

A Case-Control study on the risk factors of IBD in 258 Iranian patients

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ABSTRACT

Introduction: Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases (IBD) with uncertain etiology thought to be triggered by interactions between various environmental, genetic and immunologic factors. Role of different factors in IBD are controversial.

Materials and Methods: The aim of this study is to determine the possible risk factors in a group of Iranian patients with IBD. Ninety five consecutive cases of CD and 163 cases of UC were included. Age matched controls were randomly selected. A total of 489 controls for UC and 285 controls for CD were enrolled. A standard record concerning many variables was completed. Logistic regression analysis was used to evaluate potential confounding variables.

Results: A statistically significant protective effect for smoking in UC was found (OR=0.18 95% CI=0.064-0.504, $p < 0.05$). The risk of UC increases with prolonged exposure to OCP (OR=0.99, 95% CI=0.98-0.99, $p < 0.05$). In patients with CD, 15 cases (15.8%) reported a previous history of appendectomy compared with 19 controls (6.7%) (OR=2.6, 95% CI= 1.2-5.4, $p < 0.05$). Tonsillectomy was reported by 16 patients (16.8%) with CD compared with 25 controls (8.8%) (OR= 2.1, 95% CI= 1.07-4.1, $p < 0.05$). The logistic regression analysis showed that both appendectomy and tonsillectomy are risk factors in CD. No association with other variables was found for either disease.

Conclusion: Current smoking was a significant protective factor in UC. We observed a relationship between duration of OCP use and UC. Duration of using OCP in UC cases was significantly more than controls. Both appendectomy and tonsillectomy were risk factors in CD in this study

Keywords: Ulcerative colitis; Crohn's disease; risk factors; Iran

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INTRODUCTION

The inflammatory bowel disease (IBD) which consists of Crohn's disease (CD) and ulcerative colitis (UC) is recognized as a group of chronic idiopathic inflamma-

tory disorders of the gastrointestinal tract. Both UC and CD have defined pathologic and clinical characteristics, but no study clarified the exact pathogenesis up to now (1).

Although the exact causes and mechanisms of IBD have not been understood completely yet, Our concept of IBD nature and underlying pathophysiological mechanisms has been expanded by numerous researches during the last two decades (2,3). The hypothesis of involving immune response, in a genetically predisposed individual, as the result of a complex interaction among the environmental factors, microbial factors, and the intestinal immune system,

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are accepted by enough progress (4).

The IBD has traditionally been considered as a common disease in the western world; however recent studies represent an increasing rate of IBD in many developing countries around the world as well. One of the suggested reasons that IBD is increasing in developing countries including Asian countries are Modernization and westernization (3, 5, 6).

Although the incidence and prevalence of IBD in Iran are still unidentified, but there are some studies indicating the gradual increasing in this country (7-10). Due to the lack of true population-based registries it is difficult to reach to any firm conclusion from these studies. Since Iran is a geographically wide country of different ethnicities, a lot of studies are needed to determine infrequent disease etiopathogenesis aspects.

Due to the recent worldwide rise, and the geographic variation in incidence and prevalence of IBD, the role of environmental factors is highly considered (11,12). A variety of environmental factors such as infantile infectious diseases, infantile nutrition (breastfeeding, formula feeding or cow milk), tonsillectomy, appendectomy, diet, domestic hygiene, food refrigeration, timescales of socio-economic evolution, the use and duration of Oral contraceptive pills (OCPs) and NSAIDs, taking antibiotics and their duration, smoking, intestinal pathogens and measles vaccination were mentioned in different studies as risk factors for IBD (8,11,13-17).

There are some investigations which have been indicated the domestic hygiene as a risk factor of IBD. These studies showed that, the lack of exposure to the enteric pathogens, especially in childhood, caused CD in adulthood especially those who are genetically sensitive against CD. Several childhood infections and poor hygiene have been suggested as protective factors in CD because of the immunity and tolerance increasing against the factors which lead to CD (18-21). Considering this we checked socioeconomic factors in this study. It is obvious that people in better economical and social status are supposed to use more improved sanitary facilities so it is less probable for them to become infected with different infections. Food refrigeration is another suggested risk factor of CD. There are some studies about the cold chain hypothesis which confirm the connection between CD and domestic refrigeration. So we address the issue of cold chain hypothesis in this study (2,7,22-24).

