Crohn's disease severity in familial and sporadic cases

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Abstract

***Background*—Having a relative with inflammatory bowel disease increases the risk for Crohn's disease but may also increase its severity in affected patients.**

***Aims*—To evaluate the influence of a family history on Crohn's disease course and severity.**

***Methods*—1316 patients followed in the same unit were studied retrospectively. Age at onset, duration of illness, site, and extent of disease were determined in patients with and without a family history. Additionally, disease severity was estimated by the need for medical therapy (steroid and immunosuppressive requirement) and the frequency and extent of excisional surgery.**

***Results*—152 (12%) patients had a family history of inflammatory bowel disease. Duration of follow up was longer in patients with a family history and there were more operations for perforating complications in familial cases. However, the importance of medical therapy, and the incidence and extent of excisional surgery were similar in familial and and sporadic cases. Kaplan-Meier estimated time to prescription of immunosuppressive drugs and first intestinal resection were similar in familial and sporadic cases. When the 152 patients with familial Crohn's disease were paired for sex, location of disease at onset, date of birth, and date of diagnosis with 152 patients with sporadic Crohn's disease, the disease severity remained similar in the two groups of paired patients.**

***Conclusion*—Patients with Crohn's disease and a family history of inflammatory bowel disease do not have a more severe course.**

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Keywords: Crohn's disease; familial diseases; environmental factors; immunosuppressive drugs

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Prevalence of Crohn's disease is increased in relatives of patients with inflammatory bowel disease (IBD).[1–4] The strongest risk factor for Crohn's disease is having a relative with the disease. The age corrected risk of Crohn's disease for all first degree relatives has been estimated recently to be 3.9%, 13 times greater than the age corrected risk for relatives of controls.[4] Epidemiological data have suggested that a major recessive gene with complete or incomplete penetrance might explain inheritance of Crohn's disease.[5 6] However, many features of familial Crohn's disease and ulcerative colitis are consistent with a polygenic model of inheritance.[7] Several susceptibility loci for Crohn's disease have been located recently, using genome wide search studies. Hugot *et al* have found evidence for a linkage with the pericentromeric region of chromosome 16 in Crohn's disease.[8] Satsangi *et al* showed an association between inflammatory bowel diseases and regions on chromosomes 3, 7, and 12. Furthermore, they found that markers on chromosomes 2 and 6 were associated with increased suceptibility to ulcerative colitis and a region on chromosome 16 was associated with increased susceptibility to Crohn's disease.[9] Studies are underway to determine the gene(s) responsible for predisposition to Crohn's disease. A family history increases the risk of having Crohn's disease but may also affect disease location and clinical course. A high degree of concordance with regard to the type of disease (Crohn's disease or ulcerative colitis) and disease location has been reported among relatives with Crohn's disease.[4 10 11] Several studies have compared clinical characteristics of familial and sporadic forms of Crohn's disease. Some,[11–13] but not all[3 14] found that familial Crohn's disease starts at a younger age and is associated with a lower proportion of patients with an exclusive colonic involvement and an increased proportion of patients with small bowel involvement. However, none of these studies has addressed the question of the clinical course of Crohn's disease in familial cases. In other words, is family history a risk factor for a more severe clinical course? It has been claimed that patients with an inherited disease that starts early in life are at risk of having a more severe course than patients with later disease onset and are more likely to have similarly affected relatives.[15] This could be explained by a greater contribution of disadaptive genes to the heritability of the disease in question.

Table 1 Familial link and diagnosis in the relatives of the 152 patients with familial Crohn's disease

	Ulcerative colitis	*Crohn's disease*
Mother/father	2	26
Aunt/uncle	4	6
Sister/brother	8	65
Cousin	3	24
Daughter/son	1	9
Niece/nephew	0	4

When the patient had several affected relatives, the table indicates only the closest one. When the patient had both one affected parent and one affected sibling, the table indicates only the sibling.

Abbreviations used in this paper: IBD, inflammatory bowel disease.

