Risk Factors for Postoperative Recurrence of Crohn's Disease

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ABSTRACT

BACKGROUND

Postoperative relapse is a common feature of Crohn's disease (CD) in Western countries but its frequency and risk factors have not been studied in the Middle East where there is a rapid upsurge in the incidence of CD. This study aims to research the frequency and risk factors of its recurrence after surgery among 566 Iranian patients with CD in Tehran, Iran.

METHODS

All 566 patients diagnosed with Crohn's disease that enrolled in Digestive Diseases Research Center (DDRC) Inflammatory Bowel Disease (IBD) from April 1991 until November 2011 were included in our study. We reviewed clinical data that included time of surgery, possible risk factors and follow up after surgery. Multivariate regression analysis was performed to seek possible risk factors for early postoperative recurrence.

RESULTS

The mean age of patients was 30.85 (range: 12-88) years at the onset of enrollment. During a mean follow up of 55 months, 139 (24.5%) out of 566 Crohn's disease patients underwent at least one surgery while 32 (23%) required additional surgery during the period after their first surgical intervention. Cigarette smoking was a risk factor for both initial (p=0.001) and additional surgery (p<0.0001). The penetrating behavior of Crohn's disease, in addition to its effect on surgery (p<0.001), showed a significant influence on disease recurrence (p<0.0007) along with perianal involvement which was significantly associated with relapse (p=0.001). Although disease duration of more than ten years was a significant risk factor for surgery (p=0.043) its effect on recurrence was insignificant (p=0.059).

CONCLUSION

The rate of initial and additional surgery is much lower in this region of the world, which is partially due to the relatively new occurrence of Crohn's disease in the Middle East. Cigarette smoking, disease duration over ten years, penetrating behavior of CD, and perianal disease were the main risk factors for surgery.

KEYWORDS

Crohn's disease; Postoperative; Recurrence

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INTRODUCTION

Crohn's disease (CD) is a relapsing chronic inflammatory disease of the gastrointestinal tract (GI) that has an unknown etiology and partially understood pathophysiology.[1] It is a multifactorial entity that has several possible environmental risk factors such as smoking and diet in addition to a probable genetic susceptibility.[2] There are five types of CD: ileocolitis, ileitis, gastroduodenal Crohn's disease, jejunoileitis, and Crohn's colitis. There is some evidence that the surrogate markers of childhood hygiene, which result in lack of early childhood exposure to infectious and parasitic agents, are significantly associated with the risk of inflammatory bowel disease (IBD).[3] Sufficient evidence exists to confirm an outbreak of Crohn's disease in developing countries, including Iran, during the last two decades of the twentieth century following progressive standardization of the modern life-style in this region.[4-8]

One of the main outcomes of Crohn's disease is the need for surgery during the course of the disease. Surgery is usually warranted following an emergency presentation such as pseudo-appendicitis, in cases with obstructive symptoms, or those intractable to medical therapy.[1,9,10] Obstruction, fistula, perforation, and bleeding are among the common causes of surgery. Up to 50% of patients at referral centers are unresponsive to medical therapy necessitating a need for surgery during the first 3 years of presentation.[11,12] Early subspecialty GI care has shown to reduce the risk of first surgery among Crohn's disease patients.[13] For most patients, surgery results in a sustainable short term remission and a decreased need for additional health-care expenditure [14] but is not curative, as more than 90% of cases develop endoscopic postoperative recurrence and close to 50% become symptomatic within three years after surgery.[15-18] Postoperative management to prevent relapse and the need for repeated surgery is therefore pivotal. Several strategies for maintenance of remission are currently available. Antibiotics, thiopurines, mesalamine, and biologic anti-TNF alpha have been shown to reduce the rate of Crohn's disease relapse.[19-21] Predictive factors for recurrence include history of smoking, genetics, disease pattern, type of surgery, clinical characteristics, and disease duration. A shorter duration of disease onset prior to surgery has a higher risk for recurrence, as well as disease spread that involves the duodenum and jejunum, and disease involvement of the colon, all of which are associated with higher endoscopic and clinical recurrence.[22-27] Other factors are stricture, fistula, perianal involvement and method of surgery.[22] We aim to study the demographic characteristics and risk factors for surgery and recurrence in 566 Iranian patients with Crohn's disease.

