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TRABAJO FIN DE MÁSTER

Asociación familiar en enfermedad inflamatoria intestinal: severidad y requerimientos terapéuticos/

Disease severity and treatment requirements in familial inflammatory bowel disease

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I. Aspectos preliminares:

1. **Título/Tittle:** Asociación familiar en enfermedad inflamatoria intestinal: severidad y requerimientos terapéuticos/ Disease severity and treatment requirements in familial inflammatory bowel disease.

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5. **Resumen/Abstract:**

Introducción y objetivos

Numerosos estudios han demostrado una prevalencia y concordancia aumentada de Enfermedad Inflamatoria Intestinal (EII) entre los familiares de pacientes. Otros estudios sugieren que la influencia genética está sobre-estimada. Los objetivos de este estudio son evaluar la expresión fenotípica y los requerimientos terapéuticos en función de la presencia de asociación familiar; estudiar la relación entre el número de familiares y el grado de parentesco con la agresividad de la enfermedad; y cuantificar el impacto de la agregación familiar comparado al de otros factores ambientales.

Material y métodos

Estudio analítico, observacional, de 1211 pacientes controlados en nuestra unidad. Analizamos, en función de la presencia de asociación familiar, el número de familiares afectos y el grado de parentesco, la expresión clínica de la enfermedad, el desarrollo de complicaciones, síntomas extraintestinales, la necesidad de tratamiento con fármacos inmunomoduladores, biológicos, dilatación endoscópica y cirugía así como la mortalidad atribuida a la enfermedad. Realizamos un análisis multivariante que considera además el consumo de tabaco y antiinflamatorios no esteroideos (AINEs).

Resultados

El 14.2% de los pacientes tenían antecedentes familiares de EII. La mediana de edad al diagnóstico tiende a adelantarse en casos con historia familiar de 32 a 29 años, p=0.07. En la CU, se observa mayor frecuencia de enfermedad extraintestinal en pacientes con agregación familiar: artropatía periférica (OR=2.3, p=0.015) y eritema nodoso (OR=7.6, p=0.001). Los pacientes con EC e historia familiar presentan un mayor uso de recursos terapéuticos: inmunomoduladores (OR=1.8, p=0.029), biológicos (OR=1.9, p=0.011) y cirugía (OR=1.7, p=0.044). La frecuencia de absceso abdominal aumenta con el número de familiares afectos: 5.1% en EII esporádica, 7% con 1 familiar afecto y 14.3% con dos o más, p=0.039. Estas asociaciones se mantienen en el análisis multivariante.

Conclusiones

La asociación familiar se considera un factor de riesgo para el desarrollo de EII más agresiva con mayor necesidad de tratamientos, tendencia a un debut más precoz, mayor frecuencia de absceso abdominal y manifestaciones extraintestinales; manteniéndose como factor de riesgo al analizar la influencia de factores ambientales como el tabaco y los AINEs

Background and aims

Several studies demonstrate an increased prevalence and concordance of Inflammatory Bowel Disease among the relatives of patients. Other studies suggest that genetic influence is over-estimated. The aims of this study are to evaluate the phenotypic expression and the treatment requirements in familial Inflammatory Bowel Disease, to study the relationship between number of relatives and degree of kinship with disease severity and to quantify the impact of family aggregation compared to other environmental factors.

Methods

Observational analytical study of 1211 patients followed in our Unit. We analyzed, according to the existence of familial association, number and degree of consanguinity, the phenotypic expression, complications, extraintestinal manifestations, treatment requirements and mortality. A multivariable analysis considering smoking habits and non-steroidal-anti-inflammatory drugs was performed.

Results

14.2% of patients had relatives affected. Median age at diagnosis tended to be lower in the familial group, 32 vs 29, p=0.07. In familial ulcerative colitis, there was a higher proportion of extraintestinal manifestations: peripheral arthropathy (OR=2.3, p=0.015) and erythema nodosum (OR=7.6, p=0.001). In familial Crohn's disease, there were higher treatment requirements: inmunomodulators (OR=1.8, p=0.029); biologics (OR=1.9, p=0.011); surgery (OR=1.7, p=0.044). The abdominal abscess increased with the number of relatives affected: 5.1% (sporadic), 7.0% (one) and 14.3% (two or more), p=0.039. These associations were maintained in the multivariate analysis.

Conclusions

Familial aggregation is considered a risk factor for more aggressive disease and higher treatment requirements, a tendency for earlier onset, more abdominal abscess and extraintestinal manifestations, remaining a risk factor analyzing the influence of some environmental factors.

6. Palabras clave/ Keywords:

Asociación familiar, agresividad de la enfermedad, requerimientos terapéuticos/ familial aggregation, disease severity, treatment requirements.

