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Helicobacter pylori and Migraine: Is Eradication of *Helicobacter pylori* Effective in Relief of Migraine Headache?

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ABSTRACT

Background: Association between *Helicobacter pylori* (HP) infection and migraine and the effect of HP eradication on relief of migraine headache have been studied but the results are controversial.
Objectives: To evaluate the effect of HP eradication in treatment of patients affected by migraine.
Materials and Methods: Eighty consecutive HP infected patients affected by migraine without aura were enrolled in this clinical trial. They have referred to an endoscopy clinic for work-up of HP infection from October 2013 to November 2014. Patients were randomly assigned in 2 groups using 2 different regimens; Group A: migraine treatment and a 14-day triple therapy for HP infection and Group B: migraine treatment without HP eradication. The mean duration (hour), headache severity (MIDAS) and the frequency (per month) of clinical headache attacks were calculated upon enrollment in the study and at 6 months and 12 months after treatment. All data were analyzed using SPSS version 16. Comparison of categorical variables across the groups was performed using Chi-square test.
Results: In group A, HP infection was eradicated in 34 of 40 patients (85%). After treatment in eradicated patients compared with the control group there was significant decrease in severity and frequency (but not in duration) of the migraine attacks at 6 months (p<0.001) and significant decrease in intensity, frequency and duration of the migraine attacks at 12 months (p<0.001).
Conclusion: HP should be considered and examined in migranous patients and eradication treatment can be beneficial for relief of clinical attacks.

Keywords: *Helicobacter pylori*; Disease Eradication; Migraine Disorders

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Introduction

Migraine headache is a common discomfort clinical event, which has been associated with hypoxia, neurogenic, vascular and endothelial events, but the pathogenesis is still obscure (1). Migraine is one of the most frequent kinds of

primary headache, affecting about 18% of females and 6% of males of the general population (2). The pathophysiology of migraine is still unclear. The brainstem hypothesis for migraine should incrementally be able to explain all major physiological, pharmacological, and clinical phenomena of migraine (3).

Helicobacter pylori (HP) infects approximately half of the world population and the prevalence of the disease among asymptomatic patients appears to be age-related. Gastric infection by HP is actually considered to be the most relevant cause of chronic gastritis and peptic ulcer (5). It is also associated with an increased risk of mucosa associated lymphoid tissue (MALT) lymphoma and gastric cancer (6). In the past years an association between HP and various extraintestinal pathologies such as coronary heart disease and Raynaud phenomenon have been described (7-10). A relation between HP chronic infection and migraine has been studied but the results of these studies are controversial (11-14).

Human inflammatory response to HP is characterized by activation of neutrophils, monocytes and lymphocytes into the gastric mucosa, which is followed by the release of a large variety of cytokines with proinflammatory and vasospastic properties (1). The reduction of the vasoactive substances determined by bacterium eradication may be one of the physiopathogenetic mechanisms underlying these observations (11). The bacterium releases toxins and hydrolytic enzymes in the infected tissue promoting the peculiar cascade of events. This cascade is associated with the host immune response and alterations of vascular permeability, as a result of released vasoactive substances (15). Superoxide radicals and nitric oxide are also produced (16). Therefore, the prolonged oxidative injury caused by the persistent infection and the release of vasoactive substances might be involved in regional cerebral blood flow changes during migraine (4). Moreover, HP eradication leads to a gradual decrease of the gastric infiltrate, which is followed by a decrease of cytokines (17). HP eradication would decrease the production of such substances, thus inducing the disappearance or the improvement of migraine.

In this study, we aimed to evaluate the effects of HP eradication during a one-year follow-up in a population of patients affected by migraine without aura. One year follow-up study was necessary to avoid possible seasonal variations of migraine.

Materials and Methods

This randomized clinical trial has been conducted in an academic hospital (5 Azar) in Gorgan - Iran on the patients referred to the endoscopy clinic from October 2013 till November 2014 for work-up of HP infection. This study was approved by ethics committee of Golestan University of Medical Sciences (code number: 23279208124).

