 30.5 years (range: 10 to 60 years) in CD patients. In Figure 1, the age-specific frequency rates by IBD type are shown.

Male to female ratio was 0.8:1.0 for UC and 1.3:1.0 for CD, showing a slight predominance for males in CD but for females in UC patients. The vast majority of the subjects were residing in urban areas (95.9% and 97% for UC and CD patients, respectively). Meanwhile, more than two-thirds of IBD cases held high school certificate or a higher degree of education. History of breast-feeding during infancy was reported in 343 (85.5%) UC

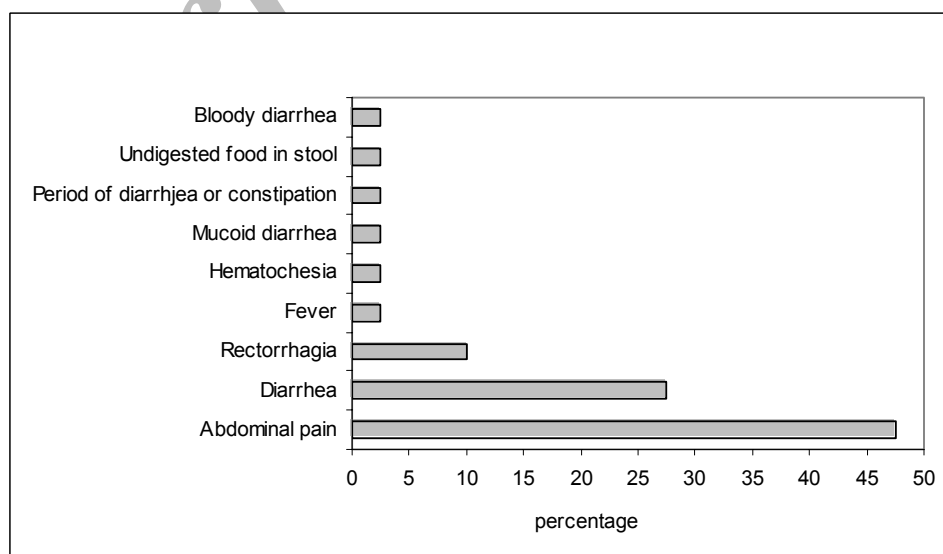


Figure 3. The predominant chief complaints of Crohn's disease patients.

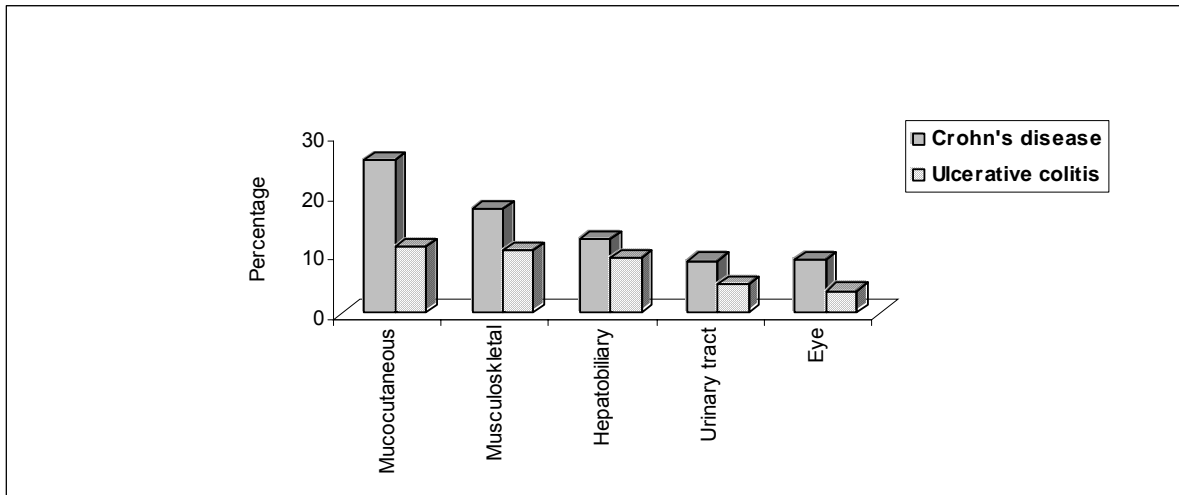


Figure 4. Frequency of extraintestinal diseases in ulcerative colitis and Crohn's disease patients.

and 45 (95.7%) CD patients.

