World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i45.17120

World J Gastroenterol 2014 December 7; 20(45): 17120-17126
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

RETROSPECTIVE STUDY

Similar clinical characteristics of familial and sporadic inflammatory bowel disease in South Korea

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Received: February 26, 2014 Revised: April 29, 2014
Accepted: July 24, 2014
Published online: December 7, 2014

Abstract

AIM: To investigate differences of clinical characteristics and disease courses between familial and sporadic inflammatory bowel disease (IBD) patients.

METHODS: We obtained clinical data on Crohn's disease (CD) (n = 691) and ulcerative colitis (n = 1113) from a tertiary referral medical center between 2005 and 2012. Seventeen patients (2.5%) with CD and 27 patients (2.4%) with ulcerative colitis (UC) were identified as having a familial history of IBD, including the first and second degree relatives. For each control case, three times the number of age-, sex-, and diagnosis year-matched CD and UC patients, without a family history of IBD, were randomly selected in this case control study.

RESULTS: There were no significant differences in age or main symptom at diagnosis, extraintestinal manifestation, location/extent, behavior of disease activity, number of hospitalizations, number of operations, operation type, number of relapses, or oral medical treatment between familial and sporadic CD and UC patients. Median (min-max) follow-up periods after diagnosis of familial CD and sporadic CD patients were 84 (24-312) and 36 (8-240) mo, respectively (P = 0.008). Familial CD patients more frequently used anti-tumor necrosis factor (TNF) antibodies compared to sporadic CD patients (17.6% *vs* 0%, P = 0.014).

CONCLUSION: In conclusion, a family history of IBD does not seem to be an important predictive factor affecting clinical characteristics or disease course even if there is a more frequent use of anti-TNF antibodies in familial CD patients compared to sporadic CD patients.

Key words: Inflammatory bowel disease; Family history; Crohn's disease; Ulcerative colitis; Clinical characteristics

Core tip: We investigated differences of clinical characteristics and disease courses between familial and sporadic inflammatory bowel disease (IBD) patients. Despite several other studies of IBD, there is still insufficient knowledge regarding the clinical characteristics in familial IBD. We report that a family history of IBD does not seem to be an important predictive factor affecting clinical characteristics or disease course. Not only genetic background but also environmental factors might affect the disease course of IBD.

Chung SH, Park SJ, Lee HS, Hong SP, Cheon JH, Kim TI, Kim WH. Similar clinical characteristics of familial and sporadic inflammatory bowel disease in South Korea. *World J Gastroenterol* 2014; 20(45): 17120-17126 Available from: URL: http://www.

wjgnet.com/1007-9327/full/v20/i45/17120.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i45.17120

INTRODUCTION

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). Although it is suggested that genetic, environmental, and immunologic factors are involved in the pathogenesis of IBD, the etiology of IBD is still not completely understood. Some suggest that a family history of IBD may be one of the most important risk factors[1]. A family history of IBD was shown to increase the risk of developing IBD 10- to 15-fold in unaffected first-degree relatives and three-fold among close relatives of IBD patients[2-4]. In the first-degree relatives of patients with IBD from Korean and western countries, the rates of familial IBD were reported to be 1.88% (South Korea) and 5%-18% (western countries)[5-12]. Even if genetic factors are associated with familial IBD[13], a family history of IBD does not mean that all patients with IBD share a specific gene, as family members of IBD patients could be exposed to similar environmental factors[14]. Some studies showed that there were no differences in clinical characteristics between familial and sporadic IBD[15,16]. Even if other studies demonstrated differences between familial and sporadic IBD, there have not been consistent results[17-19]. Despite several studies of familial IBD, there is still insufficient knowledge regarding the differing characteristics between familial and sporadic IBD. Therefore, we aimed to investigate the differences in clinical characteristics and disease course between familial and sporadic IBD patients.