Upper GI endoscopy using fiberoptic endoscope (Olympus GIF-XQ260, Japan) was performed for all of the study subjects in standard conditions. Biopsy samples were obtained from each patient with biopsy forceps during endoscopy for histology (two samples from the antrum for HP evaluation). The patients with positive result for HP were examined by a neurologist and if the diagnosis of migraine was made according to International Classification of Headache Disorders 3rd edition (ICHD-3 beta) (19), they have been proposed to participate in the

study. Finally eighty consecutive HP infected patients affected by migraine without aura enrolled in the study. All participants signed an informed consent form. They were aware about possible benefits and side effects of treatment. The patients who enrolled in this study had normal laboratory results (whole blood count, plasma sugar, liver and renal functions, sedimentation rate) and computerized tomography of the brain before treatment. Pregnant women and patients with history of smoking, alcohol and oral contraceptives consumption were excluded.

At first demographic data was recorded, and then the patients were randomly assigned using two different regimens. We used block randomization to randomly assign participants to groups of A and B by designed quadripartite blocks.

According to the Maastricht III Consensus Report (18) in the management of HP infection, no patient in both groups had strong recommendations for HP eradication. The subjects in 2 groups showed similar endoscopic findings. No ulcer was found in gastric and duodenal area in both groups. In group A, 52.5% of endoscopic findings were normal and mild to moderate esophagitis in 30%, non-erosive gastritis in 35% and mild duodenitis in 37.5% of patients were found. In group B, 50% of endoscopic findings were normal and mild to moderate esophagitis in 32.5%, non-erosive gastritis in 32.5% and mild duodenitis in 42.5% of patients were seen. (p=0.91).

Group A (Case group, n=40): the patients were given classic migraine treatment and a 14-day standard triple therapy for HP infection eradication with 20 mg Omeprazole *bid*, 1000 mg Amoxicillin *bid* and 500 mg Clarithromycin *bid*; Group B (Control group, n=40): in this group the patients were given classic migraine treatment without HP eradication treatment. A 13C-urea breath test was performed for eradication assessment 6 weeks after completion of the treatment in group A patients. The classic migraine prevention used was the tricyclic antidepressant (amitriptyline; starting dose 10 mg, increasing dosage in a range of 20 to 50 mg at bedtime). The patients in migraine attacks used 1000 mg of acetaminophen.

The mean duration (hours) and mean severity of headache: [1=mild (6-10 score), 2=moderate (11-20 score), 3=severe (21+score) according to the migraine disability assessment scale (MIDAS)], and the frequency (clinical headache attacks per month) were calculated at first before treatment. These parameters (*i.e.*, severity, duration and frequency of clinical headache attacks) of all the patients were re-evaluated 6 months and 12 months after treatment. The neurologist was blinded to evaluation of migraine.

All the data were analyzed using SPSS 16 for Windows (SPSS Inc., Chicago, IL, the United States), and the statistics were shown as mean±SD for continuous variables and percentages for categorical variables. Comparisons of categorical variables across the groups were performed using an overall Chi-square test or Fisher's exact test if required. A *p-value*<0.05 was considered to be significant.

Results

We studied 80 HP infected patients affected by migraine without aura; 40 patients in case group with mean age of 37.3±7.8 year and the others with mean age of 38.1±7.4 in control group (p=0.639). Twenty-eight patients in case group and twenty–seven

patients in control group were women and the others were women (p=0.809). The means of Body Mass Index (BMI) of patients in case and control groups were 24.1±3.3 and 23.8±2.9 kg/m² with no statistically significant difference (p=0.667). The duration of involvement by migraine in case (24.5±18.3 months) and control (25.7±19.8 months) groups was not statistically different (p=0.779).

In group A, HP infection was eradicated in 34 of 40 patients (85% eradication rate), so the six remained non-eradicated patients have been evaluated as control subjects with group B. The severity, duration and frequency of clinical headache attacks of all the patients before, 6 months and 12 months after treatment were summarized in tables 1-3. There was significant decrease in severity and frequency (but not in duration) of the migraine attacks at 6 months after HP eradication (p<0.001) (Table 1,2) and a significant decrease in severity, frequency and duration of the migraine attacks at 12 months after HP eradication in eradicated patients (p<0.001). (Table 1,2,3)

Table 1: Comparison the mean severity of migraine attacks based on MIDAS* score between HP eradicated patients and control patients in the assessment time points.

