The association between inflammatory bowel diseases and Helicobacter pylori infection: a case-control Romanian study

Camelia R. Prunduș, Lidia Ciobanu, Sorana D. Bolboacă, Marcel Tanțău, Daniela Matei, Carmen Cruciat, Cristina Pojoga, Vasile Andreica

Abstract. Aim: The main objective of this study was to investigate the association between inflammatory bowel disease (IBD) and Helicobacter pylori (Hp) infection, on a Romanian population. A secondary analysis studied the association of previous Hp eradication therapy and the onset of IBD. Methods: A case-control study was conducted with a 1:2 design (age- and gender-matched controls). The study was conducted in an outpatient department in a single center. The participants answered the same questionnaire about previous history of IBD and Hp infectious status, and blood samples were obtained to determine Hp serology. Results: The study included 145 patients known with IBD (73.8% had ulcerative colitis (UC), 26.2% had Crohn’s disease (CD)) and 290 age and sex match controls. Hp was positive in 22.4% of IBD patients and 34.2% of controls. The presence of Hp proved a protective factor for IBD as compared to the controls: OR= 0.440 (95%CI: 0.285 to 0.680, p<0.001). The rate of previous Hp eradication therapy in patients with IBD was lower and statistically different from that observed in the control group (5.5% (95%CI: 1.8 to 9.2) and 19% (95%CI: 14.5 to 23.5), respectively, p<0.001). Conclusions: We observed a negative association between Hp infection and IBD. Further prospective studies about the relation between Hp infection and IBD have to take in consideration more variables.

Key Words: Helicobacter pylori, inflammatory bowel disease, ulcerative colitis, Crohn’s disease.

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Corresponding Author: Camelia R. Prunduș, email: raluca_postei@yahoo.com

Introduction

Inflammatory bowel disease (IBD) is an inflammatory, chronic, relapsing diseases of the gastrointestinal tract. Crohn’s disease (CD) and ulcerative colitis (UC) represents the principal types of IBD (Danese et al 2006). According to the most assumptions, environmental factors can trigger IBD at humans with genetic susceptibility by altering the intestinal mucosal barrier and influencing the gut microbiota. The result is an aberrant immune response of the gut (de Souza 2017). Helicobacter pylori (Hp) are spiral or curve Gram-negative bacteria, divided into entero-hepatic Helicobacters and gastric Helicobacters, depending on the part of the gastrointestinal tract colonized (Sonnenberg 2013). Helicobacter bacteria are found in gastric mucosal microbiota and also can influence other intestinal bacterial communities (Schulz et al 2018). Infection with Hp is involved in chronic gastritis (Valle et al 1996), peptic ulcers (Asaka et al 2010), gastric cancer (Uemura et al 2001), gastric mucosa-associated lymphoid tissue (MALT) lymphoma (Nakamura et al 2012). Hp has also been proved to be involved in causing iron-deficiency anemia (Qu et al 2010), idiopathic thrombocytopenic purpura (Suzuki et al 2005) and vitamin B12 deficiency (Malferttheiner et al 2017).

Some studies have evaluated the relationship between Hp and IBD (Thomson et al 2011, Laharie et al 2009). Numerous observational studies and a meta-analysis demonstrated a negative association between Hp infection and IBD (Rokkas et al 2015). Changes in gut microbiota and immune response may be involved in the development of IBD after antibiotic therapy for Hp infection (Rosania et al 2018). The main objective of this study was to investigate the association between inflammatory bowel disease (IBD) and Hp infection, on a Romanian population. A secondary analysis studied the association of previous Hp eradication therapy and the onset of IBD.

Materials and method

The study was approved by the Ethics Committee of Regional Institute of Gastroenterology and Hepatology “Prof. Dr. Octavian Fodor” Cluj-Napoca (IRGH), Romania. All patients included in the study signed a written informed consent. A prospective case-control (1:2) experimental design was used to evaluate the association between Hp infection and IBD on a Romanian population. The target population was represented by subjects with IBD (cases) monitored at the outpatient Department of Regional Institute of Gastroenterology and Hepatology “Prof. Dr. Octavian Fodor” Cluj-Napoca, Romania; 2 Regional Institute of Gastroenterology and Hepatology “Prof. Dr. Octavian Fodor” Cluj-Napoca, Romania; 3 Department of Medical Informatics and Biostatistics, “Iuliu Hatieganu” University of Medicine and Pharmacy Cluj-Napoca, Romania.
Hepatology “Prof. Dr. Octavian Fodor” Cluj-Napoca, Romania from January 2016 to July 2016. Patients with confirmed IBD receiving or not a biological therapy (i.e. Infliximab, Adalimumab) were eligible for the study. Controls were recruited from patients addressed to the same department for investigations, without any dyspeptic symptoms. The controls were gender and age-matched (± 5 years) to the cases. The participants received the same questionnaire, containing dates regarding demographics, medical history and previous therapy for Hp infection. The controls with previous Hp eradication therapy were asked about the symptoms they had, the type of test used for diagnosis of infection and the regimen used for eradication therapy.