MATERIALS AND METHODS

Patients

We used electronic IBD registry data including CD (691 cases) and UC (1113 cases) from Severance Hospital, Yonsei University College of Medicine from January 2005 to February 2012. Seventeen patients (2.5%) with CD and 27 patients (2.4%) with UC were identified as having a familial history of IBD, including first- and second-degree relatives. For each control case, three times the number of age-, sex-, and diagnosis year-matched CD and UC patients, without a family history of IBD, were randomly selected in this case control study. We compared the clinical characteristics and disease courses between familial CD and UC patients and sporadic CD and UC patients, respectively. UC and CD were subclassified by Montreal classification[20]. Regarding the extent of UC, ulcerative proctitis (E1) was defined as inflammation limited to the rectum. Left-sided UC (E2) was defined as inflammation limited to the splenic flexure. Extensive UC (E3) was defined as inflammation extending proximal to the splenic flexure. Regarding the location of CD, L1 was defined as involvement of the ileum. L2 was defined as involvement of the colon. L3 was defined as involvement of the ileocolon. L4 was defined as L1-L3 with presenting concomitant upper gastrointestinal disease. Regarding CD behavior, B1 was defined as a nonstricturing, nonpenetrating, inflammatory type. B2 was defined as a stricturing type. B3 was defined as a penetrating type. Mayo index and CDAI at diagnosis were calculated at the time of initial diagnosis at the hospital. UC relapse was defined as a partial Mayo score $\geqslant$ 4 or surgery for disease aggravation[21]. CD relapse was defined as a CDAI score $\geqslant$ 250, a CDAI score 150 $\leqslant$ CDAI score $<$ 250 with a 75 point increase above the initial value during three consecutive weeks, surgery for progressed Crohn's disease, aside from perianal surgery[22]. Additionally, any change in therapies because of clinical aggravation was included in the criteria of relapse of IBD[23].

Statistics analysis

The normality of the data was analyzed by the Shapiro-Wilks test. For continuous variables, the Mann-Whitney *U*-test was used for nonparametric data, and Student's *t*-test was used for parametric data. Categorical data were analyzed using Pearson's χ^2 test or Fisher's exact test. All statistical analyses were performed using SPSS Statistics (version 18.0.0, IBM Corp., Armonk, NY, United States). $P \leqslant 0.05$ was considered statistically significant.

RESULTS

Demographics of familial and sporadic IBD

The numbers of male patients with familial CD and UC were 14 (82.4%) and 15 (55.6%), respectively (Table 1). There were no differences in age at symptom onset or main symptom at diagnosis between familial and sporadic IBD. Regarding extraintestinal manifestations, episcleritis was more prevalent in familial UC than sporadic UC (18.5% *vs* 4.9%, $P = 0.042$).

Family relations and relatives of familial CD and UC

In familial CD (Figure 1), the numbers of patients with CD, UC, and intestinal Behçet's disease were 9 (52.9%), 6 (35.3%), and 2 (11.8%), respectively. In familial UC (Figure 2), the numbers of patients with UC, CD, and intestinal Behçet's disease were 6 (19.2%), 16 (76.2%), and 1 (4.8%), respectively.

Differences of clinical characteristics and disease courses

Location/extent and behavior of disease: There were no differences in location/extent and behavior of disease between the familial and sporadic IBD patients including CD and UC (Table 2). In both familial and sporadic CD patients, most lesions were located at the ileocolon (70.6% *vs* 60.8%, $P = 0.568$). In familial and sporadic UC patients, the most common extent was proctitis (40.7% *vs* 34.6%, $P = 0.645$). In Table 3, the mean scores of CDAI at diagnosis of familial and sporadic CD were 120.5 ± 68.2 and 107.8 ± 82.1, respectively ($P = 0.207$). The mean Mayo scores at diagnosis were 3.6 ± 2.0 and 3.7

Table 1 Demographic data of familial inflammatory bowel disease and sporadic inflammatory bowel disease

