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The relationship between Helicobacter infection and endoscopic upper gastrointestinal diseases and migraine

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Abstract

Objectives: Migraine is often associated with various gastrointestinal (GI) symptoms and disorders, including *Helicobacter pylori* (Hp) infection. The aim of this study was to investigate both the relationship between migraine and Hp infection and the relationship between migraine and endoscopic upper GI diseases. *Methods:* This prospective observational case-control study involved 91 migraine patients and 80 control individuals with no history of migraines presenting with upper GI symptoms. Both groups underwent upper GI endoscopy, and gastric biopsy specimens were histopathologically examined. Headache frequency, duration and pain intensity (measured by VAS) were re-evaluated in the Hp-positive migraine group at week 8 post-eradication. *Results:* There was no statistically significant difference between migraine and control groups regarding Hp prevalence *(p=0.117).* Gastroesophageal reflux disease (GERD) was the most prevalent endoscopic upper GI condition in migraine patients (52.7%) than control group. It was statistically significant ($p < 0.001$). There was no statistically significant association detected between GERD and Hp in migraine subgroups ($p = 0.966$), indicating independence of GERD from Hp. 40.7% of migraine patients had moderate chronic inflammation in the gastric antrum, while this rate was 25.0% in the control group *(p=0.037*). 30.8% of migraine patients had moderate acute inflammation in the gastric antrum, while this rate was 28.7% in the control group *(p=0.036).* While moderate acute inflammation was 45.3% in Hp-positive migraine patıents, it was 10.5% in Hp-negative migraineurs*(p <0.001).* While severe chronic inflammation was present in 7.5% of Hp-positive migraine patients, it was absent in Hp-negative migraineurs. Moderate chronic inflammation was observed in 52.8% of Hp-positive and 23.7% of Hp-negative migraine patients, with a significant positive relationship between chronic inflammation and Hp in migraine patients (*p<0.001).*Although no significant differences in attack frequency and average attack duration was detected between the Hp-positive and Hp-negative migraine subgroups. The pain intensity between migraine subgroups exhibited a significant difference being higher in Hp-positive migraine patients *(p= 0.044).* In addition, in the Hp-positive migraine group, significant differences were observed in attack frequency(day/month), attack intensity(visual analog scale) and average attack duration(hours) at the 8th week post-eradication compared to the pre-eradication period.The attack frequency in the Hp-positive migraine group who have been treated was 10.0 before treatment and 6.0 after treatment(*p<0.001).* The attack intensity was 8.0 before treatment and 5.0 after treatment*(p<0.001).* The average attack duration was 5.0 before treatment and 4.0 after treatment(*p<0.001).*
Conclusion: We conclude that Hp causes more chronic active inflammation in migraine sufferers than in individuals with upper GI symptoms without a history of migraine. In addition, migraine sufferers infected with Hp experienced more severe levels of inflammation compared to those not infected with the bacterium. In Hp-infected migraine patients, the presence of the bacteria may be related to the severity of the pain attacks. Hp eradication therapy may potentially play an important role in headache management in Hp-positive migraineurs with upper GI symptoms in addition to conventional migraine treatments. A positive association was also found between GERD and migraine patients independent of Hp status.

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INTRODUCTION

The bidirectional interaction between the gut and the brain axis plays a important role in various neurological conditions.[1-3] Autonomic dysfunction affecting both migraine and gastric diseases involves alterations in the intestinal microbiota profile, influenced by hormonal and cytokine signaling.[4] Emerging evidence suggests a potential link between the intestinal microbiota and neurological conditions such as migraine.[5]

Despite numerous publications, the relationship between migraine and *Helicobacter pylori* (Hp) infection remains inconclusive. A meta-analysis by Su *et al*. revealed conflicting results, with some studies indicating a strong positive assosiation between migraine and Hp infection, while others showed negative findings, highlighting the influence of ethnic differences and study heterogeneity.[6]

Hp, a gram-negative microorganism, colonizes the stomach lining of over half the global population, causing chronic inflammation and systemic effects.[7] Its colonization of the gastric mucosa leads to systemic and permanent inflammation manifested with elevated levels of free radicals, chemokines and cytokines along with neurotransmitter release and increased neuropeptide levels. Consequently, Hp infection may disrupt the blood-brain barrier and induce axonal/neuronal injury.[8] Many researchers have found that eradication of the infectious agent significantly reduces the frequency and severity of migraine attacks. According to a review article, the data suggest that Hp eradication relieves migraine symptoms.[9]

While the presence of abnormal findings in upper gastrointestinal system (GIS) endoscopy in migraine patients has an extremely low prevalence, both epidemiological data and pathophysiological evaluations suggest a possible relationship between migraine and GIS disorders.[10,11] Further investigation into this relationship is warranted, as it may have important therapeutic implications.