In addition, patients with IBD disease were asked about the onset of the disease. IBD activity was evaluated by the Mayo Clinic score and the Harvey-Bradshaw Severity Index for patients with UC and CD, respectively (Peyrin-Biroulet et al 2016). Blood samples for routine laboratory tests and Hp serology were obtained for all patients included in the study. The exclusion criteria for controls was receiving Hp eradication therapy less than 12 months before enrollment, because cases published in the literature described new-onset IBD diagnosed 6-12 months after eradication therapy (Jovanovic et al 2001, Tursi 2006, Chiba et al 2016, Rosania et al 2018). The participants who were seropositive for Hp infection and/or proved previous Hp infection were considered Hp positive.

Quantitative data are expressed as mean and standard deviation (SD) since data passed the Kolmogorov-Smirnov test for normality. Qualitative (nominal) data were summarized as a percentage and associated 95% confidence interval (CI) calculated with an exact method (Jäntschi L et al 2010). Student t test for independent samples was used to compare the age of patients in case group with those in control group. Z-test for proportions was used to test the significance of frequencies in the same group and in different groups. The association in the 2 by 2 contingency table was tested with Chi-square ($\chi^2$) tests. Statistical analysis was performed using Statistica (v. 8, StatSoft, Tulsa, USA). Graphical representations were done with Microsoft Excel. A p-value < 0.05 regardless the used statistical test was considered statistically significant. The association between IBD onset and Hp infection was estimated using odds ratios (OR) with corresponding 95% confidence intervals (CIs) (https://www.openepi.com/TwobyTwo/TwobyTwo.htm).

Results

Four hundred and thirty-five subjects were included in the study, one hundred and forty-five with IBD. The age of patients varied from 18 years old to 85 years. The mean age of cases (44.8 (16.1)) was not statistically significant compared to the mean age of controls (45.1 (15.7)) (p = 0.8). In case group 36.6% (95%CI: 28.8 to 44.4) from subjects were from rural area, while in the control group 34.5% (95%CI: 29.1 to 39.9) were from rural area, without significant differences between groups (p=0.6). Both case and control groups contained 48.3% (95%CI: 40.2 to 56.4 in case group and 95%CI: 42.6 to 54.1 in control group) women and 51.7% (95%CI: 43.6 to 59.8 in case group and 95%CI: 54.2 to 65.4 in control group) males.

The age of onset of IBD varied from 16 to 80 years, with a mean of 38 years (SD=15.1). The ulcerative colitis (UC) was observed on 107 (73.8%) (95%CI: 66.6 to 80.9) while Crohn disease (CD) was observed on 38 (26.2%) of investigated cases (95%CI: 19.1 to 33.4), with significantly higher frequency of UC compared to CD (Z test for proportion = -12.9, p<0.001). Majority of subject regardless the IBD type were in remission (Figure 1), but the frequency of remission in CD was significantly higher than the frequency of remission in UC (Z-statistic = -3.86, p< 0.001).

Majority of patients in the case group received non-biological therapy (74.5%, 95%CI: 67.4 to 81.6; Z-statistic =-14.0, p<0.001). A higher percentage of patients with CD received biological therapy compared to those with UC, but the difference was not statistically significant (Figure 2).

Thirty-eight of the patients with IBD (30(28%) with UC and 8(21%) with CD) and one hundred and twenty-nine subjects from control group had a positive Hp result, with a significantly smaller frequency among those with IBD (Figure 3).

The presence of Hp proved a protective factor for IBD as compared to the controls: OR= 0.440 (95%CI: 0.285 to 0.680, $\chi^2=14.0$, p< 0.001). The rate of previous Hp eradication therapy in patients with IBD was lower and statistically different from that observed in the control group (5.5% (95%CI: 1.8 to 9.2) and 19% (95%CI: 14.5 to 23.5), respectively, P<0.001). Eight patients in the IBD group (6 with UC and 2 with CD) (5.5%, 95%CI: 1.8 to 9.2) received Hp eradication therapy before onset of the disease. Indications for Hp testing and eradication therapy before IBD onset was dyspeptic symptoms in all 8 patients. Hp was diagnosed by urease
It’s well known that Hp causes chronic gastritis (Valle et al 1996) and that the bacteria induce at the level of gastric mucosa an inflammatory response that is due to the fact that the bacteria stimulate the host’s immune system. It leads to a T helper type 1 (TH1) response and high levels of Th1 cytokines (Smythies et al 2000). The systemic release of cytokines may downregulate systemic immune responses and even suppress autoimmunity and this may link Hp infection with autoimmune disorders (van Amsterdam et al 2006, Ram et al 2013). Th1 immune responses is dominant in CD and Th2 or Th1/Th2 immune responses may be more frequently seen in UC (MacDonald et al 1994, Parronchi et al 1997, Fuss et al 1996). Those facts lead to the conclusion that the fact that Hp is present in the stomach of a human may influence the host’s immune responses. It can induce modifications in immune response that may be protective or may predispose the host to IBD (Papamichael et al 2014). In one study this inverse association between Hp infection and IBD was observed in CagA positive strain only on CD (Lord et al 2017). A limitation of our study was the lack of serum depiction of the CagA antigen of Hp.