II. Cuerpo del trabajo/ Original article:

1. Introduction

Several studies have demonstrated an increase in the prevalence of Inflammatory Bowel Disease (IBD) among the relatives of patients with Crohn's disease (CD) and ulcerative colitis (UC). Thus, family history of IBD is considered a risk factor for developing the disease [1-5]. The agreement in disease characteristics among relatives has also been analyzed, showing a greater clinical concordance between individuals of the same family [6-8]. Furthermore, phenotypic expression of the disease has been compared between familial and sporadic IBD with contrasting results. Whereas some studies show earlier disease onset and higher disease extent in familial disease [1-4], other studies suggest that genetic influence has been over-estimated and that other environmental factors may determine important disease features such as disease type [9-10]. Despite the numerous studies of familial aggregation in IBD, to our knowledge, there is none that analyses the influence of familial history in terms of treatment requirements –other than surgery- among patients with IBD.

The main aim of this study is, first of all, to evaluate the phenotypic expression of IBD and the treatment requirements based on the presence of familial association. Secondary objectives are to determine the relationship between number of family members affected and degree of kinship with disease severity; and to quantify the impact of family aggregation compared to other environmental factors: smoking habits and non-steroidal anti-inflammatory drugs (NSAIDs) consumption.

2. Materials and Methods

Patients

The study included 1211 IBD patients (617 UC and 594 CD) treated in the IBD Unit of the University Clinic Hospital of Valencia between 2006 and 2015. Epidemiological and clinical data were prospectively registered from the date of inclusion of the patient

in the database. Events occurring before the patient's inclusion were retrospectively acquired from direct interview with the patient and clinical record. Patients diagnosed with other types of IBD (microscopic colitis, indeterminate or unclassified) were excluded. Informed consent to participate in the database was obtained from all patients. The study was approved by the institutional ethics committee of the hospital.

Variables

Data collection included demographic data, IBD type, gender, age at diagnosis, smoking habits (active smoker, exsmoker or never a smoker), NSAIDs consumption, family history of IBD including number of affected relatives and degree of kinship, disease extent (for UC) and disease localization, behavior and perianal involvement (for CD), complications, extraintestinal immune-related manifestations (EIMs), treatment requirements (immunomodulators (IMM), biologic therapies, endoscopic dilation and surgery) and mortality due to the disease.

Definitions

Familial IBD was defined as the presence of one or more relatives of first (parents and offspring), second (siblings, grandparents, grandsons and granddaughters), third (aunts, uncles, nephews and nieces), and fourth or higher degree (cousins, great aunts, great uncles, grand nieces, grand nephews...) with either UC or CD. In the case of more than one family member affected, the one with stronger degree of kinship was taken into consideration for the analysis.

Diagnosis of UC and CD was made by local gastroenterologists based on standard clinical, endoscopic, radiological, surgical and/or pathological reports according to the ECCO consensus guidelines [11-12]. Disease extent for UC and disease localization and behavior for CD were determined with at least one image technique (endoscopy, barium small bowel follow through, or a cross-sectional imaging technique) and ileocolonoscopy (and upper endoscopy when pertinent). UC extension, CD localization and CD behavior were classified according to the Montreal classification [13]. The maximum extent and the most aggressive form of disease at any time since diagnosis were assigned for each patient. Complications considered were megacolon, bleeding, intraabdominal abscesses or bowel perforation. The EIMs taken into account were peripheral arthropathy, ankylosing spondylitis, sacroiliitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, iritis, episcleritis, primary sclerosing

cholangitis and thrombosis.

Statistical analysis

An observational analytical study was performed. The distribution of the variables was obtained by the analysis of normality with the Kolmogorov-Smirnov and the Shapiro-Wilk test. Quantitative variables showing normal distribution were expressed as mean and standard deviation and the quantitative variable that did not show normal distribution were expressed as median and interquartile range (IQR). Qualitative variables were expressed by frequencies (%).

In the analytical study, quantitative variables with two categories and normal distribution were compared with the T-student test, while the U-Mann Whitney test was used for those variables without normal distribution. Quantitative variables with more than two groups were compared with the ANOVA and the Scheffé test. Dichotomous qualitative variables were compared using the Chi-square test and in case of ordinal qualitative variables a linear per linear association test was performed; in those variables that showed more than 25% of the categories with an expected value lower than 5, the exact value was calculated with the Fisher test or the Monte Carlo test. Measures of association between qualitative variables were reported as odds ratio (OR) with 95% confidence intervals (95% CI). Finally, a multivariable analysis using logistic-regression was performed to consider the adjusted effect of simultaneous variables.

All p values were two-sided. A p-value of <0.05 was considered statistically significant. Analyses were performed with the SPSS V17.0 software package.

3. Results

Study population and familial IBD

The cohort included 1211 IBD patients, 617 diagnosed with UC (50.9%) and 594 with CD (49.1%). The distribution by sex was 573 (47.3%) female and 638 (52.7%) male with no significant differences within groups. The median age at diagnosis was 32 years old (IQR: 21). At the time of diagnosis, 533 patients (44.0%) were active smokers or ex-smokers, and 203 patients (16.8%) agreed to having consumed NAIDs. One hundred sixty patients (14.2%) had a positive family history for IBD (95% CI=12.2-16.2), with similar distribution in UC (14.2; 95% CI=11.32-17.05) and CD (14.2; 95% CI=11.31-17.11), p=0.9 (supplementary table 1).

