

ORIGINAL ARTICLE

Helicobacter Pylori Infection in Migraine Patients: A Case Control Study

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ABSTRACT

Key words:

Migraine, Helicobacter pylori, Stool antigen test, Migraine Disability Assessment Test

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Background: Worldwide about 12-15% of population complains of migraine at some point of their lives. Gastrointestinal disorders and infections including *Helicobacter pylori* (*H. Pylori*) have been the focus of many researches to delineate their relationship with migraine headache **Objectives:** To assess the coexistence of *H. pylori* and migraine headache and to assess the effect of *H. pylori* eradication on migraine impact among Egyptian patients. **Methodology:** In this case control study, eighty migraine patients and eighty age and sex matched healthy controls were enrolled. Migraine impact on patient's life was assessed on initial case evaluation by Migraine Disability Assessment Test (MIDAS1). *H. pylori* stool antigen test was done for all participants. *H. pylori* infected cases received levofloxacin based triple therapy and symptomatic control group received first line clarithromycin based therapy for 2 weeks. *H. pylori* stool antigen test was repeated 4 weeks after treatment regimen was completed. Reassessment of all cases by MIDAS2 was also done after 3 months of completing therapy. **Results:** The predominance of female gender was reported in migraine patients. Case group had statistically significant more GIT manifestations as heart burn, epigastric pain and GIT bleeding compared with control volunteers. There was significantly higher prevalence of *H. pylori* infection in patient group than controls ($P < 0.05$). *H. pylori* eradication rate was significantly higher in levofloxacin based regimen than clarithromycin based one ($P < 0.05$). *H. pylori* eradication caused statistically significant reduction of MIDAS score after treatment ($P < 0.001$). **Conclusions:** The frequency and severity of migraine headache may be postulated to *H. Pylori* infection. Eradication of *H. pylori* gastric infection induces marked clinical improvement of migraine. Levofloxacin based therapy is more efficient than clarithromycin based therapy in *H. pylori* eradication in Egyptian patients.

INTRODUCTION

Migraine headache is the second most common type of recurrent headache, affects approximately 12% of the world population at some point of their life. Migraine headache severity may range from mild to severe. During migraine attack, patient may have one or all of the following symptoms such as photophobia, sensitivity to noise, sensitivity to smell, nausea and vomiting¹.

According to the International Headache Society classification published in the International Classification of Headache Disorders (ICHD) in 2013, migraines are divided into seven subclasses including classic migraine (with aura), common migraine (without aura) and other types of migraine including ophthalmological migraine, proximate migraine,

migraine with complication, children's migraine and abdominal migraine².

Migraine is a complex neurovascular condition involving vasodilatation of intracranial and extracerebral blood vessels. This results in activation of trigeminal sensory nervous pain pathway leading to headache. Serotonin and reserpine (serotonin evacuator) play a notable role in the development of migraine headache by increasing cerebral blood flow³.

Many factors have been accepted as possible migraine facilitating or triggering factors. These factors include food, medications, sleep disorders, stress, menstruation, trauma, alcohol and environmental conditions for instance noise, light and various odors⁴.

Infectious diseases, immune responses and disorder of digestive system impacts on migraine headaches have been noted⁵.

Helicobacter pylori (*H. pylori*) is an important pathogen associated with gastric infection. *H. pylori* infection affects approximately fifty percent of the world's population mainly people of developing nations⁶.

The vast majority of *H. pylori* infected individuals may stay asymptomatic for long time. Nevertheless, *H. pylori* causes a number of digestive problems, including gastritis, gastric ulcers, duodenal ulcers and occasionally gastric carcinoma⁷. Besides gastric problems, *H. pylori* has been linked to a number of chronic diseases such as type 2 diabetes, ischemic heart disease, ischemic cerebrovascular disease, atherosclerosis, Raynaud's phenomenon and some dermatological disorders⁸.

Helicobacter pylori can induce serotonin secretion from platelets, so it plays a role in migraine headache pathogenesis. In addition, central nervous system and digestive system are interconnected by nervous, hormonal and immunological pathways. The interconnection between the brain and gut (gut-brain axis) is bidirectional⁹. Researches on the role of gut microbiota in the gut-brain axis advocate that the gut microbiome may be associated with central nervous system disorders, such as migraines¹⁰.

