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A population-based study of familial clustering of inflammatory bowel disease in Florence

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In the frame of a population-based epidemiological study in the metropolitan area of Florence in a 15 year period (1978–1992) all prevalent patients affected with ulcerative colitis (UC) or Crohn's disease (CD) (alive and resident in the area at the end of the study) were investigated in order to identify familial clustering. Only 45 patients (5.2%) reported at least 1 relative with a diagnosis of inflammatory bowel disease (IBD). Among these, 25 patients reported a first-degree relative affected with IBD (2.9%). All the 28 families were contacted and detailed personal interviews were carried out in order to collect family trees. The affected relatives living outside the study area were also identified and their IBD diagnoses were verified. Fifteen families included only affected members with a diagnosis of UC; 5 had only CD, while 8 families had members affected with both forms. Two large families had 4 affected members and 2 other families had 3. Overall 9 parent-child affected pairs were identified (1 out of every 3 families). The high concordance within families for the type of disease (p=0.015) suggests that the disease susceptibility is specific. The authors discuss these findings and a possible interpretation of the low proportion of familial cases in this area.

Key words: Crohn's disease, family history, inflammatory bowel disease, prevalence, ulcerative colitis

Ulcerative colitis (UC) and Crohn's disease (CD) are considered together in the group of inflammatory bowel disease (IBD). Their causes are not well understood.

In Italy only a few studies have provided epidemiologic data: although a low incidence has been often reported,[1–3] incidence rates comparable to those of Northern European countries have been recently found in the metropolitan area of Florence.[4]

An increasing trend has also been reported in the incidence of both UC and CD in other Mediterranean countries.[5–7]

IBD incidence shows a peak in younger people (around 20–30 years of age in CD and 20–40 years in UC).[4,8,9]

The causes of IBD are largely unknown although several observations support the concept that genetic factors may predispose patients to the development of both UC and CD.[10–13] Familial clustering, however, could also reflect a common exposure to environmental factors.

A high proportion of cases reporting a positive familial history in first- and second-degree relatives has been described, with the frequency varying from 6.1 to 35.8% and being highest in Northern Europe and the USA.[8,14–17]

The aim of this report is to describe a series of families, identified within a population-based IBD prevalence study, in which at least 2 members had an IBD diagnosis (CD and/or UC) and to evaluate the concordance of IBD type among affected members of the same family.

PATIENTS AND METHODS

A retrospective study of IBD incidence in the period January 1978–December 1987 has been recently carried out in the metropolitan area of Florence;[4] subsequently all newly diagnosed cases between January 1988 and December 1992 have also been identified. The study included both in-patients and out-patients referred to all gastroenterological and surgical departments of the area. Private gastroenterologists and family doctors were also asked to report their patients. At the time of the October 1991 national census the study area had a population of approximately 633,100 inhabitants. The IBD diagnoses were verified on the basis of well-established clinical, endoscopical, radiological, histological and surgical criteria as described elsewhere.[4] Patients with an undefined type of IBD were not considered in this report.

Among the IBD patients defined as 'prevalent' on 31 December 1992 (alive and resident in the area), we identified all those who reported at least 1 affected relative (however distant genetically) and collected information in order to confirm his/her IBD diagnosis. A proband was defined as a prevalent case resident in the area on 31 December 1992 able to report at least 1 relative already diagnosed with IBD whether alive or dead at that date. If 2 or more affected relatives were living in the study area the 'proband' was defined as the second relative who had received the IBD diagnosis. If only 1 member of the family

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was living in the study area this patient was considered as the proband.

Following the study protocol, demographic information for each IBD patient was collected from the local town offices and a study nurse carefully interviewed all the patients by telephone or face to face. The patients were asked to provide detailed information about all the IBD-affected members of their families including date of birth, residence, consanguinity, date of death and date of diagnosis. When the information was not considered exhaustive, another relative was interviewed. Family trees were collected in detail and computerized. Fisher's exact test was used to evaluate the statistical significance of concordance for the IBD type within the families, comparing the proband of each family with the affected relative(s). A few large families were identified and within each of these all possible proband-affected relative pairs were considered for concordance analysis (2 pairs for each 3 member family and 3 pairs for each 4 member family).