The aims of this study were to investigate both the relationship between migraine and Hp infection as well as the relationship between migraine and endoscopic upper GI diseases.

METHODS

Study population

This prospective observational case-control study received approval from the Siirt University Ethics Committee (approval number: 27.02.2023-4324) and was carried out in accordance with the Declaration of Helsinki. The study enrolled a total of 91 patients diagnosed with migraine and 80 control individuals with no history of migraines at all. Participants were recruited from the neurology and general surgery outpatient clinics of Siirt Training and Research Hospital between May 2023 and August 2024. Sample size calculation, significance level determination, and effect size estimation were performed using the G-Power 3.1 program. Assuming a large effect size (effect size = 0.3) and accepting a difference between groups, a minimum sample size of 88 cases was calculated for 80% power and an alpha significance level of 0.05. Migraine diagnosis was established based on the criteria defined in the ICHD-3 beta version.[12] All patients diagnosed with migraine, including those with episodic or chronic migraine with or without aura, and regardless of preventive treatment status were included. The age range for inclusion was >18 to <70 years. Other diagnostic imaging modalities, including computed tomography or magnetic resonance imaging were conducted when deemed necessary to exclude secondary headache causes.

Detailed demographic information and clinical parameters, including attack frequency (day/month), attack intensity evaluated using a visual analog scale (VAS), average attack duration (in hours) and associated symptoms such as nausea, vomiting, phonophobia, photophobia, and non-attack upper GI symptoms, were recorded for the migraine group. The VAS, ranging between 0 (no pain) and 10 (worst pain), used by migraine patients for pain intensity assessment. 80 individuals without a history of migraine who presented to the general surgery outpatient clinic with upper GI symptoms (nausea, vomiting, bloating, epigastric pain, dyspepsia, gastroparesis) were questioned individually by a neurologist to exclude migraine headache.

Exclusion criteria comprised known GI disorders (e.g., cholecystitis, celiac disease, inflammatory or irritable bowel syndrome, GI neoplastic lesions), prior Hp eradication treatment, GI bleeding observed on endoscopy,

drug intolerance at any stage of the study, and recent use of antibiotics, H_2 blockers, or proton pump inhibitors within the last two weeks.

Protocol and application

After obtaining written consent from participants upper GI procedures were conducted by two general surgeons who were completely blinded to migraine-control groups using a Fujinom brand endoscope. Premedication involved intravenous administration of 0.00-0.05 mg/kg midazolam and 1-3 mg/kg propofol 1-2 minutes before the procedure under anesthesia. Biopsy material was obtained from the gastric antrum in cases without mucosal changes, whereas 2-3 biopsy specimens were collected from areas exhibiting mucosal changes (e.g., edema, nodularity, hyperemia, ulcer, polyp, erosion) using forceps. These specimens were subsequently fixed in 10% buffered formalin and embedded in paraffin. The 2-micron-thick slides were stained with hematoxylin & eosin for routine examination and with modified Giemsa for Hp detection by a pathologist who was completely blinded to migraine-control groups. Biopsies were then assessed based on the Sydney classification, and Hp status was categorized as negative (-), mild (+), moderate (++), or severe (+++). Gastritis classification and grading are performed according to the Sydney classification, which grades the severity of acute inflammation based on neutrophil density, the severity of chronic inflammation, glandular atrophy, intestinal metaplasia and H. pylori density.[13] We excluded glandular atrophy and intestinal metaplasia from the evaluation in this study.

Endoscopic diagnoses of upper GI diseases included esophagitis, gastritis, proximal duodenitis, esophageal ulcer, gastric and duodenal ulcer, alkaline reflux, GERD (non-erosive), non-functional pylorus, gastric diverticulum, and gastric polyps.

