Original Article

Epidemiologic Characteristics of 500 Patients with Inflammatory Bowel Disease in Iran Studied from 2004 through 2007

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Background: Despite claims of rarity, some studies indicate that the prevalence of inflammatory bowel disease has increased in Iran during the past decades. Establishment of a registry and the clinical characteristics are presented in this study.

Methods: Two hundred ninety-three patients with ulcerative colitis and 207 with Crohn's disease, referred to tertiary referral gastrointestinal centers in Tehran from 2004 through 2007, were assessed. Demographic and clinical features, intestinal and extraintestinal manifestations, inflammatory bowel disease in relatives, measles infection and vaccination, nutrition during infancy, and drugs and surgical interventions were assessed.

Results: The mean±SD age at the diagnosis was 33.8±12.9 years in Crohn's disease and 37.1±13.7 years in ulcerative colitis. Male:female ratio was 0.9:1.0 for Crohn's disease and 0.7:1.0 for ulcerative colitis. A total of 177 (85.5%) patients with Crohn's disease, and 254 (86.7%) patients with ulcerative colitis had never smoked. Measles vaccination was mentioned in 150 (72.5%) of Crohn's disease and 214 (73%) of ulcerative colitis patients. Breastfeeding during infancy was reported in 178 (86%) and 257 (87.7%) of Crohn's disease and ulcerative colitis patients, respectively. Appendectomy was reported in 37 (17.9%) of Crohn's disease and 16 (5.5%) of ulcerative colitis patients, whereas tonsillectomy was reported in 11.6% of each group.

Conclusion: Demographic and clinical characteristics of inflammatory bowel disease patients are similar to that of other developing countries, in this study, more inflammatory bowel disease cases have been assessed in comparison with previous studies, which may be due to different time scales of socioeconomic evolution and environmental factors in Iran.

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Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases (IBDs) with uncertain etiology thought to be triggered by interactions between various environmental, genetic, and immunologic factors.[1] Role of different factors in IBD including infectious diseases and nutrition during infancy, tonsillectomy, appendectomy, diet, domestic hygiene, refrigeration of food, time scales of socioeconomic evolution , drugs (nonsteroidal anti-inflammatory drugs [NSAIDs] and oral contraceptive pills [OCPs]), smoking, intestinal pathogens, and measles vaccination are mentioned in various studies.[2,3–6]

Although IBD is reported to be relatively more prevalent in northern and western Europe as well as North America,[1,7–10] recent studies show a gradually increasing rate of IBD in many developing countries in Africa, South America, and Asia.[7,11–15] The incidence and prevalence of IBD in Iran is still unclear. However, according to

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recent studies, it appears that neither UC nor CD is rare in Iran; indeed their incidence appears to have increased during the recent years.

Improvements in general health and hygiene have been incriminated as a significant contributor to the growing incidence of IBD around the globe, although the evidence for specific factors that underlie such a theory is still unclear. Exposure to *H. pylori*, helminths, cold chain hypothesis, measles infection and vaccination, use of antibiotics, breastfeeding, family size, urban upbringing, day care attendance and domestic hygiene, and westernization of lifestyles including dietary habits as well as environmental changes caused by industrialization and urbanization are probably responsible for the change in the incidence.[16] Differences in the pattern of incidence and natural history of IBDs in various parts of the world may provide some clues as to the cause of the disease. It is difficult to draw any firm conclusion from the studies due to lack of true population-based registries. Since Iran is a geographically wide country with various ethnicity, many studies are needed to determine epidemiologic aspects of this disease.

We conducted this study to determine the demographic features and clinical characteristics in a large group of patients with IBD who were followed in the last years who had been referred from all over the country to different gastrointestinal clinics in Tehran during a four-year period (2004 – 2007).

Materials and Methods

Through a case-series study, we evaluated 500 patients with IBD referred to three gastro-enterology (GE) clinics in Tehran between 2004 and 2007. These centers are well-known GE centers in Tehran, which are tertiary care referral centers and welcome patients with GE problems with failing primary and secondary care treatment from all around the country.

