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ORIGINAL ARTICLE

Unexplained iron deficiency anemia: does *Helicobacter pylori* have a role to play?

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Abstract

Background and aim: Testing for *Helicobacter pylori* (Hp) infection is recommended for work-up of unexplained iron deficiency anemia (IDA), although the evidence supporting this recommendation is scant. The aim of this study was to investigate the association between Hp infection and unexplained iron deficiency (ID) or IDA in the older adult population without significant upper gastrointestinal source of blood loss.
Methods: Retrospective single-center cohort study; 523 out of 1253 consecutive patients who underwent esophagogastroduodenoscopy with no significant upper and/or lower gastrointestinal source for blood loss or risk factors for IDA. Comparisons were made between the Hp-positive and Hp-negative groups using Fisher exact test, chi-square test and Student's t-test. Univariate and multiple logistic regression analyses were used to identify significant risk factors associated with ID and IDA.
Results: One hundred and three subjects (19.7%) had Hp infection and 420 (80.3%) were negative for Hp. Sixty-eight (22.1%) out of 307 subjects with available serum iron profile had unexplained ID and 28 (5.4%) out of 510 subjects with available hemoglobin profile had unexplained IDA. No association was found between ID/IDA and Hp infection in univariate and multiple logistic regression analyses.
Conclusion: We found no association between unexplained ID or IDA and Hp infection in older adult population without peptic ulcer disease or significant upper gastrointestinal source of blood loss.

Key words: *Helicobacter pylori*; anemia; iron deficiency

Introduction

Helicobacter pylori (Hp) is the most common chronic bacterial infection in humans [1,2]. Iron deficiency anemia (IDA) is also a common condition with a prevalence of 1–2% of the adult population in the USA [3] and up to 16.6% in older adults [4]. More recent reports suggest a variable and higher prevalence of anemia in older adults, ranging between 2.9% and 61%, depending on the population studied and definition of anemia [5]. The major cause of iron deficiency (ID) in developed countries is overt or occult gastrointestinal blood loss [6]. Existing practice guidelines support the practice of performing upper and lower

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gastrointestinal endoscopic evaluation in patients with IDA and wireless video capsule endoscopy in those with unrevealing bidirectional endoscopic evaluation [7]. Despite these diagnostic modalities, the etiology of obscure gastrointestinal bleeding may remain elusive in approximately 30% of the patients [8].

Peptic ulcer disease caused by Hp infection can lead to gastrointestinal blood loss and IDA. Whether Hp infection can lead to IDA in the absence of peptic ulcer disease is controversial. Most of the data supporting association of Hp infection and IDA come from clinical studies conducted in children and pre-menopausal women with a relatively high iron requirement [9–11] and in those living in areas with a high prevalence for Hp infection [12]. The majority of the epidemiological studies that support this association have used serologic tests that do not necessarily diagnose active Hp infection. In addition, most of these studies have not ruled out the major causes of IDA such as peptic ulcer disease by esophagogastroduodenoscopy (EGD) [13]. Thus, the applicability of the available study findings in adult population living in areas with low prevalence for Hp infection who are not vulnerable to ID is controversial. The available data supporting association between Hp infection and ID do not prove cause and effect [14].

Nevertheless, the Maastricht IV Consensus on the management of Hp infection recommends testing and treatment for Hp infection in patients with unexplained IDA [15]. Hence our study was performed to evaluate the association between Hp infection and unexplained IDA in adult patients without obvious risk factors for ID living in areas with low prevalence for Hp infection.

Methods

Patients

The study involved collection of Hp infection data on 1253 consecutive patients undergoing diagnostic or therapeutic upper gastrointestinal endoscopy at the Veterans Affairs Medical Center, Syracuse, from 1 January 1998 to 28 April 2004. All patients underwent EGD with Hp testing by standard biopsy protocol (two antral and two gastric body biopsies) as part of a previous Institutional Review Board-approved study investigating new diagnostic tests and treatment protocols for Hp infection [16,17]. One biopsy each from the antrum and body was sent for histology and rapid urease testing/Campylobacter-like organism (CLO) test. A subgroup of these patients (from 1 January 1998 to 31 December 1999) had consented to collection and storage of fasting serum samples prior to endoscopy. Serum iron tests were performed on these samples. A review of medical records was performed in all the subjects to determine the presence of ID/IDA.

