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Post-infectious irritable bowel syndrome after a laboratory-proven enteritis

TEODORA IACOB[1], DOINA F. ȚĂȚULESCU[1], MIHAELA S. LUPȘE[1] and DAN L. DUMITRAȘCU[2]

[1]Department of Infectious Diseases, 'Iuliu Haţieganu' University of Medicine and Pharmacy, 400348 Cluj-Napoca; [2]Second Medical Department, 'Iuliu Haţieganu' University of Medicine and Pharmacy, 400006 Cluj-Napoca, Romania

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Abstract. There are scarce data on risk factors for post-infectious irritable bowel syndrome (PI-IBS). The objective of this study was to determine the risk factors of developing PI-IBS following an acute infectious gastroenteritis (AGE) episode in which, by laboratory tests, the etiological agent was isolated. The study was conducted on patients admitted to a tertiary center of infectious diseases during three consecutive years. The patients were divided into two groups: a group consisting of patients admitted with AGE (with an isolated etiological agent) and a control group consisting of patients admitted for an acute upper respiratory tract infection (URTI). The subjects were recalled in our center 6 months after the admission and were evaluated with Rome III IBS diagnostic questionnaire and Bristol Stool Form Scale. The questionnaires were paper printed and directly filled in by the subjects. The response rate in the case group was 5% and in the control group 100%. The prevalence of PI-IBS was higher in patients with AGE, presenting a relative risk (RR) of 4.16 [95% confidence interval (CI), 1.89-9.17], statistically significant (P<0.001) vs. URTI. From 28 female patients, 22 patients (79%) developed PI-IBS and from 17 male patients, 3 patients (18%) had developed PI-IBS with a risk of 4.4 (95% CI, 1.56-12.65), P<0.001. Regarding the infectious etiology of the AGE, *Campylobacter jejuni* had the highest risk of developing PI-IBS, RR=1.2 (95% CI, 0.13-3.11), P=0.04 compared with the other agents with a lower risk. The risk to develop PI-IBS after AGE infection is 4.16 higher than after URTI. Female sex is a risk factor for PI-IBS, 79% of the female patients developed PI-IBS after AGE. The incidence of PI-IBS is highest in patients with *Campylobacter jejuni* AGE compared with the other agents.

Correspondence to: Dr Dan L. Dumitrașcu, Second Medical Department, 'Iuliu Haţieganu' University of Medicine and Pharmacy, 3-6 Clinicilor Street, 400006 Cluj-Napoca, Romania
E-mail: ddumitrascu@umfcluj.ro

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Introduction

Post-infectious irritable bowel syndrome (PI-IBS) is characterized by the onset of the symptoms mentioned in the diagnostic criteria for irritable bowel syndrome (IBS) (the most recent criteria being those in Rome IV) (1). They occur as a result of an episode of acute infectious gastroenteritis (AGE) characterized by two or more of the following symptoms: diarrhea, vomiting, fever, and a positive result of the etiologic agent in the stool (2). A recent systematic review and meta-analysis have shown that the risk of developing IBS increases six times after a gastrointestinal infection and is maintained at least 2-3 years after infection (3,4). The data in the literature are limited regarding the risk of PI-IBS (5). Among the first studies that raised the suspicion of a link between IBS and intestinal infection was 6 decades ago, the study by Stewart (6). In 1962, Chaudhary and Truelove reported that one third of patients with a history of gastroenteritis continued to develop symptoms of IBS. All these studies have demonstrated an incidence or prevalence of PI-IBS between 5 and 32% (7-21). Unlike sporadic IBS, PI-IBS has a defined onset moment. The risk of PI-IBS appears to correlate with the severity of acute enteric infection (14,16).

Despite the fact that there are no reported sex differences in the severity of the initial infectious disease or in the immune response, the reported risk of developing PI-IBS is higher in women than in men with a relatively adjusted risk between 1.47 and 2.86 (14,16,22-24).

