

Clinical Presentation of Crohn's Disease. Association between Familial Disease, Smoking, Disease Phenotype, Extraintestinal Manifestations and Need for Surgery

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ABSTRACT

Background/Aims: Recent molecular data suggest that genetic factors may underlie the disease heterogeneity observed in Crohn's disease (CD). It was also suggested that familial inflammatory bowel disease (IBD) is a homogenous subgroup, phenotypically different from sporadic disease. Our aim was to determine the clinical presentation in a large CD population.

Methodology: 564 CD patients (m/f: 278/286, age: 37.4 (SD 12.7) yrs, duration: 8.4 (7.1) yrs) were included. Disease phenotype was determined according to Vienna classification. Familial disease, extraintestinal manifestations (EIM), need for surgery and smoking habits were also analyzed.

Results: Familial IBD was present in 73 (12.9%) patients. Age at onset and presence of EIMs was asso-

ciated with familial disease. Penetrating (44.6% vs. <10yrs: 29.1%, $P<0.0001$) and ileocolonic disease (54.4% vs. 42.8%, $P=0.03$) were more common in patients with a disease duration of ≥ 10 yrs. In a logistic regression model female gender, colonic/ileocolonic location, smoking and familial IBD were independent risk factors for EIMs, while ileal and non-inflammatory disease increased the risk for resections. Smoking was also associated with frequent relapses.

Conclusions: Familial IBD was associated with the presence of EIMs, while ileal involvement and non-inflammatory behavior independently increased the risk for surgery. Since penetrating and extensive disease was more frequent in patients with longer disease duration our data support a possible change in location and behavior during the course of disease.

KEY WORDS:

IBD;
Crohn's disease;
Phenotype;
Familial

ABBREVIATIONS:

Crohn's Disease (CD);
Inflammatory Bowel Disease (IBD);
Extraintestinal Manifestations (EIM); Primary Sclerosing Cholangitis (PSC); Odds Ratio (OR)

INTRODUCTION

Inflammatory bowel diseases (IBD) are multifactorial, polygenic diseases with probable genetic heterogeneity. In this hypothesis, different genetic backgrounds may explain different clinical patterns of the disease (1-3). In addition to genetic predisposition, various environmental and host factors (e.g. genetic, epithelial-, immune and non-immune) play a major role in the pathogenesis of IBD. Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract. Extensive heterogeneity is observed in terms of disease presentation, behavior, and response to treatment (4-6).

CD has a strong genetic component; recently NOD2/CARD15 mutations were shown by independent groups to be associated with susceptibility to CD (7,8). However there were significant geographical differences regarding the frequency of these alleles, as

they are not found in Japan and China (9,10), and other disease modifying genes may also exist (8). A lifetime risk of 10-20% to develop IBD was reported in the presence of an affected first degree relative (4,11,12). CD patients have an affected first-degree relative with CD in 2.2-16.2% of cases and with IBD in 5.2-22.5% of cases (13). The concordance rate of affected siblings was reported to be as high as 60-80% (14).

Disease phenotypes that may be genetically determined have been suggested, including: age at onset, disease site, behavior, presence of extraintestinal manifestation and need for surgery (11,14-16). Age of onset was found to be significantly less in familial compared to sporadic disease (17,18), but this was not replicated in all studies (19). Polito *et al.* (18) also showed that stratification for age at diagnosis of CD is associated to age-specific phenotypes. Concordance rates of 56-86% for location and 49-82% for behavior were reported in

parent-child pairs and sibling pairs (14,17). There is no consistent difference in location and behavior of CD between familial and non-familial (sporadic) disease. Higher frequency of ileal disease, less ileocolonic disease (19), more colonic disease (20) and also no difference (21) was reported in familial patients.