Phenotype	Familial CD (n = 17)	Sporadic CD (n = 51)	P value	Familial UC (n = 27)	Sporadic UC (n = 81)	P value
Sex			> 0.999			> 0.999
Male	14 (82.4)	42 (82.4)		15 (55.6)	45 (55.6)	
Female	3 (17.6)	9 (17.6)		12 (44.4)	36 (44.4)	
Age at diagnosis	28.2 ± 10.3	29.2 ± 10.5	0.742	36.2 ± 14.7	36.4 ± 12.8	0.951
⩽ 16 yr (A1)	0 (0)	0 (0)	0.849	0 (0)	0 (0)	> 0.999
17-40 yr (A2)	14 (82.4)	43 (84.3)		13 (48.1)	39 (48.1)	
> 40 yr (A3)	3 (17.6)	8 (15.7)		14 (51.9)	42 (51.9)	
Age at symptom onset, yr	22.6 ± 9.5	23.5 ± 9.3	0.438	36.2 ± 14.5	36.7 ± 12.7	0.710
Main symptom at diagnosis						
Abdominal pain	10 (58.8)	32 (62.7)	0.773	5 (18.5)	30 (37.0)	0.098
Diarrhea	5 (29.4)	16 (31.4)	0.880	11 (40.7)	22 (27.2)	0.232
Weight loss	0 (0.0)	2 (3.9)	> 0.999	0 (0.0)	0 (0.0)	> 0.999
Fever	0 (0.0)	1 (2.0)	> 0.999	0 (0.0)	0 (0.0)	> 0.999
Abdominal mass	0 (0.0)	0 (0.0)	> 0.999	0 (0.0)	0 (0.0)	> 0.999
Hematochezia	2 (11.8)	9 (17.6)	0.718	21 (77.8)	66 (81.5)	0.780
EIM	0	3		10	19	
Somatitis	0 (0.0)	0 (0.0)	> 0.999	0 (0.0)	2 (2.5)	0.061
Arthritis and arthralgia	0 (0.0)	2 (4.2)	> 0.999	1 (3.7)	8 (9.9)	0.445
Erythema nodosum	0 (0.0)	1 (2.1)	> 0.999	4 (14.8)	5 (6.2)	0.223
Episcleritis	0 (0.0)	0 (0.0)	> 0.999	5 (18.5)	4 (4.9)	0.042

Data are presented as number (percentage) or mean ± SD. CD: Crohn's disease; UC: Ulcerative colitis; EIM: Extraintestinal manifestation.

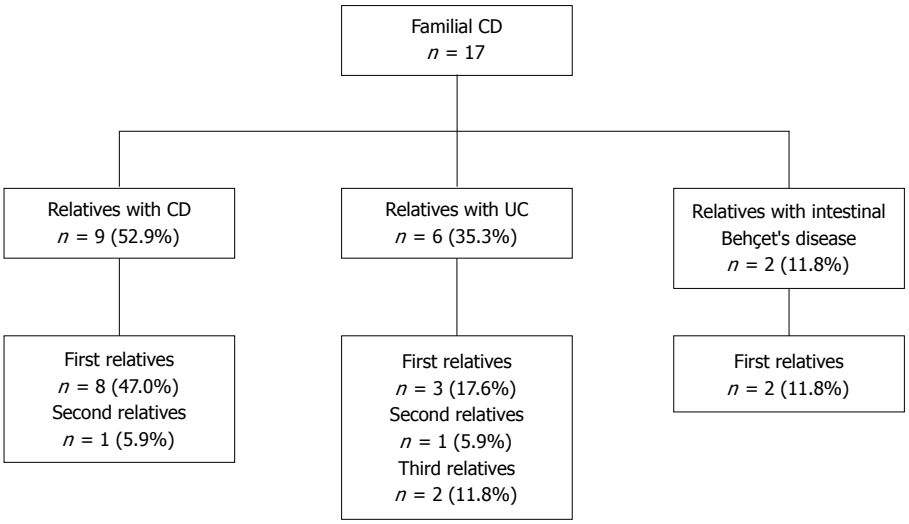

Figure 1 Family relations and relatives of familial Crohn's disease. CD: Crohn's disease; UC: Ulcerative colitis.

± 1.8 for familial and sporadic UC patients, respectively (P = 0.673). Median (min-max) follow-up duration in familial and sporadic CD patients was 84 (24-312) and 36 (8-240) mo, respectively (P = 0.008). Median (min-max) follow-up duration in familial and sporadic UC patients was 96 (12-240) and 60 (12-85) mo, respectively (P = 0.170). There was no significant difference in number of bowel resections between the familial and sporadic IBD patients (Table 4). There was no significant difference in oral medical treatments with 5-aminosalicylates (5-ASA), oral steroids, and azathioprine between familial and sporadic IBD patients (Table 5). However, familial CD patients more frequently used anti-TNF antibodies than sporadic CD patients (17.6% *vs* 0%, P = 0.014). Familial UC patients more frequently used suppositories or enemas containing 5-ASA and steroids compared to sporadic UC patients (5-ASA: 11.1% *vs* 1.2%, P = 0.047; steroids: 66.7% *vs* 43.2%, P = 0.047).

