Migraine, dyspepsia, and Helicobacter pylori: Zeroing in on the culprit

Nayereh Akbari¹, Ahmad Hormati², Ehsan Sharifipour¹, Seyed Amir Hejazi¹, Fatemeh Jafari¹, Seyed Ali Mousavi-Aghdas³, Samad EJ Golzari⁴,⁵

¹ Neuroscience Research Center, Qom University of Medical Sciences, Qom, Iran
² Gastroenterology and Hepatology Research Center, Qom University of Medical Sciences, Qom, Iran
³ Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
⁴ Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
⁵ Road Traffic Injury Research Center, Health Management and Safety Promotion Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran

Keywords
Migraine; Dyspepsia; Helicobacter Pylori; Peptic Ulcer

Abstract
Background: Numerous studies have evaluated the impact of Helicobacter pylori (H. pylori) eradication on the number, severity, and recurrence of migraine attacks. But the association of migraine, H. pylori, and gastrointestinal (GI) presentation is challenging. The aim of the current study was to investigate the correlation between migraine, H. pylori, and peptic ulcers among patients with dyspepsia undergoing upper GI endoscopy.

Methods: 305 patients with dyspepsia referring to our endoscopy ward, Shahid Beheshti Hospital affiliated to Qom University of Medical Sciences, Qom, Iran, for upper GI endoscopy filled out the study questionnaire. If a patient was experiencing headaches and the migraine was confirmed by neurologists, he/she was asked to answer the questions related to migraine, H. pylori, and peptic ulcers. Of all the 305 patients, 133 (43.6%) had confirmed episodic migraine headaches (MHs) and 177 patients (58.04%) had positive RUT for confirming H. pylori contamination, of which 123 (69.5%) had confirmed migraine. 52 (17.0%) had duodenal peptic ulcer(s), of which, 49 (94.2%) had a positive rapid urease test (RUT) (P < 0.001). 20 (6.5%) of all patients had the gastric peptic ulcer(s) which did not have a significant relation with H. pylori contamination. There was a significant relationship between the peptic ulcer site and migraine. In total, 177 patients (58.0%) had a positive RUT. History of migraine was significantly positive in those with positive H. Pylori contamination. Notably, multivariable analysis demonstrated a significant relation of H. pylori and migraine at younger ages.

Conclusion: The prevalence of H. pylori and migraine in patients with dyspepsia seems to be high. Moreover, there is a meaningful association between migraine, duodenal peptic ulcers, and H. pylori infection, too.
Introduction

Migraine is a common episodic syndrome of unilateral throbbing headache accompanied by nausea, vomiting, and photophobia.\(^1\) Since migraine attacks are debilitating and prevalent, they have a huge economic burden on the society.\(^3\) The exact pathophysiology of migraine is unclear but inherited nature and also repeated triggers by exogenous and endogenous stimulants are of the important aspects of this disorder.\(^4\) Most frequent triggering factors are limited to stress, fatigue, fasting, alcohol, sleep deprivation, climatic conditions, and hormonal, visual, olfactory, and auditory stimuli.\(^5\) Also several mechanisms such as serotonergic pathways and pain mediators like calcitonin-gene-related peptide (CGRP) alterations and inflammation are believed to be involved in the process of triggering migraine onset.\(^6\)\(^-\)\(^9\)

Helicobacter pylori (H. pylori) is a helical gram-negative bacterium involved in peptic ulcer disease, gastric adenocarcinoma, and lymphoma.\(^10\) The association between H. pylori and numerous extragastric diseases such as coronary artery diseases (CADs), insulin resistance, urticaria, rosacea, Parkinson’s disease (PD), idiopathic thrombocytopenic purpura (ITP), and iron deficiency anemia has been previously shown.\(^11\)\(^,\)\(^12\) Also some studies reported a significant correlation between H. pylori contamination and migraine, and demonstrated that after H. pylori eradication, migraine symptoms reduced in the majority of the studied patients.\(^13\)\(^-\)\(^16\) Furthermore, numerous studies have shown the efficacy of H. pylori eradication on the number, severity, and recurrence of migraine attacks.\(^15\)\(^,\)\(^17\) On the other hand, some studies have demonstrated the protective role of H. pylori [especially, cytotoxin-associated gene A (cagA) positive strain] against reflux-induced esophagitis, Barrett’s esophagus, and possibly esophagogastric junction adenocarcinoma.\(^18\)\(^-\)\(^20\) Thus, careless eradication of H. pylori may be unbeneﬁcial in asymptomatic patients.\(^21\) Altogether, the current data are limited about the exact correlation, especially regarding the relationship between the migraine and the peptic ulcers. In this study, we investigated the correlation between migraine and H. pylori contamination among patients with dyspepsia undergoing upper gastrointestinal (GI) endoscopy in a referral hospital in Iran.