Times	Eradicated patients (n=34)	Non-eradicated control patients (n=46)	*p-value*
Baseline	2.1±0.8	2.0±0.8	0.495
6 months after treatment	1.1±0.4	1.7±0.6	< 0.001
12 months after treatment	0.9±0.4	1.8±0.7	< 0.001
* Migraine Disability Assessment Scale: 1 to 3: 1= mild, 2= moderate, 3= severe			

Table 2: Comparison the frequency* of migraine attacks between HP eradicated patients and control patients in the assessment time points

Times	Eradicated patients (n=34)	Non-eradicated control patients (n=46)	*p-value*
upon enrollment in the study	8.3±1.1	8.1±1.3	0.459
At 6 months after treatment	6.1±1.2	7.9±1.5	< 0.001
At 12 months after treatment	4.5±0.9	7.4±1.2	< 0.001
* Number of clinical attack per month			

Table 3: Comparison the duration (hours) of migraine attacks between HP eradicated patients and control patients in the assessment time points

Times	Eradicated patients (n=34)	Non-eradicated control patients (n=46)	*p-value*
upon enrollment in the study	16.1±5.6	15.0±4.9	0.353
6 months after treatment	13.4±5.2	14.6±5.1	0.169
12 months after treatment	10.2±4.7	15.4±5.2	< 0.001

Discussion

In this study we observed a significant improvement of severity, duration and frequency of the migraine attacks at 12 months after HP eradication. Some studies strongly suggested a relation between HP infection and migraine. Yiannopoulou *et al.* studied 49 outpatients affected by migraine without aura. Control subjects consisted of 51 patients without any primary headache history. Both groups underwent upper gastrointestinal endoscopy for investigation of anemia or non-ulcer dyspepsia. The prevalence of HP infection was significantly higher in the migraineurs without aura compared to controls (p=0.016). The results seem to highlight the role of HP infection as a probable independent environmental risk factor for migraine without aura, especially in

patients that are not genetically or hormonally susceptible to migraine (20).

Gasbarrini *et al.* studied 200 patients affected by primary headache (tension type headache, cluster headache, and migraine with or without aura). 40% of patients were positive for HP infection with 13C-urea breath test. Eradication of the bacterium resulted in a significant decrease in intensity, duration and frequency of headache (7). In another similar study, Gasbarrini *et al.* studied 225 patients; HP was detected in 40% of the patients with 13C-urea breath test. With HP eradication, intensity, duration and frequency of migraine attacks were significantly reduced (8). Tunca *et al.* detected HP in 57.1% of the patients and got similar benefit from eradication treatment (1).

However, contradictory results are present in some literatures. Pinessi *et al.* examined 98 migrainous patients without aura and 5 patients with aura. The results showed that chronic HP infection is as frequent in patients with migraine as in controls and that this infection is not associated with any significant variation in the clinical features of the disease (13). Savi *et al.* searched the effects of HP eradication therapy in patients with migraine in a small study group and found no significant variation in the associated symptoms of migraine attacks (14).

About the relationship between *Helicobacter pylori* (HP) and migraine is said that the host inflammatory response to HP is characterized by infiltration of neutrophils, monocytes and lymphocytes into the gastric mucosa. Recruitment and activation of immune cells in the underlying mucosa involves bacterium chemotaxins, epithelial derived chemotactic peptides (chemokines) such as IL-8 and GRO-α (Growth-Regulated Oncogen alpha), and proinflammatory cytokines released by mononuclear phagocytes (*e.g.*, tumor necrosis factor-alpha, IL-1 and IL-8) as part of nonspecific immunity (21-22). The multiplicity and large quantity of vasoactive substances produced may induce a hyperreactivity of cerebral vessels to various well-known trigger factors, such as psychological or physical stress, peculiar foods, female hormones, and others, which are capable of determining the clinical manifestation of the disease (23-24).