Follow-up

Triple therapy comprising clarithromycin (500 mg; bid), amoxicillin (1000 mg; bid) and lansoprazole (30 mg; bid) was administered to all histopathologically Hp-positive patients for 14 days to achieve eradication. Hp fecal antigen testing was conducted via immunochromatographic test at 4 weeks and negativity was evaluated. Headache variables were reassessed in Hp positive migraine patients 8 weeks after eradication.

Statistical analysis

The collected data were analyzed using IBM SPSS for Windows version 29.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests, and homogeneity of variances was evaluated with Levene's test.

Headache-related continuous variables, including attack frequency (days/month), attack duration (hours), and pain intensity (VAS score), did not meet normality assumptions and exhibited right-skewed distributions with ceiling effects. Therefore, these variables were consistently analyzed using non-parametric statistical methods and are presented as medians with minimum–maximum ranges.

Descriptive statistics are reported as medians (min–max) for non-normally distributed continuous variables, means ± standard deviations for normally distributed variables, and frequencies as n (%). Between-group comparisons of continuous variables were performed using the Mann–Whitney U test for independent samples and the Wilcoxon signed-rank test. Parametric tests were applied only to variables that satisfied normality assumptions.

Categorical variables were analyzed using the chi-square test, Yates' continuity correction, Fisher's exact test, or the Fisher–Freeman–Halton test, as appropriate, based on the number of categories and expected cell counts. A two-sided p value of < 0.05 was considered statistically significant.

RESULTS

The study comprised 91 migraine patients and 80 control individuals. Demographic characteristics and group comparisons between migraine and control groups are detailed in Table 1. Females constituted 86.8% (79 individuals) of migraine patients ($p < 0.001$). This indicated a significant difference in gender distribution between the migraine group and the control group. However, the difference in average age between migraine patients (40.20 ∓ 11.63 years) and the control group (41.14 ∓ 11.96) was not statistically significant ($p = 0.604$). Migraine patients experienced an average of 10 headache days per month, with a median VAS score of 8.0 (range: 1.0 to 10.0). The majority (73.6%) of patients had a disease duration exceeding 12 months. Nausea, vomiting, photophobia, and phonophobia were reported by 89.0%, 37.4%, 85.7%, and 84.6% of

Table 1: Comparison of migraine and control groups regarding demographic characteristics, histopathological findings, and endoscopic upper GI diseases

	Migraine n=91 (53.2%)	**Control n=80 (46.8%)**	**p-value**
Gender			
Female	79 (86.8%)	42 (52.5%)	**<0.001**[a]
Male	12 (13.2%)	38 (47.5%)	
Age	40.20∓11.63	41.14∓11.96	0.604[b]
Attack frequency (day/month)	10.0 (2.0-25.0)		
Attack intensity (VAS)	8.0 (1.0-10.0)		
Average attack duration (hrs)	5.0 (1.0-72.0)		
Duration of disease			
<12 months	24 (26.4%)		
≥12 months	67 (73.6%)		
Nausea			
No	10 (11.0%)		
Yes	81 (89.0%)		
Vomiting			
No	57 (62.6%)		
Yes	34 (37.4%)		
Photophobia			
No	13 (14.3%)		
Yes	78 (85.7%)		
Phonophobia			
No	14 (15.4%)		
Yes	77 (84.6%)		
Hp			
(-)	38 (41.8%)	43 (53.8%)	0.117[a]
(+)	53 (58.2%)	37 (46.2%)	
Hp intensity			
None	38 (41.8%)	43 (53.8%)	
Mild	21 (23.1%)	17 (21.3%)	0.176[a]
Moderate	18 (19.8%)	7 (8.8%)	
Severe	14 (15.4%)	13 (16.3%)	
Acute inflammation			
None	23(25.3%)	8 (10.0%)	
Mild	38(41.8%)	46 (57.5%)	**0.036**[c]
Moderate	28(30.8%)	23 (28.7%)	
Severe	2(2.2%)	3 (3.8%)	
Chronic inflammation			
None	6 (6.6%)	14 (17.5%)	
Mild	44 (48.4%)	44 (55.0%)	**0.037**[c]
Moderate	37 (40.7%)	20 (25.0%)	
Severe	4 (4.4%)	2 (2.5%)	

