Prevalence of irritable bowel syndrome (IBS) in first-degree relatives of patients with inflammatory bowel disease (IBD)

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KEYWORDS
Prevalence; Irritable bowel syndrome; First-degree relatives; Inflammatory bowel disease

Abstract

Background: Epidemiological studies have shown a greater prevalence of irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) among first-degree relatives of patients diagnosed of these diseases. However, it is not known whether relatives of patients with IBD have a greater prevalence of IBS than the general population.

Aims: To analyse the prevalence of IBS among first-degree relatives by consanguinity (parents, siblings and offspring) and affinity (spouses) of patients with IBD.

Materials and methods: A prevalence study was conducted identifying 490 relatives of 91 patients with IBD. Of these, 404 met inclusion criteria; and 360 (response rate: 89.1%) answered the questionnaires. Subjects were invited to participate in the study through index cases (patients with IBD). The following variables were collected: age, sex, history of digestive diseases, kinship and cohabitation with the index case. The relatives completed a questionnaire to identify those who met Rome I and Rome II criteria for IBS.

Results: The overall prevalence of IBS among the first-degree relatives of patients with IBD was 49.4% and 10% according to Rome I and Rome II criteria respectively. IBS prevalence was higher in first-degree blood relatives than in spouses of patients (Rome I: 53.1% vs 29.1%, p = 0.001; Rome II: 10.8% vs 5.4%, NS). No differences were found in IBS prevalence depending on whether relatives were living with the index case or not.

Conclusion: IBS prevalence in first-degree relatives of patients with IBD is elevated. It is significantly greater in blood relatives, which suggests involvement of genetic and psychological factors rather than environmental factors.

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1. Introduction

Irritable bowel syndrome (IBS) is a prevalent functional gastrointestinal disorder (FGID) and a frequent reason for medical consultation.1,2 In Spain, an IBS prevalence in the general adult population of 12.1% based on Rome I criteria and 3.3% based on Rome II criteria has been estimated.3 IBS is considered to be a multifactorial disorder for which changes in intestinal motility and visceral hypersensitivity or psychological factors have been proposed as possible etiopathogenic mechanisms.4 Other potential mechanisms, such as inflammatory or genetic factors, have recently been proposed.5,6 There is increasing evidence supporting a probable involvement of inflammatory mechanisms in the etiopathogenesis of IBS, which has suggested the existence of a close relationship between IBS and inflammatory bowel disease (IBD).7,8 It has been seen in several studies that during periods of remission in IBD, these patients may have symptoms compatible with IBS, with a prevalence higher than in the general population. Speculation also exists about the potential existence of familial clustering (genetic predisposition) because consistent information is available about the increased prevalence of IBS and IBD respectively in first-degree relatives of patients with those diseases.9,10 Accurate information is currently lacking about the prevalence of IBS in relatives of patients with IBD. Our aim was to analyse the prevalence of IBS among first-degree relatives by consanguinity and spouses of patients diagnosed with Crohn’s disease (CD) or ulcerative colitis (UC).

2. Materials and methods

2.1. Study design and subjects

This was an observational, cross-sectional epidemiological study conducted from February 2006 to January 2009 in Valencia (Spain). The study sample (first-degree relatives of patients with IBD) was recruited using as index cases a cohort of patients aged 18 years or more previously diagnosed with IBD according to the diagnostic criteria described by Lennard-Jones11 who attended the Gastroenterology Unit of our hospital. Exclusion criteria for index cases were: a) distal ulcerative colitis; b) history of gastrointestinal surgery (except for appendectomy) or any other organic bowel disease; c) intellectual disability to complete the questionnaires; and d) refusal to participate in the study. All first-degree relatives by consanguinity (parents, siblings, and offspring) and by affinity (spouses) of patients with IBD, aged 18 years or more were recruited. Exclusion criteria were: a) a prior diagnosis of IBD (CD or UC); b) inability to contact with the family; c) intellectual disability to complete the questionnaires; and d) refusal to participate in the study.