In addition to genetic factors, environmental contributions significantly affect clinical phenotypes and disease course. The percentage of current smokers in a group of patients with CD is significantly higher than that observed in a control population matched for sex and age (45-55 vs. 30-40%) (6). A meta-analysis by Calkins (22) and a study by our group (6) estimated an odds ratio of around 2.0 in current smokers when compared to lifetime non-smokers to develop CD. Tobacco use had been a risk factor for ileal rather than colonic-only disease and, particularly heavy tobacco use, increases disease activity, risk of surgery, postoperative relapses, and accumulation of fistulae and abscesses (23,24). However, the harmful effect of smoking on the course of CD is not a universal finding. No differences were found in the need for operation or for immunosuppressants between smokers and non-smokers in patients from Israel (25,26), and patients with colonic involvement only are less sensitive to the harmful

effect of smoking (27).

A positive association between disease location and behavior was also reported (28), however this was not replicated in all studies (29). Patients with perianal disease were more likely to have colonic disease (30) whereas patients with internal fistulizing disease were more likely to have ileal or ileocolonic disease and are more likely to require intestinal resection (31).

In this study we investigated disease phenotype in a large Crohn's disease population. We also aimed to investigate the association between familial disease, smoking and disease phenotype, and identify factors affecting disease phenotype, presence of extraintestinal manifestations and need for resection.

METHODOLOGY

564 unrelated Hungarian patients with CD (male/female: 278/286, age: 37.4 (SD 12.7) years) were investigated. CD patients with a convenient diagnosis and with a follow-up time of at least one year were included. Average disease duration was: 8.4 (7.1) years. The diagnosis was based on Lennard-Jones criteria (32) and each patient has read and signed the informed consent form.

The disease phenotype was assessed by filling in a questionnaire. Age, age at presentation, familial IBD, location, behavior [according to the Vienna classification (28): A1: <40 years at onset, A2: >40 years at onset, L1: ileal, L2: colonic, L3: ileocolonic, L4: upper GI, B1: inflammatory, B2: stenosing, B3: penetrating], perianal involvement, frequent flare up, presence of extraintestinal manifestations [EIM; arthritis: peripheral and axial, ocular manifestations: conjunctivitis, uveitis, iridocyclitis, skin lesions: erythema nodosum, pyoderma gangrenosum, and hepatic manifestations: primary sclerosing cholangitis (PSC)], therapeutic effectiveness (e.g. steroid and/or immunosuppressive use and resistance), need for surgery (resections), and smoking habits were determined (**Table 1**). Familial IBD was present in 73 patients (12.9%, 41 1st degree relatives with CD and 11 with UC; 8 2nd degree relatives with CD and 13 with UC).

The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (81/2003).

Statistical methods: Variables were tested for normality by Shapiro Wilk's W test. T-test with separate variance estimates, ANOVA, factorial ANOVA with post hoc Scheffe test, χ^2 -test and χ^2 -test with Yates correction and logistic regression was used to test differences in disease phenotype between subgroups of CD patients. Odds ratios (OR) were calculated. Pearson correlation was used to compare age at onset, age class and year of birth data. A *P* value of <0.05 was considered as significant. For the statistical analysis Statistica 6.1 (Statsoft Inc, OK, USA) was used.

RESULTS

Age at onset was 28.9 (SD 11.5) years and disease

TABLE 1 Clinical Characteristics of Crohn's Disease Patients, according to the Presence of Familial IBD