Table 1: (continued)

	Migraine n=91 (53.2%)	Control n=80 (46.8%)	p-value
Upper GI diseases			
Normal	10 (11.0%)	3 (3.8%)	
Gastritis	21 (23.1%)	44 (55.0%)	
Prox. duodenitis	1 (1.1%)	0 (0.0%)	
Esophagitis	2 (2.2%)	2 (2.5%)	
Esophageal ulcer	0 (0.0%)	1 (1.3%)	
Alkaline reflux	0 (0.0%)	24 (30.0%	
GERD(non-erozive)	48 (52.7%)	0 (0.0%)	
Gastric ulcer	4 (4.4%)	0 (0.0%)	**<0.001**[c]
(Prox. duodenitis + Afunctional pylorus)	1 (1.1%)	0 (0.0%)	
(Esophagitis + Esophageal Ulcer)	3 (3.3%)	1 (1.3%)	
(Gastric diverticulum + gastritis)	1 (1.1%)	1 (1.3%)	
Gastric polyp	0 (0.0%)	1 (1.3%)	
(Gastritis+prox duodenitis)	0 (0.0%)	3 (3.8%)	

GERD: gastroesophageal reflux disease, GI: gastrointestinal, VAS: visual analog scale. [a]*chi-square test,* [b]*independent samples t-test,* [c]*Fisher-Freeman-Halton test. Significant p values are written in bold.*

migraine patients, respectively.

Within the migraine group, 38 patients (4.8%) were Hp-negative, while 53 patients (58.2%) were Hp-positive; in the control group, 43 individuals (53.8%) were Hp-negative and 37 individuals (46.2%) were Hp-positive. The groups exhibited no significant differences in Hp status (p = 0.117). Similarly, there was no significant differences in Hp density between the migraine and control group, with proportions of 19.8% and 8.8%, respectively ($p = 0.176$). GERD was the most prevalent endoscopic upper GI condition in migraine patients (52.7%) than control group (0.0%). This difference is statistically significant ($p < 0.001$).

The relationship between endoscopic and histopathological findings of migraine and control groups with Hp intensity and eradication effectiveness is presented in Table 2. While moderate acute inflammation was present in 45.3% of Hp-positive migraine patients, it was only 10.5% in Hp-negative patients. Severe acute inflammation was exclusively detected in Hp-positive migraine patients (3.8%). The relationship between acute inflammation and Hp was statistically significant in Hp-positive migraine patients compared to Hp-negative patients ($p < 0.001$). Similarly, while severe chronic inflammation was present in 7.5% of Hp-positive migraine patients, it was absent in Hp-negative migraine patients. Moderate chronic inflammation was observed in 52.8% of Hp-positive and 23.7% of Hp-negative migraine patients, with a significant positive relationship between chronic inflammation and Hp in migraine patients ($p = 0.000$). There was no statistically significant association detected between GERD and Hp in migraine subgroups ($p = 0.966$), indicating independence of GERD from Hp.

An eradication protocol was applied to both Hp positive 53(100%) migraine patients and Hp positive 37(100%) controls. Hp antigen negativity in stool samples analysed by immunochromatographic test at the fourth week after H.Pylori eradication in migraine patients and control group was statistically significant ($p < 0.001$). In Hp positive migraine patients, the absence of Hp antigen in faeces after eradication was 84.9%, while the presence of Hp antigen was 9.4%.

A comparison of the relationship between headache parameters and Hp in migraine patients is presented in Table 3. The difference between the gender distribution of migraine patients was not statistically significant between both groups

Table 2: Comparison of endoscopic and histopathological findings of migraine and control groups in relation to H.pylori as well as eradication efficiency