A questionnaire was designed to evaluate the patients prospectively, including date and place of birth, gender, ethnicity, religion, marital status, level of education, place of longest living, urban or rural living, family history of IBD, monozygotic twin with IBD, date of diagnosis, age at diagnosis, and body mass index (BMI). The second part of the questionnaire included questions on breast /formula or cow's milk feeding, measles infection during infancy, measles vaccination, smoking, history of appendectomy and tonsillectomy, consumption of antibiotics during the recent five years, and using OCPs and NSAIDs and their duration. Another part of the questionnaire included various questions about the chief complaints, medical treatment, type and extent of disease, intestinal and extraintestinal manifestations, intestinal surgical interventions, history and causes of bowel resection, and perirectal diseases (abscess and fistula). Questionnaires were completed through a face to face interview. Finally, the time between the onset of symptoms and the definite diagnosis was recorded.

The diagnosis of IBD was verified based on a well-established clinical, endoscopic, radiologic, histologic, and surgical criteria as described earlier by Lennard-Jones.[17] Two separate gastroentero-logists reviewed each patient's diagnosis and if they disagreed, opinion of a third gastroentero-logist was sought.

Extraintestinal manifestations included musculoskeletal, mucocutaneous, hepatic, ophthalmic, and urinary tract involvements. UC was diagnosed when there was evidence of diffuse mucosal disease of colon with different proximal extensions from the rectum, superficial inflammation, crypt abscess, cryptitis, and rectal involvement without any evidence of small bowel involvement other than backwash ileitis.

CD was defined as skip lesions at endoscopy, cobblestone appearance, mucosal ulceration on colonoscopy, aphtus lesion found during upper endoscopy, deep inflammation or chronic terminal ileal inflammation with or without radiologic evidence of skip lesions, stricturing disease, fistulizing disease, existence of perianal disease (skin tags, abscess, fistula), or small intestinal involvement and noncaseating granulomas.

Indeterminate colitis (IC) was defined as an active and patchy architectural distortion, in the absence of small bowel involvement after radio-logic evaluation, ileal intubations, an inconclusive endoscopic appearance, and histologic features that were not specifically diagnostic for CD or UC.[1,18]

Statistics

Data collection was done by including all patients diagnosed as IBD (new and previous cases) who were referred to the mentioned GE clinics during a four-year period of the study.

Descriptive statistical analyses were performed by SPSS version 13 (SPSS Inc., Chicago, IL).

Ethical consideration

Explaining our goals, each patient was asked to participate in our study. All patients signed the informed consent forms. They could stop their cooperation whenever they desired.

Results

A total of 500 patients were included during the three-year period of the study from 2004 through 2007. Among them, 207 (41.4%) were diagnosed as CD and 293 (58.6%) as UC patients. None of the patients was diagnosed as IC. Demographic and clinical characteristics are given in Table 1 and Figure 1.

Ninety percent of the IBD patients were born in urban areas. Different degrees of education, under high school, high school, above high school, and above bachelor degree (BA or BSc) were reported in 20.4%, 33.2%, 38.2%, and 5.6% of the patients, respectively. Two point six percent were illiterate.

A total of 177 (85.5%) patients with CD, and 254 (86.7%) patients with UC had never smoked. The prevalence of smoking was 13.3% in UC (28 men and 11 women) and 14.5% in CD (23 men and seven women) patients.

Among the female patients, 40.6% had a history of using OCP—79 patients with CD, and 124 patients with UC. The mean±SD duration of using OCP was 30.3±11 months in CD and 40.1±12 months in UC patients. Using NSAIDs for a mean±SD period of 94.5±16 months and 49.1±10 months was observed in 24.2% of the patients with CD and 30% of the patients with UC, respectively. History of using antibiotics during the last five years, (less than two episodes per year, more than two episodes per year, and none) was mentioned in 54.6%, 35.8%, and 9.6% of CD and 48.9%, 32.3%, and 18.8% of UC patients. The predominant chief complaint of the patients was abdominal pain in CD and rectal bleeding in UC patients.