A total of 339 (84.5%) UC and 39 (82.9%) CD patients had never smoked. As mentioned in 159 female patients, 50 (31.4%) were oral contraceptive pill (OCP) users (32% in UC and 26.9% in CD patients).

The predominant chief complaints of UC patients were rectorrhagia (41.9%), bloody diarrhea (31%), and chronic diarrhea without blood (14.5%). On the other hand, the predominant chief complaints of CD patients were abdominal pain (47.5%), diarrhea (27.5%), and rectorrhagia (10%) (Figures 2 and 3).

Of 241 UC patients, 139 (57.7%) stated that they had other diseases, among which hemorrhoid and thyroid abnormalities were more prevalent (30

and 24 individuals, respectively). Of 32 CD patients, however, 17 (53.1%) complained of other diseases, among these inguinal hernia was reported by two individuals (6.25%).

CD-related surgeries appeared to be common in patients with CD. Twenty-three (48.9%) patients with CD underwent at least one operative procedure; of these, 9 (19.1%) underwent colectomy, 5 (10.6%) had ileal resection, and 3 (6.4%) underwent diagnostic laparoscopy. Furthermore, history of appendectomy was revealed in 5 (10.6%) patients with CD. On the other hand, 8 (1.9%) patients with UC underwent appendectomy. A total of 22 (5.5%) UC patients and one (2.1%) CD patient noted the previous history of tonsillectomy.

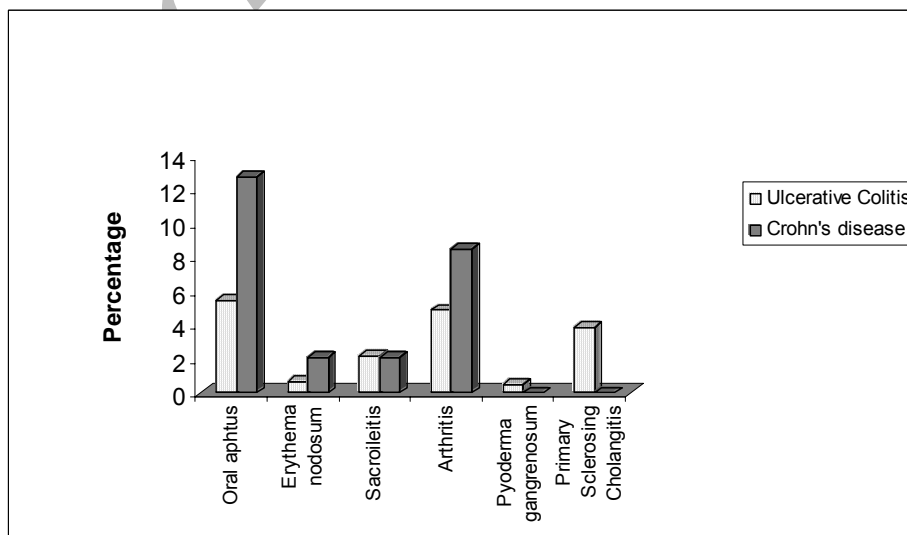


Figure 5. Frequency rates for extraintestinal diseases in ulcerative colitis and Crohn's disease.