RESULTS

Overall 869 patients were identified as prevalent IBD cases resident in the Florence metropolitan area on 31 December 1992 and met the eligibility criteria for inclusion in the study. Six hundred and fifty-three were classified as UC patients and 216 as CD patients and 3 were undefined (502 males and 367 females).

A positive family history (at least 1 first- and/or second-degree relative) was reported in 45 prevalent cases. The overall proportion in the total series was 5.2% (45/869), ranging between 4.2% in males (21 out of 502) and 6.5% in females (24 out of 367), with 4.3% for UC (28 out of 653) and 7.9% for CD (17 out of 216). Out of 45 cases only 25 reported at least 1 affected first-degree relative, an overall proportion of 2.9% (25 out of 869); according to IBD type, this prevalence was 2.3% (15 out of 653) and 4.6% (10 out of 216) among UC and CD patients, respectively.

The 45 prevalent cases were contained in 28 separate families. In addition there were 16 other relatives in these families with a diagnosis of IBD but who lived outside the study area and, hence, were not included in the Florence prevalence study. For each of these 16 affected relatives direct confirmation of diagnosis was obtained. Overall, in 28 families, the 61 affected subjects were divided equally according to gender (30 males and 31 females); 41 were diagnosed as UC (22 males and 19 females) and 20 were affected by CD (8 males and 12 females).

Among all these IBD familial patients no case of colorectal cancer was reported.

All the families were contacted and provided detailed family information for analysis. Results are presented here for these 28 families: 15 families included only members with UC (2 including 4 affected members), 5 families only members with CD (1 family including 3 affected members) and 8 families had members affected by either UC or CD (1 including 3 affected members). In the latter group a proband had a first diagnosis of UC later modified to CD.

Additional families were also identified as having a positive familial history for IBD but were not considered in this analysis because all members lived outside the study area (5) or because the diagnosis of the proband occurred after 31 December 1992 (3).

Overall, the mean age at diagnosis for the 45 prevalent cases was 41 years (males, 40 years; females, 42 years; UC, 44 years; CD, 37 years) and ranged between 14 and 74 years. Their mean age in December 1992 was 49 years. One proband reported a deceased relative who had received a UC diagnosis and lived outside of the study area.

The 24 families with 2 members affected are shown in *table 1*; the most frequent combination was a parent-child pair (9 out of 24). Overall, these families provided 24 comparisons between the proband and his/her affected relative: in 18 out of 24 families (75%) the same type of disease was reported. The concordance was 84.6 and 63.6%, respectively, in families with pairs of first-degree and second-degree affected relatives.

A detailed description of the 4 families reporting more than 2 subjects with an IBD diagnosis follows:

- Family 3 (4 members, all UC)

The female proband had a UC diagnosis when she was 41 years old. Her brother had a diagnosis of UC at 35 years and 2 nephews (one of them being the son of her affected brother) had UC diagnoses at 21 and 36 years, respectively.

- Family 9 (3 members, 1 CD and 2 UC)

The male proband had a first diagnosis at 40 years of age; later the diagnosis was modified to CD (50 years). His father and a cousin had UC diagnoses at 74 and 33 years, respectively.

- Family 11 (3 members, all CD)

The female proband had a CD diagnosis at 57 years. Her brother and a cousin had CD diagnoses at 58 and 59 years, respectively.

- Family 20 (4 members, all UC)

The female proband, her paternal aunt, a nephew and a niece had UC diagnoses when they were 46, 75, 27 and 24 years, respectively.

In these 4 large families 10 additional comparisons were possible between each proband and the 2–3 affected relatives. Overall, the 28 families showed a high concordance for the IBD type of their affected members ($p=0.015$); in 26 out of 34 comparisons (76.5%) the same

Table 1 Distribution of 24 families with 2 members affected according to inflammatory bowel disease (IBD) type – ulcerative colitis (UC) or Crohn's disease (CD) – and relationship between the proband and the affected relative

	IBD type			
Relationship	Both UC	Both CD	UC and CD	Total
Parent–child	6	1	2	9
Siblings	2	2	–	4
Cousins	1	1	1	3
Aunt/uncle–niece/nephew	4	1	3	8
Total	13	5	6	24

disease was reported (*table 2*). In contrast no concordance was shown for gender. The inclusion of the additional 8 families living outside the study area or identified after the prevalence study increased the number of comparisons to 42 and an even higher concordance was shown ($p<0.002$).