One of the earliest reports of PI-IBS refers to unexplained diarrhea and abdominal discomfort, symptoms that started after an episode of amniotic dysentery (25). Another study conducted in Sheffield examined 75 individuals who reported themselves to an infectious disease unit with the diagnosis of gastroenteritis. It was observed that 25% of them developed IBS when assessed 6 months after infection (26). Various bacterial pathogens such as *Shigella*, *Salmonella*, *Campylobacter* and *Escherichia coli* (14,15,18-20,27,28) were involved in PI-IBS development, but it remains unclear whether all these micro-organisms give an equivalent risk.

The risk of developing *Clostridium difficile* community infection is steadily rising, reaching up to 20-40% of all CDI cases (29). Two current studies have shown that 4-12% of the population may experience PI-IBS symptoms following a *Clostridium difficile* infection. Another retrospective study among military personnel revealed an incidence of PI-IBS of 5-9/100,000, years after CDI (30). The viral etiology seems to provoke a transient form of PI-IBS compared with bacterial etiology (4,13). Prospective studies provide strong evidence that the development of PI-IBS involves an interactive multifactorial etiopathogenic process (31-33). Probiotics have been shown to be effective in preventing or attenuating the symptoms of acute gastroenteritis (34-36). However, no study has yet evaluated the efficacy of interventions that modulate intestinal flora for the prevention or treatment of PI-IBS (4).

The objective of this study was to determine the risk factors of developing PI-IBS following an acute AGE. We assessed the incidence of PI-IBS by sex distribution and regarding the etiology of the infectious gastroenteritis.

Patients and methods

The type of the study was case control. The data collected were retrospective. The variables studied were qualitative and quantitative.

The target population was formed by patients admitted to a tertiary center of infectious diseases, the Clinical Hospital of Infectious Diseases, Cluj-Napoca, Romania in a time interval of three consecutive years (1.01.2013-31.12.2015). The target group was divided into two subgroups.

The case group was composed by patients with an AGE episode in which the etiological agent was isolated by direct examination: microscopy, coproparasitological examination of the stool specimens; bacteriological examinations: coproculture-Hektoen enteric (HE) agar for the isolation of *Shigella* and *Salmonella* from stool specimens, Campy CVA Agar selective medium for the primary isolation of *Campylobacter jejuni* from stool specimens, CIN (Cefsulodin, Irgasan, Novobiocin). Agar selective differential medium for the isolation of *Yersinia enterocolitica* from stool specimens; immunological examinations: rapid *Rotavirus/Adenovirus/Norovirus* test (coloured chromatographic immunoassay for the simultaneous qualitative detection of *Rotavirus, Adenovirus* and *Norovirus* in stool samples), *Giardia lamblia* antigen (coloured chromatographic immunoassay for the qualitative detection of *Giardia* in stool samples), determination of toxins A and B for *Clostridium difficile* (enzyme-linked fluorescent assay in stool samples).

The type of identification of the etiological agent was chosen based on clinical examination and the epidemiological data of the patient. The control group consisted of patients admitted to the same medical service for acute upper respiratory tract infection (URTI).

Inclusion criteria were: patients over the age of 18 with an AGE in which the infectious etiologic agent could be determined or a URTI episode. Exclusion criteria were: patients under the age of 18, gastroenteritis where the infectious etiological agent could not be isolated, HIV-infected patients, patients who died during the course of this study, and patients previously diagnosed with IBS.

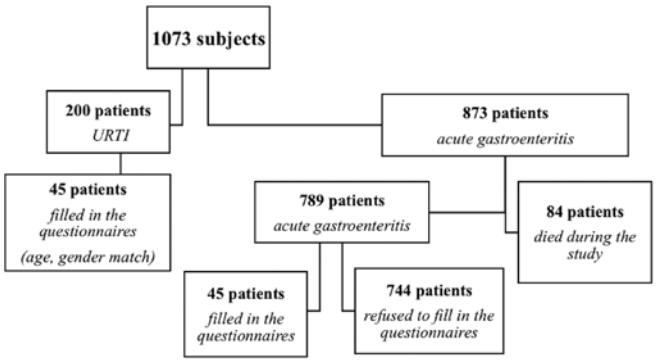

Figure 1. Study population and the response rate. URTI, upper respiratory tract infection.

The patients filled the Rome III questionnaire for IBS (37) and identified the stool consistency with the Bristol Stool Form Scale (38). The questionnaires were filled in 6 months after the acute infectious episode in both groups. The questionnaires were paper printed and directly filled in by the subjects, after being recalled to our center to be evaluated. The average response time was 5 min.