	Migraine		p-value	Control		p-value
	Hp (-)	Hp (+)		Hp (-)	Hp (+)	
Hp intensity						
0 (none)	38 (100.0%)	0 (0.0%)	0.000[a]	43 (100.0%)	0 (0.0%)	<0.001[b]
1 (mild)	0(0.0%)	21 (39.6%)		0(0.0%)	17 (45.9%)	
2 (moderate)	0(0.0%)	18 (34.0%)		0(0.0%)	7 (18.9%)	
3 (severe)	0(0.0%)	14 (26.4%)		0(0.0%)	13 (35.1%)	
Acute inflammation						
0 (none)	17 (44.7%)	6 (11.3%)	0.000[b]	6 (14.0%)	2 (5.4%)	**0.007**[a]
1 (mild)	17 (44.7%)	21 (36.6%)		30 (69.8%)	16 (43.2%)	
2 (moderate)	4 (10.5%)	24 (45.3%)		6 (14.0%)	17 (45.9%)	
3 (severe)	0 (0.0%)	2 (3.8%)		1 (2.3%)	2 (5.4%)	
Chronic inflammation						
0 (none)	6 (15.8%)	0 (0.0%)	0.000[b]	12 (27.9%)	2 (5.4%)	**0.023**[b]
1 (mild)	23 (60.5%)	21 (39.6%)		22 (51.2%)	22 (59.5%)	
2 (moderate)	9 (23.7%)	28 (52.8%)		9 (20.9%)	11 (29.7%)	
3 (severe)	0 (0.0%)	4 (7.5%)		0 (0.0%)	2 (5.4%)	
Upper GI diseases						
Normal	5 (13.2%)	5 (9.4%)	0.966[b]	3 (7.0%)	0 (0.0%)	0.245[b]
Gastritis	8 (21.1%)	13 (24.5%)		23 (53.5%)	21 (56.8%)	
Prox.duodenitis	1 (2.6%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Esophagitis	1 (2.6%)	1 (1.9%)		1 (2.3%)	1 (2.7%)	
Esophageal ulcer	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (2.7%)	
Alkaline reflux	0 (0.0%)	0 (0.0%)		12 (27.9%)	12 (32.4%)	
GERD(non-erozive)	21 (55.3%)	27 (50.9%)		0 (0.0%)	0 (0.0%)	
Gastric ulcer	1 (2.6%)	3 (5.7%)		0 (0.0%)	0 (0.0%)	
(Prox.duodenitis + afunctional pylorus)	0 (0.0%)	1 (1.9%)		0 (0.0%)	0 (0.0%)	
(Esophagitis + esophageal ulcer)	1 (2.6%)	2 (3.8%)		0 (0.0%)	1 (2.7%)	
(Gastric diverticulum+gastritis)	0 (0.0%)	1 (1.9%)		1 (2.3%)	0 (0.0%)	
Gastric polyp	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (2.7%)	
(Gastritis + prox. Duodenitis)	0 (0.0%)	0 (0.0%)		3 (7.0%)	0 (0.0%)	
Fourth week Hp antigen in stool						
Antigen not investigated	12 (31.6%)	3 (5.7%)	0.000[b]	0(0.0%)	0(0.0%)	<0.001[c]
Antigen (+)	6 (15.8%)	5 (9.4%)		0(0.0%)	14 (37.8%)	
Antigen (-)	20 (52.6%)	45 (84.9%)		43(100%)	23 (62.2%)	

GERD: gastroesophageal reflux disease, GI: gastrointestinal, Hp: Helicobacter pylori. [a]chi-square test, [b]Fisher-Freeman-Halton test, [c]Yates' chi-square test. Significant p values are written

Table 3: Comparison of the relationship between headache parameters and H. pylori in the migraine subgroups

	Migraine Hp (-) n (%) or mean±SD and median (range)	Migraine Hp (+) n (%) or mean±SD and median (range)	p-value
Gender			
Female	32 (84.2%)	47 (88.7%)	0.759[a]
Male	6 (15.8%)	6 (11.3%)	
Age	42.03∓11.83	38.89∓11.41	0.206[b]
Attack frequency (day/month)	10.0 (2.0-25.0)	12.0 (2.0-25.0)	0.444[c]
Attack intensity (VAS)	7.0 (1.0-10.0)	8.0 (5.0-10.0)	**0.044[c]**
Average attack duration (hrs)	3.5 (1.0-72.0)	6.0 (1.0-72.0)	0.189[c]
Duration of disease			
<12 months	10 (26.3%)	14 (26.4%)	0.992[a]
≥12 months	28 (73.7%)	39 (73.6%)	
Nausea			
No	4 (10.5%)	6 (11.3%)	1.000[c]
Yes	34 (89.5%)	47 (88.7%)	
Vomiting			
No	26 (68.4%)	31 (58.5%)	0.334[a]
Yes	12 (31.6%)	22 (41.5%)	
Photophobia			
No	7 (18.4%)	6 (11.3%)	0.515[d]
Yes	31 (81.6%)	47 (88.7%)	
Fonofobi			
No	7 (18.4%)	7 (13.2%)	0.700[d]
Yes	31 (81.6%)	46(86.8%)	