MATERIALS AND METHODS

Patients

All data from patients with Crohn's disease who referred to the Digestive Disease Research Center at Shariati Hospital were prospectively collected via questionnaires. There were 690 Crohn's disease cases selected that had an admission diagnosis of Crohn's disease. We chose patients with definitive diagnoses as confirmed by endoscopy or colonoscopy and biopsy results. This process excluded 124 patients who did not meet the criteria. Next, we categorized patients according to their Crohn's disease surgical histories. Any missing data were completed by contacting the patient by telephone. Interviews were conducted by a general physician who obtained all demographic and medical information, such as: patient's name, age, sex, age at presentation, chief complaint, disease duration, site of gastrointestinal (GI) involvement, perianal disease, disease behavior, type of medication, number of surgeries, reason for first surgery, family history, cigarette smoking.

Inclusion and exclusion criteria

Patients with complete medical histories and Crohn's disease confirmed by pathological, radiological and clinical diagnosis were included in the study while those with inadequate profiles or deceased patients were excluded.

Diagnosis of Crohn's Disease

We considered CD as the diagnosis when at least two of the following criteria were present and the

other possible diseases have been excluded: i) compatible clinical history of abdominal pain, diarrhea, weight loss, malaise and/or rectal bleeding; ii) endoscopic findings of cobblestoning, discrete linear or circumferential ulcers, "skip" areas or perianal disease; iii) radiological findings of stricture, fistula, cobble stoning or discrete ulceration with "skip" areas; iv) macroscopic evidence of bowel wall induration, mesenteric lymphadenopathy and creeping fat during surgery; or v) histopathologic findings of transmural inflammation or noncaseating epithelioid granulomas.

Definitions

As above, we made the diagnosis of Crohn's disease based on a combination of clinical, radiological, gross endoscopic, laboratory and histopathological findings. Surgery was defined as any condition that necessitated a bowel operation due to active disease. All surgeries due to Crohn's disease or its complications after the initial surgery were considered to be recurrent. Penetrating behavior was defined as any condition that resulted in a compromise to the integrity of the entire intestinal thickness, and included any types of fistula and/or perforations of the intestinal wall. We considered patients to be smokers if they smoked at least seven cigarettes per week during the previous six months.[28] Recurrence was any state that required additional medical or surgical interventions to relieve active Crohn's disease. Perianal disease was any involvement of the perianal area due to complications from Crohn's disease.

Statistical analysis

After data collection, we imported the data to SPSS version 18 and performed descriptive statistical analysis. Data were analyzed by the chi-square test and Pearson correlation. Odds ratio (OR) was calculated according to the following variables: number of surgeries, smoking habit, gender, penetrating behavior, age of onset, family history, infliximab and azathioprine use, and disease duration(Table1).

We performed regression analysis to interpret the relationship between smoking and risk of surgery. The sample t-test was performed to compare patients' mean ages between those who underwent surgery to those with no surgical intervention.

Table 1: Risk factors and incidence of surgery.

Risk factors	*p*-value	Odds ratio (OR)	95% confidence interval (95% CI)
Cigarette smoking	0.001	3.93	1.65–9.31
Penetrating behavior of CD	0.001	11.01	5.35–25.36
Family history of CD	>0.05	2.35	0.92–5.98
Infliximab use	>0.05	-	-
Duration above ten years	0.043	1.534	1.029–2.288

RESULTS

Of the 566 patients with confirmed Crohn's disease who enrolled in this study, 51.76% were males. Enrolled patients had a mean age of 30.9 years. At the mean follow up of 55 months, 139 (24.5%) cases (mean age: 30±14 years) underwent at least one surgical intervention. Following the first surgical intervention, 32 (22%) cases relapsed. Among this group, there were 14 (46.3%) females. The mean time between the first presentation of symptoms and surgery was 63 months and the median was 48 months. Demographic and clinical features of Crohn's disease cases are shown in Table 2 and the recurrence rate is listed in Table 3. According to Figure 1, there is a rather steep rise in the prevalence of Crohn's disease in our clinic in recent years, particularly after 2000.