Table 2 Clinical details in familial and sporadic Crohn's disease

	Familial Crohn's disease (n=152)	*Sporadic Crohn's disease (n=1164)*	*p Value*
Male/female	63/89	458/706	NS
Age at diagnosis (years)*	26.8 (12.1)	28.9 (12.9)	0.06
Delay between onset of symptoms and diagnosis (months)*	19.1 (37.5)	15.8 (32.8)	NS
Mean duration of illness (months)*	125 (112)	92 (88)	0.0005
Ethnicity			
Non-Jewish whites	88 (58%)	927 (80%)	$<10^{-6}$
Jews	43 (28%)	126 (11%)	$<10^{-6}$
Arabs	19 (12%)	83 (7%)	0.02
Asians	0	2 (0.2%)	NS
Blacks	2 (1%)	26 (2%)	NS
Smoking status			
Smokers	85 (56%)	626 (54%)	NS
Non-smokers	57 (37%)	420 (36%)	NS
Unknown	10 (7%)	118 (10%)	NS
Initial site of disease			
Colon only	43 (28%)	381 (33%)	NS
Small bowel only	42 (28%)	372 (32%)	NS
Small bowel and colon	65 (43%)	399 (34%)	0.04
Other	2 (1%)	12 (1%)	NS
Anoperineal disease at onset	25 (16%)	252 (22%)	NS
Extra-intestinal manifestations	57 (38%)	422 (36%)	NS

*Mean (SD).

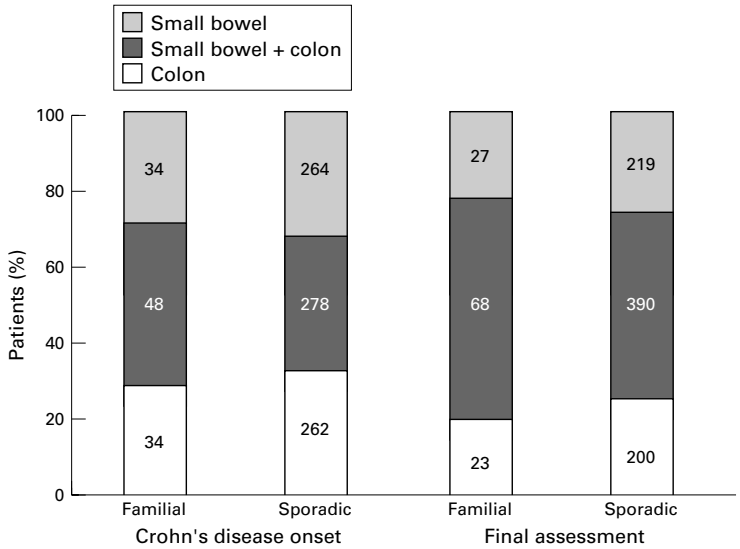

Figure 1 Distribution of Crohn's disease in patients with or without a family history, in whom duration of illness lasted more than three years (n=118 and n=809 respectively). Follow up was 156 (110) months in familial patients and 126 (85) months in sporadic patients (p=0.006). At the last assessment, patients with familial Crohn's disease tended to have a higher frequency of Crohn's disease involving the small bowel and the colon compared with sporadic patients (68/118 (57.6%) versus 390/809 (48.2%); p=0.06).

The present study describes the clinical features of Crohn's disease in patients with or without a family history and examines the influence of a family history on the clinical course and severity of Crohn's disease.

Patients and methods

PATIENT POPULATION

A total of 1322 patients with Crohn's disease, who were seen in our unit between 1974 and December 1995, was studied retrospectively. Our institution is a tertiary referral centre: 966 patients came from Paris or its suburbs, 330 came from provincial France, and 26 from foreign countries.

FAMILY HISTORY

The data were obtained from the medical charts. Additionally, in 844 patients (64%) seen after January 1995, family history status was completed by a standardised interview. Crohn's disease was considered to be familial if at least two first or second degree relatives were affected with IBD. Diagnosis of IBD in the family member was assured in 68 patients (62 with Crohn's disease, six with ulcerative colitis) who belonged to 31 families followed in our unit. In the remainder, the patient or affected family member, or his or her physician was contacted by phone and the diagnosis was confirmed in all but six patients. These six patients were excluded. Thus 152 familial cases were studied. Crohn's disease was considered to be sporadic in the other 1164 cases.