Hp: Helicobacter pylori, VAS: visual analog scale. [a]chi-square test, [b]independent samples t-test, [c]Fisher's exact test, [d]Yates' chi-square test. Significant p values are written in bold.

(p= 0.759). The difference between the average ages of migraine patients in the Hp-positive and Hp-negative groups was not statistically significant (p = 0.206). No significant difference was detected between Hp-positive and Hp-negative migraine patients with respect to attack frequency and average attack duration (p = 0.444 and p = 0.189, respectively). However, the pain intensity between migraine subgroups exhibited a significant difference (p = 0.044) being higher in Hp-positive patients.

The differences in attack frequency, attack intensity, and average attack duration in migraine patients at 8 weeks after eradication compared to before treatment were statistically significant (p < 0.001) (Table 4).

At week 8, there was a decrease in attack frequency, attack intensity, and average attack duration (Figure 1).

DISCUSSION

Migraine is a prevalent and incapacitating primary headache disorder that exhibits a higher prevalence in females (19.8%) compared to males (9.8%).[14] Migraine is characterized as a recurrent headache disorder with moderate or severe headache attacks accompanied by

Table 4: Comparison of headache parameters before and after eradication in the H. pylori-positive migraine group

	Initiation	8th week	p-value[a]
	Mean±SD and median (range)	Mean±SD and median (range)	
Attack frequency (day/month)	10.0 (2.0-25.0)	6.0 (1.0-12.0)	**<0.001**
Attack intensity (Vas)	8.0 (1.0-10.0)	5.0 (3.0-7.0)	**<0.001**
Average attack duration (hrs)	5.0 (1.0-72.0)	4.0 (1.0-12.0)	**<0.001**

VAS: visual analog scale.[a]Wilcoxon signed-rank test.Significant p values are written in bold.

nausea and/or vomiting, photophobia and phonophobia that may last 4-72 hours.[12] Nausea (especially vomiting) accompanying headache is an important factor that increases migraine disability.[15] A large-scale study in the USA reported that 73% of migraineurs had symptoms of nausea and 29% had symptoms of vomiting .[16] Our study involving 91 migraine patients, predominantly comprised females 86.8% with 89.0% experiencing nausea and 37.4% reporting vomiting alongside their migraine attacks.

Studies such as the HEAD-HUNT survey in Norway have demonstrated a higher prevalence of headaches among individuals reporting GI symptoms.[17] A web-based survey indicated that 22% of migraine patients reported experiencing GERD[18], while a clinic study found a higher prevalence of GERD in migraineurs (42%), compared to those without migraine (18%).[19] While the precise mechanism underlying this association remains unclear, autonomic nervous system dysfunction is often implicated[20-24] with delayed gastric emptying (gastric stasis) and gastroparesis identified as potential contributors to GERD development.[25] Katić *et al.* found that among 1,800 migraine patients, approximately half had GERD.[20] Hormati *et al*. reported that 78 (71.56%) of 109 GERD patients had migraines.[26] In our study, in parallel with the literature, the prevalence of GERD among upper GI diseases in the migraine group was 52.7%, and it was positively associated with migraine. Additionally, no significant association was observed between Hp infection and upper GI diseases in Hp-positive migraine patients.

Meucci *et al.* reported that 90% of migraine patients exhibiting symptoms such as nausea, vomiting, and other GI dysmotility-like symptoms had completely normal endoscopic findings .[11] Research has also indicated a low occurrence of irregularities detected during upper GI endoscopy and esophageal pH monitoring in migraine patients.[10] However, in our study we found that only 10 (11.0%) migraine patients had normal upper GI endoscopy results, indicating a higher prevalence of abnormal endoscopic GI findings among migraine patients.