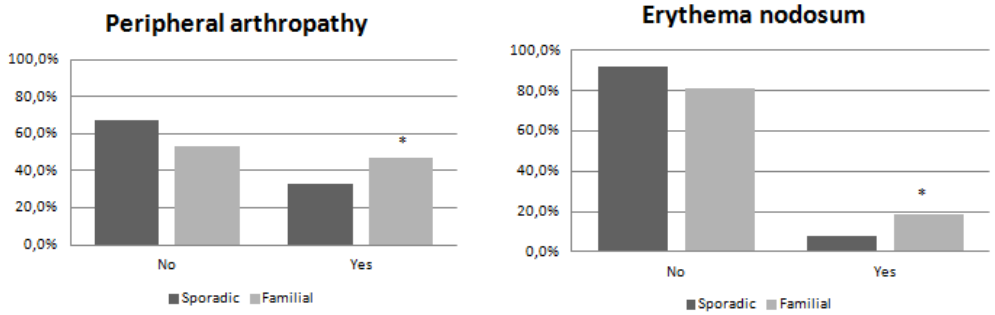
In the analysis of IBD in general, the median age at diagnosis tended to be lower in

the familial group, 32 years (IQR: 20) vs 29 years (IQR: 21), p=0.070. In familial IBD there was a higher proportion of patients with EIMs compared to sporadic cases: peripheral arthropathy 47.2% vs 33.1% (OR=1.8, 95% CI=1.2-2.7, p=0.007) and erythema nodosum, 18.8% vs 7.7% (OR=2.8, 95% CI=1.4-5.3, p=0.004) (supplementary figure 1). As well, there was a higher use of biologic therapies in the familial group, 36.3% vs 27.7% (OR=1.5, 95% CI=1.04-2.1, p=0.035) (supplementary figure 2).

Supplementary table 1. Characteristics of study population

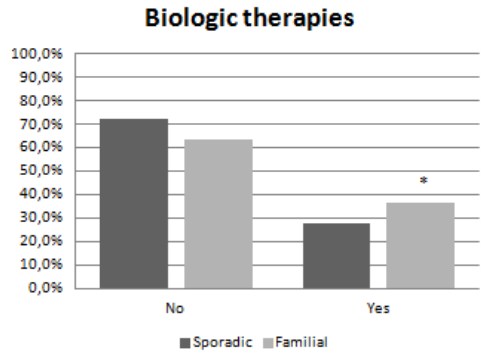
	Patients with UC	**Patients with CD**	**Patients with IBD**
Number of patients	617 (50.9%)	594 (49.1%)	1211 (100%)
Sex (F/M) N (%)	280 (45.4)/337 (54.6)	293 (49.3)/301 (50.7)	573 (47.3)/638 (52.7)
Age at diagnosis (yr) median (IQR)	36 (22)	28 (17)	32 (21)
Smoking habits[a] N (%)	235 (38.1)	310 (52.2)	533 (44.0)
NAIDs consumption N (%)	109 (17.7)	96 (16.2)	203 (16.8)
Family history N (%)	81 (14.2)	79 (14.2)	160 (14.2)

N: sample. [a.] smoker or ex-smoker.



*Statistically significant results.

Supplementary figure 1. Prevalence of peripheral arthropathy and erythema nodosum comparing sporadic and familial cases in IBD.



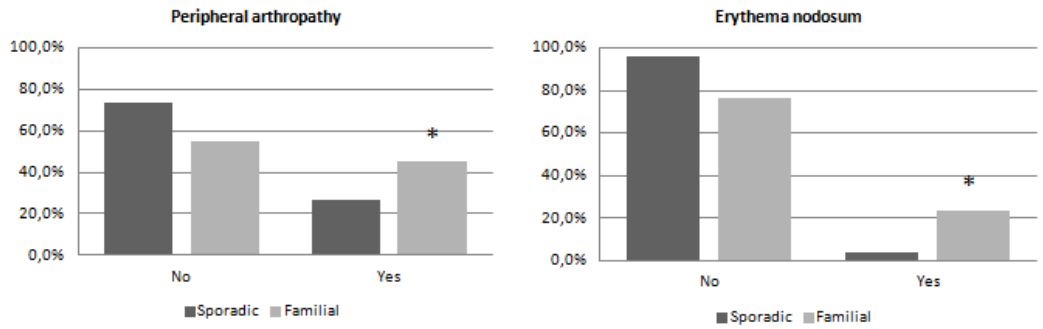
*Statistically significant results.

Supplementary figure 2. Prevalence of biologic therapies requirement comparing sporadic and familial cases in IBD.

Familial UC

A total of 617 patients with UC were included, 536 in the sporadic group (85.8%) and 81 in the familial group (14.2%). Distribution by sex was 280 (45.4%) female and 337 (54.6%) male.

Median age at diagnosis was not significantly lower in the familial group compared to the sporadic group, 34 years (IQR: 20) vs 36 years (IQR: 22), p=0.133. No differences were observed in disease extent or disease-related complications. There was a higher proportion of patients with EIMs in the familial cases compared to sporadic cases: peripheral arthropathy, 44.9% vs 26.6% (OR=2.3, 95% CI=1.2-4.2, p=0.015) and erythema nodosum, 23.5% vs 3.9% (OR=7.6, 95% CI=2.7-21.3, p=0.001) (Figure 1). Treatment requirements and mortality due to the disease were similar in both groups, sporadic and familial UC (Table 1).