	Total (n=564)	Familial IBD (n=73)	Sporadic IBD (n=491)
Male/female	278/286	33/40	245/246
Age (years)	37.3±12.7	36.3±12.6	37.5±12.8
Age at presentation (years)	28.9±11.5	28.1±11.4	29.1±12.0
Duration (years)	8.4±7.1	8.3±6.6	8.4±7.2
Location			
L1	140 (24.8%)	18 (24.6%)	122 (24.8%)
L2	155 (27.5%)	24 (32.9%)	131 (26.7%)
L3	264 (46.8%)	31 (42.5%)	233 (47.5%)
L4	5 (0.9%)	0	5 (1.0%)
Behavior			
B1	232 (41.1%)	28 (38.4%)	204 (41.6%)
B2	138 (24.5%)	19 (26.0%)	119 (24.2%)
B3	194 (34.4%)	26 (35.6%)	168 (34.2%)
Perianal disease, n (%)	152 (26.9%)	26 (35.6%)*	126 (25.7%)*
Frequent relapse, n (%)	203 (36.0%)	32 (43.9%)	171 (34.9%)
Extraintestinal manifestations, n (%)	202 (35.8%)	36 (49.3%)#	166 (33.8%)#
Arthritis, n (%)	173 (30.7%)	34 (46.6%)##	139 (28.3%)##
Ocular, n (%)	28 (5.0%)	4 (5.5%)	24 (4.9%)
Erythema nodosum/ Pyoderma, n (%)	51 (9.1%)	4 (5.5%)	47 (9.6%)
PSC, n (%)	22 (3.9%)	1 (1.4%)	21 (4.3%)
Steroid use/refractory, n (%)	475 (84.2%) / 64 (13.5%)	64 (87.7%) / 13 (20.3%)	411 (83.7%) / 51 (12.4%)
Azathioprine /refractory, n (%)	349 (61.9%) / 24 (6.9%)	51 (69.9%) / 5 (9.8%)	298 (60.7%) / 19 (6.4%)
Operation, n (%) / multiple resection (%)	237 (42.0%) / 64 (11.3%)	27 (37.0%) / 6 (8.2%)	210 (42.9%) / 58 (11.8%)
Smoking habits			
no	328 (58.1%)	40 (54.8%)	288 (58.6%)
yes	184 (32.6%)	25 (34.3%)	159 (32.4%)
previous	52 (9.3%)	8 (10.9%)	44 (9.0%)

**P*=0.051, #*P*=0.01, ##*P*=0.002 between patients with family history of IBD and without by Yates-corrected χ^2 .

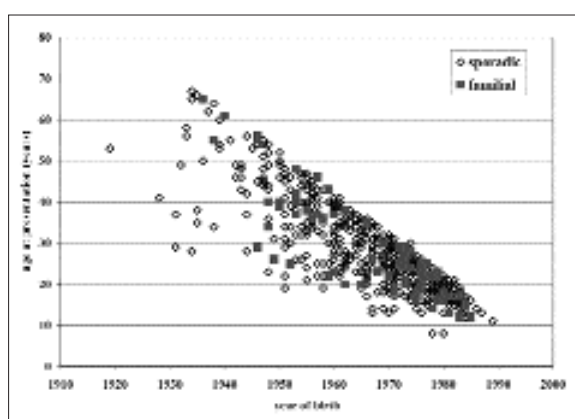


FIGURE 1 Association between age at onset and year of birth in CD patients. $r = -0.83$, $P < 0.0001$ in sporadic CD patients and $r = -0.85$, $P < 0.0001$ in patients with familial IBD.

duration 8.4 (7.1) years, not different in patients with and without familial IBD (**Table 1**). Age, age at onset and duration was mildly lower in males [35.0 (11.7) yrs vs. 39.7 (13.3) yrs, $P = 0.00001$ age at onset: 27.4 (11.2) yrs vs. 30.5 (11.6) yrs, $P = 0.001$ and duration 7.6 (6.3) yrs vs. 9.1 (7.7) yrs, $P = 0.01$]. There was no association between age at onset and familial IBD (**Table 1**). A strong negative correlation was found between age at onset and year of birth ($r = -0.83$, $p < 0.0001$, **Figure 1**). No difference was detected between familial IBD and sporadic cases.