Triggering of pain pathways originating from parasympathetic trigeminal nerve fibers in migraine leads to the secretion of CGRP

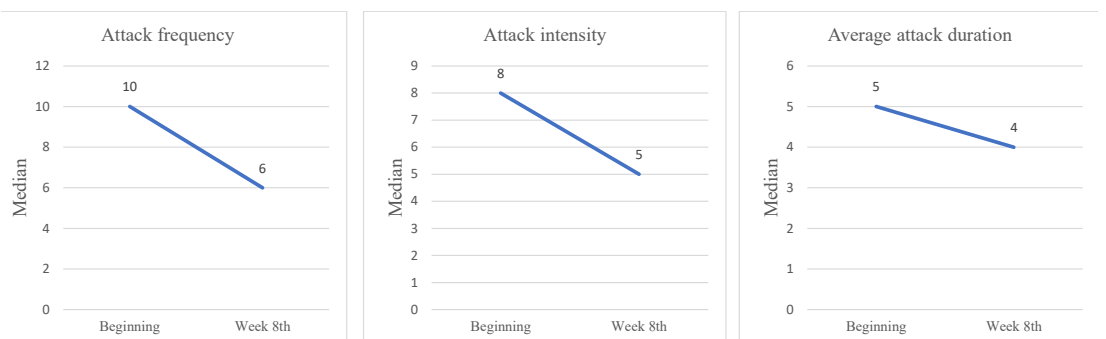

Figure 1. Variability in headache parameters between before and after eradication in H. pylori -positive migraine patients.

and pro-inflammatory agents impacting the pathophysiology of both migraines and GI ailments.[27,28] The stress triggered by physical and psychological factors in gastric diseases is thought to instigate changes in the intestinal microbiota and permeability alongside the release of pro-inflammatory cytokines. Additionally, alterations in serotonergic signaling play a pivotal role, activating the trigeminovascular system implicated in initiating migraine pain. These changes may precipitate gastric symptoms like nausea, vomiting, and delayed gastric emptying.[4,28,29]

Research findings offer inconclusive evidence regarding the link between migraine and Hp infection.[6] A meta-analysis by Bawand et al.'s comprising 12 observational studies, eight of which were case-control, revealed a potential relationship between migraine and Hp infection despite exhibiting relatively high heterogeneity ($p < 0.01$).[30] A high-quality study involving 98 patients with migraine without aura and 5 with aura revealed that the prevalence of Hp infection did not differ significantly between the migraine and control group and did not notably alter the clinical features of migraine.[31] Similarly, another study found no significant assosiation between Hp infection and migraine headaches in children.[32] Gasbarrini *et al.* conducted a high-quality study that showed similar prevalence rates of Hp in both migraine patients and controls.[33] In this study, we did not find a statistically significant result between migraine and control groups in terms of bacteria intensity(concentration). But unlike the studies mentioned, our histopathological data show that the presence of bacteria in the gastric antrum is effective in migraine pain severity independent intensity of bacteria. Migraine is associated with more severe levels of inflammation when Hp infection is present.

Hp is recognized for its role in inducing chronic active inflammation.[7] The bacterium has developed mechanisms to circumvent the immune system, including the inhibition of effector T cell responses and manipulation of immune receptors, which can vary depending on whether specific bacterial virulence factors are present or absent.[34] Consequently, the host's immune response can trigger the local secretion of inflammatory mediators, including interleukins (IL-1,6,8,10,12, IFN gamma, TNF-alpha), which may enter the bloodstream, exerting systemic effects.[35,36] The sustained existence of these pro-inflammatory agents locally and systemically can result in neuroinflammation and toxicity, resulting in axonal/neuronal damage and the generation of free radicals and vasoactive intestinal peptides.[37] In the current study, histopathological analysis of the biopsy specimens revealed a higher prevalence of chronic inflammation in Hp-positive migraine patients than in non-migraineurs. In addition, acute and chronic inflammation in biopsy specimens was higher in hp-positive migraine group than in hp-negative migraineurs. The observed relationship between inflammation caused by the bacteria and the severity of migraine pain suggests a potential association. These histopathological findings underscore the significance of Hp infection as a potential contributing factor in migraine pathology.