*Statistically significant results.

Figure 1. Prevalence of peripheral arthropathy and erythema nodosum comparing sporadic and familial cases in UC.

Table 1. Characteristics of UC, comparing sporadic disease and familial aggregation

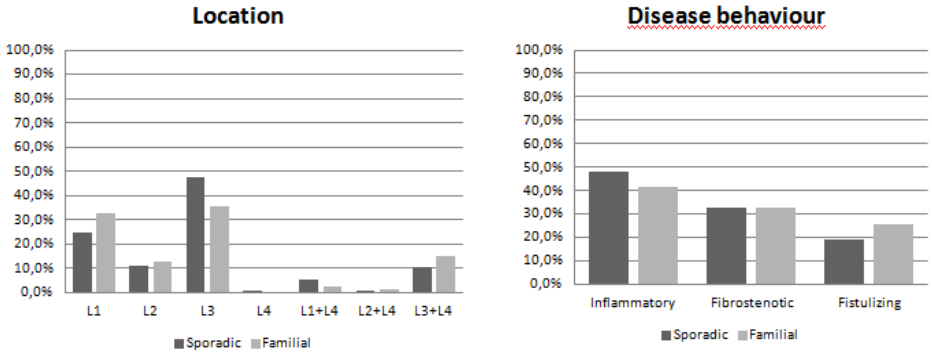
	Sporadic UC	Familial UC	p value
Patients	536	81	
Age at diagnosis (yr) median (IQR)	36 (22)	34 (20)	0.133
Disease extent (Montreal) (%)			0.655
- **E1**	12.9	8.6	
- **E2**	29.9	34.6	
- **E3**	57.3	56.8	
Complications (%)	3.9	5.3	0.797
EIMs (%)	29.7	48.1	0.002*
- **Peripheral arthropathy**	26.6	44.9	0.015*
- **Erythema nodosum**	3.9	23.5	0.001*
Treatment requirements (%)			
- **Immunomodulators**	30.0	29.6	1.000
- **Biologic therapies**	17.1	18.5	0.885
- **Endoscopic dilation**	0.0	0.7	1.000
- **Surgery**	11.6	6.2	0.204
Mortality (%)	2.9	3.0	1.000

*Statistically significant results.

Familial CD

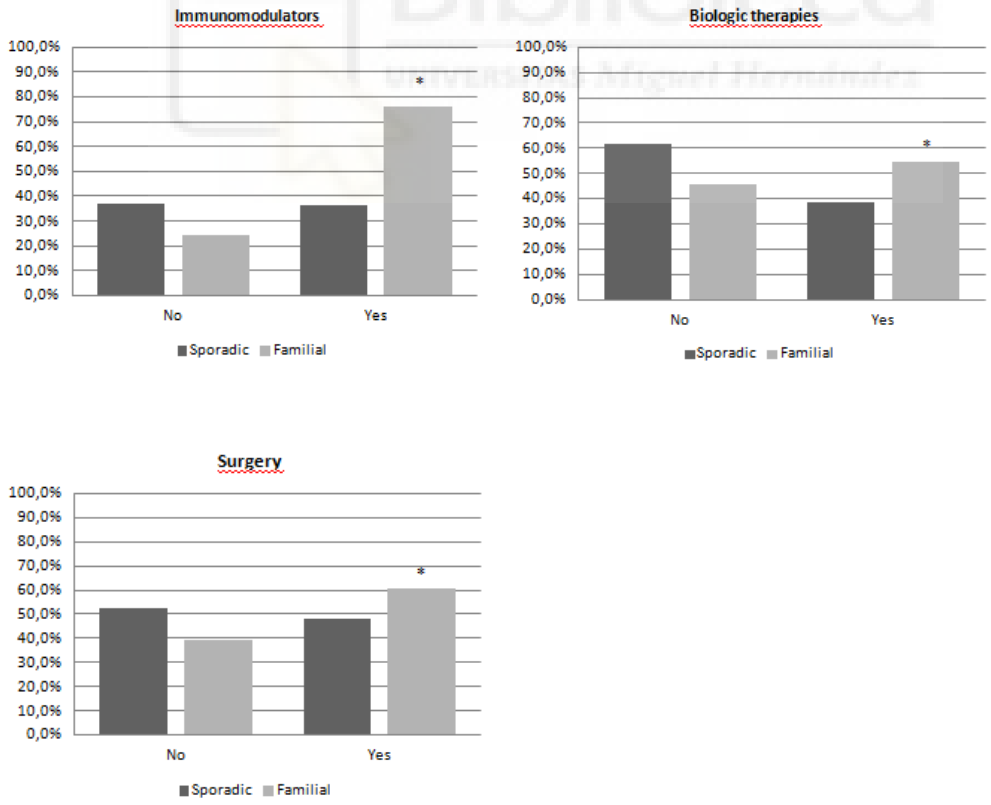
Five hundred ninety-four patients were diagnosed with CD. There were 515 cases (85.8%) in the sporadic group and 79 (14.2%) in the familial group. Distribution by sex was 293 (49.3%) female and 301 (50.7%) male.