In order to explain the low prevalence of Hp infection in IBD patients, the idea that treatments used for IBD may be responsible for Hp eradication, has been raised (el Omar et al 1994). Other studies showed that treatment with sulfasalazine or other 5-aminosalicylic acid (5 ASA), steroids, thiopurines (Guslandi et al 2002, Song et al 2009) and even newer therapeutics such as anti-tumor necrosis factor (TNF) treatment have no impact on Hp status in IBD patients (Triantafillidis et al 2014). Another hypothesis was that using antibiotics for long time in IBD patients could lead to the eradication of Hp infection (Papamichael et al 2014). A study made by Matsumura in 2001 showed a significantly lower prevalence of Hp infection in patients with CD who had received antibiotics for more than 2 weeks (Matsumura et al 2001). Other studies proved that in IBD patients treated with ciprofloxacin and/or metronidazole there was no modification regarding the Hp status (Pronai et al 2004, Guslandi 2004). On the other hand, the changes of gut microbiota after Hp eradication therapy (one proton pump inhibitor plus two antibiotics) (Dethlefsen et al 2011, Rashid et al 2015) might lead to the development of IBD on a subset of individuals, under certain circumstances (Rosa et al 2018). Eight of our IBD patients received antibiotics for Hp eradication before the IBD was diagnosed. Only five of these patients received eradication therapy for Hp six to twelve months before the diagnosis of IBD was made. This underlines the idea that there are some other factors implicated in the onset of IBD along with Hp infection eradication. Thus, assessing gut microbiota prior and after Hp eradication could be what we need for understanding the exact role of microbiota in IBD onset (Rosa et al 2018). Some genetic and environmental factors that favor Hp acquisition or IBD development might be implicated. There are studies that proved that IBD is associated with high preoccupation for hygiene, and that can be detrimental to Hp acquisition (Mendall et al 1992, Elliot et al 2000). Further prospective studies about the relation between Hp infection and IBD have to take in consideration more variables.

A strength of our study was the fact that IBD patients received non-only biological therapy, but also 5 ASA, steroids and thiopurines, while prior study was referring only on IBD controls on biological therapy (Rosa et al 2018). Another strength point was the selection of controls from a group of patients without dyspeptic symptoms that referred to the same outpatient unit (IRGH Cluj Napoca, Romania). As data from literature indicated a time frame for the development of IBD after eradication therapy for Hp of 6-12 months (Jovanovic et al 2001, Tursi et al 2006, HVM Bioflux http://www.hvm.bioflux.com.ro/)
Chiba et al (2016), we excluded from the study the controls that received eradication therapy less than 1 year before enrollment. Limitations of the study were: the missing the exact data regarding the prior antibiotic use, this information not being reliable when collected on a patient’s history method and the lack CagA antigen depiction.

**Conclusion**

In our study population we found that between Hp infection and IBD there is a negative association. We consider that further investigations about the implication of Hp in other extra-gastric manifestations and disorders are needed. It remains to be proved whether the presence of Hp itself has an apparent protective effect on IBD or that is due to other variables. More studies to investigate the role of the eradication of Hp infection as risk factor for developing IBD are needed.

**References**


Authors

- Camelia Raluca Prunduș, “Iuliu Hatieganu” University of Medicine and Pharmacy, 8 Victor Babes street, Cluj-Napoca, Romania; raluca_postei@yahoo.com
- Lidia Ciobanu, “Iuliu Hatieganu” University of Medicine and Pharmacy, 8 Victor Babes street, Cluj-Napoca, Romania; ciobanulidia@yahoo.com
- Sorana D. Bolboaca, “Iuliu Hatieganu” University of Medicine and Pharmacy, 8 Victor Babes street, Cluj-Napoca, Romania; sbolboaca@gmail.com
- Marcel Tantau, “Iuliu Hatieganu” University of Medicine and Pharmacy, 8 Victor Babes street, Cluj-Napoca, Romania; matantau@gmail.com
- Daniela Matei, “Iuliu Hatieganu” University of Medicine and Pharmacy, 8 Victor Babes street, Cluj-Napoca, Romania; dmatei68@gmail.com
- Cristina Pojoga, Regional Institute of Gastroenterology and Hepatology, 19-23 Croitorilor street, Cluj-Napoca, Romania; cristinapojoga@yahoo.com
- Vasile Andreica, “Iuliu Hatieganu” University of Medicine and Pharmacy, 8 Victor Babes street, Cluj-Napoca, Romania; andreicav@umfcluj.ro

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