Iranian Journal of Neurology

Original Paper

Iran J Neurol 2019; 18(1): ???-???

Migraine, dyspepsia, and Helicobacter pylori; zeroing in on the culprit

Received: 12 Sep. 2018
Accepted: 05 Nov. 2018

Nayereh Akbari[1], Ahmad Hormati[2], Ehsan Sharifipour[1], Seyed Amir Hejazi[1], Fatemeh Jafari[1], Seyed Ali Mousavi-Aghdas[3], Samad EJ Golzari[4,5]

[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 dyspeptic patients 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, which were prepared exactly from Migraine Disability Assessment (MIDAS) questionnaire. The relation between migraine and confirmed H. pylori contamination was investigated using statistical models.

Results: Of all the 305 patients, 133 (43.6%) had confirmed episodic migraine headaches (MHs). 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: Patients with dyspepsia seem to have more migraine attacks. Also, it seems that there is a meaningful association between migraine, duodenal peptic ulcers, and H. pylori.

How to cite this article: Akbari N, Hormati A, Sharifipour E, Hejazi SA, Jafari F, Mousavi-Aghdas SA, et al. Migraine, dyspepsia, and Helicobacter pylori; zeroing in on the culprit. Iran J Neurol 2019; 18(1): ???-???.

Email: ijnl@tums.ac.ir

Corresponding Author: Ehsan Sharifipour
Email: sharifipour.e@gmail.com

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.[2] 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.[3] Most frequent triggering factors are limited to stress, fatigue, fasting, alcohol, sleep deprivation, climatic conditions, and hormonal, visual, olfactory, and auditory stimuli.[4] 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.[5-8]

Helicobacter pylori (H. pylori) is a helical gram-negative bacterium involved in peptic ulcer disease, gastric adenocarcinoma, and lymphoma.[9] 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.[10,11] 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.[12-14] Furthermore, numerous studies have shown the efficacy of H. pylori eradication on the number, severity, and recurrence of migraine attacks.[13,15] 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.[16-18] Thus, careless eradication of H. pylori may be unbeneficial in asymptomatic patients. Altogether, the current data are limited about the exact correlation, especially regarding the relationship between the migraine and the peptic ulcers.[19] 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 patients undergoing upper GI endoscopy in a tertiary specialized center: Shahid Beheshti Hospital affiliated to Qom University of Medical Sciences, Qom, Iran. Patients were recruited from May 2016 to May 2017. Using MedCalc statistical software (version 16.4.3, MedCalc Software bvba, Ostend, Belgium), the sample population of 304 was calculated considering the results from the reliable and correlate studies.

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] the patients were asked to answer the questions related to migraine from the study questionnaire (designed for this study) which were prepared exactly from the Migraine Disability Assessment (MIDAS) questionnaire.[20] Questions related to findings from endoscopy (iron deficiency anemia, vomiting, epigastric pain, melena, hematemesis, rectorrhagia, dyspepsia, etc.), findings in esophagus (reflux, erosive esophagitis, stricture, varices, neoplasia, etc.), stomach, and duodenum (peptic ulcer, erosive gastritis, hernia, neoplasia, etc.), rapid urease test (RUT) results, and laboratory results from liver function test [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin]. RUT, unlike the enzyme-linked immunosorbent assay (ELISA) for antibacterial antibody, has the advantage of showing present infection. Two researchers assisted patients while answering the questionnaire. To evaluate the validity and accuracy of the questionnaire, a trial was performed on 30 patients and errors in the questionnaire were corrected. Primary outcome of the present study was the evaluation of the correlation between migraine and peptic ulcers

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/m^2)	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)	00-07	0.94 ± 0.40

BMI: Body mass index; MH: Migraine headache; MIDAS: Migraine disability assessment; SD: Standard deviation

among patients with dyspepsia undergoing upper GI endoscopy considering the role of confirmed and present H. pylori contamination.

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.

To present the data, we used descriptive statistical methods such as mean, standard deviation (SD), and frequency and to assess the correlation between variables. All of our statistical analyses were performed by SPSS software (version 22, IBM Corporation, Armonk, NY, USA). More precisely, student's t-test (for quantitative variables), Fisher's exact test (for categorical variables), and chi-square test were used for data analysis. A P-value less than 0.050 was considered statistically significant.

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). 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. 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).

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)	-
P	< 0.001	-	-

H. pylori: Helicobacter pylori

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	Yes	13 (65.0)	7 (35.0)	0.514
Ulcer [n (%)]	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

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.

Discussion

The current cross-sectional study demonstrated that migraine was a common complain among patients with dyspepsia. Moreover, it seems that 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.[21-23] 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.[14,19,24]

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.