No significant difference in age at diagnosis was found comparing the familial group with the sporadic group, 26 years (21) vs 28 years (17), p=0.185. No differences were observed in the frequency of disease location, perianal disease or behavior (Supplementary figure 3). No differences were found in the prevalence of complications or EIMs.



Supplement figure 3. Prevalence of disease location and disease behavior comparing sporadic and familial cases in CD.

The familial group of CD had higher treatment requirements with IMM, 75.9% vs 63.1% (OR=1.8, 95% CI=1.07-3.2, p=0.037); biologic therapies, 54.4% vs 38.6% (OR=1.9, 95% CI=1.2-3.1, p=0.011) and surgery, 60.8% vs 47.8% (OR=1.7, 95% CI=1.04-2.8, p=0.044) (Figure 2). Mortality showed no differences in either group (Table 2).



*Statistically significant results.

Figure 2. Prevalence of treatment requirements comparing sporadic and familial cases in CD.

Table 2. Characteristics of CD, comparing sporadic disease and familial aggregation

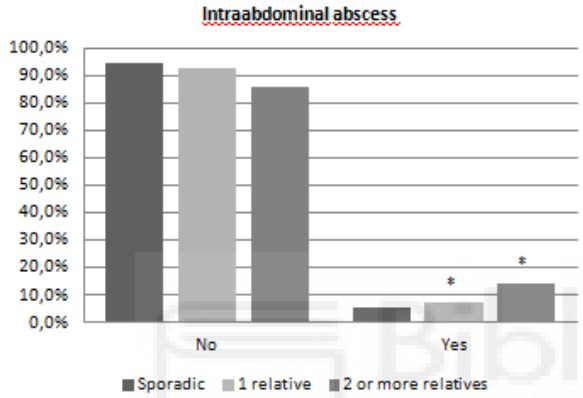
	Sporadic CD	Familial CD	p value
Patients	515	79	
Age at diagnosis (yr) median (IQR)	28 (17)	26 (21)	0.185
Disease location (Montreal) (%)			0.876
- **L1**	24.8	32.9	
- **L2**	10.9	12.7	
- **L3**	47.3	35.4	
- **L4**	0.6	0.0	
- **L1+L4**	5.5	2.5	
- **L2+L4**	0.2	1.3	
- **L3+L4**	10.7	15.2	
Perianal disease (Montreal) (%)	35.3	33.3	0.835
Disease behavior (Montreal) (%)			0.184
- **B1**	48.0	41.8	
- **B2**	32.9	32.9	
- **B3**	19.1	25.3	
Complications (%)	15.1	17.3	0.743
EIMs (%)	43.6	47.4	0.630
Treatment requirements (%)			
- **Immunomodulators**	63.1	79.9	0.037*
- **Biologic therapies**	38.6	54.4	0.011*
- **Endoscopic dilation**	6.4	11.4	0.207
- **Surgery**	47.8	60.8	0.044*
Mortality (%)	5.0	6.0	1.000

*Statistically significant results

Number of family members affected and degree of kinship

Among the cases with familial IBD, 128 patients (80.0%) had 1 family member affected, while 28 patients (17.5%) had 2 or more relatives affected by IBD (22 with two members, 3 with 3 members, 2 with 4 members and 1 with 6 members); the number of family members affected could not be obtained from 4 patients. In UC the distribution was: 68 patients (83.9%) had 1 relative affected by IBD while 12 patients (14.8%) had 2 or more members affected; this information could not be obtained from 1 patient. In CD: 60 patients (75.9%) had 1 relative affected, while 16 patients (20.3%) had 2 or more relatives affected by IBD; the number of relatives affected could not be registered from 3 patients.

The median age at diagnosis did not show differences when compared the sporadic group, the group with one family member affected and the group with two or more relatives affected. No differences were observed between groups in the disease extent (in UC), disease location, perianal involvement and disease behavior (in CD). Considering the complications, the frequency of intra-abdominal abscess increased with the number of family members affected in the proportion of 5.1% in the sporadic group, 7.0% with one relative affected and 14.3% with two or more relatives affected, p=0.039 (Supplementary figure 4).



*Statistically significant results.

Supplement figure 4. Proportion of intra-abdominal abscess according to the number of family members affected with IBD.

Among the EIMs, the frequency of peripheral arthropathy according to the number of family members was: 33.1% in the sporadic group, 48.9% with one family member with IBD and 35.3% with two or more family members with IBD, p=0.029. In the case of erythema nodosum, the frequency was: 7.7% in the sporadic group, 20.3% with one family member and 9.1% with two or more relatives affected with IBD, p=0.010. No differences were observed either in treatment or in mortality rate between groups (Table 3).