The results were statistically processed with the program SPSS Statistics 24.

All procedures performed in the study involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee (Committee chiar - Felicia Loghin; members: Anca Buzoianu, Ioana Cristolțan, Vasile Fluieraș; jurist - Luminița Gocan; reference no. 132/11.04.2014) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the patients included in the study.

Results

The target population consisted of 1,073 patients, divided into two groups. The case group consisted of 873 patients with an infectious gastroenteritis episode were the etiological agent was isolated. In this group, 84 patients (10%) died during the course of this study. In the case group, 45 patients filled in the questionnaires (5%) they were aged 18-80 years (average, 57.36). The reasons for the refusal to fill in the questionnaires in the case group were: lack of time, they did not want to be part of the study and to disclose medical data, without interest for the field of medical research. The sex distribution was: 17 male patients (38%) and 28 female patients (62%). Of these, 56% were diagnosed with irritable bowel syndrome (25 patients) and 44% were without irritable bowel syndrome (20 patients).

In the control group, out of 200 patients admitted for URTI, 45 patients were selected by age and sex matching; all patients selected filled in the evaluation questionnaires. The response rate in the control group was 100%. The reasons for completing the questionnaires in the control group were because the subjects wanted to take part in the study. Of the 45 patients with URTI, 13% were diagnosed with irritable bowel syndrome (6 patients) and 87% were without irritable bowel syndrome (39 patients) (Fig. 1).

Table I. The incidence of PI-IBS within the study population.

Patients (N=90)	IBS N=31	No IBS N=59	RR for IBS RR (95% CI)	P-value
AGE	25 (56%)	20 (44%)	4.16 (1.89-9.17)	0.00002
URTI	6 (13%)	39 (87%)		

PI-IBS, post-infectious irritable bowel syndrome; AGE, acute infectious gastroenteritis; URTI, upper respiratory tract infection; IBS, irritable bowel syndrome; RR, relative risk.

Table II. The incidence of PI-IBS within the study population by sex distribution.

Patients (N=45) AGE	IBS N=25	No IBS N=20	RR for IBS RR (95% CI)	P-value
Male	3 (18%)	14 (82%)	4.4 (1.56-12.65)	0.0006
Female	22 (79%)	6 (21%)		
Patients (N=45) URTI	**IBS N=6**	**No IBS N=39**	**RR for IBS RR (95% CI)**	**P-value**
Male	2 (13%)	13 (87%)	1 (0.20-4.85)	0.1169
Female	4 (13%)	26 (87%)		

PI-IBS, post-infectious irritable bowel syndrome; AGE, acute infectious gastroenteritis; URTI, upper respiratory tract infection; IBS, irritable bowel syndrome; RR, relative risk.

Table III. PI-IBS subtype distribution in the case group.

AGE PI-IBS subtype	N=25
IBS-D	8 (32%)
IBS-C	5 (20%)
IBS-M	10 (40%)
IBS-U	2 (8%)

PI-IBS, post-infectious irritable bowel syndrome; AGE, acute infectious gastroenteritis; IBS-D, diarrhea predominance subtype of irritable bowel syndrome; IBS-C, constipation predominance subtype of irritable bowel syndrome; IBS-M, mixed subtype of irritable bowel syndrome; IBS-U, unsubtyped irritable bowel syndrome.

Table IV. PI-IBS distribution in the case group according to the etiology of the AGE.

Etiological agent	PI-IBS N=25	No PI-IBS N=20
Clostridium difficile	17 (52%)	16 (48%)
Salmonella spp.	5 (62%)	3 (38%)
Campylobacter jejuni	2 (67%)	1 (33%)
Rotavirus	1 (100%)	0

PI-IBS, post-infectious irritable bowel syndrome.

After statistical analysis, we observed that patients who had an AGE were at a higher risk of developing PI-IBS at a relative risk (RR) of 4.16 (95% CI, 1.89-9.17). By comparing the two subgroups, statistically significant data were obtained that are in favor of the alternative hypothesis (P=0.00002, P<0.05), so the case group showed an increased incidence of PI-IBS compared with the control group (Table I).