Medical, laboratory and pharmacy electronic records from 6 months before to 6 months after the performance of the endoscopy were reviewed. Demographic and clinical data included history of medical conditions known to cause ID, obvious causes for acute and/or chronic blood loss or impaired iron absorption, prior gastrointestinal surgery, alcohol or drug abuse, prescription/over-the-counter medication use (non-steroidal anti-inflammatory, proton pump inhibitor, iron supplementation, anticoagulant and antiplatelet medications), pertinent laboratory results, endoscopy and pathology reports.

Patients with significant source of chronic and/or acute gastrointestinal blood loss identified on upper endoscopy and/or lower endoscopy [18,19], abnormal small bowel biopsies, clinical diagnosis consistent with celiac disease or other malabsorption syndromes, obvious cause of non-GI blood loss such as epistaxis or heavy menstrual bleed, previous treatment for Hp, indeterminate Hp status, ongoing iron therapy and insufficient clinical data were excluded.

Determination of Hp status

Hp status was determined by CLO test and presence of Hp organisms on histological evaluation of gastric biopsies. Positive Hp status was defined as positive CLO test and presence of Hp on histology. Negative Hp status was defined as negative CLO test and absence of Hp on histology. In patients with discordant results by CLO and histology, positive Hp serology or presence of chronic active gastritis on biopsy was used to determine the presence of active Hp infection. Patients with discordant CLO/histology results, who were on proton pump inhibitors (PPIs) and had no serology tests were deemed indeterminate.

Determination of ID and IDA

Blood hemoglobin level of <13 and <12 g/dL in men and women respectively was used to define anemia [20]. Patients were considered iron-deficient if serum ferritin level was <41 ng/mL. Prior studies conducted in anemic patients have shown that a cutoff serum ferritin level of 41 ng/mL has a sensitivity and specificity of 98% [21,22]. In those with anemia, we also used a higher cutoff ferritin level of 100 ng/mL [23] to ensure capture of ID in those with potentially coexistent anemia of chronic disease.

Statistical analysis

Demographic data, clinical characteristics and laboratory parameters including serum iron results were compared in the Hp-positive and Hp-negative groups. Fisher exact test or chi-square test was employed for analysis of categorical variables and Student's *t*-test was used for analysis of continuous variables. A probability value of <0.05 was considered statistically significant. Similar univariate analysis of demographic data, clinical characteristics, Hp status and medication use [non-steroidal anti-inflammatory drugs (NSAIDs) and PPIs] was also performed in the groups with ID and IDA. Multiple logistic regression analysis was then performed using variables that were statistically significant on univariate analysis in the groups with ID and IDA.

Results

A total of 1253 consecutive patients who underwent EGD and standard testing for Hp infection from 1 January 1998 to 28 April 2004 were eligible for inclusion in the study. Seven hundred and 30 patients were excluded [endoscopic identification of a significant gastrointestinal bleeding source (n = 557), other causes for ID including celiac disease (n=60), inadequate data (n=74), previous treatment for Hp (n=27) and indeterminate Hp infection status (n=12)].

The final study population consisted of 523 subjects, of whom 488 (93.3%) were males and 35 (6.7%) were females. All the patients underwent EGD and 72% (n=378) underwent flexible sigmoidoscopy or colonoscopy. Out of the 523 subjects, 103 had Hp infection (19.7%) and 420 were negative for Hp (80.3%) (Table 1). The female patients were relatively younger as compared to the males (mean age 51.9 vs 61.8 years, data not shown). Age, gender, race, mean ferritin level, hemoglobin level or ID was not associated with Hp infection.

Table 1. Comparison of variables in 523 patients with and without *Helicobacter pylori* (Hp) infection

	Hp-positive (n=103)	Hp-negative (n=420)	p-value	Odds ratio	95% confidence interval
Gender			0.66	0.82	0.36–1.85
Male	95 (19.5)	393 (80.5)			
Female	8 (22.9)	27 (77.1)			
Race			0.24		
Caucasian	93 (19.0)	396 (81.0)			
African American		14 (63.6)			
Others	2 (16.7)	10 (83.3)			
Age, years	61.7 ± 11.7	61.0 ± 13.1	0.62		
Hemoglobin, g/dL	14.3 ± 1.8 (n=102)	14.1 ± 1.9 (n=408)	0.27		
Ferritin, ng/mL	174.1 ± 215.0 (n=71)	185.1 ± 251.6 (n=236)	0.74		
Iron deficiency	12 (17.6)	56 (82.4)	0.26	0.65	0.33–1.30

Data are presented as mean ± standard deviation or number (percentage).