CHARACTERISTICS OF CROHN'S DISEASE

The characteristics of Crohn's disease were taken from the medical charts. Diagnosis of Crohn's disease relied on accepted clinical, radiological, and histological criteria.[16] The onset of Crohn's disease was set as the time of diagnosis, itself defined as the date of the first detection of inflammatory abnormalities of the intestine, as assessed from radiological, endoscopic, or peroperative observations. The initial site of the disease was determined during the first six months following diagnosis, by small bowel *x* rays, colonoscopy, or barium enema in most of the patients seen after 1975. The majority of patients were followed clinically two to four times per year. Anoperineal examination was performed at least annually. Endoscopies, barium enemas, and small bowel *x* rays were performed in relapses, new symptoms, and when considering surgery or immunosuppressive drugs. A total of 297 patients (22.5%) was seen only once in our unit, either for advice or for a short therapeutic course.

Based on the results of endoscopic and radiological procedures, Crohn's disease was classified into three forms: small bowel, colon, and Crohn's disease affecting both the small bowel and the colon. The distribution of the disease process was assessed at onset in the whole series. It was compared at the onset of Crohn's disease and at the last assessment in patients whose duration of illness lasted more than three years.

The type of disease, whether perforating or not was assessed in operated patients by the medical charts and the pathological examination of resected bowel, as described by Greenstein *et al*.[17] Only intestinal resections were considered for this classification; stricturoplasties, anoperineal drainage, intestinal bypasses, and operations for postoperative complications were not taken into account. Patients who underwent an intestinal resection for acute perforation, abscess, or fistulae were considered as having a perforating Crohn's disease. Patients who underwent an intestinal resection because of obstruction, colectasia, bleeding, or failure to improve with medical therapy, were classified as non-perforating Crohn's disease. When a patient had both perforating and non-perforating indications for surgery, he was classified as having a perforating Crohn's disease.

DISEASE SEVERITY

Overall severity of the disease was estimated by two criteria. Firstly, the importance of medical

Table 3 Severity in familial and sporadic Crohn's disease

	Familial Crohn's disease (n=152)	*Sporadic Crohn's disease (n=1164)*	*p Value*
Corticosteroids	128 (84%)	949 (82%)	NS
Nutritional support	39 (26%)	265 (23%)	NS
Immunosuppressive drugs	48 (32%)	314 (27%)	NS
No surgical resection	78 (51%)	646 (55%)	NS
One resection	50 (33%)	363 (31%)	NS
More than one resection	24 (16%)	155 (13%)	NS
Postsurgical handicap index*	14 (18)	12 (16)	NS

*Mean (SD).

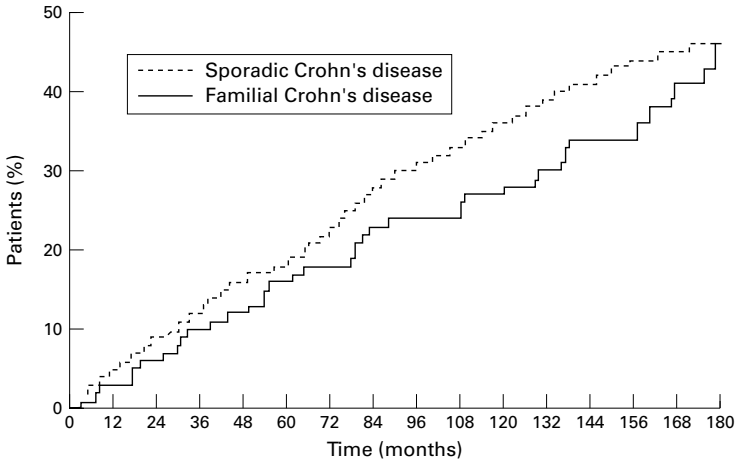

Figure 2 Kaplan-Meier estimated time to first prescription of immunosuppressive drugs in familial (n=152) and sporadic Crohn's disease (n=1164; NS).