Materials and Methods

In this cross-sectional study, we assessed the correlation between H. pylori contamination and migraine among 305 patients undergoing upper endoscopy in a tertiary specialized center, Shahid Beheshty hospital, affiliated to Qom University of Medical Sciences, Qom, Iran. Patients were recruited from May 2016 to May 2017. 305 patients with refractory dyspepsia referring to our endoscopy ward for upper GI endoscopy filled out the study questionnaire. Patients having used antibiotics or proton-pump inhibitors (PPIs) in the last 2 weeks were excluded. The questionnaire consisted of sex, age, height, weight, occupation, education, family history of headaches, previous medical history (headaches, diabetes, ischemic heart diseases, respiratory diseases, chronic kidney diseases (CKDs), rheumatologic diseases, etc.). If a patient was experiencing headaches, he/she was referred to an experienced neurologist. If the diagnosis of MH (with or without aura) was confirmed by the expert neurologists using the International Classiﬁcation of Headache Disorders-3rd Edition (ICHD-3) (beta version).\(^1\)

Patients with conﬁrmed migraine were asked to answer the study questionnaire which were prepared exactly from the Migraine Disability Assessment (MIDAS) questionnaire with eleven-point pain scale.\(^22\)\(^-\)\(^23\) Questions related to ﬁndings from endoscopy (iron deﬁciency anemia, vomiting, epigastric pain, melena, hematemeses, rectorrhagia, dyspepsia, etc.), ﬁndings in esophagus (reflux, erosive esophagitis, stricture, varices, neoplasia, etc.), stomach, and duodenum (peptic ulcer, erosive gastritis, hernia, neoplasia, etc.), H. pylori contamination using rapid urease test (RUT) results, and laboratory results from liver function test [alanine aminotransferase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP), and bilirubin]. Two researchers assisted patients while answering the questionnaire. Primary outcome of the present study was to investigate the correlation between migraine with H. pylori contamination and peptic ulcers among patients with dyspepsia undergoing upper gastrointestinal endoscopy.

The current study was approved by the Ethical Committee of Qom University of Medical Sciences, in accordance with the Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients. Patients unwilling to participate in the study were excluded.
Table 1. Demographic characteristics of the study patients

| Variables                        | Minimum-Maximum | Mean ± SD |
|----------------------------------|------------------|-----------|
| Age (year)                       | 12-88            | 43.94 ± 15.13 |
| Weight (kg)                      | 37-155           | 66.91 ± 13.84 |
| Height (cm)                      | 100-192          | 164.03 ± 10.00 |
| BMI (kg/m²)                      | 13.10-47.00      | 26.04 ± 4.79 |
| MH attack duration (hour)        | 0.5-72.0         | 15.49 ± 8.30 |
| MH history (year)                | 0.5-30.0         | 4.88 ± 3.20 |
| MH severity*                     | 1-10             | 4.21 ± 4.04 |
| MIDAS score                      | 4-40             | 12.64 ± 8.12 |
| MH Disability (days in one month)| 0-7              | 0.94 ± 0.40 |

BMI: Body mass index; MH: Migraine headache; MIDAS: Migraine disability assessment; SD: Standard deviation
*Based on eleven-point pain scale

To present the data, we used descriptive statistical methods such as mean, standard deviation, and frequency. More precisely, independent Student’s t (for quantitative variables), Fisher’s exact (for categorical variables), and chi-square tests were used for data analysis. A P-value less than 0.05 was considered statistically significant. All of the statistical analyses were performed on IBM SPSS software (version 22, IBM Corp., Armonk, NY, USA).

Results

A total number of 305 patients were included in our study. Demographic characteristics of the patients are presented in table 1. The female sex formed 60.3% of the entered population. 68.9% of the patients had education level of lower than diploma. Prevalence of migraine in patients with dyspepsia was 43.6% (133 patients, all suffering from episodic migraine without any chronic migraine) and this was significantly higher in female than male patients (48.9% vs. 35.5%, respectively) (P < 0.010). Of all the patients, 129 (42.3%) had a positive family history of headaches in their 1st or 2nd degree relatives. Detailed data related to MH of patients is demonstrated in table 1.