DISCUSSION

IBD has complex causes including environmental factors and genetic susceptibility[24]. Familial history of IBD is known to be an important risk factor for IBD[4,25,26]. However, the etiologies of IBD are still not completely understood[26]. A positive family history of IBD has been shown to increase the risk of developing IBD 10- to 15-fold for first-degree relatives and three-fold for close relatives of IBD patients[2-4,27]. A family history of IBD does not necessarily mean that a specific gene exists in all patients, as they are also more likely to be exposed to the same environmental risk factors for developing IBD as

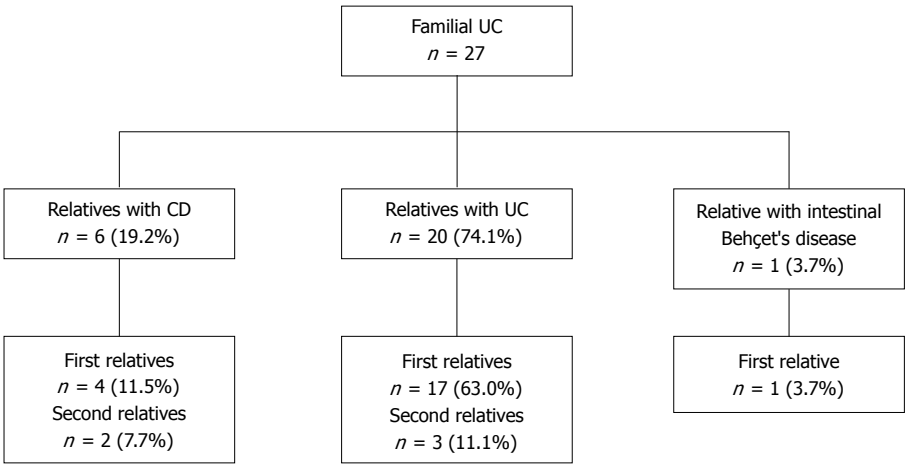

Figure 2 Family relations and relatives of familial ulcerative colitis. CD: Crohn's disease; UC: Ulcerative colitis.

Table 2 Comparison of location/extent and behavior of disease between familial and sporadic inflammatory bowel disease using the Montreal classification *n* (%)

Type of IBD	Familial CD (*n* = 17)	Sporadic CD (*n* = 51)	*P* value	Familial UC (*n* = 27)	Sporadic UC (*n* = 81)	*P* value
Location/extent[1]						
1	3 (17.6)	11 (21.6)	> 0.999	11 (40.7)	28 (34.6)	0.645
2	2 (11.8)	9 (17.6)	0.718	15 (55.5)	47 (58.0)	0.826
3	12 (70.6)	31 (60.8)	0.568	1 (3.8)	6 (7.4)	0.677
4	0 (0.0)	0 (0.0)	> 0.999			
CD behavior[2]			0.668			
1	9 (52.9)	33 (64.7)	0.391			
2	3 (17.6)	8 (15.7)	> 0.999			
3	5 (29.5)	10 (19.6)	0.504			
Perianal fistula	4 (23.5)	12 (23.5)	> 0.999			

[1]CD location: 1 = L1 (ileum), 2 = L2 (colon), 3 = L3 (ileocolon), 4 = L4 (upper intestine); Extension of UC: 1 = E1 (proctitis), 2 = E2 (left-sided colitis), 3 = E3 (pancolitis); [2]CD behavior: 1 = B1 (nonstricturing, nonpenetrating, inflammatory), 2 = B2 (stricturing), 3 = B3(penetrating). IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis.

Table 3 Comparison of clinical characteristics between familial and sporadic inflammatory bowel disease *n* (%)