Colonoscopy and small bowel series were done in all patients. Barium enema was also done in about 20% of the patients. Extension of disease was evaluated by total colonoscopy in all CD and UC patients. Of 293 UC patients, 149 had proctitis (inflammation up to 15 cm from anus), 94 had left-sided colitis (inflammation up to the splenic flexure), and 50 had pancolitis. Rectum was involved in all cases. Involvement of the small intestine was seen only in 19.3%, large intestine in 35.7%, and both the small and large intestine in 44% of all 207 patients with CD. In only two patients with CD, the involvement of the upper gastrointestinal tract was seen. The relative frequency of intestinal involvement is given in Table 2.

Different types of CD including inflammatory, fistulizing, and fibrostenosing type were reported in 75%, 13.5%, and 11.5% of the patients with CD.

Most of the patients were treated with prednisolone (16.6%), azathioprine (12.4%), sulfasalazine (13.2%), or mesalasine (9%). Thirty-eight point six percent of the patients with CD and 20.4% with UC were treated with other regimens.

CD-related surgeries appeared to be more common than UC. Intestinal resection was reported in 19 (9.7%) patients with CD and in nine (3.07%) with UC. Severe perianal diseases leading to surgery, such as abscess drainage and anal fistulotomy, were reported in 11 (5.3%) of CD and three (1%) of UC patients.

The most frequent intestinal complications of CD were fistula, abscess, obstruction, and massive bleeding, reported in 13.5%, 8.2%, 7.5%, and 3.8%

Table 1. Different demographic and historical characteristics of IBD patients.

Variable	Crohn's disease (*n*=207)	Ulcerative colitis (*n*=293)
Gender (M/F)	0.9/1	0.7/1
Age, mean (SD)	33.8 (12.9)	37.2 (13.7)
BMI, mean (SD)	22.6 (3.9)	23.7 (4.2)
Smoking, *n* (%)	30 (14.5)	39 (13.3)
First degree IBD history, *n* (%)	18 (8.7)	28 (9.6)
Infantile feeding, *n* (%)		
Breast	178 (86)	257 (87.7)
Formula	25 (12.1)	28 (9.6)
Cow's milk	4 (1.9%)	8 (2.7)
History of measles infection, *n* (%)	74 (35.7)	123 (42)
History of measles vaccination, *n* (%)	150 (72.5)	214 (73)
Previous appendectomy	37 (17.9)	16 (5.5)
Previous tonsillectomy	24 (11.6)	34 (11.6)

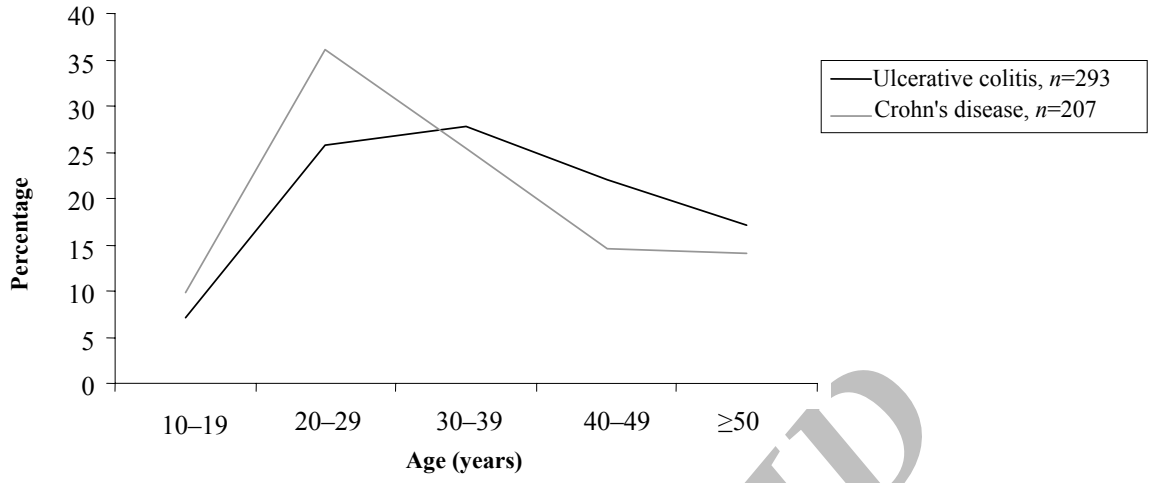

Figure 1. Age-specific frequency for UC and CD.