DISCUSSION

The present study describes the IBD patients reporting at least 1 relative affected by UC or CD in a population-based series including all the prevalent cases in the Florence metropolitan area on 31 December 1992. Familial cases represented 5.2% of the total. This proportion is lower than that reported by other studies from high risk areas in Northern Europe, where the frequency of 'familial' cases is higher than 10%,[12,16] but is consistent with another report recently published from Italy: 5.5% (36/652) of IBD cases from a large multicentre clinical series reported a positive familial history.[18]

We also found that 4.6% of prevalent CD patients in Florence reported a first-degree relative affected by IBD; in a recent review this proportion in 5 studies of Crohn's disease ranged between 4.7 and 16.5%.[19]

In our study the frequency of female patients with a positive familial history was slightly higher than that for males, in agreement with Lashner et al.;[10] moreover the proportion of familial cases among CD patients tended to be higher than among UC cases in agreement with several studies,[20–22] although, in a large clinical series from Northern Italy,[18] the overall prevalence of IBD familial cases was slightly higher among UC patients than CD patients. This could reflect geographical differences or different interactions between genetic and environmental factors. Familial occurrence partially reflects the background prevalence rates: in fact the proportion of 'familial' cases in Florence is lower than that reported in high-risk areas, but not so much in relative terms (a twofold difference; while considering the overall IBD prevalence or incidence rates a higher ratio between high- and low-risk areas can be found). Paradoxically, the interpretation could be that susceptibility has a stronger role in low-risk areas compared to high-risk areas. In other words, when environmental risk factors for IBD are introduced in a population, individuals with a genetic predisposition are more frequently represented among those who are first affected by the disease and it is more likely that familial cases represent real genetic clusterings. Repeating this study in the same area in 10 or 20 years from now, one would expect to find a higher 'familial' occurrence of IBD with the percentage of cases with a positive family history increased to levels currently found in high-risk areas (10%). However, the relative risk for relatives of IBD patients in comparison to the general population would probably be decreased. This interpretation is also in agreement with the results of a study focused on the role of susceptibility and the risk of gastric cancer in different regions of Italy[23] where low-risk areas showed a much lower occurrence of 'familial' cases (9.3 versus 23.9%) but the relative risk associated with a positive family history tended to be higher in low- rather than in high-risk areas (at least twofold).

A statistically significant concordance of type of disease was also found: probands affected by UC tended to have relatives affected by UC rather than by CD, while probands affected by CD tended to have relatives affected by CD rather than by UC. In the 24 families with 2 affected members the concordance tended to be higher when 2 first-degree relatives were affected. These findings suggest that CD and UC are distinct diseases following a separate inheritance pattern, even if it is possible to identify a smaller subgroup of patients showing a susceptibility for IBD as one entity. Common exposure to specific environmental factors is an unlikely explanation for this disease-specific familial clustering; moreover pairs of siblings were only rarely involved in our study.

Lewkonia and McConnel[24] suggested that CD and UC are polygenic hereditary diseases sharing genes conferring susceptibility. According to their hypothesis CD results when a higher number of such genes are present in a given individual, while UC results when that number is lower. Other studies suggested the presence of a recessive gene with incomplete penetrance as the most likely explanation for susceptibility to CD;[25] the relatively high frequency of parent–child clusters in our case series, however, could point to a possible dominant inheritance pattern as suggested for the hereditary pattern of UC.[11]

Table 2 Concordance of inflammatory bowel disease type (ulcerative colitis (UC) or Crohn's disease (CD)) between each of 28 probands and his/her affected relative(s)[a]

		Affected relative	
		UC	CD
Proband	UC	19	3
	CD	5	7

Fisher's exact test, p=0,015
a: In 4 large families multiple comparisons were possible between the proband and his/her 2 or 3 affected relatives

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