The purpose of this study was to determine the role of different environmental factors in IBD in Iran.

MATERIALS AND METHODS:

Cases and controls

The study was set up as a population-based case-control study in Tehran University in Iran. 163 patients with UC and 95 patients with CD, visiting three major private clinics in Tehran, Iran, were enrolled consecutively in this study, during a 2-year period (January 1, 2008 to December 31, 2009). The diagnosis of IBD was confirmed by clinical, laboratory, endoscopic, and histological findings in accordance with Leonard-Jones criteria (25).

Controls were randomly selected from the same clinics, from the patients with IBS or functional GERD, which have been diagnosed at least three months prior to the course of the study in these clinics. IBS was diagnosed by Rome II criteria and rolling out the organic causes of symptoms by physical examination, lab tests, endoscopy and colonoscopy. The diagnosis of GERD was based on clinical manifestations. Finally we enrolled 489 controls for UC patients and 285 controls for CD patients which have been matched by sex and age during this study. Using these numbers we matched controls by cases in a 3 to 1 matching design. All cases and controls signed a written informed consent for this study. The ethics committee of Tehran University School of Medical Sciences approved the study protocol.

Questionnaire

All participants were guided and interviewed to complete a structured multi-item questionnaire which has been taught by an expert co-investigator.

We asked several questions from participants, such as demographics, disease characteristic findings, including clinical manifestations, radiologic, endoscopic and histological findings, type and extent of disease, intestinal and extra intestinal manifestations, childhood dietary and duration (breastfeeding, formula feeding, cow milk), smoking habits, history of childhood measles infection and vaccination, history of appendectomy and tonsillectomy, use of OCPs (type and duration), taking antibiotics during last five years, the frequency of weekly tooth brushing, family history of IBD and monozygote twin with IBD, the number of family members (before 12 years old, current family members), socioeconomic conditions and

food refrigeration.

Regarding the socioeconomic condition, we asked about the use of several facilities such as personal car, personal bath, refrigerator, freezer, washing machine, microwave, central heating system and personal computer. The questions included whether they use the facilities or not, the date of starting to use and the quality of the facilities. The quality classified as well or poor. By well quality it means the continuous use of them and by poor quality it means as the lack of their use for at least one month consecutively.

The participants were classified as current smokers, if they had smoked more than 1 cigarette per day within 6 months before the diagnosis of IBD, nonsmokers, if they never or rarely smoked and ex-smokers who were defined as patients who quit smoking more than 6 months before the diagnosis of IBD. Our classification was in accordance with the definitions of smoking in the National Health Interview Survey. By oral contraceptive use it means to use it at least 1 month for any indication including birth control, hormone replacement therapy, regulation of menstrual disorders, or other reasons.

Statistical Analysis

Statistical analyses were performed using SPSS16 software (SPSS, Inc, Chicago, IL). Chi square test was performed to compare frequencies of risk factors between the IBD patients and controls. Multiple logistic regression analysis was performed to evaluate multiple risk factors for IBD. *p* value less than 0.05 considered significant. Odds ratios (OR) and 95% confidence intervals (CI) were measured.

RESULTS

A total of 163 cases with UC (male, 43.6%; female, 56.4%; mean age (\pm SD):37.1(\pm 13.8); range: 13-74) and 489 controls (male, 39.3%; female, 60.7%; mean age (\pm SD):37.9(\pm 13.8); range: 14-84) were recruited in the study. 95 cases with CD (male, 38.25%; female, 61.75%; mean age (\pm SD):32.6 (\pm 12.6); range: 13-60) and 285 controls (male, 44.2%; female, 55.2%; mean age (\pm SD):33.3 (\pm 11.9); range: 14-64) were enrolled in this study. All cases had at least three-matched control. Comparing several demographic factors between cases and controls, we didn't find any association between demographic variables including sex, age, marital status, race, BMI, place of birth, place of longer living, level of education and ethnicity in both UC and CD.

A significant protective effect of smoking was found in UC. As it was mentioned we categorized smoking habits as none smokers, ex smokers and smokers. We observed a significant protective effect of current smoking in UC (OR=0.18, CI=0.064-0.504). But this protection didn't include ex smoking and none smoking. Also no connection was detected between smoking and CD (Table 1).

