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Original Article

Exacerbation causes among inflammatory bowel disease patients in Guilan Province north of Iran

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ABSTRACT

Objective: Numerous factors may contribute as triggers to the exacerbation of the condition of patients with inflammatory bowel disease.
Methods: The medical files of 109 patients with the positive history of inflammatory bowel disease exacerbation between March 2016 and March 2017 were assessed retrospectively. Data were obtained using the inflammatory bowel disease data bank software. The parameters were obtained from the inflammatory bowel disease data bank software. The mentioned parameters were assessed in terms of type and severity of disease using chi-square test in SPSS software. Moreover, binary logistic regression test was used to assess the associations between season of disease onset and inflammatory bowel disease exacerbation as odds ratios with 95% confidence intervals (95% CI).
Results: Overall, (88.1%) of cases with inflammatory bowel disease exacerbation, had ulcerative colitis. The mean age of patients was 38.14 ± 14.66 years. The disease duration in all patients (ulcerative colitis and Crohn's disease) was 35.43 and 38.85 months, respectively. About 50% of patients with infection were strongyloides stercoralis positive. The occurrence of mild inflammatory bowel disease exacerbation was significantly higher in spring in comparison to other seasons (OR = 3.58; 95% CI 0.1–1.04). Most patients with ulcerative colitis were prescribed salicylates alone (53.12%). Most patients with Crohn's disease with mild and severe activity were non-smokers ($p = 0.058$). This difference was marginally significant.
Conclusion: It is suggested that in future studies, the evidences of distribution of SS infections among patients with inflammatory bowel disease and the history of exacerbation along with other environmental factors such as enhancing nutritional quality and surface water be taken into consideration.

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Causas de exacerbação entre pacientes com doença inflamatória intestinal na província de Guilan, norte do Irã

Palavras-chave:
Doença inflamatória intestinal
Doença de Crohn
Exacerbação
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RESUMO

Objetivo: Em pacientes com doença inflamatória intestinal, vários fatores podem servir como gatilhos para a exacerbação do quadro.
Métodos: Os prontuários de 109 pacientes com história de exacerbação da doença inflamatória intestinal entre março de 2016 e março de 2017 foram avaliados retrospectivamente. Os dados foram obtidos usando o software do banco de dados sobre doença inflamatória intestinal, que também foi usado para a definição dos parâmetros do estudo. Esses parâmetros foram avaliados quanto ao tipo e severidade da doença usando o teste do qui-quadrado no software SPSS. Além disso, o teste de regressão logística binária foi utilizado para avaliar as associações entre a estação do início da doença e a exacerbação da doença inflamatória intestinal, expressados em razão de probabilidade (*odds ratio*) com intervalos de confiança de 95% (95% CI).
Resultados: No geral, 88,1% dos casos de exacerbação da doença inflamatória intestinal foram observados em pacientes com colite ulcerativa. A média de idade dos pacientes foi de 38,14 ± 14,66 anos. Em todos os pacientes, a duração média da doença (colite ulcerativa e doença de Crohn) foi de 35,43 e 38,85 meses, respectivamente. Cerca de 50% dos casos de infecção apresentaram cultura positiva para *Strongyloides stercoralis*. A ocorrência de leve exacerbação da doença inflamatória intestinal foi significativamente maior na primavera em comparação com outras estações (OR = 3,58; 95% CI: 0,1-1,04). A maioria dos pacientes com colite ulcerativa foi medicada apenas com salicilatos (53,12%). A maioria dos pacientes com doença de Crohn com atividade classificada como leve ou grave era não fumante (p = 0,058). Essa diferença foi marginalmente significativa.
Conclusão: Sugere-se que, em estudos futuros, as evidências de distribuição das infecções por *Strongyloides stercoralis* em pacientes com doença inflamatória intestinal e história de exacerbação sejam levadas em consideração em conjunto com outros fatores ambientais, como qualidade nutricional e da água de superfície.

