Irritable bowel syndrome after *Clostridioides difficile* infection

Teodora Iacob (teodora.iacob@yahoo.com)
Spitalul Clinic de Boli Infectioase Cluj-Napoca https://orcid.org/0000-0001-7159-983X
Mihaela Sorina Lupșe
Spitalul Clinic de Boli Infectioase Cluj-Napoca
Dan Lucian Dumitrașcu
Universitatea de Medicina si Farmacie Iuliu Hatieganu

Research article

Keywords: post-infectious irritable bowel syndrome, Clostridioides difficile infection, polymerase chain reaction

Posted Date: April 24th, 2020

DOI: https://doi.org/10.21203/rs.2.13407/v2

Abstract

Background Post-Infectious Irritable Bowel Syndrome (PI-IBS) is a common complication of *Clostridioides difficile* infection (CDI).

The objectives of this study were to asses the risk of PI-IBS following a CDI. We also evaluated if there is a correlation between the onset of PI-IBS and the severity of CDI.

Methods The study group consisted of 69 patients consecutively admitted in a tertiary center with an acute gastroenteritis episode, suspected of having a *Clostridioides difficile* infection. PCR for CDI from feces were performed to assess the infection. The subjects were divided into two groups. A group consisted of patients with CDI and the other group where the CDI was ruled out. The patients were evaluated for PI-IBS 6 months after the episode of CDI by Rome III IBS diagnostic questionnaire and the Bristol Stool Form Scale. In these patients CDI recurrence was ruled out by PCR; patients were retested. Severity of CDI was stratified according to the need for hospitalization or not. Other evaluated parameters for severity at patients were the level of serum creatinin, C-reactive protein (CRP) and white blood cell count (WBC). The questionnaires were paper printed and directly filled in by the subjects.

Results The response rate to the questionnaire was 100%. During the course of this study 31 patients died. Out of 38 patients, 37% (14 patients) were diagnosed with CDI. After CDI, 57% (8 patients) developed PI-IBS and 43% (6 patients) where without PI-IBS with a relative risk (RR) of 2.29 (95 % confidence interval CI 0.99 – 5.23), p=0.04. In the group of patients with a severe form of CDI, 90% (9 patients) developed PI-IBS with a RR of 2.72 (95% CI 0.80 – 9.24), p=0.04, compared to the group of patients with light and moderate forms CDI.

Conclusion Our study shows that, 6 months after CDI, PI-IBS develops in 57% patients, higher than in the control group where CDI was ruled out by PCR (43%), statitstically significant (p=0.04). The severity of CDI was a risk factor for PI-IBS, 90% of patients with severe forms of CDI developed PI-IBS.

Background

Irritable bowel syndrome (IBS) is a combination of chronic and recurrent symptoms such as constipation, diarrhea, bloating and/or abdominal pain, which do not appear to have a base of biochemical or structural anomalies detectable by conventional laboratory methods. IBS affects approximately 9-13% of the general population at any time [1].

IBS is defined by recurrent abdominal pain, on average at least one day per week over the last 3 months; abdominal pain episodes must be associated with two or more of the following: to be related to defecation, the intestinal transit frequency to be modified, a change in the consistency of the seat to occur. Symptoms must have started at least 6 months before in accordance with the Rome IV diagnostic criteria [2].

Post-Infectious Irritable Bowel Syndrome (PI-IBS) is characterized by the occurrence of the symptoms mentioned in the diagnostic criteria for IBS (the most recent criteria being those in Rome IV) [3]. They occur as a result of an episode of acute infectious gastroenteritis characterized by two or more of the following symptoms: diarrhea, vomiting, fever, and a positive result of the etiologic agent in the stool [4].

The incidence of *Clostridioides difficile* infection (CDI), formerly known as *Clostridium difficile* and often called *C. difficile* or *C. diff*, has increased over the last decade and has become an important cause of mortality, morbidity and a challenge to the current medical system [5, 6, 9].