We observed a relationship between duration of using OCPs and UC (*p* value=0.02) (OR=0.99, 95%CI=0.98-0.99). It seems that UC cases are more likely to use OCPs for a longer time in our study. The mean (\pm SD) duration (months) of using OCPs in UC patients and controls were 42.6 (\pm 57.3) and 23.4(\pm 45.7), respectively. But we failed to find any association between types of OCPs and UC (Table2). The comparison of different types of infantile feeding in UC and CD, between cases and controls, didn't

Table 1: Smoking in UC cases and controls, CD cases and controls*

Variables	Ulcerative colitis cases (n=163)	Controls of ulcerative colitis (n=489)	p - value	Crohn's disease cases (n=95)	Controls of Crohn's disease (n=285)	p - value
Smoking						
Smoker	4	61	0.001**	11	28	0.52
Non-smoker	142	390		77	238	
Ex-smoker	17	38		7	19	
Mean(SD) number of pack year	8.05 \pm 13.26	7.48 \pm 13.36	0.85	9.52 \pm 5.00	9.07 \pm 5.83	0.86

*As a result of missing data, the number of cases and controls of UC and CD for some variables may be less than 168, 489, 95 and 285 respectively. **
P value less than 0.05 is significant.

Table 2: OCPs use in cases and controls of UC and CD*.

Variables	Ulcerative colitis cases (n=163)	Controls of ulcerative colitis (n=489)	<i>p</i> - value	Crohn's disease cases (n=95)	Controls of Crohn's disease (n=285)	<i>p</i> - value
OCPs ever used**						
Yes	53	171	0.96	24	86	0.25
No	39	127		29	81	
Mean duration(SD) of using OCPs(months)	42.57 ± 57.34	23.40 ± 45.71	0.02	24.04 ± 47.25	24.32 ±52.92	0.98
Time of using OCPs						
Current	8	17	0.60	3	13	0.58
In the last year	5	19		2	15	
More than one year ago	40	136		19	69	
Type of OCPs						
LD	36	101	0.60	19	63	0.23
HD	8	14		3	8	
Compound	1	17		0	10	
Unknown	8	40		2	16	

* As a result of missing data, the number of cases and controls of UC and CD for some variables may be less than 168, 489, 95 and 285 respectively.

** Questions about OCPs were only asked of females. OCPs refer to oral contraceptive pills.

Table 3: History of infantile feeding in cases and controls of UC and CD*.

Variables	Ulcerative colitis cases (n=)	Controls of ulcerative colitis (n=)	p - value	Crohn's disease cases (n=)	Controls of Crohn's disease (n=)	p - value
Breast Milk						
Yes	148	439	0.33	83	30	0.47
No	15	50		12	255	
Mean (SD) duration of breast milk(month)	18.43 ± 6.70	17.96 ± 7.40	0.69	18.17 ± 7.40	17.77 ± 7.50	0.57
Formula feeding						
Yes	26	76	0.92	24	233	0.19
No	137	413		71	52	
Mean (SD) duration of formula feeding	9.04 ± 7.06	10.47 ± 7.1	0.42	10.71 ± 6.91	9.98 ± 6.80	0.30
Cow Milk						
Yes	13	34	0.58	4	24	0.13
No	150	455		91	261	
Mean (SD) duration of cow milk(month)	10.54 ± 9.09	10.62 ± 7.72	0.96	6.25 ± 4.57	10.96 ± 7.28	0.50

*As a result of missing data, the number of cases and controls of UC and CD for some variables may be less than 168, 489, 95 and 285 respectively.

Table 4: History of measles infection/ vaccination/ appendectomy/ tonsillectomy, frequency of use antibiotic*.

Variables	Ulcerative colitis cases (n=153)	Controls of ulcerative colitis (n=489)	<i>p</i> - value	Crohn's disease cases (n=95)	Controls of Crohn's disease (n=285)	<i>p</i> - value
History of measles						
Yes	69	186	0.31	30	101	0.18
No	46	126		39	88	
Unknown	48	176		26	96	
History of measles vaccination						
Yes	110	312	0.67	70	203	0.24
No	26	82		9	41	
Unknown	27	95		16	41	
History of appendectomy						
Yes	7	37	0.24	15	19	0.007
No	156	452		80	266	
History of tonsillec-tomy						
Yes	17	53	0.88	16	25	0.02
No	146	436		95	260	
Frequency of using Antibiotic						
2<episodes per year	89	260	0.93	39	146	0.22
2>episodes per year	46	140		36	88	

*As a result of missing data, the number of cases and controls of UC and CD for some variables may be less than 168, 489, 95 and 285 respectively.

show us any significant connection (Table 3).