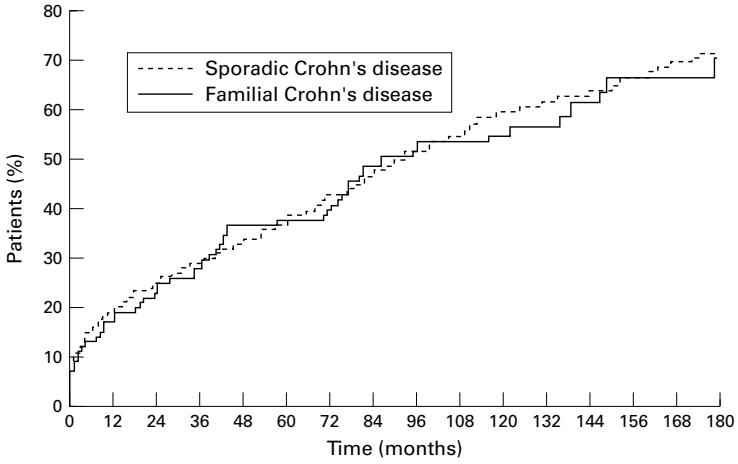

Figure 3 Kaplan-Meier estimated time to first intestinal resection in familial (n=152) and sporadic Crohn's disease (n=1164; NS).

therapy was assessed by the need for corticosteroids, immunosuppressive drugs (azathioprine or methotrexate in the case of failure of or intolerance to azathioprine), and nutritional support, according to the treatment policy followed in our unit.[18] Secondly, the frequency and extent of excisional surgery was measured by the postsurgical handicap index.[19]

STATISTICS

Data are expressed as mean (SD). Quantitative variables were compared in patients with familial and sporadic Crohn's disease using the Student's *t* test, when appropriate (that is, when the Bartlett test of homogeneity of variances was not significant). Discrete variables were compared using the χ^2 test. The same comparisons, using the same statistical tests were performed between patients with familial Crohn's disease and a subset of patients with sporadic Crohn's disease, paired for sex, location of disease at onset, date of birth, and date of diagnosis. These statistical tests were performed using the EPI-INFO software (EPI-INFO, Stone Mountain, Georgia, USA). The need for immunosuppressive drugs and for excisional surgery was determined using actuarial curves, starting at the date of diagnosis, using the Kaplan-Meier method. Actuarial curves were compared by means of the log rank test, using Statview software (Abacus concept, Berkeley, California, USA).

Results

The percentage of familial Crohn's disease was 12% (152/1316 patients). It did not change significantly with time: 39/287 (14%) were diagnosed before 1981, 26/238 (11%) between 1981 and 1985, 39/330 (12%) between 1986 and 1990, and 48/461 (10%) since 1990. Table 1 shows the family members of patients with familial Crohn's disease.

CLINICAL DATA

As shown in table 2, the age at diagnosis tended to be younger and duration of illness was significantly longer in patients with familial Crohn's disease than in patients with sporadic Crohn's disease. Patients with familial Crohn's disease were more often Jews or Arabs and had a higher frequency of Crohn's disease involving the small bowel and the colon (table 2 and fig 1). Additionally, patients with a family history were more often operated on for perforating complications than patients with sporadic Crohn's disease (33/71 (46%) versus 164/479 (34%); p=0.04).

DISEASE SEVERITY

The importance of medical therapy, and the incidence and extent of excisional surgery, as measured by the postsurgical handicap index, were similar in familial and sporadic Crohn's disease (table 3). Time to prescription of immunosuppressive drugs and first intestinal resection was similar in familial and sporadic cases (figs 2 and 3).