Introduction

Inflammatory Bowel Disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory disorders of the gastrointestinal tract identified by episodes of relapse and remission. These two identified subtypes of the disease involve the gastrointestinal tract in different patterns.[1] Although numerous studies have been conducted during the last several decades in order to investigate the etiology of IBD, causative factors in disease pathology are not yet fully understood. IBD is thought to result from interaction between genetic and environmental factors.[2] There have been many studies in recent decades seeking to identify the environmental factors that affect the course of IBD, including seasonal variations and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) usage. However, the majority of these studies have been performed in Western countries. The incidence and prevalence of IBD in Asia have been rapidly increasing in recent years,[3] but few studies have been conducted regarding the seasonal patterns of IBD in Asian populations.[4] Data from an Italian study indicates that the onset of CD symptoms occurred more frequently during spring and summer; a similar trend was observed with UC.[5] The use of NSAIDs has been associated with the onset of IBD or with a clinical flare-up of IBD in a number of case reports.[6] In some studies no relationship has been reported between NSAIDs consumption and exacerbation of underlying IBD.[7,8] It is now fully accepted that UC predominantly affects non-smokers and ex-smokers, and that smoking exerts a universal protective effect against developing UC. Previous family studies have assessed the impact of smoking on patients with IBD. A high degree of concordance has been recognized for the association of smoking and the IBD phenotype within a family, UC occurred in non-smokers and CD in smokers.[9,10] Previous studies revealed that different factors such as infectious diseases, lifestyle factors, domestic hygiene, and intestinal pathogens play a role in IBD exacerbation.[1] Although the prevalence and incidence of IBD have not been accurately studied in Iran, our country has an increasing rate of IBD.[11] This study aimed to survey the IBD exacerbation causes on the basis of disease severity.

Methods

Study design and patients

This retrospective cross-sectional study was conducted on patients with definite histological diagnosis of IBD (CD or UC)

according to standard endoscopic criteria and referring to the gastroenterology ward of Razi Hospital, Iran, due to disease recurrence between March 2016 and March 2017. Patients were included using local IBD Data Bank Software in the Gastrointestinal and Liver Diseases Research Center (GLDRC), Rasht, Iran, which records information on all IBD diagnosed patients of Guilan Province, Iran. The included patients were assessed based on disease severity and the probable causes of exacerbation.

Exacerbation causes

Active infection such as amoeba, parasite, bacterial, and viral infections in blood smear and/or stool culture, Cytomegalo-Virus (CMV) pp65 antigen, clostridium difficult toxin a and b antigen, Anti-amoeba, and Strongyloides, seasonal exacerbation pattern, use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), drugs compliance, and type of current treatment [corticosteroid, salicylates, immunosuppressive drugs, and anti-Tumor Necrosis Factor (TNF)] were considered as exacerbation causes.

Disease severity

In the IBD Data Bank Software, the severity of disease was recorded for UC and CD according to the Modified Truelove Witts Severity Index (MTWSI) and Harvey Bradshaw Severity Indices (HBSI), respectively.

Data extraction

Informed consent was obtained through phone calls from all patients in order to use their recorded data. Data regarding age, gender, education level, place of residence (rural or urban), job status (employed or unemployed), UC or CD duration, history of smoking, seasonal disease exacerbation pattern, mainte-

Table 1 – Demographic and disease-related characteristics of patients with UC or CD as well as exacerbation.

