

Helicobacter pylori is Associated with Less Fistulizing, Strictureing, and Active Colitis in Crohn's Disease Patients

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Abstract

Introduction

A potential protective role of *Helicobacter pylori* (HP) infection against the development of Crohn's disease (CD) has been postulated. There is a lack of studies evaluating the association of HP with CD phenotypes. The aim of this study was to investigate the clinical features and disease activity of patients with CD who were diagnosed with HP infection.

Methods

The charts of 306 consecutive patients from the inflammatory bowel disease (IBD) database at the University of Florida College of Medicine, Jacksonville from January 2014 to July 2016 were reviewed. Ninety-one CD patients who were tested for HP were included, and the frequencies of strictures, fistulas, and colitis in surveillance biopsies in these patients were evaluated.

Results

Of the 91 CD patients tested for HP, 19 had HP infection. A total of 44 patients had fistulizing/strictureing disease, and 62 patients had active colitis. In the univariate analysis, patients with HP infection had less fistulizing/strictureing disease (21.1% vs. 55.6%, $p = 0.009$) and less active colitis (42.1% vs. 77.1%, $p = 0.005$). In the multivariate analysis, HP infection remained as a protective factor for fistulizing/strictureing disease phenotype (OR: 0.22; 95%CI: 0.06-0.97; $p = 0.022$) and active colitis (OR: 0.186; 95%CI: 0.05-0.65; $p = 0.010$).

Conclusion

HP infection was independently associated with less fistulizing/strictureing disease and less active colitis in CD patients. Our study suggests CD patients with a history of HP infection are less prone to complications.

Categories: Gastroenterology, Internal Medicine, Infectious Disease

Keywords: gastroenterology, inflammatory bowel disease (ibd), helicobacter pylori infection, crohns disease, fistulizing crohn's disease, autoimmune

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Introduction

Helicobacter pylori (HP) is a Gram-negative bacterium that colonizes the gastric epithelium and is the most common bacterial infection worldwide, infecting approximately half of the world's population [1]. A higher prevalence of HP infection is seen in developing countries with most of the infections being acquired during childhood and persisting throughout adulthood [2]. HP is associated with the development of chronic gastritis, peptic ulcer disease, gastric cancer and mucosa-associated lymphoid tissue lymphoma [3]. In addition, the association of HP infection with extra-gastric disease has been suggested by several researchers [4-12].

Crohn's disease (CD) is characterized by transmural inflammation of the digestive system and may affect the gastrointestinal tract from mouth to the perianal area. The prevalence is more significant in developed countries with higher latitudes, with prevalence ranging from 10 to 200 per 100,000 people [13]. Complications such as fistulas, perforation, and strictures develop in up to 53% of patients at 10 years follow-up and are associated with significant morbidity [14-15]. Up to 50% of patients will require surgical intervention over the first five years of disease, and many CD patients require multiple abdominal surgeries over their lifetime [16].

The diagnosis of HP infection is associated with a lower incidence and prevalence of CD [17-20]. HP infection is thought to have a protective effect on the development of CD that persists despite eradication treatment and is thought to be secondary to the association of chronic HP infection with the immune system and microbiome modulation [17]. There is a lack of studies in the literature evaluating HP infection in patients diagnosed with CD. The aim of this study was to investigate the clinical features and disease activity of patients with CD who were diagnosed with HP infection.

Materials And Methods

A total of 306 consecutive charts of patients from the inflammatory bowel disease (IBD) database at the University of Florida College of Medicine, Jacksonville from January 2014 to July 2016 were reviewed. Ninety-one CD patients who were tested for HP infection by standard gastric biopsies were included in this study. Detailed clinical data pertaining to HP infection and CD were obtained in this retrospective case-control study. The study was approved by the Institutional Review Board of the University of Florida College of Medicine, Jacksonville and was conducted in accordance with principles in the Declaration of Helsinki.

Inclusion and exclusion criteria

Inclusion criteria were patients with (1) biopsy-proven CD who had a surveillance colonoscopy and (2) esophagogastroduodenoscopy (EGD) gastric biopsies for evaluation of HP. Patients with ulcerative colitis were excluded. Patients without surveillance colonoscopy reports available in our electronic record were also excluded from this study.

Study and control groups

The study group consisted of patients with CD and history of HP, and the control group was patients with CD without HP infection.

Endoscopic diagnosis

The diagnosis of HP was confirmed by gastric biopsies that were fixed in 10% formalin, embedded in paraffin wax, which had 5-mm sections stained with hematoxylin and eosin for histology and with Giemsa staining to evaluate HP status. Random biopsies were collected throughout the colon for the purpose of evaluating CD activity. Those lesions that displayed evidence of dysplasia were followed by surveillance colonoscopies.