Table 3. Characteristics of familial IBD, comparing sporadic disease and number of family members

	Sporadic IBD	**1 relative affected**	**2 or more relatives affected**	**p value**
Patients	1051	128	28	
Age at diagnosis (yr) median (IQR)	32 (20)	29 (21)	27 (22)	0.220
UC: Disease extent (Montreal) (%)				0.862
- **E1**	12.9	5.9	25.0	
- **E2**	29.9	35.3	33.3	
- **E3**	57.3	58.8	41.7	
CD: Disease location (Montreal) (%)				0.894
- **L1**	24.8	36.7	25.0	
- **L2**	10.9	11.7	12.5	
- **L3**	47.3	30.0	50.0	
- **L4**	0.6	0.0	0.0	
- **L1+L4**	5.5	3.3	0.0	
- **L2+L4**	0.2	1.7	0.0	
- **L3+L4**	10.7	16.7	12.5	
CD: Perianal disease (Montreal) (%)	26.0	25.0	12.5	0.327
CD: Disease behavior (Montreal) (%)	48.0	38.3	50.0	0.216
- **B1**	32.9	38.3	18.8	
- **B2**	19.1	23.3	31.3	
- **B3**				
Complications (%)	9.5	10.7	16.7	0.281
- **Intra-abdominal abscess**	5.1	7.0	14.3	0.039*
- **Erythema nodosum**	7.7	20.3	9.1	0.010+
EIMs (%)	36.6	48.4	48.1	0.010*
- **Peripheral arthropathy**	33.1	48.9	35.3	0.029*
Treatment requirements (%)				
- **Immunomodulators**	46.3	51.6	53.6	0.197
- **Biologic therapies**	27.7	38.3	28.6	0.074
- **Endoscopic dilation**	3.5	5.9	4.5	0.280
- **Surgery**	29.5	33.6	32.1	0.384
Mortality (%)	3.9	2.8	16.7	0.274

*Statistically significant results.

Analyzing the degree of kinship, 53 patients (33.1%) had a first-degree relative affected by IBD, 60 (37.5%) had a second-degree relative affected, 14 (8.8%) had a third-degree relative and 25 (15.6%) had a fourth of higher-degree relative affected; 8 patients did not know the degree of consanguinity. Distribution according to degree of consanguinity in UC was: 33 patients (40.7%) with a first-degree relative, 27 (33.3%) with a second-degree relative, 8 (9.9%) with a third degree relative and 10 (12.3%) with a fourth or higher-degree relative affected; information on the degree of kinship could not be obtained from 3 patients. While in CD there were 20 patients (25.3%) with a first-degree relative affected by IBD, 33 (41.8%) with a second-degree relative, 6 (7.6%) with a third-degree relative and 15 (20.0%) with a fourth or higher degree relative affected; information on the degree of kinship could not be obtained from 5 patients.

No differences were observed in median age at diagnosis, disease extent (in UC), disease location, perianal involvement, disease behavior (in CD), complications or mortality due to the disease. Among EIMs, the proportion of peripheral arthropathy was: 33.1% in the sporadic group, 35.3% in patients with a fourth or higher-degree relative, 63.6% in patients with a third degree relative, 47.5% in patients with a second degree relative and 41.2% in patients with a first degree relative affected, p=0.029. In the case of erythema nodosum, the frequency was: 7.7% in the sporadic group, 7.7% in patients with a fourth or higher-degree relative, 30.0% in patients with a third degree relative, 18.2% in patients with a second degree relative and 21.7% in patients with a first degree relative affected, p=0.001. A higher need of biologic therapies was observed according to the degree of kinship: 27.7% in the sporadic group, 36.0% in patients with a fourth degree relative, 28.6% in patients with a third degree relative, 41.7% in patients with a second degree relative and 34.0% in patients with a first degree relative affected, p=0.031 (Table 4).

Table 4. Characteristics of familial IBD, comparing sporadic disease and degree of kinship

	Sporadic IBD	**Fourth or higher-degree**	**Third degree**	**Second degree**	**First degree**	**p value**
Patients	1051	25	14	60	53	
Age at diagnosis (yr) median (IQR)	32 (20)	26 (18)	26 (20)	27 (19)	30 (21)	0.506
UC: Disease extent (Montreal) (%)						0.560
- **E1**	12.9	0.0	37.5	3.7	9.1	
- **E2**	29.9	50.0	25.0	37.0	30.3	
- **E3**	57.3	50.0	37.5	59.3	60.6	
CD: Disease location (Montreal) (%)						0.810
- **L1**	24.8	26.7	33.3	39.4	30.0	
- **L2**	10.9	20.0	16.7	6.1	15.0	
- **L3**	47.3	46.7	16.7	39.4	25.0	
- **L4**	0.6	0.0	0.0	0.0	0.0	
- **L1+L4**	5.5	0.0	0.0	0.0	5.0	
- **L2+L4**	0.2	0.0	0.0	0.0	5.0	
- **L3+L4**	10.7	6.7	33.3	15.2	20.0	
CD: Perianal disease (Montreal) (%)	26.0	33.3	33.3	21.2	15.0	0.308
CD: Disease behavior (Montreal) (%)						0.489
- **B1**	48.0	40.0	33.3	30.3	65.0	
- **B2**	32.9	40.0	50.0	33.3	25.0	
- **B3**	19.1	20.0	16.7	36.4	10.0	
Complications (%)	9.5	8.7	7.1	13.8	8.5	0.696
EIMs (%)	36.6	36.0	64.3	51.8	44.2	0.013*
- **Intra-abdominal abscess**	33.1	35.3	63.6	47.5	41.2	0.029*
- **Erythema nodosum**	7.7	7.7	30.0	18.2	21.7	0.001*
Treatment requirements (%)						
- **Immunomodulators**	46.3	64.0	50.0	60.0	35.8	0.788
- **Biologic therapies**	27.7	36.0	28.6	41.7	34.0	0.031*
- **Endoscopic dilation**	3.5	13.0	7.1	5.5	2.2	0.678
- **Surgery**	29.5	36.0	21.4	46.7	17.0	0.895
Mortality (%)	3.9	0.0	0.0	8.3	4.8	0.438