Characteristic	UC*n* (%)	CD*n* (%)	*p*-Value
Age			0.016
<20	11 (12)	1 (8)	
20–39	37 (38)	11 (84)	
40–59	37 (38)	1 (8)	
>60	11 (12)	0 (0)	
Gender			0.130
Female	51(53)	4 (31)	
Male	45 (47)	9 (69)	
Education			0.788
<High school	39 (41)	5 (38)	
High school	54 (56)	8 (62)	
<High school	3 (3)	0 (0)	
Place of residence			0.207
Urban	74 (77)	12 (92)	
Rural	22 (23)	1 (8)	
Job status			0.211
Worker	13 (14)	1 (8)	
Employed	17 (17)	6 (46)	
Self-employed	15 (15)	3 (23)	
Unemployed	38 (40)	1 (8)	
Student	13 (14)	2 (15)	
Type of treatment			<0.001
Salicylates	51 (53.1)	4 (30.7)	
Salicylates + Immunosuppression drugs (Azathioprine)	12 (12.5)	0 (0)	
Salicylates + Prednisolone	9 (9.4)	1 (7.7)	
Salicylates + Prednisolone + Immunosuppression drugs (Azathioprine)	7 (7.3)	0 (0)	
Salicylates + Prednisolone + Immunosuppression drugs + Anti-TNF (Azathioprine)	1 (1)	3 (23.1)	
Without drug	16 (16.7)	3 (23.1)	
MTX + Anti-TNF	0 (0)	1 (7.7)	
Salicylates + Anti-TNF	0 (0)	1 (7.7)	
Anti Amibiasis Antibody	0 (0)	1 (7.7)	
Strongyloides stercoralis antibody	7 (7.3)	0 (0)	
Infection			0.015
CMV pp65 Ag	3 (3.1)	2 (15.4)	
Without enteric infection	85 (88.5)	10 (76.9)	
Anti Amibiasis Antibody + Strongyloides stercoralis antibody	1 (1.1)	0 (0)	

UC, ulcerative colitis; CD, Crohn's disease; Anti-TNF, anti-tumor necrosis factor; MTX, methotrexate.

nance therapy drugs compliance, active enteric infections, history of NSAIDs usage, and the above-mentioned exacerbation causes were extracted from the software.

Analysis

Statistical analysis of quantitative and qualitative data was conducted using chi-square test in SPSS software (version 20, IBM Corporation, Armonk, NY, USA). In addition, $p \leq 0.05$ was considered as statistically significant. In order to assess associations between season and IBD exacerbation, binary logistic regression test was used which presented as Odds Ratio (OR) with 95% confidence interval (95% CI).

Ethical consideration

The present study was approved by the ethics committee of Guilan University of Medical Sciences, Iran.

Results

A total of 109 registered patients with IBD exacerbation were included in the current study; 96 patients had UC. The demographic and disease-related characteristics of patients with UC or CD as well as data related to exacerbation are presented in Table 1. There was no significant association between education level, place of residence, and job status in patients with IBD exacerbation (Table 1). The mean duration of disease was 35.43 and 38.85 months in patients with UC and CD, respectively. Most of the patients had suffered from UC and CD for less than 5 years. While most patients with CD had moderate and severe disease (69.2%), patients with UC had mild disease (56.3%). However, this difference was not statistically significant ($p = 0.084$) (Fig. 1). No significant relationship was reported between NSAIDs treatment and disease severity ($p = 0.307$). The mild IBD pattern mainly occurred in spring with a significant relationship in comparison to other seasons (OR = 3.58; 95% CI 0.1–1.04) (Table 2). Disease severity did not differ significantly among patients based on smoking habits (smokers: $p = 0.903$; nonsmokers: $p = 0.463$). However, in patients with CD, the relationship between smoking and disease severity was marginally significant ($p = 0.058$) (Table 3). There were no significant differences between those with drug compliance for maintenance therapy and those without compliance ($p = 0.106$). There was a significant association between active enteral infection and UC exacerbation, but there was no significant relationship between enteral infection and CD exacerbation ($p = 0.188$) (Table 3). Among the 96 patients with UC exacerbation, enteric infection was found in 11 patients (11.46%), Strongyloides Stercoralis (SS) antibody was detected in 7 (64%) individuals. Moreover, CMV pp65 antigen was detected in 3 (27%) participants. Of the 13 cases with CD exacerbation, infection was detected in 3 patients (23.08%); CMV pp65 antigen was detected in 2 (66.67%) instances (Table 1). In patients with positive CMV pp65 antigen test, the symptoms were eliminated with ganciclovir usage. Single maintenance therapy with salicylates was the most common treatment method in patients with UC 51 (53.12%), but in patients with CD, combination therapy was the most reported method ($p < 0.001$) (Table 2).