Sample size calculations were based on the prevalence rates of IBS previously reported for the general Spanish population: 12.1 and 3.3% according to Rome I and Rome II criteria respectively.2 Assuming a prevalence of IBS in first-degree relatives of patients with IBD two times greater than that of the general Spanish population, a significance level of 0.05, and an 80% statistical power, the estimated number of relatives needed to be evaluated was 65 according to Rome I criteria, and 288 according to Rome II criteria. Up to 4 relatives were expected to be included on average per each index patient with IBD. Assuming a 20% loss of relatives, recruitment of relatives of 100 patients with IBD was considered to be adequate.

2.2. Methods

Demographic characteristics (sex and age) and data related to the disease of the patient with IBD (date of diagnosis, type of disease [UC or CD], disease location and behaviour pattern, and clinical severity with modified Truelove–Witts index for UC and Best index or CDAI – Crohn’s Disease Activity Index – for CD) were collected using a structured clinical survey administered by the physician which included the family tree of the first-degree relatives of the patient. Subjects (first-degree relatives) were invited to participate in the study through index cases (patients with IBD). General and clinical variables of relatives were also collected (age, sex, history of colorectal cancer, celiac disease or IBD, kinship and cohabitation with index case) and a questionnaire to evaluate use of healthcare resources (medical consultations for their bowel symptoms in the past year) and to assess whether they met the diagnostic criteria for IBS defined according to Rome I and Rome II criteria.12 IBS according to Rome I criteria, is defined as continuous or recurrent symptoms of: 1) abdominal pain, relieved with defecation, or associated with a change in frequency or consistency of stool; and/or 2) disturbed defecation (two or more of): a) altered stool frequency, b) altered stool form, c) altered stool passage, d) presence of mucus, e) bloating or feeling of abdominal distension. Rome II criteria are defined by the presence at least 12 weeks (which need not be consecutive) in the preceding 12 months, of abdominal discomfort or pain that has two out of three of these features: 1) relieved with defecation, 2) onset associated with a change in frequency of stool, 3) onset associated with a change in form (appearance) of stool. Subjects who met the Rome II criteria were categorised as constipation-predominant, diarrhoea-predominant, or alternating type IBS. This questionnaire, once completed, should be sent by post or handed in by patients themselves at the next scheduled visit.

2.3. Statistical analysis

Qualitative variables are reported in absolute frequencies and percentages, and as mean and range for continuous variables. Prevalence estimates are also expressed in their corresponding 95% confidence interval (CI95%). Univariate analyses were performed using for qualitative variables a Chi-square test, or a Fisher’s exact test if the conditions for use of the previous test were not met. A Student’s t test or a Mann–Whitney test for independent samples was used as appropriate to assess differences between quantitative variables. A logistic regression was used for the multivariate analysis to assess the association of IBS with different independent variables (age, sex, IBS type and activity, kinship and cohabitation with index case). For all analyses, a value of p<0.05 was considered statistically significant.
2.4. Ethical considerations

Each subject was assigned a code known to the researcher only in order to preserve confidentiality. The local research ethics committee approved this study.

3. Results

3.1. Characteristics of the selected sample

One hundred and eight patients with IBD were recruited (52 with UC and 56 with CD). Of these, 91 (41 with UC and 50 with CD, with no significant differences in sociodemographic characteristics between these patients and those initially recruited) completed the questionnaires (response rate 84.2%). Patients had a mean age of 39 years (range: 19–78 years), and 54.9% were males. Mean time to disease progression from diagnosis was 9 years and 10 months (range: 11 months–30 years). The location of the disease according to the Vienna classification was: terminal ileum (L1) in 18 patients with CD (36%), colon (L2) in 10 (20%), ileocolon (L3) in 20 (40%), and upper gastrointestinal tract (L4) in 2 (4%), while disease behaviour was: inflammatory (B1) in 20 patients (40%), stricturing (B2) in 14 (28%), and penetrating (B3) in 16 (32%). As regards UC, 16 patients (39%) had left-sided ulcerative colitis and 25 (61%) extensive ulcerative colitis. At study entry, the mean CDAI score in patients with CD was 109 (range: 7–359) while the mean modified Truelove–Witts index score in UC patients was 10.3 (range: 9–19). Sixty (65.9%) of 91 patients were in remission (38.7% CD and 61.3% UC) at the time of inclusion.