METHODOLOGY

Study design and Participants

This case-control study was executed in Neurology, Gastroenterology Outpatient's Clinics and Medical Microbiology and Immunology Department of Zagazig University during the period from January 2017 to January 2019. In current study 80 migraine patients referred to the Neurology Clinic were enrolled as the case group. Migraine headache was diagnosed according to the International Headache Society (IHS) criteria. Control group included 80 age and sex matched healthy participants with no primary headache history.

Exclusion criteria:

Patients with chronic headache not fulfill migraine criteria, patients less than 18 years and participant refusal.

Ethical concerns

The study committed to the ethical guidelines of declaration of Helsinki. Written informed consents were obtained from all participants.

Work-up:

Initial evaluation:

Interviewing and completing a questionnaire for participants (case and control) were used to collect required data including age, sex, sleep disorder, history of migraine in family members, gastro-intestinal (GI) disorder and previous *H. pylori* eradication therapy. The questionnaire included a modified list of stress inducing life events according to social readjustment rating scale. The total score of events encountered during the

preceding year by participant was calculated. Participants whose score ≥ 300 were reported to have stress. Score over 300 indicates higher risk of getting a stress related illness¹¹.

For case group on enrolment, calculation of Migraine Disability Assessment Test score (MIDAS) was done to assess migraine disabling effect and impact on life (MIDAS 1). Disability score was calculated by summation of the number of work days missed, the number of work days and household tasks with productivity reduction by half or more, the number of days in which the patient missed social activity, the number of days with headache and severity of migraine in the last 3 months¹².

All participants were tested for *H. pylori* infection by the noninvasive, cost convenient stool antigen test. Stool Antigen Test (SAT) was performed by lateral flow Immunochromatographic assay using *H. pylori* antigen rapid test (Aria, Philippines).

Therapy:

All patients (infected and non-infected) received migraine symptomatic therapy. Migraine patients with positive *H. pylori* antigen in stool received salvage levofloxacin based triple treatment for *H. pylori* for 2 weeks (levofloxacin 500 mg/24h, amoxicillin 1 g/12 h and pantoprazole 40 mg/12 h) irrespective of previous *H. pylori* therapy. According to updated clinical guidelines¹³, symptomatic control group naïve regarding any *H. pylori* therapy with gastrointestinal complaint and positive stool antigen test received first line triple standard treatment of *H. pylori* for 2 weeks (omeprazole 20 mg/12h, amoxicillin 1 g/12 h and clarithromycin 500 mg/12 h).

Reevaluation:

Stool antigen test was repeated 4 weeks after *H. pylori* eradication therapy was completed for all infected participants. Any proton pump inhibitor was stopped at least 1 week before repeating stool antigen test. All migraine patients were reevaluated clinically to assess migraine intensity and effect by MIDAS test (MIDAS 2) after 14 week of enrolment.

Statistical analysis

All data were analyzed using computerized software (SPSS version 23, Chicago, IL, USA). Comparison of categorical variables across the groups was performed using Chi-square test. For comparison of continuous variables, T- test and Mann-Whitney test were used.

RESULTS

This study enrolled 80 migraine patients diagnosed according to criteria of international society of headache, included 47 women (58.75%) and 33 men (41.25 %) with statistically significant predominance of female gender ($P < 0.05$).

Table (1) summarizes predisposing factors of migraine in both case and control group showing that,

sleep disorder was reported by 22 migraine patients (27.5%) and only 5 of control group (6.25%) experienced sleep disorder ($P < 0.05$). There is significant difference regarding family history of migraine and sleep disorder ($P < 0.05$).

Table 1: Predisposing factors of migraine in case and control groups

	Case n=80 N (%)	Control n=80 N (%)	P value
Stress	71 (88.75)	69(86.25)	0.866
Sleep disorder	22 (27.5)	5 (6.25)	0.001
Family history of migraine	37 (46.25)	1 (1.25)	0.000

Gastrointestinal symptomatology of case and control groups in table (2) shows significant difference between patients and control volunteers including heart burn, epigastric pain and GIT bleeding ($P < 0.05$).