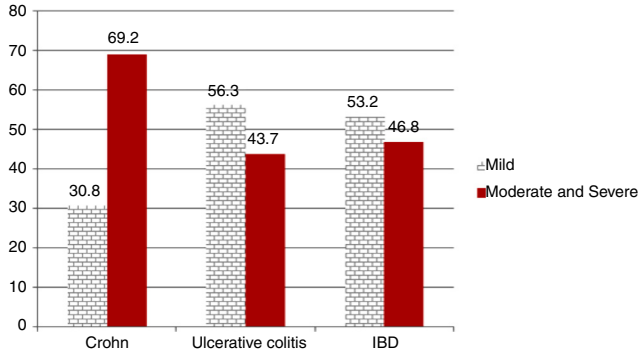

Fig. 1 – Severity of disease variation in inflammatory bowel disease and ulcerative colitis and Crohn's disease.

Discussion

Several types of studies with different settings have been conducted in order to distinguish the factors which are related to exacerbation and remission of IBD symptoms as well as activity with several indexes related to both clinical symptoms and biomarkers in model-based or human researches.[12–16] However, there is not a unique list of causes to guide physicians or health care providers in the establishment of management strategies to alleviate these exacerbation occurrences. Thus, people all around the world are exposed to different exacerbation factors while the global trend of IBD appears to be increasing significantly.[17] Hence, exploring local disturbance factors is essential. It is argued that the westernization and industrialization of Asian countries with consideration of some environmental risk factors are contributing to the increase in the incidence and prevalence of IBD.[18,19] IBD is one of the gastrointestinal diseases with the most economical implication and no medical cure, so it requires a lifetime management.[20] According to this study, in Guilan Province, it seems IBD has involved individuals who are in their productive ages, this places a long-term financial burden on the patients, health care system, and society.[21] Lee et al. conducted a retrospective study to compare the clinical features and disease behavior of UC among individuals diagnosed at younger and older ages.[22] They found the severity of certain clinical features and the extent of disease in patients with UC to be higher in younger patients, although their disease course and prognosis might not differ from that of elderly patients.[22] In the present study patients with CD exacerbation were younger than patients with UC. Furthermore, there was inverse gender dominance in these two groups; a higher rate of men had CD and a higher rate of women had UC. However, in the study by Larsson et al., women with CD experienced exacerbation more which illustrates that it is a more complicated and serious condition in medical terms.[23] In a systematic review and meta-analysis, a positive association was found between urban environment and both CD and UC.[24] As was the case in the present study, in some studies it seems that the role of education levels and employment status was not highlighted in disease exacerbation in patients with UC and CD.[23] The current study results showed that the symptom of IBD exacer-

Table 2 – Association of disease severity with season and treatment medications.

Disease severity	IBD		p-Value
	Mildn (%)	Moderate and severen (%)	
Season			0.061
Spring	19 (70.4)	8 (29.6)	
Summer	14 (40)	21 (60)	
Autumn	15 (62.5)	9 (37.5)	
Winter	10 (43.5)	13 (56.5)	
Treatment medications			0.050
Salicylates	35 (63.6)	20 (36.4)	
Salicylates + Immunosuppressive Drugs (Azathioprine)	4 (33.3)	8 (66.7)	
Salicylates + Prednisolone	3 (30)	7 (70)	
Salicylates + Prednisolone + Immunosuppressive drugs (Azathioprine)	4 (57.1)	3 (42.9)	
Salicylates + Prednisolone + Immunosuppressive drugs + Anti-TNF (Azathioprine)	0 (0)	4 (100)	
Without Drug	12 (63.2)	7 (36.8)	
MTX + Anti-TNF	0 (0)	1 (100)	
Salicylates + Anti-TNF	0 (0)	1 (100)	

IBD, inflammatory bowel disease; Anti-TNF, anti-tumor necrosis factor; MTX, methotrexate.

Table 3 – Smoking and active enteric infection in association of different types of disease severity.