In total, 177 patients (58.0%) had a positive RUT for confirming present H. pylori contamination. Of all patients with confirmed H. pylori, 123 patients (69.5%) had confirmed migraine, but of 128 non H. pylori contaminated patients, only 10 patients (3.27%) were suffered from migraine. The relation between H. pylori contamination and presence of migraine in patients with dyspepsia was significant (P < 0.001) (Table 2).

Furthermore, of all patients undergoing upper GI endoscopy, 52 (17.0%) patients had duodenal peptic ulcer(s), of which, 49 (94.2%) had a positive RUT (P < 0.001). 20 (6.5%) of all patients had gastric peptic ulcer(s) which did not have a significant relation with H. pylori contamination. Although the relation between H. pylori contamination with age and education was not significant, there was significant association between H. pylori contamination and positive family history of headaches (P < 0.001) (Table 3).

Interestingly, the association between migraine and duodenal peptic ulcer was significant (P = 0.002); nevertheless, the association between migraine and gastric peptic ulcer was not significant (Table 4). Also, there was a significant association between migraine and positive family history of headaches, and migraine was significantly more prevalent in women (P < 0.001 and P < 0.050, respectively).

The relations of MH with age and education were not significant (Table 4). Notably, multivariable analysis demonstrated the significant relation of H. pylori and migraine at younger ages.

Table 2. The relation between Helicobacter pylori (H. pylori) contamination and migraine

| H. pylori contamination | Migraine | Total [n (%)] |
|-------------------------|----------|---------------|
|                         | Positive [n (%)] | Negative [n (%)] | |
| Positive                | 123 (40.32) | 54 (17.70) | 177 (58.04) |
| Negative                | 10 (3.27) | 118 (38.68) | 128 (41.96) |
| Total                   | 133 (43.60) | 172 (56.40) | - |

H. pylori: Helicobacter pylori
Discussion

The current cross-sectional study demonstrated that migraine is a common complain among dyspeptic patients. Also, there is a meaningful correlation between migraine, duodenal peptic ulcers, and H. pylori.

It seems that there is an association between migraine and GI presentations (clinically or sub-clinically). In addition, recent studies addressed that H. Pylori infection had the association with some extra GI disorders such as migraine. Although some studies insist on the possible role of H. pylori infection in migraine precipitation, the others (spatially epidemiological sources) only emphasize the idea of a simple co-occurrence of these two.

Results from a meta-analysis are also in consistence with our findings. In the mentioned study, a total number of 903 patients were included and it was shown that patients with migraine were more commonly contaminated with H. pylori.

At least one positive test for H. pylori infection including serology, RUT, mucosal biopsy, polymerase chain reaction (PCR), or urea breath test (UBT) was needed in this study. In our study, we used RUT because it is cost-effective and a positive RUT indicates present contamination.

Table 3. The relation between Helicobacter pylori (H. pylori) contamination and other variables

| Variables                        | H. pylori contamination | P       |
|----------------------------------|-------------------------|---------|
|                                  | Positive | Negative |
| Sex [n (%)]                      | Male | 72 (59.5) | 49 (40.5) | 0.673 |
|                                  | Female | 105 (57.1) | 79 (42.9) |       |
| Education [n (%)]                | Below diploma | 123 (58.6) | 87 (41.4) | 0.937 |
|                                  | Diploma | 33 (58.9) | 23 (41.1) |       |
|                                  | Associate | 4 (66.7) | 2 (33.3) |       |
|                                  | Bachelor | 14 (51.9) | 13 (48.1) |       |
|                                  | Master or above | 3 (50.0) | 3 (50.0) |       |
| Family history of MHS [n (%)]    | Yes | 94 (72.9) | 35 (27.1) | < 0.001 |
|                                  | No | 83 (47.2) | 93 (52.8) |       |
| Duodenal ulcer [n (%)]           | Yes | 49 (94.2) | 3 (5.8) | < 0.001 |
|                                  | No | 128 (50.6) | 125 (49.4) |       |
| Gastric Ulcer [n (%)]            | Yes | 13 (65.0) | 7 (35.0) | 0.514 |
|                                  | No | 164 (57.5) | 121 (42.5) |       |
| Age (year) (mean ± SD)           | 44.36 ± 13.18 | 43.36 ± 17.51 | 0.306 |