Table 2. Comparison of variables in patients with and without iron deficiency (serum ferritin results available in 307 patients)

	ID-positive (n=68)	ID-negative (n=239)	p-value	Odds ratio	95% confidence interval
Hp infection	12 (16.9)	59 (83.1)	0.26	0.65	0.33–1.30
Gender			0.004	0.27	0.12–0.62
Male	56 (19.9)	226 (80.1)			
Female	12 (48.0)	13 (52.0)			
Race			0.48		
Caucasian	65 (23)	218 (77)			
African American	3 (18.8)	13 (81.2)			
Others	0 (0.0)	8 (100.0)			
NSAID use	36 (22.2)	126 (77.8)	0.99	1.01	0.59–1.75
PPI use	27 (20.3)	106 (79.7)	0.58	0.83	0.48–1.43
Age, years	62.3 ± 12.7	61.9 ± 13.2	0.81		

Data are presented as mean ± standard deviation or number (percentage). ID, iron deficiency; Hp, *Helicobacter pylori*; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Out of the 307 subjects with available serum ferritin results, 68 subjects (22.1%) were iron-deficient and 239 subjects had no ID (Table 2). Female gender was significantly associated with ID on univariate as well as multiple regression analysis (48% vs 20%, $p = 0.004$). Other variables such as Hp infection, age, gender, race, PPI use or NSAID use were not associated with ID.

Out of the total of 523 subjects, 510 subjects had hemoglobin levels available and they were classified as anemic and not anemic. IDA was present in 28 (5.4%) with available ferritin results, when a cutoff of <41 ng/mL was used for serum ferritin level to define ID (Table 3). Using a higher cutoff for serum ferritin level of <100 ng/mL in those with anemia, IDA was present in only 46 subjects (9.0%). No significant association between IDA and Hp infection was found even with using a higher cutoff for serum ferritin level of <100 ng/mL in those with anemia (data not shown). However, the patients in this subgroup with IDA and higher serum ferritin cutoff were found to be significantly older compared to those without IDA (mean age, 66.04 vs 60.71 years, $p < 0.01$) (data not shown).

Logistic regression analysis showed female gender to be the only significant factor associated with ID (Table 4). The significance of gender however did not hold true in those with IDA on univariate or multivariate analysis (data not shown).

Discussion

Our study did not show an association between ID/IDA and Hp infection in adult population, using strict (ferritin level of <41ng/mL) and liberal (ferritin level of <100 ng/mL) criteria to define ID/IDA. This lack of association may be attributed to the low vulnerability of our patients to ID/IDA (predominantly adult males with no increased risk for ID living in areas with low prevalence for Hp infection) as well as the exclusion of upper and/or lower gastrointestinal source of blood loss and confirmation of the presence of active Hp infection. The prevalence of Hp infection in our study population was 19.7% compared to 30.1–39.5% in other epidemiologic studies performed in the USA [13]. This lower prevalence is likely explained by the use of serology for detecting Hp infection in the above studies and the exclusion of patients with indeterminate Hp infection status, previous treatment for Hp infection, and upper and/or lower gastrointestinal source of blood loss in our study. Although female gender was the only significant factor associated with ID in multiple logistic regression, there was no significant difference in the Hp infection status in females with and without ID. However, the small number of female patients in our study (6.7%) limits further interpretation.

The mechanisms by which Hp infection is postulated to cause IDA are Hp-associated chronic gastritis resulting in hypo- or achlorhydria, reduced ascorbic acid secretion and reduced intestinal iron absorption, occult blood loss due to chronic erosive gastritis, and sequestration and utilization of iron by Hp [24]. The major studies that have reported Hp infection to be an independent risk factor for IDA in North America were conducted in school-aged children residing in rural Alaska with a

Table 3. Comparison of variables in patients with and without iron deficiency anemia (hemoglobin levels available in only 510 patients)

	IDA-positive (n=28)	IDA-negative (n=482)	p-value	Odds ratio	95% confidence interval
Hp infection	4 (3.9)	98 (96.1)	0.63	0.65	0.22–1.93
Gender			0.43	0.59	0.17–2.07
Male	25 (5.3)	450 (94.7)			
Female	3 (8.6)	32 (91.4)			
Race			0.76		
Caucasian	26 (5.5)	450 (94.5)			
African American	2 (9.1)	20 (90.9)			
Others	0 (0.0)	11 (100.0)			
NSAID use	15 (5.7)	250 (94.3)	0.84	1.12	0.51–2.44
PPI use	11 (4.4)	239 (95.6)	0.33	0.66	0.30–1.43
Age, years	65.4 ± 12.2	61 ± 12.8	0.07		

