Clinical Characteristics of Crohn's Disease in 72 Families

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Background & Aims: **Familial aggregation argues for genetic susceptibility to Crohn's disease. The aim of this study was to compare the age of onset and the clinical features of Crohn's disease between patients with familial disease and those with sporadic disease and investigate the concordance for disease location and type among relatives with Crohn's disease.** ***Methods:*** **Seventy-two families with 2 (n = 55), 3 (n = 8), 4 (n = 6), and 5 or more (n = 3) affected first-degree relatives were selected for the study. A population of 1377 patients with sporadic nonfamilial Crohn's disease was used for comparison.** ***Results:*** **Clinical data were obtained from 176 patients with familial Crohn's disease (79 men and 97 women). Median age at onset was younger in familial Crohn's disease than in sporadic cases: 22 vs. 26.5 years ($P < 0.01$). In familial cases, fewer patients had exclusively colonic involvement and more patients had both small bowel and colonic involvement. Among relatives of families with 2 affected members, 56% were concordant for disease location and 49% for disease type. These percentages reached 83% and 76%, respectively, within families with more than 2 affected members.** ***Conclusions:*** **Patients with familial Crohn's disease are characterized by an early age at onset with more extensive disease and may represent a homogeneous clinical subgroup with a particularly strong genetic influence.**

A number of studies have shown an increased prevalence of inflammatory bowel disease (IBD) among relatives of patients with Crohn's disease (CD) and ulcerative colitis.[1–5] These reports are of importance because some evidence shows that IBD is at least partly determined by genetic predisposition. Although there are many reports about familial risk of IBD, few describe clinical characteristics of familial aggregations. Several investigators note that there seems to be an earlier age of onset in familial cases than in sporadic cases. Scattered publications have described unique clinical similarities in affected relatives. In a preliminary report, Tokayer et al. reported a high degree of concordance for intestinal site and transmural aggressiveness among relatives in 35 families with CD.[6] This apparent specificity of lesion is particularly interesting because it might help to define phenotypic groups well-suited for genetic studies.

In northern France, IBD is characterized by a high incidence of CD and the existence of large familial aggregations of CD within a stable population.[7–9] The aim of this study was to describe the clinical characteristics of patients with CD recruited from 72 French families, including concordance for site and type of the disease, and to test the hypothesis that the clinical characteristics of familial CD would differ from those of sporadic CD.

Materials and Methods

Patients

Seventy-two families that had 176 patients with CD were studied. The families were included if they had at least 2 first-degree relatives affected with CD. We did not include "mixed" families with CD and ulcerative colitis in this study. Twenty-eight families were identified via hospital records, and 44 families were identified in a population-based study through the Register of IBD of northwestern France. The median calendar year of cases' ascertainment was 1987 (1962–1993) in the hospital-identified cases and 1988 (1961–1993) in the population-identified cases (NS). The methods used for collecting information within families and the diagnostic criteria for CD were similar to those described previously in our incidence study.[7] The present study used an interviewer practitioner who went to the different centers participating in the study and collected data from the charts using a standardized questionnaire. If necessary, missing data were collected from the gastroenterologist (in private or hospital practice)

0016-5085/96/$3.00

and/or general practitioner in charge of the patient. The questionnaire included a family history (pedigree, year of birth, and sex) of all first-degree relatives. The following data were collected for each patient with CD: age at onset (first symptom), disease location at onset (small bowel only, colon only, or small bowel plus colon), and disease type at onset (primarily fibrostenotic [i.e., cicatrizing], primarily inflammatory, or primarily penetrating [i.e., fistulizing]).[10] The type of disease was inferred from the dominating clinical and morphological features as follows: in the fibrostenotic type, patients had clinical and radiological evidence of stenosis; in the fistulizing type, patients could present with an acute, free perforation, subacute perforation with abscess formation, or chronic perforation with internal fistula; and in the inflammatory form, such as jejunoileitis, patients had no evidence of stenosis and fistula. Presence of anoperineal disease at onset was also recorded. When present, similar information was obtained from second-degree affected relatives.