Familial aggregation appears to be more or less the same in both groups. In the UC group, there were 44 patients (10.9%) with first and 12 patients (2.9%) with second degree relatives affected by inflammatory bowel disease. Regarding CD patients, these figures were 3 (6.4%) and 4 (8.5%), respectively. Extension of disease was evaluated with total colonoscopy in 283 UC and 32 CD patients. Of 283 UC patients, 147 (51.9%) had proctitis (inflammation up to 15 cm from anus), 85 (30%) had left-sided colitis (inflammation up to the splenic flexure), and 51 (18.1%) had pancolitis. Among CD patients, terminal ileum was the most common affected site (43.7%).

Based on data retrieved from medical files of the patients, 126 (31.4%) UC patients and 19 (40.4%) CD patients have had one of the five major studied extraintestinal diseases. Surprisingly, 36 UC (8.9%) and 5 CD (10.6%) patients had multiple extraintestinal diseases. In Figure 4, the frequency of extraintestinal diseases is shown by their subtypes. Mucocutaneous lesions were the most common extraintestinal disease for each of the CD (25.7%) and UC (11.2%) groups.

Primary sclerosing cholangitis (PSC) and pyoderma gangrenosum were solely found in 16 (3.9%) and 2 (0.5%) UC patients, respectively. Erythema nodosum was more common in patients with CD (2.1%) than in patients with UC (0.7%) (Figure 5).

Perianal diseases were reported in 24 (51.1%) CD patients. Among these, 14 (29.8%) developed hemorrhoid, 8 (17%) had perianal fistula, 3 (6.4%) manifested fissure, and 2 (4.3%) had perianal fissure as well as abscess. Colorectal cancer was developed in one UC (0.2%) and one CD (2.1%) patient.

Of the 132 patients first visited by the doctors who were not gastroenterologists, 115 (87.1%) were referred to the gastroenterologist for definite diagnosis. The mean lag time between the onset of complaints and definite diagnosis was 13.9 and 17.7 months for UC and CD, respectively. Those CD patients who had been visited by internists came to the definite diagnosis averagely 47.3 months following their first symptoms.

Discussion

UC and CD are chronic inflammatory bowel diseases whose pathogenesis and pathologic state still remain to be clearly defined. Knowledge of various incidence and prevalence rates as well as

clinical features of IBD in different geographic areas or races may provide insight into possible risk factors and mechanisms that contribute to the occurrence of IBD. During the past decade, unofficial reports have claimed that the incidence appears to be increasing.⁴⁻⁶ The possible causes of such an increase may include westernization in life style (such as dietary habits and smoking), changes in the living environment, and development in diagnostic modalities.

Despite this rapid increment, due to lack of true population-based registries, studies about the clinical characteristics and natural history of IBD are few in Iran. Meanwhile, the high prevalence of acute and chronic infections has fostered the belief that IBD is a rare disease in the country. Thus, like other problems, it appears that the clinical characteristics of IBD may be different from those of western countries. However, our study revealed that the demographic pattern and clinical picture of IBD are more or less similar to that of other countries, although the rarity of CD is noted.

Compared to people living in urban areas and having higher education, it seems that the detection rate of IBD is lower in those living in rural areas and having lower education.

Our 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.^{2, 6, 7} Nevertheless, unlike other Asian countries and conflicting with a previous study performed by Malekzadeh et al in Iran, our study showed that another smaller second peak exists among aged persons.^{6, 8, 9}

Secondly, a slight male predominance of CD was in accordance to the regions with low incidence rates, but in contrast to Malekzadeh et al study.^{6, 10, 11} In addition, unlike other studies, we found a slight female predominance in UC.^{12 - 14} Thirdly, 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.¹⁵ Our data supports the hypothesis of smoking in UC. However, it is hard to draw any firm conclusion regarding CD since the sample size is quite small and the smoking habits of general population is not known.

