

Irritable bowel syndrome after *Clostridium difficile* infection

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Research article

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Abstract

Background and Aim

Post-Infectious Irritable Bowel Syndrome (PI-IBS) is a common complication of Clostridium difficile infection (CDI). The objectives of this study were to assess 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 Clostridium 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. Severity of CDI was stratified according to the need for hospitalization or not. 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) were 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%), statistically 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.

Introduction

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 stool 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 *Clostridium difficile* infection (CDI) 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 assess 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.

Materials 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 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 in which PCR for *Clostridium 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.

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

[Insert Fig. 1 Here]

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

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).

[Insert Table 1 Here]

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 ruled 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).

[Insert Table 2 Here]

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 previously 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.

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 of CDI and hospitalized previously compared to 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%), statistically 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 chair - 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

References

1. Gwee KA. Irritable bowel syndrome in developing countries—a disorder of civilization or colonization? *Neurogastroenterol Motil* 2005;1: 317–324.
2. Drossman DA, Chang L, Chey WD, Kellow J, Tack J, Whitehead WE. Rome IV Multidimensional Clinical Profile for Functional Gastrointestinal Disorders: MDCP (Second Edition), Rome Foundation, 2016.
3. Drossman DA, Hasler WL. Rome IV-Functional GI disorders. *Gastroenterology* 2016, 150, 1257–1261
4. Ericsson CD, Hatz C, DuPont AW. Postinfectious Irritable Bowel Syndrome. *Clin Infect Dis.*2008;46(4):594–599.
5. Dubberke ER, Olsen MA. Burden of *Clostridium difficile* on the healthcare system. *Clin Infect Dis.* 2012; 55 Suppl 2():S88–92.
6. Lessa FC, Winston LG, McDonald LC. Burden of *Clostridium difficile* infection in the United States. Emerging Infections Program C. *difficile* Surveillance Team. *N Engl J Med.* 2015 Jun 11;372(24):2369–70.
7. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology.* 2009;136:1979–1988.
8. Grover M. Role of gut pathogens in development of irritable bowel syndrome. *Indian J Med Res.* 2014;139:11–18
9. Gupta A, Khanna S. Community-acquired *Clostridium difficile* infection: an increasing public health threat. *Infect Drug Resist.* 2014;7:63–72.
10. Sethi S, Garey KW, Arora V, Ghantaji S, Rowan P, Smolensky M, et al. Increased rate of irritable bowel syndrome and functional gastrointestinal disorders after *Clostridium difficile* infection. *Hosp Infect.* 2011;77(2):172–3.

11. Gutiérrez RL, Riddle MS, Porter CK. Increased risk of functional gastrointestinal sequelae after *Clostridium difficile* infection among active duty United States military personnel (1998–2010). *Gastroenterology*. 2015;149(6):1408–14.
12. Iacob T, Țățulescu DF, Dumitrașcu DL. Therapy of the postinfectious irritable bowel syndrome: an update. *Clujul Med*. 2017; 90(2): 133–138.
13. Iacob T, Țățulescu DF, Cijevschi Prelipcean C, Dumitrașcu DL. Pathogenic Factors in Postinfectious Irritable Bowel Syndrome - An Update. *Rev Med Chir Soc Med Nat Iasi*. 2016; 120(3): 515–21.
14. Wadhwa A, AlNahas MF, Dierkhising R, Patel R, Kashyap P, Pardi D, et al. High risk of post-infectious irritable bowel syndrome in patients with *Clostridium difficile* infection. *Aliment Pharmacol Ther*. 2016;44(6): 576–582.
15. Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. *J Gastrointestin Liver Dis*. 2006;15(3):237–41
16. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32(9):920–4

Tables

Due to technical limitations, Tables 1 & 2 are only available to download from the Supplementary Files section.

Figures

Fig. 1 *Clostridium difficile* infection and the PI-IBS incidence within the study population

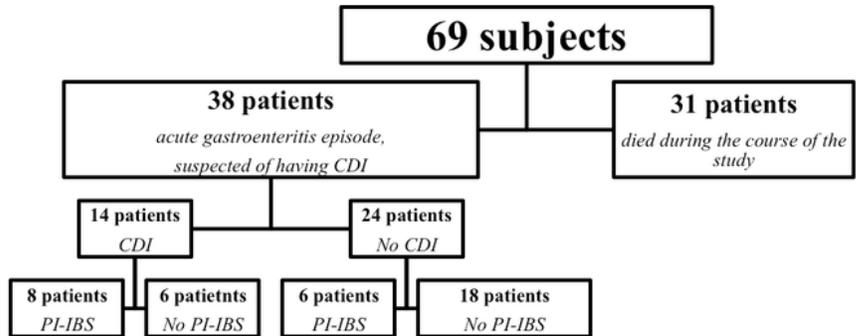


Figure 1

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

Supplementary Files

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