of the patients, respectively. Massive bleeding in 21 (7.1%) patients was the most frequent complication of UC. Colorectal cancer was developed in only one (0.3%) patient with UC and none of the patients with CD.

In our study, 64.6% of CD and 62.4% of UC patients had one of the five major studied extraintestinal diseases. Musculoskeletal lesions were the most extraintestinal manifestations reported in 42% of the patients with CD and 38.5% with UC. Mucocutaneous, hepatobiliary, urinary tract, and ophthalmic involvement were reported in 8.2%, 4.3%, 4.8%, and 5.3% of CD patients and 3%, 10.5%, 7.7%, and 5.3% of UC patients, respectively. Different types of extraintestinal diseases are given in Table 3. Primary sclerosing cholangitis (PSC) which had been confirmed by magnetic resonance cholangiopancreatography (MRCP) in all of these patients was seen in 28 (9.5%) patients with UC, and six (2.8%) with CD. In these patients, anemia (Hb<13 g/dL in men, and Hb<11 g/dL in women) was seen in three patients. Alkaline phosphatase >140 IU was seen in almost 75% and total bilirubin >1 mg/dL was seen in about 60% of the patients with PSC. SGOT (AST) and SGPT (ALT) >40 IU were seen in about 43% of PSC patients.

Erythema nodosum was reported in none of the patients with UC. However, it was mentioned in four patients with CD.

The mean±SD lag time between the onset of complaints and definite diagnosis was 24.4±10.1 and 22±8.1 months for CD and UC, respectively.

Discussion

In the recent decades, western countries have witnessed a gradual increase in the incidence of UC followed, a few years later, by a similar increase in CD. At the same time, reports coming from developing countries like India, China, Singapore, indicate that although both the incidence and prevalence of IBD in Asian countries are still low compared with Europe and North America, but it is increasing rapidly.[19–25]

Most of the previous reports from Iran, from 1996 through 2002, insist on the increasing rate of UC but rarity of CD.[11,26,27] Only in 2000, it was reported by Malekzadeh et al. that CD is a rapidly increasing disease. For the first time, they showed

Table 2. Percentage of intestinal involvement in IBD patients.

Variable	Proctitis, *n*(%)	Left- sided colitis, *n*(%)	Pancolitis, *n*(%)
Ulcerative colitis (*n*=293)	149 (51)	94 (32)	50 (17)
	Only small intestine, *n*(%)	**Only large intestine, *n*(%)**	**Both small and large intestine, *n*(%)**
Crohn's disease (*n*=207)	40 (19.3)	74 (35.7)	91 (44)
		Proctitis, *n* (%) 25 (15)	
		Right- sided colitis, *n* (%) 140 (85)	

Table 3. Clinical characteristics of IBD patients.

Variable	Crohn's disease (*n*=207)	Ulcerative colitis (*n*=293)
Extra intestinal involvement		
Sclerosing cholangitis (PSC), *n* (%)	6 (2.8)	28 (9.5)
Arthritis, *n* (%)	76 (37)	94 (32)
Sacroileitis, *n* (%)	10 (4.8)	6 (2)
Oral aphtus, *n* (%)	11 (5.3)	6 (2)
Erythema nodosum, *n* (%)	4 (1.9)	—
Pyoderma gangranosum, *n* (%)	1 (0.4)	3 (1)
Complications		
Obstruction, *n* (%)	14 (7.5)	1 (0.3)
Massive bleeding, *n* (%)	8 (3.8)	21 (7.1)
Fistula, *n* (%)	28 (13.5)	1 (0.3)
Abscess, *n* (%)	17 (8.2)	4 (1.3)
Toxic megacolon, *n* (%)	—	—
Perforation, *n* (%)	1 (0.4)	—
Cancer, *n* (%)	—	1 (0.3)

