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Familial ulcerative colitis in Israeli Jews: its prevalence and clinical severity compared to sporadic disease

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Abstract

Background A family history of inflammatory bowel disease (IBD) is present in some ulcerative colitis (UC) patients. We aimed to investigate the familial occurrence of UC and its impact on disease severity.

Methods A structured questionnaire was distributed to patients with UC. Parameters pertaining to disease severity were compared for patients with or without positive family history of IBD.

Results The study group consisted of 168 UC patients with a total of 952 first degree relatives. Positive family history for IBD in a first degree relative was reported in 24 patients (14%). Six of the 336 parents (1.8%) had IBD (all with UC). There were 13 siblings with IBD (4 CD, 9 UC) out of 249 (5.4%). Seven of 376 (1.9%) offsprings had IBD (4 CD, 3 UC). Familial patients were more commonly females and have reported significantly more disease exacerbations than the sporadic group (17.7±15 versus 6.8±11, respectively, p=0.006). On multivariate analysis, familial disease was significantly and independently associated with both female sex (OR 4.1, 95% CI 1.1-14.9, p=0.04) and more exacerbations per year (annual OR 1.05, 95% CI 1.01-1.1, p=0.02). However, similar proportions of sporadic and familial patients wherever hospitalized, underwent colectomy or were treated by immune-suppressors.

Conclusions Familial occurrence of UC is not uncommon among Jewish patients in Israel. The familial-genetic component may preferentially influence disease occurrence among females, and is possibly associated with more disease flares although other parameters of disease severity do not seem to be impacted.

Keywords Crohn's disease, ulcerative colitis, inheritance

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Introduction

The etiopathogenesis of ulcerative colitis (UC) is still undefined although interplay between a predisposing genetic background with alterations in immune system functions brought about by unknown triggers has been suggested. The prevalence of UC varies among different ethnicities, and was reported to be particularly high among Jewish descendents [1]. However, the concordance rate among monozygotic twins was found to be merely 16% thereby indicating that genetic components may play a different and perhaps more minor role in UC compared to Crohn's disease (CD) where the respective concordance rate is greater than 50% [2]. Familial occurrence of disease is another manifestation of genetically inherited pathogenic factors, and has been reported to be present in 10-20% of patients in Caucasians but in only 2-5%

of Southeastern Asians [1,3-5]. In a single survey, 22% of Jewish UC patients residing in the US had a familial disease compared to only 11% of their non-Jewish counterparts [6]. However, the prevalence of familial disease among Jews residing in Israel has not been investigated.

We and other groups have previously examined whether familial CD confers a greater risk of a more severe course of disease and have found no such association [7,8]. In contrast, the handful of studies examining this question in UC yielded conflicting results regarding the association of familial disease with a particular patient sex, disease extent and severity [3,9,10].

Therefore, the aim of the present study was to investigate the prevalence of familial UC among Jewish CD patients residing in Israel, and to examine if a positive family history of inflammatory bowel disease (IBD) is associated with a more severe disease course.

Materials and Methods

A structured anonymous questionnaire was designed to inquire about demographical data and clinical characteristics pertaining to UC course and treatment, as well as to disease occurrence in family members. Severity of UC was evaluated by the following outcome parameters: The need for colectomy, past or present use of corticosteroids or immunomodulators including biologics, the follow up in a community clinic or in hospital referral center clinics, the number of hospitalizations, the number of flares requiring change of treatment, and the subjective assessment of percentage of time with active disease during the last year. The questionnaires were disseminated among patients attending the Israeli Crohn's & Colitis Foundation meeting held in February 2008, and among CD patients attending the Sheba Medical Center and Rambam Health Care Campus gastroenterology clinics. Patients who had at least one first degree relative with IBD were designated as familial, whereas patients without IBD in their first degree relatives were designated as sporadic. Questionnaires of two members of the same family were analyzed as a single questionnaire for familial prevalence calculation.