Type of disease severity	IBD		p-Value	UC		p-Value	CD		p-Value
	Mildn (%)	Moderate and severe n (%)		Mildn (%)	Moderate and severe n (%)		Mildn (%)	Moderate and severe n (%)	
Smoking									
No	41 (54.7)	34 (45.3)	0.903	39 (59.1)	27 (40.9)	0.463	2 (22.2)	7 (77.8)	0.058
Ex-smoker	4 (50)	4 (50)		4 (66.7)	2 (33.3)		0 (0)	2 (100)	
Active-smoker	13 (50)	13 (50)		11 (45.8)	13 (54.2)		2 (100)	0 (0)	
Active enteric infection									
Yes	3 (21.4)	11 (78.6)	0.059	3 (27.3)	8 (72.7)	0.040	0 (0)	3 (100)	0.188
No	55 (57.9)	40 (42.1)		51 (60)	34 (40)		4 (40)	6 (60)	

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

bation with mild pattern occurred mainly in the spring. Koido et al. declared that the clinical onset of UC in Japan was significantly more common in winter and spring.[25] A significant increase in the onset of UC (but not CD) was reported during December in Norway by Moum et al.[26] Taghavi et al.[27] and Romberg-Camps et al.[28] found no relation between the onset of IBD and seasons. The mechanism of action of some factors such as presence of cytomegalovirus,[29–31] intestinal protozoa infections,[12] enteropathogenic virus,[32] clostridium difficile,[33] and acute viral enteritis[34] in causing relapse or symptom exacerbations among patients with IBD has been widely studied. Surprisingly, in this study, most of the patients with IBD had no enteric infection, while SS was more common among patients with UC and CMV pp65 Ag was observed in patients with CD. Irving and Gibson reported similar findings.[35]

Furthermore, other probable factors such as NSAIDs consumption,[36] disease onset at a young age,[22] seasonality patterns,[37] depression,[38] and Quality Of Life (QOL)[23] are linked to IBD exacerbation. It has been noted that the use of NSAIDs has been associated with the onset of IBD or with a clinical flare-up of IBD in a number of case reports[6]; in contrast, no relationship was reported between NSAIDs treatment and exacerbation of underlying IBD by Bonner et al.[7] and Dominitz et al.[8] According to a recent retrospective study among patients with IBD, intake of either celecoxib or rofecoxib is linked to clinical relapse of the intestinal disease in 39% of cases, as well as resolution of symptoms after COX-2 inhibitor withdrawal.[39] In the present study, no significant relationship was observed between NSAIDs treatment and exacerbation of IBD in mild and moderate-severe cases of the disease. Moreover, it seems that drug compliance does not have a vital role in the prevention of IBD exacerbation. This study showed that most of the patients with UC exacerbation were treated with 5 amino salicylic acid only, but patients with CD exacerbation were treated with a combination of salicylates and immunosuppression drugs as well as anti-TNF drugs. In a study by Shirazi et al., it was reported that the majority of patients with CD and UC were treated with only 5 amino salicylic acid.[40] One study in Iran showed that most patients were treated with a combination of salicylates and azathioprine (60% in UC and 72.3% in CD) and salicylates were the most common drugs in both groups (38.4% in UC and 25.9% in CD).[1] The majority of patients who were prescribed salicylates alone showed mild disease, while patients who were treated with combination therapy showed moderate to severe IBD exacerbation. These data can clarify the general characteristics of patients with IBD exacerbation on the basis of disease severity and improving management options. This

study had some limitation, namely the short-term study period, and the lack of measurement of the QOL of patients and control group. In addition, among those with appropriate drug compliance, the dose of salicylates was not investigated, whether the optimal dosage has been consumed or not.

Conclusion

The results of this study showed the high frequency of enteric infections, of which *SS* was the most common, in patient with UC exacerbation in Guilan Province. Therefore, patients should be assessing for this factor through stool or blood samples. The symptoms of mild IBD exacerbation occurred more frequently during spring. No relationship was observed between NSAIDs treatment and exacerbation of IBD.

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Conflicts of interest

The authors declare no conflicts of interest.

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