Table 2: GIT symptomatology of case and control groups

Symptom	Case (80) N (%)	Control (80) N (%)	P value
Heart burn	52 (65%)	38 (47.5%)	0.000
Epigastric pain	17(21.25%)	9 (11.25%)	0.000
GIT Bleeding	4 (5%)	0 (0%)	0.043

Table (3) summarizes the prevalence of *H. pylori* infection in case and control groups. Out of 80 migraine patients 57 (71.25%) had positive results regarding stool antigen test with significant difference in prevalence of *H. pylori* between patients and control participants ($P < 0.05$).

Table 3: Prevalence of *H. pylori* infection in case and control groups

	Migraine cases (n = 80)	Healthy control (n = 80)	P value
Positive SAT on enrolment	57(71.25%)	37(46.25%)	0.001

*SAT: Stool Antigen Test

Table (4) summarizes the efficiency of used treatment regimens in *H. pylori* eradication. *H. pylori* SAT turned negative in 48 out of 57 patients (84.21%) after receiving full dose of levofloxacin based triple therapy versus 21 out of 32 (65.62%) in control group who received 1st line clarithromycin based triple therapy. *H. pylori* eradication was significantly higher in levofloxacin based regimen ($P < 0.05$).

Table 4: *H. pylori* eradication success among infected case and control groups

	Levofloxacin therapy (cases) (n=57)	Clarithromycin therapy (control) (n= 32)	P value
Eradication	48 (84.21%)	21 (65.62%)	0.007

Table (5) shows the difference between calculated MIDAS score on initial examination and the score calculated 14 weeks after enrolment in the study. There was statistically significant difference between MIDAS score before (12.5833 ± 2.41303) and after (4.1458 ± 1.85644) *H. pylori* eradication ($P < 0.05$). The mean of MIDAS1 score in cases with positive stool antigen and uninfected migraine patients was (12.33 ± 2.828), (11.8473 ± 3.2661) respectively and MIDAS2 (10.22 ± 3.456), (10.8329 ± 2.65541) respectively, with no significant reduction in both groups ($P > 0.05$).

Table 5: MIDAS scores on enrolment and subsequent assessment of case group

	MIDAS1 mean \pm SD	MIDAS2 mean \pm SD	P value
Migraine patients with eradication success (n=48)	12.5833 ± 2.31303	4.1458 ± 1.85644	0.000
Migraine patients with eradication failure (n=9)	12.33 ± 2.828	10.22 ± 3.456	0.057
Migraine patients with negative <i>H. pylori</i> stool antigen (n= 23)	11.8473 ± 3.2661	10.8329 ± 2.65541	0.262

*MIDAS: Migraine Disability Assessment score

DISCUSSION

Migraine is a common disabling recurrent headache that significantly interferes with personal daily activity. Migraine has a deleterious effect on patients' quality of life. Headache disorders including migraine was ranked in the Global Burden of Disease Study 2015 (a comprehensive regional and global research program of disease burden) as the third neurological disabler in under 50 years.¹⁴ The effect of gastrointestinal disorders and GIT infections including *H. pylori* on migraine headache has been the focus of many studies.

In current study females were more affected by migraine than males. In agreement with other studies¹⁵⁻¹⁶. Sleep disorder affected case group to greater extent than control group, in accordance with another study which reported more occurrence of fatigue, poor sleep quality in chronic migraine patients. Such sleep disorder is considered both predisposing and aggravating factor of migraine¹⁷.

Positive family history of migraine in first degree relatives was (46.25 %) among case group concordant with Akbari and coworkers¹⁸ who reported positive history in 42.3% of cases. Other studies reported higher percentage of positive family history. Peroutka and Howell reported migraine in 91% of migraine patients' 1st degree relatives¹⁹. Such difference in history of family affection by migraine between diverse studies may be explained by difference in migraine type and cultural differences in pain reporting.

Lower family history of migraine in current study can be explained by findings of Yiannopoulou and coworkers¹⁹. They reported in their study that *H. pylori* infection could be primarily relevant in migraineurs with negative family history and fewer known risk factors for migraine this is consistent with the results of current study¹⁸⁻²³⁻²⁴.