Statistical analysis

Continuous variables were analyzed by two-tailed Student t-test or Mann-Whitney U-test, as appropriate, and categorical variables were analyzed by Fisher Exact test. Correlation between continuous variables was examined by Spearman correlation test. Multivariate analysis was performed by a backwards logistic regression model. All statistics were performed using MedCalc software (Mariakerke, Belgium). $P<0.05$ was considered significant.

Ethical considerations

The study was approved by the Institutional Review Boards of Sheba Medical Center and Rambam Health Care Campus.

Results

Questionnaires were returned by 169 patients. One patient was excluded due to missing data regarding family history of IBD. Thus, 168 questionnaires were available for analysis and comprised the study group. Of these, 70 were obtained during the Crohn's and Colitis Foundation meeting, and 98 were completed by patients attending the Sheba Medical Center and Rambam Health Care Campus outpatient clinics. To estimate the rate of miss-reported data, a sample of 30 questionnaires completed by patients in the outpatient clinic was reviewed against these patients' charts. This review found three inconsistencies: two patients miss-reported their disease extent and one patient who reported past usage of methotrexate despite being followed-up continuously in the Sheba hospital clinic without documentation of this drug's prescription.

There were 24 respondents who reported a positive family history in the form of a first degree relative with IBD, amounting to 14% of the 168 study participants. Two respondents reported two first degree relatives with IBD (the two parents in one case, and two offsprings in another case).

The breakdown of prevalence of IBD in family members of patients is shown in Table 1. We found no correlation between

Table 1 Prevalence and types of IBD among first degree relatives of patients with UC. One couple of 2 parents with UC was the parents of a single index respondent, and 2 CD sons were the offsprings of the same UC respondent father.

	Total number	Number with CD	Number with UC	Total number with IBD (%)
Parents	336	0	6	6 (1.8%)
Siblings	240	4	9	13 (5.4%)
Offsprings	376	4	3	7 (1.9%)
All 1st degree relatives	952	8	18	26 (2.7%)

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

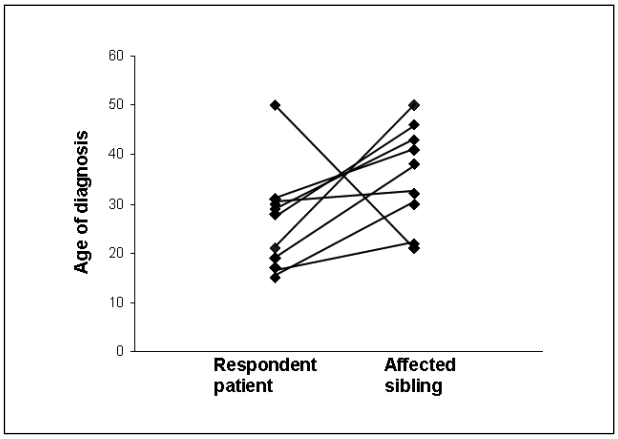

Figure 1 The age of UC onset in the pairs of affected siblings. No significant correlation was found between the age of disease onset in index questionnaire respondents on the left and their respective affected sibling on the right (r=0.26, p=0.5, n=9, Spearman correlation test).

the gender of the proband or the relative, and the type of disease (CD or UC) he/she was inflicted with. When two siblings in the same family were affected by UC, no correlation between age of disease onset in the sibling pairs was found (r=0.26, p=0.5, n=9, Spearman correlation test, Fig. 1).

We next aimed to compare the demographic and clinical characteristics of familial and sporadic patients. Table 2 shows epidemiologic and disease-specific characteristics between the 2 groups and indicated a trend for increased proportion of females in the familial cases. A comparison between the familial and sporadic groups with respect to various indicators of disease severity is shown in Table 3. The findings showed no difference in all of the parameters of disease behavior or severity between familial and sporadic cases, except for a modest increase in the number of flares in the familial patients despite a comparable duration of disease.