H. pylori: Helicobacter pylori; MH: Migraine headache; SD: Standard deviation

Table 4. The relation between migraine headache (MH) and other variables

| Variables                        | Migraine | P       |
|----------------------------------|----------|---------|
|                                  | Positive | Negative |
| Sex [n (%)]                      | Male | 43 (35.5) | 78 (64.5) | 0.021 |
|                                  | Female | 90 (48.9) | 94 (51.1) |       |
| Education [n (%)]                | Below diploma | 92 (43.3) | 119 (56.7) | 0.549 |
|                                  | Diploma | 28 (50.0) | 28 (50.0) |       |
|                                  | Associate | 2 (33.3) | 4 (66.7) |       |
|                                  | Bachelor | 11 (40.7) | 16 (59.3) |       |
|                                  | Master or above | 1 (16.7) | 5 (83.3) |       |
| Family history of headaches [n (%)] | Yes | 86 (66.7) | 43 (33.3) | < 0.001 |
|                                  | No | 47 (26.7) | 129 (73.3) |       |
| Duodenal ulcer [n (%)]           | Yes | 33 (63.5) | 19 (36.5) | 0.002 |
|                                  | No | 100 (39.5) | 153 (60.5) |       |
| Gastric ulcer [n (%)]            | Yes | 9 (45.0) | 11 (55.0) | 0.897 |
|                                  | No | 124 (43.5) | 161 (56.5) |       |
| H. pylori contamination [n (%)]   | Yes | 123 (69.5) | 54 (30.5) |       |
|                                  | No | 10 (7.8) | 118 (92.2) |       |
| Age (year) (mean ± SD)           | 42.70 ± 12.61 | 44.36 ± 16.79 | 0.398 |

H. pylori: Helicobacter pylori; SD: Standard deviation
Hosseinzadeh, et al. in a case-control study have also shown a significant relation between anti H. pylori immunoglobulin G (IgG) and immunoglobulin M (IgM) titers and severity of migraine.29 A study on childhood migraine has also suggested that H. pylori contamination is more common in this population. However, the study could not strongly recommend UBT for these patients.30 A study on 60 patients with migraine showed that those infected with H. pylori experienced less frequent and less severe migraine attacks after H. pylori eradication.31 Lee, et al. in a study used the clinical data warehouse method to analyze data regarding patients with different types of headaches and showed non-significant findings in keeping with higher prevalence of H. pylori contamination among migraine patients.32 Faraji, et al. in a double-blind clinical trial on 64 patients with migraine showed that H. pylori eradication caused a significantly larger decrease in the MIDAS score in contrast to that H. pylori eradication caused a significantly clinical trial on 64 patients with migraine showed the control group receiving placebo. 15 Doulberis, migraine attacks after H. pylori eradication.31 Lee, pylori experienced less frequent and less severe migraine showed that those infected with H. pylori and migraine in patients with dyspepsia seems to be high, and a large percentage of migraine cases in these individuals are associated with H. pylori. Moreover, there was a significant relation between the peptic ulcer site and migraine, and duodenal ulcers were significantly related to migraine. Thus, migraine could be a disease beyond just brain involvement and H. pylori seems to be one of the factors having a meaningful association on this relation. Paying more attention to digestive problems in migraine and headache in patients with dyspepsia is beneficial as well as H. pylori eradication in these patients.

Conclusion
The present study on 305 patients showed a significant correlation between dyspepsia, migraine, and H. pylori infection. The prevalence of H. pylori and migraine in patients with dyspepsia seems to be high, and a large percentage of migraine cases in these individuals are associated with H. pylori. Moreover, there was a significant relation between the peptic ulcer site and migraine, and duodenal ulcers were significantly related to migraine. Thus, migraine could be a disease beyond just brain involvement and H. pylori seems to be one of the factors having a meaningful association on this relation. Paying more attention to digestive problems in migraine and headache in patients with dyspepsia is beneficial as well as H. pylori eradication in these patients.

Conflict of interests
The authors declare no conflict of interest in this study.