A total of 490 first-degree relatives (243 of patients with CD and 247 of patients with UC) were identified (Fig. 1). Of these, 86 (17.5%) were excluded, most of them (n=59; 68.6%) because the relative could not be contacted. Finally, 404 relatives (mean age: 46 years [range: 18–84]; females: 51.4%) were eligible for the study. Of them, 360 (response rate: 89.1%; mean age: 43 years [range: 18–84]; females: 54.2%) answered and sent the questionnaire. There were no significant differences in sociodemographic characteristics between relatives identified and relatives eventually included and analysed. No relatives reported a history of colorectal cancer or celiac disease. Three relatives were excluded because they had been diagnosed with IBD (2 CD and 1 UC). Half of the relatives (n=180) lived with patients with IBD; 125 of them were blood relatives (69.4%), and the remaining 55 spouses.

3.2. IBS prevalence

Overall prevalence of IBS among the first-degree relatives of patients with IBD was 49.4% according to Rome I criteria and 10% according to Rome II criteria (41.7% diarrhoea-predominant type, 36.1% constipation-predominant type, and 22.2% alternating type) (Table 1). The mean age of relatives who met Rome I criteria was 42.7 years (range: 18–81 years), as compared to 44.9 years (range: 18–67 years) in those with IBS according to Rome II criteria. No significant sex and age differences were seen between relatives without IBS and those who met the criteria. The diarrhoea-predominant type was more common in males (46.7% vs 38.1%) and the constipation-
predominant type was more common in females (38.1% vs 33.3%), but the differences were not statistically significant.

IBS prevalence was higher in first-degree blood relatives than in first-degree relatives by affinity. According to Roma I criteria, IBS prevalence in blood relatives and spouses was 53% and 29.1% (p=0.001) respectively, and according to Roma II criteria, IBS prevalence in blood relatives and spouses was 33.3%, but the differences were not statistically significant.

In multivariate analysis, the independent variables of kinship and IBD activity were found to be factors associated to the occurrence of IBS according to Roma I and Roma II criteria respectively (Table 3). Seventy-seven (21.4%) of the 360 first-degree relatives analysed had consulted for bowel symptoms in the past year. Most of them (93.5%) were relatives who met the diagnostic criteria for IBS.

### 4. Discussion

The prevalence of IBS in first-degree relatives of patients diagnosed with IBD in our series was 49.4% and 10% according to Rome I and Rome II criteria respectively. These rates are much higher than those reported for the general population in wide series published in Western countries using the same Rome diagnostic criteria14;16; and three to four times higher than the estimated prevalence in a reference Spanish population, 12.1% based on Rome I criteria and 3.3% based on Rome II criteria.2 Among the demographic variables recorded, female sex was associated to a greater probability of having symptoms consistent with IBS, regardless of the diagnostic criterion used, although not significantly as reported in the literature in wider populations.14,16

To our knowledge, a single study, published by Scott et al.,22 as an abstract, is currently available analysing the prevalence of functional bowel disorders among first-degree relatives of patients with IBD. In this study, authors reported that IBS was the most common functional bowel disorder in those relatives. The Rome I diagnostic criteria were used to diagnose IBS, and the prevalence obtained was greater (61.5%) than the prevalence seen in our study (49.4%). This difference may be due to the sample size in the Scott et al. study, 26 first-degree relatives (19 and 7 relatives of patients with CD and UC, respectively), and particularly to the fact that only patients seeking medical care for bowel symptoms (abdominal pain or distension, diarrhoea or constipation) were recruited. This study did not specifically assess the

### Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
<th>IBS (Rome I)</th>
<th>IBS (Rome II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n% (CI95%)</td>
<td>n% (CI95%)</td>
</tr>
<tr>
<td>Global</td>
<td>360</td>
<td>178 (44.3–54.6)</td>
<td>36 (7.1–13.6)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>165 (45.8)</td>
<td>79 (40.3–55.5)</td>
<td>15 (5.1–14.5)</td>
</tr>
<tr>
<td>Female</td>
<td>195 (54.2)</td>
<td>99 (43.8–57.8)</td>
<td>21 (6.4–15.1)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–29</td>
<td>88 (24.4)</td>
<td>5 (52.3–64.3)</td>
<td>0.5 (1.8–12.8)</td>
</tr>
<tr>
<td>30–44</td>
<td>115 (31.9)</td>
<td>55 (47.8–64.8)</td>
<td>11 (4.8–6.4)</td>
</tr>
<tr>
<td>45–59</td>
<td>100 (27.8)</td>
<td>48 (38.7–57)</td>
<td>14 (4.8–6.5)</td>
</tr>
<tr>
<td>≥60</td>
<td>57 (15.9)</td>
<td>29 (37.9–58.2)</td>
<td>6 (7.8–22.4)</td>
</tr>
</tbody>
</table>

Values given are absolute frequencies (n), percentages (%), and their corresponding 95% confidence intervals (Cl95%).