	Familial CD (*n* = 17)	Sporadic CD (*n* = 51)	*P* value	Familial UC (*n* = 27)	Sporadic UC (*n* = 81)	*P* value
Disease activity (at diagnosis)	CDAI			Mayo score		
Mean ± SD	120.5 ± 68.2	107.8 ± 82.1	0.207	3.6 ± 2.0	3.7 ± 1.8	0.673
< 150	11 (64.7)	36 (70.6)	0.761	0-2, 9 (33.3)	18 (22.2)	0.428
150 ≤ and < 220	4 (23.5)	8 (15.7)		3-5, 14 (51.9)	52 (64.2)	
≥ 220	2 (11.8)	7 (13.7)		6-12, 4 (14.8)	11 (13.6)	
No. of hospitalizations			0.175			0.794
0	9 (52.9)	35 (68.6)		25 (92.6)	73 (90.1)	
1-2	6 (35.2)	14 (27.5)		1 (3.7)	7 (8.7)	
≥ 3	2 (11.7)	2 (3.9)		1 (3.7)	1 (1.2)	
No. of relapses			0.342			0.333
0	13 (76.5)	44 (86.3)		22	72	
1-2	4 (23.5)	7 (13.7)		5	9	
≥ 3	0 (0.0)	0 (0.0)		0	0	
Relapse duration after diagnosis, mo	49.3 ± 65.5	38.9 ± 44.5	0.907	58.2 ± 102.2	21.3 ± 20.5	0.898
Follow-up duration after diagnosis, mo	84 (24-312)	36 (8-240)	0.008	96 (12-240)	60 (12-85)	0.170

Ulcerative colitis (UC) relapse was defined as a partial Mayo score ≥ 4 or surgery for disease aggravation[12]. Crohn's disease (CD) relapse was defined as a Crohn's disease activity index (CDAI) score ≥ 250, a CDAI score 150 ≤ CDAI score < 250 with a 75 point increase above the initial value during three consecutive weeks, or surgery for progressed Crohn's disease, aside from perianal surgery[13].

Table 4 Comparison of number of bowel resection surgeries between familial and sporadic inflammatory bowel disease *n* (%)

Phenotype	Familial CD (*n* = 17)	Sporadic CD (*n* = 51)	*P* value	Familial UC (*n* = 27)	Sporadic UC (*n* = 81)	*P* value
Number of surgeries			0.194			0.759
0	13 (76.5)	44 (86.3)		27 (100)	79 (97.5)	
1	3 (17.6)	7 (13.7)		0 (0.0)	2 (2.5)	
2	1 (5.9)	0 (0.0)		0 (0.0)	0 (0.0)	

CD: Crohn's Disease; UC: Ulcerative colitis.

Table 5 Medication types and adverse events in patients with familial and sporadic inflammatory bowel disease *n* (%)

	Familial CD (*n* = 17)	Sporadic CD (*n* = 51)	*P* value	Familial UC (*n* = 27)	Sporadic UC (*n* = 81)	*P* value
5-ASA	16 (94.1)	50 (98.0)	> 0.999	17 (63.0)	64 (79.0)	0.124
Steroid	7 (41.2)	15 (29.4)	0.551	5 (18.5)	18 (22.2)	0.684
Thiopurines	7 (41.2)	28 (54.9)	0.406	5 (18.5)	11 (13.6)	0.540
Anti-TNF antibodies	3 (17.6)	0 (0.0)	0.014	0 (0.0)	0 (0.0)	-
Suppository						
5-ASA	1 (5.9)	0	0.250	3 (11.1)	1 (1.2)	0.047
Steroid	0	2 (3.9)	> 0.999	18 (66.7)	35 (43.2)	0.035
AEs by thiopurine	4 (23.5)	8 (15.7)	0.477	1 (3.7)	6 (7.4)	0.677
Leukopenia	4 (23.5)	7 (13.7)	0.448	1 (3.7)	4 (4.9)	> 0.999
Nausea	0	1 (2.0)	> 0.999	0 (0.0)	0 (0.0)	> 0.999
Arthralgia	0	0	> 0.999	0 (0.0)	1 (1.2)	> 0.999
Skin lesion	0	0	> 0.999	0 (0.0)	1 (1.2)	> 0.999
Pancreatitis	0	0	> 0.999	0	0	> 0.999
Elevation of liver enzyme	0	0	> 0.999	0	0	> 0.999

UC: Ulcerative colitis; CD: Crohn's disease; ASA: Aminosalicylates; TNF: Tumor necrosis factor; AE: Adverse events.