Acknowledgments
We would like to acknowledge Neuroscience Research Center of Qom University of Medical Sciences for its supports during the conduction of this study.
Migraine, dyspepsia, and Helicobacter pylori

between Helicobacter pylori infection and migraine: a meta-analysis. World J Gastroenterol 2014; 20(40): 14965-72.
15. Faraji F, Zarinfar N, Zanjani AT, Morteza A. The effect of Helicobacter pylori eradication on migraine: A randomized, double blind, controlled trial. Pain Physician 2012; 15(6): 495-8.
16. Tunca A, Turky C, Tekin O, Kargili A, Erbayrak M. Is Helicobacter pylori infection a risk factor for migraine? A case-control study. Acta Neurol Belg 2004; 104(4): 161-4.
17. Ansari B, Basiri K, Meamar R, Morteza A. The effect of Helicobacter pylori eradication on migraine: A randomized, double blind, controlled trial. Pain Physician 2012; 15(6): 495-8.
18. Chow WH, Blaser MJ, Blot WJ, Gammon MD, Vaughan TL, Risch HA, et al. An inverse relation between cagA+ strains of Helicobacter pylori infection and risk of esophageal and gastric cardia adenocarcinoma. Cancer Res 1998; 58(4): 588-90.
19. Yoshioka T, Takeshita E, Sakata Y, Hara M, Akutagawa K, Sakata N, et al. Helicobacter pylori infection status had no influence on upper gastrointestinal symptoms: A cross-sectional analysis of 3,005 Japanese subjects without upper gastrointestinal lesions undergoing medical health checkups. Esophagus 2017; 14(3): 249-53.
20. Rubenstein JH, Inadomi JM, Scheiman J, Schoenfeld P, Appelman H, Zhang M, et al. Association between Helicobacter pylori and Barrett's esophagus, erosive esophagitis, and gastroesophageal reflux symptoms. Clin Gastroenterol Hepatol 2014; 12(2): 239-45.
21. Camara-Lemarroy CR, Rodriguez-Gutierrez R, Monreal-Robles R, Marfil-Rivera A. Gastrointestinal disorders associated with migraine: A comprehensive review. World J Gastroenterol 2016; 22(36): 8149-60.
22. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. Pain 2000; 88(1): 41-52.
23. Kwong WJ, Pathak DS. Validation of the eleven-point pain scale in the measurement of migraine headache pain. Cephalalgia 2007; 27(4): 336-42.
24. Yiannopoulou KG, Efthymiou A, Karydakis K, Arhimandritis A, Bovaretos N, Tsivras M. Helicobacter pylori infection as an environmental risk factor for migraine without aura. J Headache Pain 2007; 8(6): 329-33.
25. Chabriet H, Danchot J, Michel P, Joire JE, Henry P. Precipitating factors of headache. A prospective study in a national control-matched survey in migraineurs and nonmigraineurs. Headache 1999; 39(5): 335-8.
26. Covelli V, Pellegrino NM, Jirillo E. A point of view: The need to identify an antigen in psychoneuroimmunological disorders. Curr Pharm Des 2003; 9(24): 1951-5.
27. Gabrielli M, Fiore G, Candelli M, Giacovazzo M, Pola P, Gasbarrini G, et al. Re: "Chronic Helicobacter pylori infection and migraine: A case-control study" (Pinessi L, Savi L, Pellicano R, et al. Headache. 2000; 40: 836-839). Headache 2002; 42(3): 236-7.
28. Su J, Zhou XY, Zhang GX. Association between Helicobacter pylori infection and migraine: a meta-analysis. World J Gastroenterol 2014; 20(40): 14965-72.
29. Hosseinzadeh M, Khosravi A, Saki K, Ranjbar R. Evaluation of Helicobacter pylori infection in patients with common migraine headache. Arch Med Sci 2011; 7(5): 844-9.
30. Bradbeer L, Thakkar S, Liu A, Nanar R. Childhood headache and H. pylori--a possible association. Aust Fam Physician 2013; 42(3): 134-6.
31. Bakhtishpour A, Momeni M, Ramroodi N. Effect of Helicobacter pylori treatment on the number and intensity of migraine attacks. Zahedan J Res Med Sci 2012; 14(6): 6-8.
32. Lee SH, Lee JH, Kwon Y, Kim JH, Sohn JH. Clinical implications of associations between headache and gastrointestinal disorders: A study using the Hallym Smart Clinical Data Warehouse. Front Neurol 2017; 8: 526.
33. Pinessi L, Savi L, Pellicano R, Rainero I, Valfre W, Gentile S, et al. Chronic Helicobacter pylori infection and migraine: A case-control study. Headache 2000; 40(10): 836-9.