### Table 2

<table>
<thead>
<tr>
<th>IBS</th>
<th>Blood relatives</th>
<th>Blood relatives</th>
<th>Spouses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cohabitation</td>
<td>no cohabitation</td>
<td>cohabitation</td>
</tr>
<tr>
<td></td>
<td>% (Cl95%) (n=125)</td>
<td>% (Cl95%) (n=180)</td>
<td>% (Cl95%) (n=55)</td>
</tr>
<tr>
<td>Rome I</td>
<td>56.8 (48.1–65.1)</td>
<td>50.6 (43.3–57.9)</td>
<td>29.1 (17.6–42.9)</td>
</tr>
<tr>
<td>(n=178)</td>
<td>n=71</td>
<td>n=91</td>
<td>n=16</td>
</tr>
<tr>
<td>Rome II</td>
<td>8.8 (4.4–15.2)</td>
<td>12.2 (7.4–17)</td>
<td>5.4 (1.14–15.1)</td>
</tr>
<tr>
<td>(n=36)</td>
<td>n=11</td>
<td>n=22</td>
<td>n=3</td>
</tr>
</tbody>
</table>

Values given are percentages (%) and their corresponding 95% confidence intervals (Cl95%). p* Spouses vs blood relatives with cohabitation; p** spouses vs blood relatives without cohabitation.
Irritable bowel syndrome in relatives of patients with inflammatory bowel disease

Table 3  Factors associated to the occurrence of IBS (Rome I–II criteria).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=360</th>
<th>IBS n (%)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rome I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinship</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood relatives</td>
<td>305 (84.7)</td>
<td>162 (53.1)</td>
<td>3.23 (1.64–6.67)</td>
<td>0.001</td>
</tr>
<tr>
<td>Spouses</td>
<td>55 (15.3)</td>
<td>16 (29.1)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Rome II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity IBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>101 (28.1)</td>
<td>20 (15.8)</td>
<td>2.19 (1.07–4.46)</td>
<td>0.03</td>
</tr>
<tr>
<td>Remission</td>
<td>259 (71.9)</td>
<td>16 (7.7)</td>
<td>Reference</td>
<td></td>
</tr>
</tbody>
</table>

Values given are absolute frequencies (n), percentages (%), and their corresponding 95% confidence intervals (95% CI).

The influence of the type of kinship, disease characteristics in the index cases, or cohabitation on the prevalence of IBS.

First-degree blood relatives had a greater prevalence of IBS than spouses using both Rome diagnostic criteria. This association, kinship and IBS prevalence, persisted in the multivariate analysis, but only with the Rome I criteria, probably because of the reduced sample size of the group of relatives with IBS according to Rome II criteria. In this regard, there are several studies in first-degree relatives of patients with IBS showing analogous results, i.e. blood relatives of IBS patients have a greater prevalence of IBS than spouses.9,23,24 The main reason that could account for the high prevalence of IBS among first-degree relatives of patients with IBD could be the existence of familial clustering or even a genetic predisposition between both conditions. Various epidemiological studies have shown a greater prevalence of IBS and IBD as compared to the estimated prevalence in the general population among first-degree relatives of patients with these diseases respectively.9,10,25 However, the main limitation of most these studies is that information about the condition of relatives with symptoms consistent with IBS is provided by patients but not confirmed by relatives themselves. On the other hand, the high prevalence of FGIDs in some families could be related to the involvement of environmental factors. Twin studies are a specific type of familial study to differentiate between genetic and environmental factors that may contribute to development of a disease.