*Statistically significant results.

Smoking habits and NSAIDs consumption

In the multivariate analysis that included smoking habits and NAIDs consumption, all the associations previously shown were maintained. Family history of IBD remained an independent risk factor for higher prevalence of EIMs in UC and higher treatment requirements in CD (Table 5).

Table 5. Multivariate analysis with family history, smoking habits and NAIDs consumption.

			OR	95% CI	p value
EIMs in UC	Peripheral arthropathy	family history	2.1	1.1-3.9	0.027*
		smoking habits	1.4	0.9-2.3	0.177
		NAIDs	1.3	0.8-2.4	0.311
	Erythema nodosum	family history	6.3	2.1-18.8	0.001*
		smoking habits	1.1	0.4-3.0	0.926
		NAIDS	1.6	0.5-5.1	0.419
Treatment requirement in CD	IMM	family history	1.8	1.01-3.1	0.044*
		smoking habits	1.5	1.01-2.1	0.042*
		NAIDS	1.0	0.6-1.7	0.868
	Biologic therapies	family history	1.9	1.2-3.1	0.009*
		smoking habits	1.1	0.8-1.6	0.464
		NAIDS	1.6	0.9-2.4	0.055
	Surgery	family history	1.8	1.1-2.9	0.023*
		smoking habits	1.1	0.8-1.5	0.071
		NAIDS	0.6	0.4-0.9	0.018

*Statistically significant results.

4. Discussion

Family aggregation in IBD has been documented in numerous studies. In general, our results related to phenotypic IBD characteristics are comparable with those published by North American and European medical centers [1-6]. However, this is the first study that has analyzed the influence of familial history of IBD in terms of treatment groups in the disease extent (in UC), disease location, perianal involvement and disease behavior (in CD). Considering the complications, the frequency of intra-abdominal abscess increased with the number of family members affected in the proportion of 5.1% in the sporadic group, 7.0% with one relative affected and 14.3% with two or more relatives requirements, other than the need for surgery.

Earlier results showed an increased risk of developing CD and UC among relatives

of IBD patients as compared to the general population. Moreover, the greatest risk of a positive family history was observed in siblings [4,10]. In the study of Peeters et al the prevalence of familial IBD was 20.6% in patients with CD, while only 2.1% of controls had a family member affected [4]. In the Orholm et al analyses, first-degree relatives of patients with UC or CD, had a 10-fold increase in the risk of having the same disease as the patient when compared to the general population [5]. The rate of family history for IBD in our cohort was 14.2%. In contrast to prior results where CD usually showed higher prevalence of family history, in our patients the same 14.2% rate was observed for both UC and CD. Comparing the familial cases with the sporadic ones, previous studies found an earlier age at onset [2-4], a higher prevalence of EIMs for both UC and CD and higher prevalence of ileocolic disease location, perianal disease and penetrating behavior for CD [4]. In comparison, we also found that the median age at onset tended to be lower in the familial group, which may reflect the effects of genetic factors in producing anticipation between generations [13]. Speculating whether anticipation of diagnosis in familial IBD would be a bias of diagnosis due to the higher predisposition to consider the disease among relatives of patients, we deem that a difference of 3 years in disease onset between familial and sporadic IBD is more than the possible delay that may take place between demand for attention and diagnosis. A higher proportion of EIMs was also reported in patients with CD and a positive family history. Specifically, a 7.6-fold increase in the risk of erythema nodosum and a 2.3-fold increase in the case of peripheral arthropathy were observed. In addition, the frequency of peripheral arthropathy was also higher, together with the increasing number of family members affected. This might suggest the existence of a genetic influence on this phenotypic trait. In our cohort, no differences were found in disease extent in UC and disease location, perianal disease or behavior in CD. Despite no statistically significant differences for disease behavior, there was a higher percentage of fistulizing disease in familial cases. Considering the relationship between fistulizing behaviour, perforation and internal fistula, the increase in the prevalence of intra-abdominal abscess could be explained by the higher global frequency of fistulizing disease in the familial group.

An important finding in our study was the higher treatment requirements with IMM, biologic therapies and surgery in familial CD. This can be considered an indicator of higher disease severity, due to the fact that these therapies are reserved for those patients with either more aggressive disease or refractory to first-line treatments.