affected family members[28]. Moreover, in a Spanish twin study, environmental factors were also shown to influence gene expression[29]. Familial aggregation was more prevalent in CD than in UC patients in Western societies, but the opposite was found in some Asian societies[5,9,30,31]. In several studies, 5%-15% of CD patients had a family history of IBD and 8%-14% of UC patients had a family history of IBD[17,18,30,32,33]. In South Korea, 1.51% of CD patients and 2.01% of UC patients had a positive first-degree family history of IBD[5]. A positive family history was found in 2.7% and 2.6% of familial UC and CD in a Japanese study, respectively[14]. Despite several studies about the clinical phenotypes of familial IBD, there are still inconsistent and inconclusive results[17,18,26]. In many reports, the location, disease severity, behavior of disease, and extraintestinal manifestations of CD were not significantly different in familial and sporadic disease[4,15,16,30,34-38]. However, contrary to these reports, some differences between familial and sporadic CD have been reported. Patients with familial CD had an earlier onset time[11,15,31,34], more extensive disease[11,34], greater stricturing pattern[39], a higher operation rate[39,40], and more ileal disease with less ileocolonic disease compared to patients with sporadic CD[17]. In UC studies, there was no difference in frequency of surgery or medical treatment between familial and sporadic UC[26,35]. However, in other reports, some differences between familial and sporadic UC were reported. There was worse disease severity[41], more frequent relapses[26], and more extensive colitis[1] in familial UC patients compared to sporadic UC patients. In our study, there were no significant differences in age at symptom onset, main symptom at diagnosis, extraintestinal manifestation, location/extent, behavior of disease, disease activity at diagnosis, number of hospitalizations, number of operations, operation type, number of relapses, or oral medical treatment between familial and sporadic CD and familial and sporadic UC patients, respectively. This study did find that familial CD patients more frequently used anti-TNF antibodies than sporadic CD patients. More frequent use of anti-TNF antibodies in familial CD patients might be explained by differing follow-up duration, since follow-up durations for patients with familial CD were significantly longer than those of sporadic CD patients. In our results, there was more frequent use of suppositories containing 5-ASA and steroids in familial UC compared to sporadic UC patients and more prevalent episcleritis in familial than sporadic UC. To the best of our knowledge, there have been no reports regarding the differences in usage of suppositories and frequency of episcleritis between familial and sporadic IBD.

There were several weak points in our study. First, the number of enrolled patients was small, and the study was performed in a single tertiary referral medical center. This study was performed using the hospital-based registry and was not a population-based cohort study. Therefore, a population-based cohort study will be needed in the future to evaluate the differences of clinical phenotypes between familial and sporadic IBD patients. There may have been a selection bias, and our results may not be generalizable. Even though the number of patients en-

rolled in this study is small (17 patients with familial CD; 27 patients with familial UC), we used a well-organized electronic medical database to compare the differences between familial and sporadic IBD.

In conclusion, a family history of IBD does not seem to be an important predictive factor affecting clinical characteristics or disease course, even if there is a more frequent use of anti-TNF antibodies in familial CD patients compared to sporadic CD patients.

COMMENTS

Background

Genetic, environmental, and immunologic factors are involved in the pathogenesis of inflammatory bowel disease (IBD); the etiology of IBD is still not completely understood. Some suggest that a family history of IBD may be one of the most important risk factors. A family history of IBD was shown to increase the risk of developing IBD 10- to 15-fold in unaffected first-degree relatives and three-fold among close relatives of IBD patients.

Research frontiers

Despite several other studies of IBD, there is still insufficient knowledge regarding the clinical characteristics in familial IBD. Authors report that a family history of IBD does not seem to be an important predictive factor affecting clinical characteristics or disease course. Not only genetic background but also environmental factors might affect the disease course of IBD.

Related publications

Some studies showed that there were no differences in clinical characteristics between familial and sporadic IBD. Even if other studies demonstrated differences between familial and sporadic IBD, there have not been consistent results. Despite several studies of familial IBD, there is still insufficient knowledge regarding the differing characteristics between familial and sporadic IBD.

Innovations and breakthroughs

The authors report that a family history of IBD does not seem to be an important predictive factor affecting clinical characteristics or disease course even if there is a more frequent use of anti-tumor necrosis factor (TNF) antibodies in familial Crohn's disease (CD) patients compared to sporadic CD patients. More frequent use of anti-TNF antibodies in familial CD patients might be explained by differing follow-up duration, since follow-up durations for patients with familial CD were significantly longer than those of sporadic CD patients.

Applications

The manuscript can help to understand the different characteristics between familial and sporadic IBD.

Peer review

This report analyzed the clinical features of familial and sporadic IBD including age and main symptoms at diagnosis, location/extent, behavior, number of hospitalizations, surgery, relapses and treatment. They conclude that the two forms of disease are essentially superimposable with the exception of the greater use of anti-TNF's in familial CD. This is a very good piece of work.

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