Disease location was predominantly ileocolonic (L3: 46.8%), while disease behavior was more balanced. Ileocolonic location was more frequent in patients with penetrating behavior (54.1% vs. others 42.9%) while inflammatory behavior was more frequent in patients with colonic disease (34.5% vs. others 22.8%, $P = 0.004$, **Table 2**). Age at onset was also lower in patients with ileocolonic (L3: 26.6 yrs vs. L1: 30.5 yrs and L2: 31.6 yrs, $P = 0.01$ and $P = 0.0004$ by post hoc Scheffe test) or penetrating (27.1 yrs vs. B1: 29.8 yrs, B3: 30.1 yrs, $P < 0.048$ and $P = 0.041$) disease. In patients with a disease duration of ≥ 10 yrs B3 (44.6% vs. < 10 yrs: 29.1%) and L3 disease (54.4% vs. 42.8%) was more common while B1 (27.5% vs. 48.3%, $P < 0.0001$) and L1 (18.6% vs. 28.0%, $P = 0.03$) was less prevalent (**Figure 2**). Smoking was associated with disease behavior but not location; penetrating disease was more frequent in patients currently smoking (41.9% vs. 29.5%, $P = 0.02$).

There was a tendency of increased frequency of perianal disease in patients with familial IBD ($P = 0.051$). In a logistic regression analysis investigating the association between gender, location, behavior, familial IBD and smoking; non-inflammatory behavior (OR=1.89, 95%CI=1.30-2.75, $P = 0.001$) and smoking (OR=1.67, 95%CI=1.16-2.39, $P = 0.005$) were independent risk factors for frequent relapses.

Extraintestinal manifestations were more frequent in patients with familial IBD (49.3% vs. sporadic: 33.8%, $P = 0.01$) and females (39.9% vs. males:

31.6%, $P = 0.04$). Location (L2-3: 41.3% vs. L1 22.1%) was also associated to the presence of EIMs in univariate analysis. In a logistic regression analysis investigating the association between gender, location, behavior, familial IBD, smoking and the presence of EIMs gender, behavior, smoking and familial disease were independently associated with EIMs (**Table 3**). Arthritis was also more frequent in patients with familial IBD (46.6% vs. 28.3%, $P = 0.002$). Ileocolonic or colonic location (OR=4.29, 95%CI=1.51-12.18, $P = 0.006$) and smoking (OR=1.88, 95%CI=1.04-3.39, $P = 0.02$) increased the risk of cutaneous manifestations.

Steroid and azathioprine use was more frequent in patients with ileocolonic (steroid use; L3: 89% vs. L1: 74.3%, L2: 85.2%, $P = 0.0017$, azathioprine use; 68.9% vs. L1: 52.1%, L2: 58.7%, $P = 0.007$) or penetrating disease (steroid use: 90.7% vs. L1: 76.7%, L2: 87.7%, $P = 0.0017$, azathioprine use: 73.7% vs. L1: 49.1%, L2: 66.7%, $P = 0.007$). In a logistic regression analysis both

TABLE 2 Association between Disease Location and Behavior in Patients with Crohn's Disease

	Ileal	Colonic	Ileocolonic	Upper GI	Total
Inflammatory	54 (23.3%)	79 (34.0%)	96 (41.4%)	3 (1.3%)	232
Stricturing	46 (33.3%)	27 (19.6%)	63 (45.7%)	2 (1.4%)	138
Penetrating	40 (20.6%)	49 (25.3%)	105 (54.1%)	0	194
Total	140	155	264	5	564

$P = 0.004$.