Study variables and outcome measurements

A total of 21 variables were studied. Clinical variables included were age, male sex, age at CD diagnosis, disease extension, presence of strictures, presence of fistulizing disease, active colitis on colonics biopsies, symptoms of diarrhea on CD diagnosis, symptoms of bleeding on CD diagnosis, symptoms of abdominal pain on CD diagnosis, history of *Clostridium difficile* infection, arthritis, use of 5-aminosalicylic acid (5-ASA), use of 6-mercaptopurine (6-MP)/azathioprine, use of methotrexate, use of steroids, use of biologics, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and stool calprotectin levels. The primary outcomes were to investigate the clinical features and disease activity of patients with CD who were diagnosed with HP infection.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation (SD) or N%. Univariate analysis was performed to identify potential variables associated with HP infection in CD patients. Student *t*-tests or nonparametric Wilcoxon rank sum tests were used for continuous factors, and Pearson chi-square tests were used for categorical variables. Multivariate logistic regression analysis was performed to assess the risk factors associated with disease activity in CD patients with HP. An automated stepwise variable selection method performed on 1,000 bootstrap samples was used to choose the final multivariable model. A *P*-value of 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 22 (SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. 2013.)

Results

The medical records of 306 consecutive patients with biopsy-proven IBD were reviewed. Of these, a total of 91 CD patients who were tested for HP through standard gastric biopsies were evaluated in this study. Patients were subdivided into HP positive ($n = 19$) or HP negative ($n = 72$). The median interval of CD duration was 10 years (interquartile range [IQR] of five to 22 years).

There were no differences between HP-positive and HP-negative patients with regard to age (46.5 ± 3.4 vs. 47.0 ± 1.8 ; $P = 0.896$), male sex (26.3% vs. 30.6%; $P = 0.789$), age at CD diagnosis (32.3 ± 2.9 vs. 33.7 ± 1.7 ; $P = 0.709$), disease extension (ileal 10.5% vs. 11.1%; ileocolonic 47.3% vs. 61.1%; colonic 42.2% vs. 27.8%; $P = 0.555$), diarrhea on CD diagnosis (78.9% vs. 66.7%; $P = 0.406$), bleeding on CD diagnosis (26.3% vs. 25.0%; $P = 0.560$), abdominal pain on CD diagnosis (89.5% vs. 72.2%; $P = 0.147$), history of *Clostridium difficile* infection (17.6% vs. 17.9%; $P = 0.645$), arthritis (10.5% vs. 16.7%; $P = 0.726$), use of 5-ASA (63.2% vs. 70.8%; $P = 0.580$), use of 6-MP/azathioprine (26.3% vs. 29.2%; $P = 1.000$), use of methotrexate (5.6% vs. 4.3%; $P = 1.000$), use of steroids (73.7% vs. 88.9%; $P = 0.135$), use of biologics (36.8% vs. 51.4%; $P = 0.309$), CRP level (5.7 ± 1.8 vs. 23.7 ± 5.3 ; $P = 0.112$), ESR level (25.0 ± 4.1 vs. 41.1 ± 4.3 ; $P = 0.053$) and level of calprotectin (187.5 ± 41.7 vs. 159.8 ± 42.5 ; $P = 0.727$; Table 1)

Variable	H. pylori positive (n = 19)	H. pylori negative (n = 72)	P-value
Mean age, years	46.5 ± 3.4	47.0 ± 1.8	0.896
Male sex	5 (26.3%)	22 (30.6%)	0.786
Age at CD diagnosis	32.3 ± 2.9	33.7 ± 1.7	0.709
Disease extension			
Ileal	2 (10.5%)	8 (11.1%)	0.555
Ileocolonic	9 (47.3%)	44 (61.1%)	
Colonic	8 (42.2%)	20 (27.8%)	
Diarrhea on CD diagnosis	15 (78.9%)	48 (66.7%)	0.406
Bleeding on CD diagnosis	5 (26.3%)	18 (25.0%)	0.560
Abdominal pain on CD diagnosis	17 (89.5%)	52 (72.2%)	0.147
History of <i>C. difficile</i> infection*	2 (17.6%)	10 (17.9%)	0.645
Arthritis	2 (10.5%)	12 (16.7%)	0.726
Fistulizing/stricturing disease	4 (21.1%)	40 (55.6%)	0.009
Active colitis on random biopsies	8 (42.1%)	54 (77.1%)	0.005
Use of 5-ASA	12 (63.2%)	51 (70.8%)	0.580
Use of 6-MP/AZA	5 (26.3%)	21 (29.2%)	1.000
Use of methotrexate	1 (5.6%)	03 (4.3%)	1.000
Use of steroids	14 (73.7%)	64 (88.9%)	0.135
Use of any biologic	7 (36.8%)	37 (51.4%)	0.309
CRP	5.7 ± 1.8	23.7 ± 5.3	0.112
ESR	25.0 ± 4.1	41.1 ± 4.3	0.053
Fecal Calprotectin	187.5 ± 41.7	159.8 ± 42.5	0.727

TABLE 1: Univariate analysis of risk factors associated with H. pylori

AZA, azathioprine; CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine

**H. pylori* positive (12) were tested for *C. difficile*; *H. pylori* negative (56) were tested for *C. difficile*.

A total of 44 patients had fistulizing/stricturing disease, and 62 patients had active colitis identified on random colonic biopsies. In the univariate analysis, patients with HP infection had less fistulizing/stricturing disease (21.1% vs. 55.6%, $p = 0.009$) and less active colitis (42.1%

vs. 77.1%, $p = 0.005$) on random colonic biopsies (42.1% vs. 77.1%, $p = 0.005$).