Cigarette smoking

Cigarette smoking was a strong risk factor for additional surgery [$p<0.001$, OR=7.45, 95% confidence interval (CI): 2.48–22.33]. Among those who underwent surgery, there were 19 who smoked. Of smokers, 14 cases had more than one surgery.

Penetrating behavior

Of all patients who underwent surgery, 52 cases had

penetrating behavior and 34.6% of these underwent additional surgery. This data showed the significant effect of penetrating behavior on recurrence (p<0.007, OR=3.04, 95% CI: 1.32–6.99).

Age of onset

We divided patients into two groups according to age, below 30 and above 30 years. There was no correlation between age of onset and additional surgery (p>0.05, OR=0.191–1.011).

Relation of recurrence to family history and risk of surgery

According to our data, family history was not a significant risk factor for recurrence (p=0.73, OR=3.61, 95% CI: 0.99–13.1).

Infliximab, azathioprine and relapse

We noted no significant relationship between infliximab and its effect in preventing relapse (p=0.16). Of seven cases, three experienced recurrence. There were three patients who took infliximab before the first surgery, of which none experienced a relapse. However the results showed no significant difference in comparison with the group who did not take infliximab before surgery (p=0.29), which was possibly a result of the low number of cases in this study. There was no significant relationship between azathioprine and its effect in preventing relapse (p=0.164, OR=0.49, 95% CI: 0.19–1.23).

Perianal disease

Of 31 persons with perianal disease, 14 (45.2%) experienced relapse. There were 15 (21.1%) cases without perianal involvement that relapsed and 56 (78.9%) among the ones with no perianal disease. There was a significant difference between perianal disease and relapse, which indicated that perianal disease was a strong risk factor [p=0.01, OR=3.07 (1.24-7.62)].

Table 2: **Frequency of clinical features (n=566).**

Variables	Total	One surgery	Relapse
Sex			
Male	293	58	16
Female	273	51	14
Chief complaint			
Diarrhea	126	12	8
Bloody diarrhea	148	17	9
Colicky abdominal pain	211	38	15
Present symptom			
Asymptomatic	165	43	11
Diarrhea	28	12	4
Bloody diarrhea	46	6	5
Abdominal pain	46	17	5
Draining fistulae	3	6	0
Fistulae	75	34	16
Duration of diseas >10 yrs	238	52	17
Mean age (yrs.) at onset	30.9 (SD=14.1)	32 (SD=14.9)	29.5 (SD=14.2)
Site of GI involvement			
Small bowel	132	30	12
Both small and large intestines	140	32	8
Large intestine	147	19	7
Abscess	24	10	8

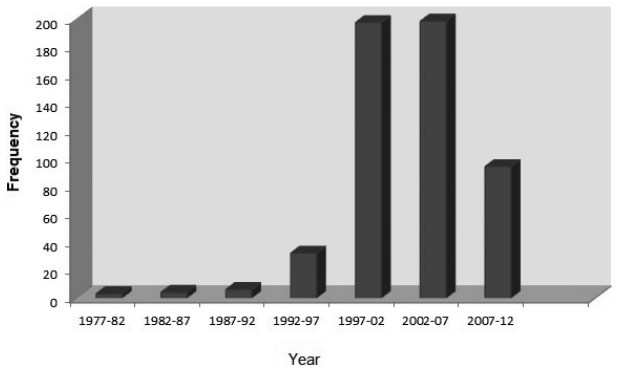

Fig1: Frequency of CD

Table 3: Frequency of surgery.