The 10-year cumulative number of CD-related surgeries was 23 (48.9%) which is comparable to other reports from western and Asian studies.^{7,16} Despite a bigger lag time between the onset of symptoms and definite diagnosis as compared with other studies,¹⁷ the need for surgery did not differ

markedly. This may reveal CD to have a milder course among Iranian population; however, drawing a precise conclusion requires studies with a bigger sample size and longer follow-up. To decide whether the previous history of appendectomy or tonsillectomy has any impact on developing IBD among Iranian population, a case-control study is suggested.

A high proportion of IBD cases have reported a positive family history. The frequency was 13.4% for UC and 12.9% for CD. As to UC, this proportion is in agreement with the reports from northern Europe and USA,^{18,19} but is higher than that reported from Italy²⁰ or even other Asian countries.^{21,22} Familial occurrence of CD has been reported only among Japanese population in Asia, where only 2.8% of CD patients had a positive family history of CD.²³ In contrast, familial aggregation appears to be higher in Iranian CD patients in our study; a fact that is consistent with western reports and the study of Malekzadeh et al.⁶ Familial occurrence of IBD may reflect the background prevalence rates. It is therefore evident that IBD is as uncommon as previously thought in Iran. Needless to say, we should bear in mind geographical differences or even different interactions between genetic and environmental factors to judge the high prevalence of IBD in Iran.

There are many factors that make the comparison of disease extent among 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.⁷ Yang et al have described the disease extent among Korean UC patients.²⁵ As compared with our results, they reported proctitis with a lower (34% vs 51.9%) but pancolitis with a higher (30.9% vs 18.1%) frequency. Extension of disease was described in 7,966 Chinese UC patients. Among these, 70.2% had proctitis; 22.5%, left-sided colitis; and 7.3%, pancolitis.²⁶ This probably reflects the fact that extension of disease in Iranian population is rather similar to western countries.

We have found that 31.4% of UC and 40.4% of CD patients had one of the five major extraintestinal diseases studied in this report. This is far greater than the 6.1% rate reported in Chinese UC patients²⁶ and the 6.2% rate reported by Bernstein et al; however in the latter study those

with peripheral arthritis were deliberately excluded.²⁷ Our data regarding the rate of extraintestinal features of CD are comparable to the 41.4% rate in Malekzadeh et al study,⁶ 34.7% in Indian population,²⁸ 24.1% in Korean patients,²⁹ and 21% to 41% in western studies.³⁰ In addition, we found PSC in UC patients with a prevalence rate of 3.9% that is consistent with Swedish group study³¹ and also reports from North America.²⁷

Furthermore, colorectal cancer was noted in one UC (0.2%) and one CD (2.1%) patient. These low rates could be partly explained by the low incidence rate of colorectal cancer among Iranian general population. These figures are similar to Asian studies⁷ but much lower than that reported from western countries.^{32, 33} Early diagnosis in addition to a consistent therapy and regular check-ups may lead to a significant reduction in extraintestinal diseases. Moreover, establishing the associations of immune-mediated diseases in extraintestinal sites may lead to better understanding of the pathogenesis of IBD.

Higher prevalence of infectious diseases and common disorders such as hemorrhoid, and lack of attention to the increased incidence of IBD in Iran are possible reasons for delayed diagnosis of IBD. Delay in the diagnosis of UC is most obvious when an internist or a surgeon first visits the patient. Delay in the diagnosis of CD is longer than that of UC; this could be partly due to a wider list of differential diagnoses and the current belief that CD is rare in Iran.

In conclusion, we did not find IBD in Iran to be a common disease; however, according to unofficial reports the incidence and prevalence of IBD continue to rise in Iran. Meanwhile, the course of IBD seems to be milder among Iranian patients.

Although studying the patterns of geographic, variations, age and gender distribution, and the impact of known risk factors may yield valuable clues to the cause of IBD, determining the prevalence and incidence rates of IBD among Iranian population are necessary. To meet this demand, a systematic registry should be set up for IBD in different referral centers similar to the one which has been established in the Research Center for Gastroenterology and Liver Disease (RCGLD), Shaheed Beheshti University of Medical Sciences.

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