A population of patients with sporadic nonfamilial CD, including 1377 incident cases of CD registered in the Register of IBD of northern France since 1988, was used for comparing age at onset and disease location and for testing the concordance for location within families. There were 606 men and 771 women, the median duration of CD was 3 years (range, 1–7 years), and 23% of sporadic cases were identified through hospitals.

Statistics

Age at onset (i.e., at first symptoms) of CD was compared between familial and sporadic cases using the Kruskall–Wallis test. Distribution of disease within the intestine and presence of anoperineal disease was compared in familial and sporadic cases using the χ^2 test.

Concordance for disease location and type of disease was defined as 2 or more members of the same family having the same site or type of disease. In families with more than 2 affected members, the percentage of concordance was calculated as the sum of concordant patients divided by the total number of patients. To establish the statistical significance of concordance for location, we compared observed concordant numbers with theoretical numbers using a χ^2 test. Theoretical numbers were calculated from values recorded in sporadic cases using the binomial theorem.[11] They represented the expected values if the distribution of sporadic cases was applied to familial cases.

Results

Clinical data at onset were obtained from 176 patients with CD (79 men and 97 women); median duration of disease was 6.8 years (range, 2–34 years). Fifty-five families had 2 affected members, 8 had 3, 6 had 4, 2 had 5, and 1 had 8. Eighty-two percent of the affected members were siblings, 29% were parents and children, and 13% were second-degree relatives. Clinical characteristics of 2 of these families have been reported in detail previously.[9]

Table 1. Comparison of Age At Onset and Disease Location At Onset Between Patients With Familial CD and Those With Sporadic CD

	Familial CD (%) (n = 176)	Sporadic CD (%) (n = 1377)
Age at onset (*yr*, median [range])	22 (5–56)	26.5 (4–83)[b]
Disease location		
Small bowel only	20	16
Colon only	19	35[b]
Small bowel + colon	61	49[a]
Anoperineal	39	19[c]

[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

Clinical Profile of Patients With Familial CD

Median age at onset of familial CD was 22 years, which was significantly younger than in sporadic cases (26.5 years; $P < 0.01$). Median age at onset was 21.5 years in families with 2 affected members and 20 years in families with 3 or more members (NS).

There was an overall difference in disease location at onset between patients with familial CD and those with sporadic CD ($P = 0.002$). Fewer patients with familial CD had exclusively colonic involvement and a higher proportion had both small bowel colonic involvement and anoperineal disease (Table 1).

In patients with familial CD, the type of disease was fistulizing in 14%, fibrostenotic in 48%, and inflammatory in 38%. There was a significant statistical link between the fibrostenotic type and the presence of small bowel involvement, with an odds ratio of 1.3 (95% confidence interval, 1.2–1.5; $P < 10^{-4}$) (Table 2).

Concordances

Among relatives of families with 2 affected members, 56% were concordant for disease location and 49% for disease type. These percentages reached 83% and 76%, respectively, within families with more than 2 affected members.

When observed concordances for location were compared within families, with theoretical numbers based on sporadic cases, an overall significant difference was found. Considering the different locations, there was an excess of concordance for small bowel location and a decreased concordance for colonic location within families (Table 3).

The percentage of concordance for anoperineal disease

was 43.5% in families with 2 members, 45% in families with >2 members, and 44% overall. When observed concordances for anoperineal disease and theoretical numbers were compared, there was a significant excess of observed concordances within families (29 vs. 16) ($P = 0.04$).

Discussion

This study, which was largely population based, provided the greatest body of information, available thus far on clinical characteristics of familial CD. In our series, patients with familial CD had an earlier age of onset. This association, which is strengthened by the particular earliness of onset of the disease (median age, 20 years) in multicase families, has already been documented in some[12–14] but not all[15,16] family studies. Some reports indicate that patients with CD and an early age at onset have an increased positive family history compared with patient populations with a more varied age of onset. Thirty-five percent of patients with CD and a disease onset before the age of 21 years followed up at the Cleveland Clinic had a positive family history of IBD.[13] Earlier age at onset in families may be caused by increased awareness of the family to disease symptoms. It could also be related to the concept of genetic anticipation, i.e., an increased severity and earlier onset of disease in subsequent generations of affected families. Recently, two groups have provided preliminary data suggesting genetic anticipation in IBD.[14,17] However, these data could also suggest increased prevalence of a transmissible agent in the household affecting the more susceptible younger members of the family.