A quarter of patients report symptoms consistent with IBS ≥6 months following their CDI episode. The results are significant considering the progressively increasing burden of CDI. This makes it important to consider the possibility of PI-IBS when patients with a history of CDI present with ongoing gastrointestinal symptoms. This patients may be retreated for CDI inappropriately. Additionally, longer duration of CDI symptoms is also moderately associated. Considering the significant incidence of CDI PI-IBS, retreatment for recurrence should only be offered after laboratory confirmation of the diagnosis [7, 8, 14]. There are studies in the literature that investigate the risk of PI-IBS and CDI, but available data is scarce [10].

The objectives of this study were to asses the risk of PI-IBS following a CDI. We also evaluated if there is a correlation between the onset of PI-IBS and the severity of CDI.

Methods

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

The target population consisted of 69 patients admitted to a tertiary center, the Clinical Hospital of Infectious Diseases, Cluj-Napoca. The patients were admitted with an episode of acute gastroenteritis, suspected of having CDI based on the clinical manifestations (watery diarrhea, sometimes bloody or with mucus), fever, abdominal pain, nausea) in association with the epidemiological history (previous hospital admissions, recent antibiotic therapy, proton pump inhibitor treatment or chemotherapy). The study was conducted from 1.01.2016 to 31.06.2018.

The inclusion criteria were patients over 18 years of age with suspicion of CDI, as mentioned above, in which PCR for *Clostridioides difficile* was performed. Exclusion criteria were patients under 18 years of age, patients without CDI suspicion, HIV infected patients, patients who died during the course of this study. Severity of CDI was stratified according to the need for hospitalization or not. Other evaluated parameters for severity at patients were the level of serum creatinin, C-reactive protein (CRP) and white blood cell count (WBC).

The patients were evaluated for irritable bowel syndrome (IBS) 6 months after the episode of CDI with Rome III IBS diagnostic questionnaire (15) and Bristol Stool Form Scale (16). In these patients CDI

recurrence was ruled out by PCR. The patients were retested.

The questionnaires were paper printed and directly filled in by the subjects. The average response time was 5 minutes.

The study was approved by the local ethic committee.

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

Results

Patients were aged between 20 and 92 years (mean 60.72). During the course of this study 31 patients out of a total of 69 patients died (Figure 1). The patients who died during the course of this study were with age >60 years and had multiple comorbidities: cardiac, neurological and/or malignant.

Of the 38 patients, 76% were living in urban area (28 patients) and 24% (10 patients) in rural area. Distribution by gender was female 37% (14 patients) and male 63% (24 patients).

The infection with *Clostridioides difficile* was confirmed in 14 patients by PCR and the infection was ruled out in 24 patients (control group).

All 38 patients in the studied population completed the above mentioned questionnaires.

Regarding severity, all patients admitted had fever, presented high WBC (>11 000/μL) , increased level of CRP (>4mg/dl) and increased level of serum creatinine (>1.8mg/dl).

In the CDI group 57% (8 patients) developed PI-IBS after six months, while 43% (6 patients) did not develop PI-IBS. In the control group 25% developed PI-IBS (6 patients) and 75% (18 patients) did not develop PI-IBS. After CDI, patients had a higher risk of developing PI-IBS compared to the group where CDI was ruled out, with a RR=2.29 (95% CI 0.99 – 5.23), data statistically significant, p=0.04 (Table 1).

Table 1 PI-IBS incidence and CDI

Patients (N=38)	PI-IBS N=14	No PI-IBS N=24	RR for PI-IBS *RR (95% CI)*	p value
CDI (PCR+), n(%)	8 (57%)	6 (43%)	2.29 (0.99 – 5.23)	0.0475

Regarding IBS subtypes, after CDI 62% (5 patients) developed IBS-D, 13% (1 patient) developed IBS-C and 25% (3 patients) developed IBS-M. In the group of patients where CDI was rulled out 17% (1 patient)

developed IBS-D, 50% (3 patients) developed IBS-C and 33% (2 patients) developed IBS-M.