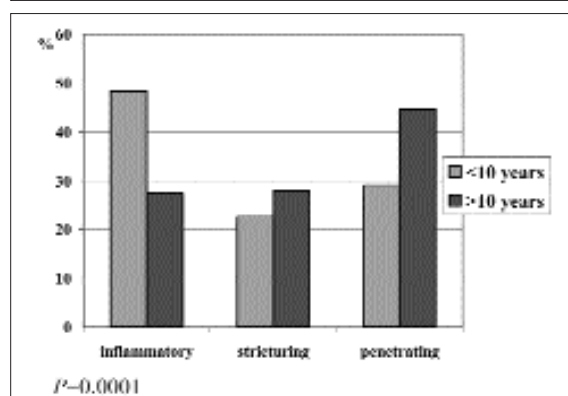
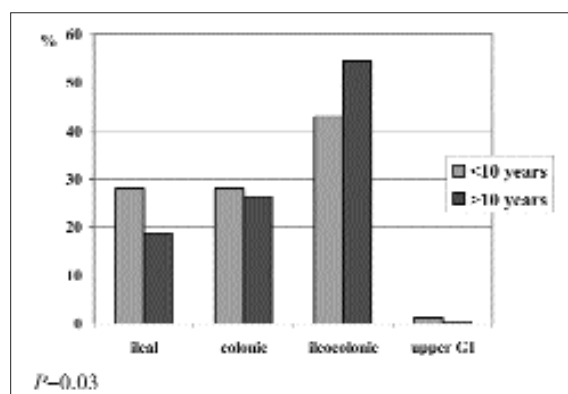


FIGURE 2 Association between Disease Location, Behavior and Duration in CD Patients with More or Less than 10 Years Disease Duration

TABLE 3 Logistic Regression: Association between Gender, Disease Location, Behavior, Familial Disease, Smoking and the Presence of Extraintestinal Manifestations

Factor	Coefficient	P value	OR	95%CI
Female gender	0.409	0.026	1.51	1.05-2.16
Ileocolonic or colonic location	0.902	<0.0001	2.47	1.57-3.88
Non-inflammatory behavior	0.308	0.10	1.36	0.94-1.96
Familial disease	0.628	0.016	1.88	1.13-3.12
Smoking	0.440	0.017	1.55	1.08-2.22

The coefficient is equivalent to the natural log of the odds ratio (OR).

TABLE 4 Logistic Regression: Association between Gender, Disease Location, Behavior, Familial Disease, Smoking and the Need for Resection

Factor	Coefficient	P value	OR	95%CI
Female gender	0.042	0.84	1.04	0.69-1.57
Ileal involvement	1.28	<0.0001	3.59	2.22-5.81
Non-inflammatory behavior	2.64	<0.0001	14.10	8.69-22.77
Extraintestinal manifestation	-0.29	0.18	0.75	0.49-1.15
Familial disease	-0.34	0.28	0.72	0.39-1.32
Smoking	-0.35	0.10	0.71	0.46-1.06

The coefficient is equivalent to the natural log of the odds ratio (OR).

location and behavior were independent predictors of steroid ($P_{\text{location}}=0.001$, $P_{\text{behavior}}<0.0001$) and azathioprine use ($P_{\text{location}}=0.002$, $P_{\text{behavior}}<0.0001$).

Logistic regression analysis was used to explore the effect of familial disease, gender, location, behavior and smoking on the need for surgery. Non-inflammatory behavior and ileal involvement were positively, independently associated to the need for resections but not gender or familial disease (Table 4). This association was analyzed also for the need of multiple resections: the effect of ileal involvement ($\text{OR}=2.91$, $95\%\text{CI}=1.27-6.65$, $P=0.01$) and non-inflammatory behavior ($\text{OR}=15.7$, $95\%\text{CI}=4.8-50.9$) remained unchanged.

DISCUSSION

In this study we investigated the characteristic traits of familial IBD and association between clinical data and disease phenotype. In concordance with previous studies (11,17,18) age at onset was not associated with familial disease with identical disease duration and similar smoking habits. Furthermore we confirmed the findings of Poilito *et al.* (18), who showed age-specific phenotype according to the age at diagnosis. In our study more stricturing (A1: 37.8% vs. A2: 17.7%, $P=0.0007$) and ileocolonic (50.0% vs. 31.3%, $P=0.004$) disease was present in A1 patients (<40 years old at diagnosis), while colonic disease (A2: 38.5% vs. A1: 25.2%) and inflammatory behavior (50.0% vs. 39.3%) was more common in patients with A2 disease.