To examine if any of these parameters were independently associated with disease classification (sporadic / familial), they were entered into a multivariate backwards logistic regression model (Table 4). In this analysis, the strength of association between familial occurrence of disease and female sex has increased and obtained statistical significance. The association of familial disease with increased rate of disease exacerbations was retained in this analysis as well.

Discussion

The present study investigated the prevalence of familial clustering of IBD among relatives of patients with UC, and examined if familial cases are associated with a more aggressive course of disease. The results showed a surprisingly high rate of 14% of patients (24 of 168) having a positive family history for IBD in first degree relatives. This rate is comparable to the prevalence of positive family history of IBD in Israeli CD patients which was 16% [8]. This surprising finding stands in contrast with studies in other ethnicities showing a lower prevalence of familial disease among UC patients compared to CD ones [10], and may attest to inheritance patterns peculiar to Jewish UC patients. However, patients in the UC cohort had on average more first degree relatives compared to patients with CD (952/168 versus 825/181, incidence rate ratio 1.24, 95% CI 1.13-1.36, P<0.001). This increases the arithmetical probability of an index UC patient to have at least one first degree relative with IBD, perhaps accounting for this seemingly comparable number of patients with

Table 2 Epidemiologic and disease specific characteristics among the patients with positive IBD history in first degree relatives (familial patients), versus those without (sporadic cases).

	All patients (n=168)	Familial patients (n=24)	Sporadic patients (n=144)	P value
Females (%)	71 (42%)	14 (58%)	57 (40%)	0.12
Median age (SD)	45±17	51±15	43±17	0.4
Born in Israel	124 (74%)	20 (83%)	104 (72%)	0.3
Ashkenazi origin	70 (41%)	11 (46%)	59 (41%)	0.9
Smokers	43 (26%)	5 (21%)	38 (26%)	0.8
Mean disease duration§	11±11	12±14	11±11	0.3
Median age of diagnosis	30±15	30±14	30±16	0.7
Mean diagnosis delay$	20±48	1.1±2	2±4	0.16
Disease location*				
Rectum	29 (19%)	7 (32%)	22 (17%)	0.14
Left sided	79 (52%)	7 (43%)	72 (39%)	0.8
Extensive / pancolitis	44 (29%)	8 (36%)	36 (28%)	0.5

**Data derived from 152 respondents. § Disease duration is expressed in years. $ Diagnosis delay denotes the duration of symptoms in months until diagnosis.*

Table 3 Disease complications and severity parameters among the patients with positive inflammatory bowel disease history in first degree relatives (familial patients), versus those without (sporadic cases).

	Familial patients (n=24)	Sporadic patients (n=144)	P value
Treatment (past or present)			
Corticosteroids	11 (46%)	90 (63%)	0.17
Thiopurines/Methotrexate	8 (33%)	33 (23%)	0.3
Cyclosporine	0	8 (5%)	0.6
Biologics	2 (8%)	8 (5%)	0.6
Underwent colectomy	2 (8%)	19 (13%)	0.7
Mean number of hospitalizations (SD)	2.7±6	1.4±4	0.3
Never hospitalized due to CD*	13 (54%)	66 (46%)	0.3
Followed at hospital out-patient clinic*	14 (64%)	92 (71%)	0.9
Mean number of exacerbations (SD)	17.7±15	6.8±11	0.006
Mean % of time with active disease in last year (SD)	33±39	33±34	0.9

** denotes data items for which some respondents did not provide data*
CD, Crohn's disease

familial disease in UC and CD. Supporting this contention is the trend towards reduced prevalence of IBD among the 952 first degree relatives of UC patients in the current cohort compared to its prevalence among 825 relatives of CD patients documented in our previous study on a similar population (2.7% versus 4.3% respectively, p=0.08). Interestingly, the present study found a higher preponderance for familial disease to occur in female UC patients. This is an intriguing observation which replicates previous findings from two studies also showing higher rates of familial disease among female UC patients compared to male patients [3,9]. It is tempting to speculate whether female predilection for familial occurrence of disease points to certain patterns of inheritance and/or genetic loci involved, but this would be best answered by future targeted genetic studies.