Patients with familial CD were characterized by a higher frequency of small bowel disease and a fibrostenotic type of disease, with a significant association between these two features. However, it is likely that these features are secondary to the early age at onset. Evidence shows that CD represents inflammation of the lymphoid tissue, Peyer's patches of the ileum, and aggregated lymphoid follicles of the colon. A potential hypothesis for the increased frequency of disease in the small bowel in the young is that Peyer's patches of the ileum, similar to the tonsils of the oral cavity, are more active in the young. Similarly, the site and type of disease are probably correlated (i.e., the small bowel is more likely to have stenosis from valve obstruction and then proximal-to-valve fibrosis and muscular hyperplasia). Interestingly, similar observations were recently made by Polito et al.; among 555 consecutive patients with CD retrospectively reviewed in Baltimore, Maryland, younger age at diagnosis was associated with a higher prevalence of family history of CD, greater small bowel involvement, and stricturing disease.[14] In contrast to our findings and those of Polito et al., no significant differences for age at onset or extension of the disease were found between patients with a positive family history of CD and those who had no known affected relatives in a study from Liverpool, England.[16] Thus, other series need to examine the question.

Our series clearly showed the clinical similarities of CD within families. These similarities were particularly striking in families with more than 2 affected members, with almost 80% of concordance for location and type. The literature contains limited evidence to suggest that complications and disease severity are consistent within families. A few reports describe relatives who have developed the same type or distribution of disease or the same complication. For instance, dilatation of the colon occurred in 2 relatives with CD,[18] and CD was characterized by an initial duodenal involvement in 2 brothers.[19] In a study of 10 families with 32 cases of IBD, 3 of 4 affected siblings who had identical HLA haplotypes had similar disease patterns.[20] However, Weterman and Pena analyzed the clinical patterns and the histopathologic features of the disease in 8 families, each with 2 siblings affected by CD, and found that the degree of similarity did not differ greatly from that observed in unrelated cases with CD.[21] More recently, Tokayer et al. reported that among relatives with CD belonging to 35 families,

Table 2. Association Between the Fibrostenotic Type and Presence of Small Bowel Involvement

	Small bowel involvement	
	Yes	No
Fibrostenotic type		
Yes	78	6
No	63	26

Relative risk, 1.3 (confidenc interval, 1.2–1.5); $P < 10^{-4}$.

Table 3. Comparison Between Observed and Theoretical Concordances for Location Within Familial Cases

	Location		
	Small bowel	Small bowel + colon	Colon
Total no. of patients	35	107	34
Concordant patients within families			
Observed no.	24[b]	79	11[a]
Theoretical no.	12	82	26

[a] $P < 0.05$.
[b] $P < 0.001$ vs. theoretical numbers.

88% were concordant for location of disease and 67% were concordant for pattern of transmural aggressiveness.[6] In their study of twins affected with IBD, Tysk et al. also noted that most of the concordant monozygotic twins had a similar distribution of disease.[22]

Together with our observations, these findings support that familial CD is a homogeneous clinical subgroup, well suited for exploring in depth possible genetic and environmental factors. Some of the families in the present report were included in a genome-wide search of a susceptibility gene for CD using a nonparametric two-point sibling-pair linkage method, allowing us to identify a putative CD susceptibility locus on chromosome 16.[23] These observations did not exclude the participation of an infectious agent in the origin of CD; perhaps some of the bacteria recently found in the intestinal tissues of patients play a role.[24] Additional studies are needed to further explore the respective roles of genetic and environmental factors in the initiation of familial CD.

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Received December 4, 1995. Accepted May 1, 1996.

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Supported in part by the Association F. Aupetit, the INSERM, and the Ministère de la Santé et de l'Action Humanitaire (Direction Générale de la Santé) (no. 92/R12), Centre Hospitalier Régional et Universitaire de Lille, Ferring France Co., and Astra Company.