We found no association between disease location, behavior and familial IBD. There is also no consistency in difference in location and behavior of CD between familial and non-familial (sporadic) disease in the literature. In two recent studies using the Vienna classification, Halme *et al.* (19) demonstrated a

greater frequency of ileal disease in familial disease (38 versus 21%) and less ileocolonic (35 vs. 50%). Freeman *et al.* (20) also found less ileocolonic disease in familial disease (32 vs. 43%) but purely colonic disease (46 vs. 29%) was more frequent in familial cases. Hampe *et al.* (21) found no difference between familial and sporadic disease in terms of disease behavior. Furthermore Carbonnel *et al.* (33) found more operations for perforating disease in familial disease.

A possible explanation for this large variation might be that the patient groups may differ also in terms of other genetic and/or environmental factors (like smoking). In our study no difference was found in smoking habits between familial and sporadic patients. A further limitation could be if the analysis was not done at the same timepoint, as disease phenotype is dynamic and changes over time (29,34), as found also in our study. Disease location was more extensive and behavior shifted towards higher prevalence of penetrating disease in patients with longer disease duration.

Extraintestinal manifestations (EIMs) were found in one third of the patients. The presence of extraintestinal manifestations was higher in familial CD cases and -beside female gender, colonic and ileocolonic disease and smoking- familial disease was an independent risk factor for EIMs in a logistic regression analysis. High concordance rates for extraintestinal manifestations were reported previously in subsequent CD generation (67-80%) (35). Furthermore in the study of Hofer *et al.* (36) beside fistulizing disease behavior, male gender and corticosteroid treatment and the presence of extraintestinal manifestations were found to be associated with earlier reoperations. In contrast in our study the presence of EIMs was not associated to need for surgery.

An important question is the clinical outcome measured by the number of relapses and the need for CD associated surgery. We found non-inflammatory behavior and smoking to be independent predictors of frequent relapses. In the study of Cosnes *et al.* (37) current smoking increases the risk of flare-up compared to never-smokers by more than 50%, the same extent found also in our study. The effect of smoking in that study was independent of gender, age, duration of disease and current therapy. Patients with colonic location were less sensitive. In concordance with previous data (38,39) smoking was associated with more frequent penetrating disease.

The deleterious effect of smoking in CD was particularly manifest in patients who had been operated on in previous studies. The cumulative rates of clinical and surgical recurrence were found to be consistently more elevated in smokers compared to non-smokers (40,41).

The need for steroids and immunosuppressants was reported to be also increased in smokers compared to non-smokers (23). Moreover, the risk of being operated on at least once during disease course was also increased in smokers in most previous studies (42). In our study ileal disease and most markedly

non-inflammatory behavior were associated with increased risk for surgery and, in concordance with data in patients from Israel (45,46), no differences were found in the need for operation or for immunosuppressants between smokers and non-smokers. Of note, in the study of Cosnes *et al.* immunosuppressive therapy was suggested to neutralize the effect of smoking on the need for surgery (43).

In IBD, anticipation was originally suggested by studies that demonstrated a younger age at onset in familial compared to sporadic disease, and younger age at onset and more serious disease in subsequent family generations (17,29,44). However, in concordance with more recent studies (45,46), our results suggested that anticipation does not occur in IBD. In this study, we could not prove an earlier age at onset, or a difference in disease location, behavior or increased need for aggressive immunosuppressive therapy and surgery in patients with familial disease

compared to sporadic patients with identical disease duration and similar smoking habits. In contrast, age at onset became lower in the later diagnosed patients, both in sporadic and familial IBD.

In summary, the presence of EIMs was associated with familial IBD. Familial disease, female gender, colonic involvement and smoking were independently associated with EIMs, while ileal disease, non-inflammatory behavior but not smoking were independent risk factors increasing the risk for surgery. Since penetrating and more extensive disease was more common in patients with longer disease duration our data support a possible change in disease location and behavior during the course of the disease.

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FOOTNOTE

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