In the multivariate logistic regression analysis, HP, fistulizing/stricturing disease, abdominal pain on CD diagnosis, and active colitis on random biopsies were included in the final model. After adjusting for all other variables in the model, HP infection remained as a protective factor against fistulizing/stricturing disease (OR: 0.22; 95%CI: 0.06-0.97; $p = 0.022$) and active colitis on biopsies (OR: 0.186; 95%CI: 0.05-0.65; $p = 0.010$; Table 2).

Variable	Adjustable OR	95% CI	p
Fistulizing/stricturing disease	0.221	0.06-0.81	0.022
Abdominal pain on CD diagnosis	4.420	0.80-24.34	0.088
Use of steroids	0.242	0.05-1.07	0.061
Active colitis on random biopsies	0.186	0.05-0.65	0.010

TABLE 2: Multivariate analysis of risk factors associated with H. pylori

CD, Crohn's disease

Discussion

HP and CD are two separate disease entities that have a profound impact on the health of affected patients [14,21]. In the present study, HP infection in patients with CD was associated with lower rates of combined fistula or strictures as well as lower rates of active colitis in surveillance colonoscopy with random biopsies. HP infection is acquired in childhood, and it generally persists for life unless treated with antibiotics [22]. HP is commonly associated with chronic gastritis, peptic ulcer disease, and gastric cancer [3]. In addition, HP has been associated with the development of extra-gastric disorders including chronic idiopathic thrombocytopenic purpura and growth retardation in children [5,23]. Strong evidence supports that HP may also be associated with a variety of other diseases such as rosacea, chronic idiopathic urticaria, hyperemesis gravidarum in pregnancy, worsening microalbuminuria in diabetics, ischemic stroke, coronary heart disease, and Grave's disease [6-11,24]. An inverse relationship with the development of allergies has also been reported [12,25].

CD affects the gastrointestinal tract and is characterized by segmental and transmural inflammation with associated complications ranging from mucosal ulcerative lesions, thickening of the bowel wall, edema of the wall, fistulas and inflammatory or fibrotic strictures with significant morbidity to patients. Given the higher prevalence of CD in developed countries, improved sanitary conditions are thought to reduce exposure to bacterial antigens which protect from auto-inflammation and development of inflammatory bowel disease [17,26]. There is still much to understand the factors affecting disease phenotype and natural history of the disease.

Several studies have shown that people infected with HP had a lower prevalence of CD suggesting a possible protective effect of HP infection against the development of CD [18-20,26]. Lars et al. found that more patients are diagnosed with CD among those who are HP negative than among those HP positive with the protective effect of HP infection persisting even after eradication [17]. In our study, HP infection in patients with CD is associated with

lower rates of combined fistulas or strictures and lower rates of active colitis in surveillance colonoscopy with random biopsies. It has been shown that certain intestinal microbial ecosystems harbor aggressive traits relevant in the induction of chronic inflammation in susceptible hosts that can theoretically interfere with CD phenotype [27]. HP infection may interfere with the natural history of CD through modulation of the gastric and intestinal microbiome [28]. Although Th1 responses which are induced by HP favor autoimmune and inflammatory diseases, a potential mechanism by which HP protects against CD has been suggested as HP induces the development of FoxP3+ regulatory T cells and impairs dendritic cell maturation with decreased intestinal inflammation [29-30]. We postulate that this finding is secondary to a potential role of chronic infection with HP to downgrade the auto-inflammatory response seen in CD, potentially changing the intestinal microbiome related to CD development.

There are limitations to our study. The number of patients with CD that had HP in this study was small, which may have compromised the power of the study. In addition, there may have been selection and referral bias since the study was conducted at a single referral center. Similarly, patients in our study may have had more severe disease and may not be representative of those seen in the general community. Because this was a retrospective study, it was not possible to evaluate other risk factors for such as genetic and inflammatory cytokines associated with different CD phenotypes. It would be interesting to confirm a cause-and-effect association between HP infection, different CD phenotypes and active colitis in CD by future prospective studies.

Conclusions

In conclusion, HP infection is associated with less fistulizing/stricturing activity in CD and less active colitis on surveillance biopsies. Further prospective studies are needed to confirm this association.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. University of Florida Jacksonville IRB-03 issued approval 201601465. The IRB-03 at the University of Florida, Jacksonville has approved this study and granted a full waiver of informed consent. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** Miguel Malespin declare(s) a grant and personal fees from Abvie, Gilead, Intercept, Novo Nordisk. The authors declare no relevant conflicts of interest. Miguel Malespin receives research funding from Abbvie, Gilead, Intercept, and Novo Nordisk. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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