No. of surgeries	Frequency	Percent	Cumulative percent
None	427	75.4	75.4
1	108	19.1	94.5
2	24	4.2	98.8
3	2	0.4	99.1
More than 3	5	0.9	100.0
Total	566	100.0	

Management of Crohn's disease

Treatment was based on clinical findings and to some extent, laboratory parameters. We defined complete clinical remission as the absence of clinical signs and symptoms in addition to normal laboratory findings. Partial remission was defined as minimal clinical findings and borderline laboratory abnormalities. Achievement of endoscopic remission (mucosal healing) and biologic remission (C-reactive protein normalization) was not considered essential for remission.

Disease duration

We categorized patients in two groups and considered ten years as the cutoff point for testing the effects of disease duration. The results showed a significant difference (p=0.043) between the two groups, which implied that disease duration of more than ten years was a risk factor for surgery. Out of 319 cases in group A with disease duration of less than ten years, 252 had no indications for surgery. In group B with disease duration of more than ten years, 70 out 247 patients underwent surgical intervention. Despite the effects of surgery, duration of disease was not statistically associated with relapse (p=0.059).

DISCUSSION

In the second part of the twentieth century there was progressive improvement in living standards and the establishment of a modern life-style in developed countries. At that time, prior to the 1950s, the first outbreak of Crohn's disease appeared in the United States. Crohn's disease had a North-South gradient of incidence in Europe,[29-33] was noted in the 1950s or before in Sweden,[34] present in the 1960s in the United Kingdom,[30,33] and later observed in Southern Europe.[31] Thus, as with Western countries, in Iran ulcerative colitis appeared first, followed by Crohn's disease which occurred about 20 years later.

Currently Crohn's disease is an important public health problem.[6-8] The age-specific incidence curve and clinical presentation of Crohn's disease in Iran is similar to Western countries and confirms other worldwide epidemiological studies.[6,7] The percentages of complications and location of Crohn's disease lesions is also similar to reports in other Crohn's disease studies from Western countries. However the percentage of patients with epithelioid granulomas is relatively low compared to Western countries, which may be explained by the shorter follow-up time and lower rate of surgery in Iran.[6-8] The current study, which is the first natural history report in Iran, notes a surgery rate of 24.5% over a five-year follow up period.

Surgery rates among Crohn's disease patients vary widely among different reports and according to a recent review, range from 25% to 60% at five years.[35] Surgical rates for Crohn's disease vary more considerably within Asia and the Middle East, which may primarily be the result of the length of follow up. Additional long term studies are needed to explore the reasons behind such differences.[36,37]

Cigarette smoking, penetrating behavior, perianal involvement and longer duration of disease were the main risk factors for surgery and recurrence. This finding was similar to other reports.[10,38-40] Gender, age of onset, type of therapy (thiopurines or infliximab) did not affect the rate of surgery or recurrence. This might have been a result of to the limited number of subjects treated with infliximab.

However due to low experiences with these medications, future studies with larger number of subjects on biologic therapy are necessary to determine the efficacy of anti-TNF-α medications compared to conventional therapy in Iran. One of the reasons for a lower rate of surgery is probably due to the recent onset of Crohn's disease in this region. As the period of follow up increases the percentage of Crohn's disease patients who require surgery for recurrent disease will also increase.

This is the first study on the natural history of Crohn's disease with special emphasis on surgery rate and risk factors for Crohn's disease recurrence in Iran. There are several limitations to our study. In a retrospective study design that reviews medical records, data abstraction may be subject to bias. DDRC serves as a national referral center for patients with IBD. There is a possibility of more complex cases that have been referred to our center, thus necessitating a greater need for surgery and the presence of higher rates of postoperative recurrence, which is a source of referral bias. In addition, biologic therapy was available for a limited number of Crohn's disease patients with special insurance coverage for this expensive medication, therefore this study was unable to evaluate the efficacy of these medications in prevention of relapse.

In conclusion our study revealed that approximately one fourth of Crohn's disease patients required surgery during the first 5 years following diagnosis. Cigarette smoking, penetrating behavior, perianal involvement and longer duration of disease were the main risk factors for surgery and recurrence.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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