In the group of patients with AGE, after processing the results, an increased incidence of PI-IBS was noted among female patients compared with males, with 79% of women (22 patients) developing PI-IBS and 18% men (3 patients) developing PI-IBS. The alternative hypothesis is valid, statistically significant (P=0.0006, P<0.05), with RR=4.4 (95% CI, 1.56-12.65). In the group with URTI, sex distribution of PI-IBS showed an RR=1 (95% CI, 0.20-4.85) for female patients, with P=0.11, P>0.05, not statistically significant. There was no higher incidence of PI-IBS in female patients in the URTI group. By correlating the data from the case group and the control group, intestinal infection is shown as a risk factor in increasing the incidence of PI-IBS in female patients in the studied population (Table II).

From the point of view of the subtypes of PI-IBS, a distribution in favor of the mixed subtype was observed (Table III).

Regarding the infectious etiology of the AGE, in the case group, there were 17 patients with *Clostridium difficile* (52%), 5 patients with *Salmonella spp.* (62%), 2 patients

Table V. PI-IBS subtype distribution depending on the infectious etiology.

PI-IBS subtype	*Clostridium difficile* N=17	*Salmonella spp.* N=5	*Campylobacter jejuni* N=2	*Rotavirus* N=1
IBS-D	6 (35%)	1 (20%)	1 (50%)	0
IBS-C	3 (18%)	2 (40%)	0	0
IBS-M	7 (41%)	2 (40%)	1 (50%)	0
IBS-U	1 (6%)	0	0	1 (100%)

PI-IBS, post-infectious irritable bowel syndrome; IBS-D, diarrhea predominance subtype of irritable bowel syndrome; IBS-C, constipation predominance subtype of irritable bowel syndrome; IBS-M, mixed subtype of irritable bowel syndrome; IBS-U, unsubtyped irritable bowel syndrome.

with *Campylobacter jejuni* (67%) and a patient with *Rotavirus (*100%) who developed PI-IBS (Table IV).

Analyzing the statistical significance test for each of the coefficients of the logistic regression model, it was observed that both *Rotavirus* (B=20.692, P=0.00001, P<0.05) and *Campylobacter jejuni* (B=0.182, P=0.04) are good predictors of the appearance of PI-IBS. The risk of IBS depending on the bacteria is RR=0.6 for *Clostridium difficile* infection (CDI) and 1.2 times higher for *Campylobacter jejuni* infection than for *Salmonella spp.* to which these values were reported.

Distribution of IBS subtypes depending on the infectious etiology of the AGE revealed that in patients with *Salmonella spp.* infection the incidence of IBS subtypes with constipation predominance (IBS-C) and mixed (IBS-M) were increased. Patients with CDI showed diarrhea predominance subtype (IBS-D) and mixed subtype similar to patients with *Campylobacter jejuni* infection. The patient with *Rotavirus* infection presented the subtype 'unsubtyped' (IBS-U). (Table V).

Discussion

Our study looked for risk factors for developing PI-IBS following AGE. The etiological agent of AGE was isolated by direct examination (microscopy, coproparasitological examination), bacteriological examinations (coproculture) and immunological examinations (rapid *Rotavirus/Adenovirus/Norovirus/Astrovirus* test, *Giardia lamblia* antigen, determination of toxins A and B for *Clostridium difficile*). The type of identification of the etiological agent was chosen based on clinical examination and the epidemiological data of the patient.

In this study we observed that PI-IBS occurs with an RR of 4.16 (95% CI, 1.89-9.17) compared with controls. The prognostic factors are female sex, the etiological agent involved in the AGE correlate with the duration of the probiotic therapy after AGE.

The limitations of our study were the fact that not all the patients filled in the questionnaires: 84 patients (10%) died during the course of this study. In the case group, 45 patients filled in the questionnaires (5%) and 744 patients (85%) refused to fill in the questionnaires. The reasons for the refusal to fill in the questionnaires in the case group were: lack of time, they did not want to be part of the study and to disclose medical data, without interest for the field of medical research. Another limitation was the fact that the evaluation was performed at 6 months after the AGE, but there was no follow-up after this.