In our study gastrointestinal complaints including heart burn, epigastric pain and GIT bleeding are significantly higher in migraineurs than control group ($P < 0.05$). In a study performed by Meucci and colleagues²¹, they observed significant difference in migraine prevalence between control group and patient group with dysmotility like dyspepsia and nausea. Another study remarked frequent association between dyspepsia and postprandial migraine. Scientists hypothesized many explanations for this association including referred pain, serotonin pathways, autonomic nervous system dysfunction, vasculopathy, and allergy to certain food²². Other studies confirmed a direct link between digestive system dysfunctions and migraine headaches.¹⁸⁻²³⁻²⁴

In the current study, there was statistically significant difference ($P < 0.05$) between prevalence of *H. pylori* infection in case and control groups which was in agreement with other studies. Actually, some studies

verified the relation between *H. pylori* infection and migraine headache.¹⁸⁻²⁵⁻²⁶⁻²⁷

While many studies assert the role of *H. pylori* infection in pathogenesis of migraine, others only emphasize the idea of a simple coexistence of these two conditions²⁸. This controversy could be resolved by the findings observed by Gasbarrini and coworkers²⁹, who reported significantly higher prevalence of cytotoxin-associated gene A (CagA) positive strains in migraine patients compared with controls, signifying the role of specific strain of *H. pylori* in migraine pathogenesis. CagA gene encodes for highly immunogenic protein that induces a robust inflammatory response leading to production of pro-inflammatory cytokines and vasoactive substances. This may be the suggested mechanism of functional vascular disorder of migraine in *H. pylori* infected patients.³⁰

Egyptian studies performed in different localities reported high prevalence of CagA gene among isolated *H. pylori*. Azza and Amira³¹ in their study found that 72.2% of *H. pylori* isolates were positive for CagA gene. Amer and coworkers³² also reported CagA gene prevalence to be 65.2%. Such high prevalence of CagA gene in isolated strains in Egypt may support the role of *H. pylori* in migraine pathogenesis in current study.

In current study migraine patients received levofloxacin salvage therapy because clarithromycin antibiotic is contraindicated to be co-administered with ergot containing drugs "symptomatic migraine therapy". Clarithromycin is potent CYP 3A4 inhibitors that predispose to acute ergot toxicity³³.

In the current study salvage therapy gave statistically significant higher eradication rate of *H. pylori* infection than first line triple therapy (84.21% versus 65.62%, $P < 0.05$). Comparable results were reported by other studies targeting *H. pylori* eradication which revealed better results of levofloxacin based therapy over 1st line therapy in Egyptian patients³⁴⁻³⁵. Wide use of standard regimen antibiotics in different gastrointestinal and respiratory infections may be the cause of antimicrobial resistance evolution. High eradication failure rates of *H. pylori* infection elucidate the need to establish local antibiotic policy for its management.

In our study, Evaluation of migraine impact on patient's life was assessed by MIDAS test. The mean of MIDAS1 score on initial examination of migraine patients with successful eradication therapy was (12.5833 ± 2.41303) before treatment. Significant reduction in MIDAS2 score following *H. pylori* eradication (4.1458 ± 1.85644) was noticed ($P < 0.05$). Our results in line with a study done by Faraji and coworkers in their randomized controlled trial on two groups of migraine patients. They reported significant reduction in frequency, intensity and duration of migraine attacks in migraineurs with eradicated

infection compared to those without *H. pylori* treatment³⁶.

Results of the current study are in agreement with other studies reported improvement of migraine in patients who received *H. pylori* therapy. It was demonstrated that during follow-up a significant reduction in all parameters of migraine attacks was observed³⁷⁻³⁸.

On the other hand, patients with failed *H. pylori* eradication and non-infected patients showed non-significant overall reduction in MIDAS score before and after treatment. This may be explained by reduction in MIDAS score individually due to seasonal variation associated with certain environmental and climatic changes improving migraine associated with allergic conditions or due to relative control of migraine attack severity by symptomatic therapy.

Treatment of *H. pylori* infection can diminish migraine headache considerably. As the eradication of bacteria concurs with the reduction in patients' disability due to migraine. *H. pylori* infection can be considered as one etiology of migraine headache in Egyptian patients.

CONCLUSION

Screening test for *H. pylori* infection seems to be justified in migraine patients as *H. pylori* infection is strongly related to migraine headache. Treatment of coexisting *H. pylori* infection leads to reduction of frequency and severity of migraine. *H. pylori* eradication could also be an adjuvant therapy for this disabling headache disorder.

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the work done in the manuscript.

- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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