From the point of view of the severity of the diseases based on hospitalizations, 53% of patients were not hospitalized (20 patients) and 47% were hospitalized (18 patients) when recruited for the study. In the group of patients with CDI who required hospitalization 90% (9 patients) developed PI-IBS and 10% (1 patient) did not develop PI-IBS, with a RR of 2.72 (95% CI 0.80 – 9.24) compared to the group of patients who did not require hospitalization for CDI. In the group of patients without CDI, those hospitalized had a RR of 3.5 (0.37 – 32.80) of developing PI-IBS, the results were not statistically significant (p = 0.2909) (Table 2).

Table 2 The correlation between PI-IBS and the severity of CDI

Patients (N=38)	*CDI (PCR+)*	*CDI (PCR+)*	**RR for PI-IBS**	**p value**
	PI-IBS	**No PI-IBS**	*RR (95% CI)*	
	N=11	**N=5**		
Hospitalized, n (%)	9 (90%)	1 (10%)	2.72 (0.80 – 9.24)	0.0493
Not hospitalized, n(%)	2 (33%)	4 (67%)		
	No CDI (PCR-)	*No CDI (PCR-)*	**RR for PI-IBS**	**p value**
	PI-IBS	**No PI-IBS**	*RR (95% CI)*	
	N=3	**N=19**		
Hospitalized, n (%)	2 (25%)	6 (75%)	3.5 (0.37 – 32.80)	0.2909
Not hospitalized, n(%)	1 (7%)	13 (93%)		

Discussions

The objective of this study was to establish the incidence of PI-IBS after CDI and to find out if there is a correlation between the onset of IBS and the severity of CDI.

In our study, after statistical analysis of the results, we observed that patients who had CDI, evidenced by PCR detection, were at a higher risk of developing PI-IBS. Patients with CDI and previous hospitalizations had a higher risk of developing PI-IBS compared to patients who were not previous hospitalized.

Our study has limitations: not all patients in the selected group filled in the questionnaires, 31 patients out of a total of 69 patients died during the course of this study. The patients who died during the course of this study were with age >60 years and had multiple comorbidities: cardiac, neurological, malignant. Being an under-funded medical center, another limitation of this study was that the number of enrolled patients with CDI was low.

The characteristics of the infectious illness such as diarrhea, abdominal cramps, increased stool frequency, bloody or mucous stools, and positive stool culture and weight loss are potent predictors of long term outcome. The risk of PI-IBS appears to correlate with the severity of the acute enteric infection [12, 13]. The above mentioned symptoms are frequently associated with CDI.

Wadhwa et al [14] showed that 25% of patients with CDI (diagnosed by PCR) without prior IBS develop PI-IBS at least 6 months after CDI which is higher than the mean incidence of PI-IBS in patients due to infection with other pathogens. Results from our study have shown that 57% of CDI patients (8 patients) diagnosed by PCR without a history of IBS have developed PI-IBS.

In another study, Gutiérrez et al [11] carried out a retrospective study on patients who presented CDI The patients were both community-based and hospitalized. The conclusion for both categories of patients was that the incidence of IBS in patients with CDI was greater than in patients who did not have CDI. In our study we observed a higher prevalence of PI-IBS in patients with severe forms if CDI and hospitalized previously compared the patients with light and moderate forms of CDI who were not hospitalized previously. Thus, CDI is considered to be one of the major risk factors for PI-IBS patients RR=6.1 (95% CI 2.9-12.9). Our data are consistent with this study.

Conclusion

Our study shows that, 6 months after CDI, PI-IBS develops in 57% patients, higher than in the control group where CDI was ruled out by PCR (43%), statitstically significant (p=0.04). The severity of CDI was a risk factor for PI-IBS, 90% of patients with severe forms of CDI developed PI-IBS.