There are several studies where concordance between monozygotic and dizygotic twins was compared, analysing the probability of experiencing a FGID, particularly IBS.26–30 A greater concordance was found between monozygotic twins as compared to dizygotic twins, which would support the genetic contribution theory. However, a greater prevalence of IBS was also found in dizygotic twins whose parents were diagnosed with IBS, which would imply that social learning (family environment) would play a similar or greater role than the genetic load. To sum up, while twin studies have provided highly consistent results supporting the genetic contribution, this does not exclude the implication of familial environmental factors (diet, lifestyle, physical, psychic, or sexual abuse) or the genetic contribution of other non-gastrointestinal conditions, such as psychiatric diseases (including somatization or generalised anxiety disorders), susceptibility to infection (post-infectious IBS), etc. It should also be noted that social learning and other aspects related to the familial environment during childhood may be confounding factors in familial and twin studies. All these studies therefore suggest that both genetic and environmental factors should play a significant role in IBS development.31–33 Future studies could elucidate the relationship between hygiene factors and the development of intestinal inflammation.

As regards study limitations, the difficulty to determine whether or not the associations are causal in cross-sectional studies should be noted. However, since the primary study objective was to assess the prevalence of IBS among first-degree relatives of patients with IBD, the study design had to be necessarily cross-sectional. In this regard, it cannot be ruled out that some of the relatives analysed may eventually be diagnosed an IBD or any other gastrointestinal diseases. It was an exclusion criteria, patients with distal ulcerative colitis, to avoid confusions with other diseases such as ischemic proctitis, lymphoid follicular proctitis, radiation or drug proctitis.

Both, IBD and IBS, are characterised by a chronic course with a natural trend to symptomatic relapse, and it is known that in a high proportion of patients with IBD, symptoms are attributed to a FGID, IBS in most cases, before final diagnosis is made.34–36 It is also known that the time from symptom start to diagnosis of IBD may be as long as 20 years.37 In our study, of all identified relatives only 3 (who were excluded from the analysis) had been diagnosed with IBD. Seventy-seven (21.4%) of the 360 relatives analysed had consulted for bowel symptoms in the past year. Most of them (93.5%) met diagnostic criteria for IBS and none were diagnosed IBD. On the other hand, a foreseeable and unavoidable limitation is the main reason for exclusion of relatives, unavailability to contact (59 subjects; 68.6% of relatives excluded). Obviously, all of them were relatives who were not living with the IBD patients, which could influence the results of our study.

IBS prevalence was investigated using Rome I and Rome II criteria, for which prevalence data in the general Spanish population were available.2 The Rome I criteria have been used in many population studies and as selection criteria in clinical trials,14,16,38 where exclusion of coexisting symptoms or diseases is very important. The Rome II criteria have been very useful for selecting patients for pathophysiological studies or for recruitment into clinical trials, but also have limitations. As they are much stricter in aspects of symptom duration and frequency, they are believed to underestimate the true prevalence of IBS.2,15,20 Following the start of the study Rome III criteria were published39; not applied retrospectively for lacking the necessary recording information of the cases included in the study. Rome III criteria were intended to achieve a balance, not to be too strict or too lax, but actually there are few data yet on the IBS prevalence in accordance with these new criteria.40 It is expected that IBS prevalence according to Rome III criteria, is closer to that obtained with Rome I criteria.

In conclusion, the results of this study show a significantly higher prevalence of IBS in first-degree blood relatives (but not in spouses) of patients with IBD as compared to the general Spanish population, regardless of cohabitation or not.
with the index case, which suggests the potential existence of a genetic predisposition to suffer IBS, rather than the involvement of environmental factors.

Future prospective studies are needed to assess the course of relatives of patients with IBD who met IBS criteria on bigger population samples. After these relatives are followed up for some time, a more comprehensive study will be able to confirm whether the high prevalence of IBS is due to genetic factors, which would support the possibility that a close relationship exists between IBD and IBS, or to environmental or other factors.

Contributors

Mariam Aguas MD PhD: data collection, statistical analysis and interpretation of data, writing of the paper and approving final version; Vicente Garrigues MD PhD: statistical analysis and interpretation of data, writing of the paper and approving final version; Guillermo Bastida MD: data collection, statistical analysis and interpretation of data, and approving final version; Pilar Nos MD PhD: data collection and approving final version; Vicente Ortíz: statistical analysis and interpretation of data, and approving final version; Alberto Fernandez: data collection and approving final version; Julio Ponce MD PhD: designing and setting up of the study, writing of the paper and approving the final version.

References