A previous study has documented an increased rate of extensive/pan-colonic UC in familial cases compared to sporadic [3], but other studies have not reproduced these findings [9,10], and the disease extent was not different between the two groups in our cohort either.

Table 4 Odds ratio and confidence interval (CI) for association of variables with familial disease.

Parameter	Odds ratio	95% CI	P value
Female sex	4.05	1.1-14.9	0.04
Number of disease exacerbations	1.05 (/1 exacerbation)	1.01-1.1	0.02
Diagnosis delay	0.8 (/1 year)	0.6-1.3	0.2
Rectal disease location	1.3	0.8-1.9	0.3
Ever used corticosteroids	0.6	0.15-2.3	0.4

Two previous studies in Western Europe did not find a correlation between disease severity and the familial form of UC [9,10]. Using similar indicators of disease behavior (colectomy rate, need for immunomodulation and hospitalizations) we also did not identify an increased severity of UC among familial patients. However, when we compared the number of flares necessitating interventions, there was a modestly increased rate of flares among the familial cases (Tables 3 & 4). This factor was not tested in the previous studies [9,10] thereby precluding any inter-population comparisons. Nevertheless, the fact that the difference in the rate of flares was minimal along with the similar rate of hospitalization, colectomy and immunomodulation usage suggests that these flares may have been of limited clinical impact. IBD patients with a positive family history of IBD are often worried that this may detrimentally affect their prognosis, marking them for a worse course of disease. Thus, we believe our findings to be important in providing corroborating reassuring evidence to UC patients that a positive history of IBD in their family probably does not entail a more severe disease course.

Unlike findings in two previous reports in CD [8,11], we did not find a correlation between the age of disease onset in two affected siblings (Fig. 1). This further attests to differences in the relative contribution of the genetic component versus environmental or other factors in CD compared to UC.

There are several limitations in our study. The use of self-reported questionnaires was associated with missing answers for some data articles (Table 2). In addition, self-reporting may arguably lead to incorrect data entry. While this possibility cannot be absolutely excluded, the results of our chart review in the sample of 30 patients show that such mistakes on behalf of the patients are minor. However, specific validation of IBD diagnosis in the family members of patients was precluded by the design of the present study. Defining a familial component in an IBD patient has some

Summary Box

What is already known:

- Familial component is known to be present in some patients with IBD
- Jews have been reported to have relatively high rate of familial disease
- Scant data suggest little impact of having a familial disease on UC severity

What the new findings are:

- Familial disease is present in 14% of Israeli Jews with UC
- The familial form preferentially affects female patients
- Patients with familial disease have more disease flares over the course of disease
- In contrast, other parameters of disease severity such as rate of hospitalizations, use of immunosuppressants and colectomy rate are not impacted by having a positive family history of IBD

arbitrary element inherent in deciding whether first, second, or any degree relative with IBD is the qualifying factor for determining familiality. We have therefore chosen a strict definition encompassing only first degree relatives. However, one should acknowledge that the results obtained may not be the same if second and third degree_relatives were allowed to be included for the sake of familial disease definition. A further limitation relates to the lack of standardization of the assessment of disease severity by the articles inquired upon by the questionnaires. Nevertheless, other population studies similarly employed such parameters to assess disease course and severity [7]. Moreover, most of these parameters represent endpoints that are a cause of great concern for patients (e.g. need for steroids or immunomodulators, need for colectomy, etc.). Thus, we believe that the parameters evaluated are useful for assessing clinically meaningful disease severity indicators.

In conclusion, the prevalence of positive familial history of IBD among Jewish UC patients in Israel is nearly 15%, and is more common among female patients. However, familial occurrence of disease has minimal, if any, impact on disease behavior and severity.

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