that CD is not as rare as it was previously thought in Iran.[28] However, in 2002, another 10-year period study also showed the rarity of CD in Iran.[26] Now, in this study, the higher rate of CD is noted by evaluating 207 patients who referred to our tertiary care centers from all over the country during a three-years period.

Our study, as well as that of Aghazadeh et al. revealed that the demographic pattern and clinical picture of IBD in Iran are more or less similar to that of other countries. However, it seems that the course of IBD is milder among Iranian patients. In other words, since IBD, especially CD, in Iran has occurred later than western countries, severe courses and more serious complications might also appear in the future by increasing the duration of disease. Our study, in agreement with other studies from the Middle East countries and previous studies by Malekzadeh et al. did not reveal a second peak among patients more than 50 years of age. This finding is in contrast to a study by Aghazadeh et al.[28, 29] Only in patients with UC, we observed that two peaks exist, 20 – 29 and 30 – 39 years age groups.

Compared with other studies, a slight female predominance of both CD and UC was found in our study.[11,30]

The number of CD-related surgeries was 14.5% which is comparable with reports from western and Asian studies.[7,31–33] However, drawing a precise conclusion requires studies with a bigger sample size and a longer follow-up.

It was found that 9.6% of UC and 8.7% of CD patients had a positive history of IBD in their first degree relatives. This proportion is similar to northern Europe and America,[32,34,35] but is more than the reports from some Asian countries.[36,37,39]

Most of the UC patients had proctitis (50.8%) followed by left-sided colitis 32.2%, which is in agreement with the results of Aghazadeh et al. [26] However, in Yang et al's. study,[14] pancolitis was reported with a higher frequency (30.9% *vs.* 17%) but proctitis with a lower frequency (34% vs. 50.8%) . It seems that extension of the disease in Iranian population is rather similar to western countries.[26]

Like other Iranian studies, and in contrast to Aghazadeh et al's. study, involvement of the iliocolic region in CD was most frequent (44.1%). Rectal bleeding, as the predominant chief complaints of UC patients in our study, as abdominal pain in CD patients, is similar to other Asian and western studies.[11,12,26,39]

Our data regarding the rate of extraintestinal features of IBD, which revealed musculoskeletal manifestations as the most frequent complications (38.5% in UC and 42% in CD), are comparable with the results of Aghazadeh et al.[26] However, like their study, colorectal cancer was only reported in one UC patient that could be explained by the low incidence of colorectal cancer among Iranian general population.

IBD results from an interaction between genetic and environmental factors, leading to an abnormal immune response of the intestinal mucosa to intraluminal antigens.[23]

The literature suggests that the hygiene hypothesis and its association with decreased microbial exposure in childhood probably plays an important role in the development of IBD, although the strength of the supporting data for each of these factors varies.[16] Among the environmental factors, less infantile breast milk feeding is suggested as an additional cause for

IBD. However, our results indicated that most of our patients were breastfed.

Infantile measles infection and measles vaccination is suggested as an additional cause of increasing prevalence and incidence of IBD. Our results with regard to measles vaccination indicate that most of our patients were vaccinated.

Increasing complications and morbidity due to IBD, which leads to increasing referral to gastroenterologists, may be another factor influencing the observed increase in the number of CD patients in this study.

Appearance of IBD is much more in urban than rural populations, in higher than lower socioeconomic groups, in breastfed and vaccinated children than others, indicating that, maybe, improved sanitation and hygiene is important in the etiopathogenesis of IBD.

Although it seems that the course of IBD is milder among Iranian patients, the total number of IBD patients reported in our study is an alarm.

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