Declarations

Ethics approval and consent to participate

All procedures performed in studies 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 number 132/11.04.2014) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The data that support the findings of this study are available from Hospital of Infectious Diseases Cluj-Napoca, Romania but restrictions apply to the availability of these data, which were used under license

for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Hospital of Infectious Diseases Cluj-Napoca, Romania.

Competing interests

The authors declare that they have no competing interests

Authors' Contributions

TI wrote the manuscript and provided data for Figure 1, Table 1, Table 2, conducted the patient interviews and conducted all statistical analyses.

DLD conceived of the study, and participated in its design and coordination and helped to draft the manuscript. MSL participated in the design of the study.

All authors read and approved the final manuscript.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Figures

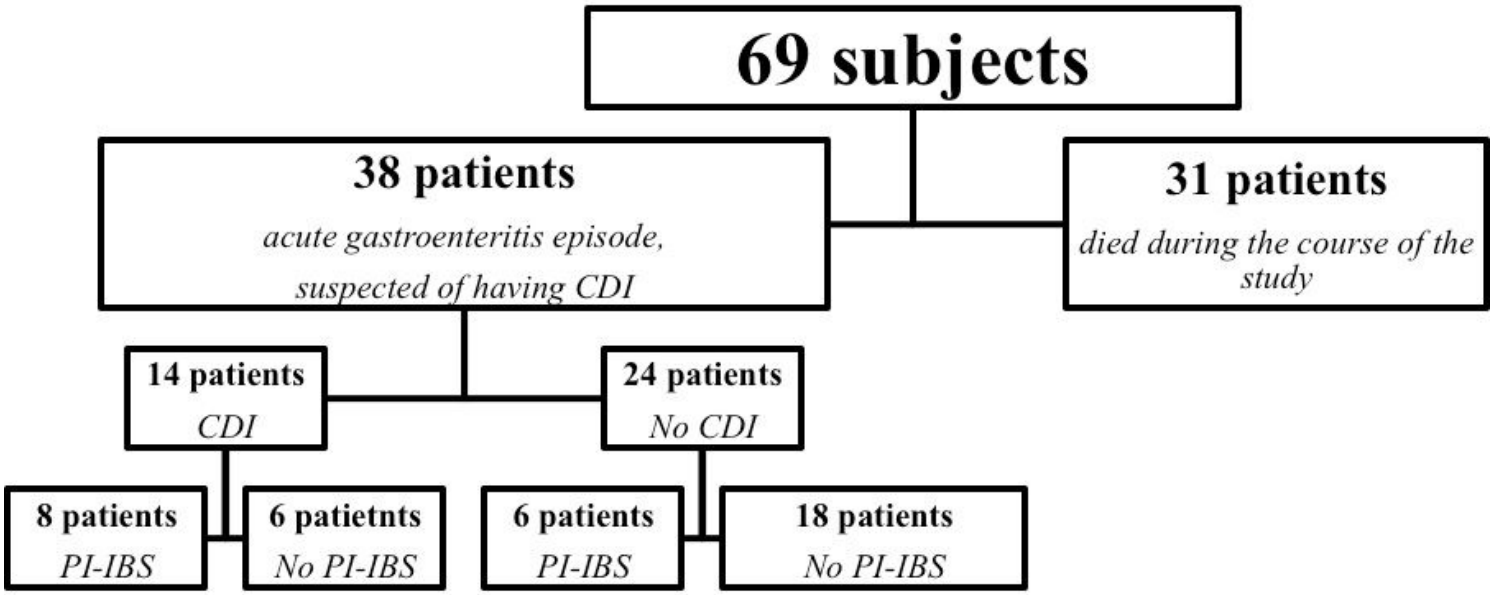

Figure 1

Clostridioides difficile infection and the PI-IBS incidence within the study population