We didn't observe any relationship between socioeconomic status, cold chain, family size (before 12 years old and current family size), oral hygiene (frequency of weekly toothbrush), and IBD.

CD was significantly associated with appendectomy in this study. 15 cases (15.8%) and 19 controls (6.7%) previous history of appendectomy was reported in. (OR=2.625, 95%CI=1.27-5.402, $p = 0.007$).

Comparing the history of tonsillectomy between CD cases and controls showed that, tonsillectomy is a risk factor too. Tonsillectomy was reported in 16 cases (16.8%) compared with 25controls (8.8%). (OR=2.106, 95%CI=1.071-4.142, $p = 0.02$)(Table 4).

DISCUSSION

Unfortunately, there are a few studies about the inflammatory bowel disease (IBD) in Iran. The inci-

dence of IBD especially CD is less frequent in Iran than western world, but the studies carried out shows the increasing of IBD in Iran (7, 27).

Many environmental factors were searched and suggested as the risk factor of IBD, however only few association has been well documented in the pathogenesis of IBD (9). We try to compare our findings with other studies reports, especially studies in Asia. One of the most important theories of the environmental factors is the relationship between smoking and IBD. Many studies have represented a negative correlation between smoking and UC, which means, smoking has a protective effect on UC developing (11). The protective effect of smoking against UC were found in the studies in China and Japan. Also there are studies in which a positive correlation between smoking and the risk of CD development observed (24,29). In our study we observed that, current smoking is a

protective factor in UC, but this protection doesn't include ex smokers. We didn't perceive any association between smoking and risk of CD which is resemble with results of Asian studies from Hong Kong and Korea (30, 31). Also it could be the result of the small size of study.

A number of studies has imported that appendectomy might be a protective factor against the development of UC (30, 32). Some Asian studies reported the same results (33,34). Regarding to a study in Iran, appendectomy is a risk factor in CD, but has a modest protective effect for development of UC (17). Unfortunately the studies about determining the risk of appendectomy on the development of CD in Asia is too rare (26). Also some studies have suggested tonsillectomy as a risk factor in UC. In contrast, tonsillectomy wasn't confirmed as the risk factor of CD in other ones (26,32).

There are paradoxical views about breastfeeding in several studies. It is suggested that breastfeeding might be a protective factor in developing IBD (9), however some studies didn't report any positive connection (9).

Some but not all studies have shown a relationship between oral contraceptive use and the IBD development (15, 35,36). We observed that the risk of UC was increased with prolonged exposure to OCPs but we didn't detect any association between OCPs and CD.

The suggestion of higher socioeconomic status which leads to better sanitary and health facilities were mentioned in some studies. Regarding this hypothesis, better hygiene could be a risk factor for IBD, so it is concluded that better socioeconomic condition could be a risk factor as well (18,19,21,37).

Some studies detected a relationship between expo-

sure to home refrigerator and the risk of CD, indicating that exposure to home refrigerator in case group is higher than that in control group, which were chosen from general population (2, 23, 24).

One of the problems in this study was the uncertainty about the exact history of measles vaccination, infantile measles infection and the history of using antibiotics during last five years. So, we recommended the patients to have their vaccination card at the time of their visit. We also asked their parents about the patient's infantile infectious history.

Regarding many helpful studies, some risk factors such as smoking and appendicitis are approved as factors which have influence on IBD process. But still there are controversial viewpoints about the efficacy of many other factors in IBD. Although studies which were done in this field are widespread and worldwide, still so many questions, which we don't know their answers yet, exist. It seems, to eliminate the ambiguous and unknown cases, studies should be continued to approve or reject the previous studies findings. In addition, it is necessary to find and suggest the new probable factors. Because the factors which are known as preventing or predisposing, are as the results of the studies like ours.

The deficiencies of IBD studies, in Asian countries including Iran, have many reasons. One of the most important reasons is that, Iran is geographically, a wide country and there are many areas which are not accessible to health care centers, so this is the reason that we don't have real population _based samples. Because of this Asian countries should be more active in the epidemiologic studies in IBD, and further studies are inevitable for better understand the potential risk factors of IBD in Asia.

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