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	118	
Age (year) (mean ± SD)		42.70 ± 12.61	44.36 ± 16.79	0.398

H. pylori: Helicobacter pylori; SD: Standard deviation

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.[12] In our study, we used RUT because it is cost-effective and a positive RUT indicates present contamination. 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.[25] 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.[26] 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.[27] 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.[28] 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 the control group receiving placebo.[13] Doulberis, et al. in a recent literature review demonstrated a higher prevalence of GI presentations among patients with migraine, although a clear pathophysiology remained unclear.[9] On the other hand, Pinessi, et al. reported that the infection of H. pylori was not more common among patients with migraine compared to control patients.[29]

In our study, the relation between H. pylori contamination and presence of migraine in patients with dyspepsia was significant. Interestingly, migraine and duodenal peptic ulcers were significantly correlated, while there was no significant relation between gastric ulcers and migraine. This may be due to significant correlation between ulcer at the duodenum and H. pylori contamination in contrast to gastric ulcer which was not significantly correlated with H. pylori infection. This finding emphasizes the migraine association of H. pylori contamination with the difference in the site of peptic ulcers (stomach or duodenum). At this study, female sex was a risk factor for migraine, but age and education level were not correlated with migraine.

Conclusion

The present study on 305 patients showed a significant correlation between dyspepsia, migraine, and H. pylori infection. Also, 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 patients with migraine is recommended and if a patient is infected by this microbe, eradication could be beneficial.

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.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013; 33(9): 629-808.
2. Haagsma JA, Graetz N, Bolliger I, Naghavi M, Higashi H, Mullany EC, et al. The global burden of injury: Incidence, mortality, disability-adjusted life years and time trends from the Global Burden of Disease study 2013. Inj Prev 2016; 22(1): 3-18.
3. Gajria K, Lee LK, Flores NM, Aycardi E, Gandhi SK. Humanistic and economic burden of nausea and vomiting among migraine sufferers. J Pain Res 2017; 10: 689-98.
4. Goadsby PJ. Pathophysiology of migraine. Neurol Clin 2009; 27(2): 335-60.
5. Peroutka SJ. What turns on a migraine? A systematic review of migraine precipitating factors. Curr Pain Headache Rep 2014; 18(10): 454.
6. Kimball RW, Friedman AP, Vallejo E. Effect of serotonin in migraine patients. Neurology 1960; 10: 107-11.
7. Deen M, Christensen CE, Hougaard A, Hansen HD, Knudsen GM, Ashina M. Serotonergic mechanisms in the migraine brain - a systematic review. Cephalalgia 2017; 37(3): 251-64.
8. Deen M, Hansen HD, Hougaard A, Norgaard M, Eiberg H, Lehel S, et al. High brain serotonin levels in migraine between attacks: A 5-HT4 receptor binding PET study. Neuroimage Clin 2018; 18: 97-102.
9. Doulberis M, Saleh C, Beyenburg S. Is there an Association between migraine and gastrointestinal disorders? J Clin Neurol 2017; 13(3): 215-26.
10. Blaser MJ. Helicobacter pylori and gastric diseases. BMJ 1998; 316(7143): 1507-10.
11. Franceschi F, Gasbarrini A, Polyzos SA, Kountouras J. Extragastric diseases and Helicobacter pylori. Helicobacter 2015; 20(Suppl 1): 40-6.

12. Wong F, Rayner-Hartley E, Byrne MF. Extraintestinal manifestations of Helicobacter pylori: A concise review. World J Gastroenterol 2014; 20(34): 11950-61.
13. Mann NS, Singh S. Helicobacter pylori and migraine: Systematic evaluation of 1084 cases with meta-analysis. International Medical Journal 2015; 22(2): 65-6.
14. Su J, Zhou XY, Zhang GX. Association 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, Turkay 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, Chitsaz A, Nematollahi S. Association of Helicobacter pylori antibodies and severity of migraine attack. Iran J Neurol 2015; 14(3): 125-9.
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. Yiannopoulou KG, Efthymiou A, Karydakis K, Arhimandritis A, Bovaretos N, Tzivras M. Helicobacter pylori infection as an environmental risk factor for migraine without aura. J Headache Pain 2007; 8(6): 329-33.
24. Chabriat 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.
25. Covelli V, Pellegrino NM, Jirillo E. A point of view: The need to identify an antigen in psyconeuroimmunological disorders. Curr Pharm Des 2003; 9(24): 1951-5.
26. 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.
27. 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.
28. Bradbeer L, Thakkar S, Liu A, Nanan R. Childhood headache and H. pylori--a possible association. Aust Fam Physician 2013; 42(3): 134-6.
29. Bakhshipour 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.
30. Lee SH, Lee JJ, 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.
31. 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.