The fecal Hp antigen test, one of the non-invasive tests employed to assess eradication efficacy and for social seroprevalence screening in the Hp-positive group was utilized in our study. In a meta-analysis of 48 studies examining the sensitivity and specificity of test results using monoclonal antibodies, the sensitivity varied between 94% and 98%, while specificity ranged from 95% to 98%. [38] In our study, immunochromatographic test of Hp antigen in stool samples at the fourth week post-eradication revealed high levels in both the migraine (84.9%) and control groups (62.2%) suggesting effective eradication. When attack frequency, attack intensity and average attack duration were compared between patients in the Hp-positive and Hp-negative migraine groups, an increase in attack intensity was observed only in Hp-positive migraineurs.

In recent investigations, Hassan *et al*. found no significant relationship between the frequency and severity of migraine attacks and H.pylori in their study published in 2022.[39] Cavestro *et al.* observed a higher incidence of headaches among Hp-negative individuals.[40] Similarly, Elnady et al. did not report a significant correlation between migraine frequency, duration, and intensity and Hp infection.[41] While the assessment methods varied across these studies, their overall findings suggest no discernible disparities in migraine symptoms and characteristics between patients with Hp infection and other migraineurs.

Eradicating Hp infection has demonstrated potential in relieving migraine headaches. These improvements manifest across various parameters, including reduced headache intensity, improved headache duration, and a decrease in the frequency of attacks.[9] Consistent with these

observations, our study revealed a significant reduction in the frequency of pain attack, attack intesity and average attack duration among our Hp-positive migraine patients evaluated at the eighth week post-eradication compared to pre-eradication.

This study was subject to certain limitations. Firstly, data were gathered from individuals attending a single training and research hospital within a regional community, thus limiting the generalizability of the findings to the broader population.

Secondly, despite the higher number of patients assessed both endoscopically and histopathologically in the Hp-positive migraine-control groups, exclusions were necessary for individuals who experienced intolerance to eradication treatment or were unable to complete clinical follow-up. These exclusions resulted in a reduction in our overall sample size.

The inability to detect antigens in some stool samples was particularly due to patient-related factors in the Hp- migraine group; however, since the Hp+ migraine and Hp+ control groups underwent eradication, this did not affect the flow of our study.

Thirdly , a significant gender imbalance was observed between the migraine and control groups, with a higher proportion of female participants in the migraine cohort. While subgroup analyses within the migraine group revealed no significant gender-related differences between Hp-positive and Hp-negative individuals, this baseline discrepancy may have influenced the overall comparisons between study groups. Therefore, the gender distribution should be considered when interpreting the generalizability and external validity of the study findings.

And finally, this study is observational, non-randomized, and not placebo-controlled. In the Helicobacter-positive migraine group, headache frequency, duration, and pain intensity assessed by VAS scores after eradication were evaluated based on the verbal reports of migraine patients. Therefore, large-population randomized, placebo-controlled studies are needed to eliminate bias from the results of our study. Furthermore, migraine preventive medications, medication overuse, sleep disorders, psychiatric problems, etc. were not excluded.

We concluded that migraine patients with upper GI symptoms (nausea, vomiting, bloating, reflux, etc.) infected with Helicobacter infection are exposed to more chronic active inflammation than controls with upper GI symptoms without migraine headache. Migraine sufferers infected with Helicobacter pylori experienced more severe levels of inflammation compared to those not infected with the bacterium. The degree of inflammation caused by the bacteria may be associated with the severity of attack in Hp-infected migraine patients. Hp eradication therapy could potentially play an important role in headache management in Hp- positive migraine patients with upper GI symptoms in addition to conventional migraine treatments. Further research is needed to confirm the efficacy of Hp eradication as a novel therapeutic approach in migraine treatment. Additionally, no significant association was observed between Hp infection and upper GI diseases in Hp-positive migraine patients. GERD was more common in migraine patients and independent of Hp status.

DISCLOSURE

Ethics: Ethics committee approval has been granted from our institution. Informed consent has been obtained from all participants.

Data availability: The data supporting this study's findings are available on request from the corresponding author.

Conflict of interests: None

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