A total of 152 patients with familial Crohn's disease was paired for sex, location of disease at onset, date of birth, and date of diagnosis with 152 patients with sporadic Crohn's disease. In paired patients with familial and sporadic Crohn's disease, in whom smoking status was known, the proportion of smokers (85/142 versus 79/135) and non-smokers (57/142 versus 56/135) was similar. Moreover, the ratio of perforated versus non-perforated disease was also similar in paired patients with familial and sporadic Crohn's disease (33/38 versus 29/47; NS). As shown in table 4, the disease severity assessed by the importance of medical therapy and the incidence and extent of excisional surgery did not differ in the two groups of paired patients. Kaplan-Meier estimated time for prescription of immunosuppressive drugs was similar in the two groups, but time to first

Table 4 Severity of Crohn's disease in patients with and without a family history, paired for sex, location of disease at onset, date of birth, and date of diagnosis

	Familial Crohn's disease (n=152)	*Sporadic Crohn's disease (n=152)*	*p Value*
Mean duration of illness	125 (112)	99 (95)	0.04
Corticosteroids	128	130	NS
Nutritional support	39	43	NS
Immunosuppressive drugs	48	43	NS
No surgical resection	78	67	NS
One resection	50	58	NS
More than resection	24	27	NS
Postsurgical handicap index	14 (18)	13 (15)	NS

intestinal resection tended to be shorter in sporadic than in familial patients (p=0.06).

Discussion

This study compared the severity of Crohn's disease in patients with and without a family history. For this purpose, a large population of patients recruited at a single centre was studied. Crohn's disease severity, assessed by the importance of medical treatment, need for surgery, and the postsurgical handicap index, was similar in familial and sporadic forms.

Retrospective collection of data is subject to error, and a word of caution is needed in the interpretation of results, particularly the distribution and extent of disease. However events such as frequency, extent of surgery (based on operative charts), and the need for corticosteroids and immunosuppressive drugs are unlikely to have been biased by the retrospective collection of data. Moreover, there is no obvious reason why a systematic error would have affected preferentially one of the two groups studied. It is noteworthy that there were more Jews and Arabs in patients with a family history. However, to our knowledge, no study has addressed the question of Crohn's disease severity among different ethnic groups and in our series, Crohn's disease severity was similar in these categories of patients compared with the others (data not shown).

In spite of the small differences regarding age at onset, duration of Crohn's disease, and disease location, familial Crohn's disease was not more severe than sporadic Crohn's disease. In fact, patients with or without a family history had a remarkably similar time to prescription of immunosuppressive drugs and first intestinal resection. These results suggest that inherited genes do not play an important role in Crohn's disease severity. At present, the only environmental factor consistently associated with Crohn's disease is smoking. Smoking tobacco not only increases the risk of having Crohn's disease, but also significantly increases its severity, whatever the disease distribution.[19] Indeed, patients who smoke, particularly women, more often require corticosteroids and immunosuppressive therapy.[19]

Other studies have also reported a significantly younger age at onset in familial Crohn's disease.[11–13] The concept of genetic anticipation—that is, an increased severity and earlier onset of disease in subsequent generations of affected families, has been suggested to be valid in IBD[4 10 20] and might explain the younger age at onset in patients with a family history. However, the fact that the members of the later affected generation have not yet lived through their later years of susceptibility (ascertainment bias) might artificially decrease the mean younger age at onset in this generation.[21] Furthermore, the hypothesis of an environmental agent affecting the more susceptible younger members of the same family cannot be excluded either. This environmental hypothesis is supported by a recent study that showed that small intestinal permeability (measured by differential urinary excretion of lactulose and mannitol) was increased in a subset of unrelated persons living in the same environment as patients with Crohn's disease.[22]

In this study, a family history was associated with an increased frequency of abscess or perforation. Studies relating Crohn's disease severity to the perforating or non-perforating type of disease have produced conflicting results. It has been shown that patients with perforating Crohn's disease more often require surgical resection.[17 23] Other studies, however, showed that perforating and non-perforating forms of Crohn's disease carried a similar time to clinical relapse[24] and reoperation.[25 26] We found that perforating Crohn's disease was less severe than non-perforating Crohn's disease.[27] These discrepancies may reflect differences in medical and surgical therapies performed rather than an inherently more severe course in patients with perforating Crohn's disease.

In summary, these results show that having a relative with Crohn's disease does not increase the severity of Crohn's disease in affected patients. Patients with Crohn's disease with a family history should be informed that their disease course is not more severe than that of sporadic Crohn's disease.

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