Regarding sex distribution, until now there are 21 studies published showing an increased incidence of PI-IBS in female patients. In a 2017 meta-analysis performed by Klem *et al* (39) based on data from 11 studies with extractable data, it was revealed that female sex was associated with a 2.2 times increase in PI-IBS (OR, 2.19; 95%, CI, 1.57-3.07). Summarizing the estimate, a substantial heterogeneity (I2=72%) was noted. On the other hand, a study led by Litleskare *et al* (40) in Norway in 2018 on the prevalence of PI-IBS after intestinal infection with *Giardia lamblia* showed that female sex is also known as a risk factor in sporadic PI-IBS.

The data in our study reveals that in the case group, female sex had 4.4 higher risk of developing PI-IBS compare to the control group.

Based on a meta-analysis of 45 studies, in 2017 Klem *et al* (39) reported that approximately one in 9 people (95% CI, 7-13) exposed to different forms of infectious enteritis can develop IBS at a rate 4 times higher than persons who are not exposed. The risk rate of developing PI-IBS among patients in our study with an exposure to infectious gastroenteritis was 4.16 times higher than the patients non-exposed (95% CI, 1.89-9.17).

Infectious etiology of gastroenteritis and the prevalence of PI IBS, in a study from Nottingham in 1996, limited only to gastroenteritis with *Campylobacter*, confirmed that 9% of the 189 infected individuals developed PI-IBS (22). However, in our subgroup of patients with *C. jejuni* infection, the percentage was higher, 67%, respectively, 2 patients in 3 had PI-IBS. Mearin *et al* (41) prospectively evaluated the evolution of dyspepsia and IBS in a cohort of adult patients affected by a *Salmonella* enteritidis epidemic one year after the acute gastroenteritis episode and observed that intestinal salmonellosis is a significant risk factor not only for IBS but also for dyspepsia; so 1 out of 7, and 1 out of 10, subjects developed dyspepsia, respectively, IBS. In our case, 3 out of 8 patients were diagnosed with IBS after intestinal *Salmonella* infection. The risk rate to develop PI-IBS following an enteritis with *C. difficile* was 52% in our study. Wadhwa *et al* (42) observed in a transversal study in which patients were contacted and evaluated by sampling (by methods similar to those used in our study) demonstrated that 25% of patients with *C. difficile*

infection without previous irritable bowel syndrome developed PI-IBS; this incidence being higher than the mean incidence of patients with PI-IBS due to infection with other pathogens. Gastroenteritis due to viral etiology is mostly associated with acute episodes of diarrhea and with low risk of residual digestive symptoms. This may be associated with a lower incidence of PI-IBS compared with infection due to bacterial pathogens. In a viral gastroenteritis outbreak, approximately a quarter of the patients reported symptoms of PI-IBS 3 months after the outbreak (13). The results obtained in our study showed that the only patient diagnosed with gastroenteritis with *Rotavirus* developed the 'unsubtype-able' form of PI-IBS. They is also an argument for the prevention of enteral infection from the hospital admission, thus avoiding subsequent development of long-term medical conditions such as PI-IBS (43).

In conclusion, the risk of developing PI-IBS after AGE infection is 4.16 higher than after URTI. The female sex is a risk factor for PI-IBS, 79% of the female patients developed PI-IBS after AGE. The incidence of PI-IBS is highest in patients with *Campylobacter jejuni* AGE compared with the other agents.

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Availability of data and materials

The data that support the findings of this study are available from the Hospital of Infectious Diseases (Cluj-Napoca, Romania); however, restrictions apply to the availability of these data, which were used under license for the current study, and are not publicly available. Data are however available from the authors upon reasonable request and with the permission of the Hospital of Infectious Diseases.

Authors' contributions

TI wrote the manuscript, provided the data for Fig. 1 and Tables I-V, conducted the patient interviews and performed all statistical analyses. DLD conceived the study, participated in the design and coordination of the study, and assisted with the drafting of the manuscript. MSL and DFT participated in the design of the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in the study involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee (Committee chiar - Felicia Loghin; members: Anca Buzoianu, Ioana Cristolțan, Vasile Fluieraș; jurist - Luminița Gocan; reference no. 132/11.04.2014) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the patients included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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