No other differences than those previously mentioned were influenced either by the

number of family members affected with IBD or by the degree of consanguinity. This makes us wonder whether genetic influence has been overestimated [9-10] and if unknown confounding factors and other environmental factors may determine important disease features. In the John C, et al study, no clinically significant differences between familial and sporadic cases were identified. However, it was reported that smoking habits determined disease type in familial cases [10].

In our study, the multivariate analysis, which included some of the environmental factors such as smoking habits and NSAIDs consumption, found that all the associations previously shown were maintained, including the positive family history as an independent risk factor for IBD. However, there is little research on the role of each of the environmental factors in the disease compared to the numerous epidemiological, familial and genome-wide association studies that have investigated genetic factors [14-16]. Therefore, additional studies are needed to explore the respective roles of environmental factors in the familial IBD.

A limitation of our study could be the fact that it is a monocentric study with a reduced number of patients with family history of IBD, as only our registered hospital cohort was analyzed. Moreover, even if epidemiological and clinical data were prospectively registered, several data were retrospectively assessed by direct interview with the patient, including some information that had missed before the statistical analysis. Another limitation that should be mentioned is that smoking habits were considered to be positive when there had been exposition at any time in the past or the present. However, the influence of exposition throughout the IBD was not analyzed.

In conclusion, familial aggregation in IBD is considered a risk factor for more severe disease, evaluated as a tendency for earlier onset, more prevalence of EIMs in UC (peripheral arthropathy and erythema nodosum) and increased treatment requirement in CD (IMM, biologics and surgery). Moreover, a higher frequency of abdominal abscess was found, with an increasing number of family members affected. EIMs (peripheral arthropathy and erythema nodosum) and biologic therapy requirements were also influenced by the number of family members and/or the degree of consanguinity. Family history remains a risk factor when analyzing the influence of environmental factors such as smoking habits and NSAIDs consumption.

These conclusions may have practical implications for patient care and open the hypothesis of whether patients with positive family history need a more aggressive therapeutic escalation. The need for more intense treatment requirements in familial

IBD that we have observed in our IBD population may be the trigger for large-scale treatment trials (to compare sporadic and family-related cases) or epidemiological studies to confirm the importance of family aggregation in IBD prognosis.

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6. Compliance with ethical standards

The study was approved by the institutional ethics committee of the hospital.

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8. Conflict of interest:

The authors declare no conflicts of interest.

III. Bibliografía/References:

1. Trier F, et al. Familial Risk of Inflammatory Bowel Disease: A Population-Based Cohort Study 1977-2011. *Am J Gastroenterol* 2015; 110:564-571.
2. Andreu M, et al. Disease severity in familial cases of IBD. *J Crohn's Colitis* 2014; 8:234-239.
3. Colombel J-F, et al. Clinical Characteristics of Crohn's Disease in 72 Families. *Gastroenterol* 1996; 111:604-607.
4. Peeters M, et al. Familial Aggregation in Crohn's Disease: Increased Age-Adjusted Risk and Concordance in Clinical Characteristics. *Gastroenterol* 1996; 11:597-603,
5. Orholm M, et al. Familial occurrence of inflammatory bowel disease. N Engl J Med 1991;324:84-8.
6. Cabré E, et al. Phenotypic concordance in familial inflammatory bowel disease (IBD). Result of a nationwide IBD Spanish database. *J Crohn's Colitis* 2014; 8, 654-661.
7. Steven R. Brant. Update on the Heritability of Inflammatory Bowel Disease: The Importance of Twin Studies. *Inflamm Bowel Dis* 2011.
8. Bayless T, et al. Crohn's Disease: Concordance for Site and Clinical Type in Affected Family Members- Potential Hereditary Influences. *Gastroenterol* 1996; 111:573-579.
9. Halfvarson J, et al. Genetic in Twins with Chron's Disease: Less Pronounced than Previously Believed?. *Inflamm Bowel Dis* 2011; 17:6-12.
10. John C, et al. Inflammatory Bowel Disease in 97 Families Each With Three or More Affected First-Degree Relatives. *Gastroenterol* 1996; 111:587-596.
11. Axel Dignass, et al. The second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. *J Crohn's Colitis* 2012;6:965-990.
12. Gert Van Assche, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohn's Colitis* 2010;4:7-27.
13. Silverberg MS, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the

2005 Montreal Congress of Gastroenterology. *Can J Gastroenterol* 2005;19:5-36.

14. Satsangi J, et al. Clinical patterns of familial inflammatory bowel disease. *Gut* 1996;38:738-41.
15. Loddo I, et al. Inflammatory bowel disease: genetics, epigenetics, and pathogenesis. *Front Immunol* 2015;6:551.
16. Gordon H, et al. Heritability in Inflammatory Bowel Disease: From the First Twin Study to Genome-Wide Association Studies. *Inflamm Bowel Dise* 2015; 21:1428-1434.
17. Weronica E, et al. The history of genetics in inflammatory bowel disease. *Ann Gastroenterol* 2014;27:294-30.