Data are presented as mean ± standard deviation or number (percentage). IDA, iron deficiency anemia; Hp, *Helicobacter pylori*; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Table 4. Logistic regression model in subjects with iron deficiency

	p-value	Odds ratio	95% confidence interval
Age (years)	0.57	1.01	0.98–1.03
Hp infection (positive vs negative)	0.16	0.59	0.28–1.23
Gender (male vs female)	<0.001	0.21	0.09–0.52
Race (Caucasian vs others)	0.20	2.34	0.63–8.64
NSAID Uses (yes vs no)	0.59	1.17	0.66–2.08
PPI use (yes vs no)	0.47	0.81	0.45–1.45

Hp, *Helicobacter pylori*; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

high prevalence of Hp infection and IDA [12] and in participants of the National Health and Nutrition Examination Survey in whom serologic tests were used for diagnosis of Hp infection [13]. Other studies that suggested a role for Hp eradication in improving IDA were conducted in children, adolescents and pre-menopausal women who have a relatively high iron requirement to meet the demands of growth and menstrual blood loss [9–11]. On the other hand, there are epidemiologic studies that showed no association between Hp seropositivity and ID/IDA [25–29]. In summary, the causal relationship between Hp infection and ID/IDA remains controversial. Our study did not show any association between Hp infection and ID/IDA.

The Maastricht IV Consensus on the management of Hp infection recommends testing and treatment of Hp infection in patients with unexplained IDA [15]. Although these guidelines may be applicable in countries with high prevalence for Hp infection, the universal adoption of this guideline in areas with low prevalence for Hp infection such as the USA may result in unnecessary testing and treatment. More importantly, this practice could delay the diagnosis of other serious conditions that could cause ID/IDA in older population. The evidence that carriage of certain Hp strains is inversely related to the prevalence of Barrett's esophagus, esophageal adenocarcinoma, asthma and atopic disorders has prompted some authors to warn against testing and treating for Hp infection in asymptomatic individuals [30]. While we concur with the current guidelines that, if testing for Hp infection is undertaken, appropriate treatment and confirmation of eradication of the infection should be ensured in all patients with positive test result for Hp infection, our study results do not support the recommendation that testing for Hp infection should be performed in all patients with unexplained IDA.

The strengths of our study include the identification and exclusion of significant upper gastrointestinal source of blood loss via EGD in all the subjects, the adoption of strict criteria to determine active Hp infection and the use of a higher cutoff for serum ferritin to capture those with potential ID. In most of the observational epidemiologic studies evaluating association between Hp infection and ID, EGD was not performed [12,13,25–27,31–40]. We used a combination of CLO testing and detection of Hp on histology to adjudicate Hp status, which provides a more accurate determination of the Hp infection status. The majority of previous studies looking at association of Hp and IDA used serology for identification of Hp infection [13,26,27,31–38]. Only a few studies used tests besides serology to determine active Hp infection [12,39–42]. However, these studies were conducted in subjects vulnerable to ID such as children and adolescent females living in areas with a high prevalence for Hp infection.

The limitations of our study include the retrospective study design, the study population comprising predominantly adult males who are typically not vulnerable to ID and the availability of lower gastrointestinal endoscopy results in only 72% of the study population. The selection of a homogenous patient population without the confounding effects of vulnerability to ID is, however, a better model to study the association between Hp infection and IDA. Although the study was retrospective in nature, a large number of our patients had biopsies for Hp performed by protocol and serum samples collected for calculation of serum iron indices prospectively at the time of EGD. While the availability of lower gastrointestinal endoscopy results on all patients would have been ideal, bidirectional endoscopy as well as appropriate small bowel imaging studies was conducted in all the patients who presented with overt or occult gastrointestinal blood loss. Additionally, all patients with a significant source of chronic and/or acute gastrointestinal blood loss identified on endoscopic or small bowel imaging tests were excluded from the study. It is to be also noted that prior studies showing association between unexplained ID and Hp infection did not have strict exclusion criteria as are used in our study and did not have upper and lower gastrointestinal endoscopy data on all patients.

In conclusion, we found no association between ID or IDA and Hp infection in older adult population without peptic ulcer disease or significant upper gastrointestinal source of blood

loss. Our study does not support routine testing for Hp infection in adult patients with unexplained IDA living in areas with low prevalence for Hp infection. More importantly, work-up of IDA, particularly in patients above 60 years of age, should not end with the diagnosis of Hp infection, as such a practice could lead to delayed diagnosis of potentially more serious underlying pathology.

Conflict of interest statement: none declared.

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