Other studies have provided evidence that migraine has a gastrointestinal origin and is related to HP infection to a certain extent. Mavromichalis *et al.* conducted a study showing that 29 of the 31 patients with migraine had an associated gastrointestinal disorder. These findings suggested that upper gastrointestinal mucosal inflammation may play an important role in the pathogenesis not only of recurrent abdominal pain, but also of migraine (25). Other researchers have found a correlation between migraine and digestive disorders in adults. They found that approximately 75.7% of patients who had migraine also suffered from digestive disorders [reflux (47.1%), gastric ulcers (17.1%), and gastritis (4.3%)], and the prevalence of HP infection was 38.6% among them (26). The explanation of this phenomenon is that gastrointestinal neuroendocrine cells can synthesize and secrete 5-hydroxytryptamine, substance P, and vasoactive intestinal polypeptides. When HP infects a cell, inflammation stimulates the cell to secrete these substances and causes a central nervous system disorder by the brain-gut axis, which indirectly proves why most patients have migraine attacks that are associated with gastrointestinal symptoms.

The limitations of our study were small sample size, lack of data about other confounding factors like hormones, duration of sleep and socioeconomic status.

Conclusion

Our findings showed that *Helicobacter pylori* infection should be considered in migranous patients and its eradication treatment will be beneficial for relief of clinical attacks. Moreover, a trial which should also include the evaluation of cytokines and the HLA typing of the patients remains necessary to verify the presence of a possible.

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Conflict of Interest

The authors have no conflict of interest.

References

1. Tunca A, Turkay C, Tekin O, Kargili A, Erbayrak M. Is *Helicobacter pylori* Infection a Risk Factor for Migraine? Acta Neurol Belg 2004; 104(4): 161-4.
2. Gabrielli M, Franceschi F, Fiore G, Candelli M, Armuzzi A, Ojetti V, et al. Beneficial Effects of *Helicobacter pylori* Eradication on Migraine: a 12-Month Follow-Up Study. J Headache Pain 2001; 2(1): 39-43.
3. Sprenger T, Goadsby PJ. Migraine Pathogenesis and State of Pharmacological Treatment Options. BMC Medicine 2009; 7:71.
4. Galletti F, Cupini LM, Corbelli I, Calabresi P, Sarchielli P. Pathophysiological Basis of Migraine Prophylaxis. Prog Neurobiol 2009; 89(2): 176-92.
5. Ciancarelli I, Di Massimo C, Tozzi M, De Matteis, Marini C, Carolei A. *Helicobacter pylori* Infection and Migraine. Cephalalgia 2002; 22(3): 222-5.
6. Bouzourene H, Haefliger T, Delacretaz F, Saraga E. The Role of *Helicobacter pylori* in Primary Gastric MALT Lymphoma. Histopathology 1999; 34(2): 118-23.
7. Gasbarrini A, Franceschi F, Gasbarrini G, Pola P. Extraintestinal Pathology Associated with *Helicobacter* Infection. Eur J Gastroenterol Hepatol 1997; 9(3): 231-3
8. Gasbarrini A, Serricchio M, Tondi P, Gasbarrini G, Pola P. Association of *Helicobacter pylori* Infection with Raynaud Phenomenon. Lancet 1996; 348(9032): 966-7.
9. Morgando A, Sanseverino P, Perotto C, Molino F, Gai V, Ponzetto A. *Helicobacter pylori* Seropositivity in Myocardial Infarction. Lancet 1995; 345(8961): 1380.
10. Vafaeimanesh J, Hejazi SF, Damanpak V, Vahedian M, Sattari M, Seyyedmajidi M. Association of *Helicobacter pylori* Infection with Coronary Artery Disease: Is *Helicobacter pylori* a Risk Factor? Scientific World Journal 2014; 2014:516354.
11. Gasbarrini A, De Luca D, Fiore G, Franceschi F, Ojetti V, Torre ES, et al. Primary Headache and *Helicobacter pylori*. Int J Angiol 1998; 7(4): 310-2.
12. Gasbarrini A, De Luca D, Fiore G, Gambrielli M, Franceschi F, Ojetti V, et al. Beneficial Effects of *Helicobacter pylori* Eradication on Migraine. Hepatogastroenterology 1998; 45(21): 765-70.
13. 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.
14. Savi L, Pellicano R, Rainero I, Valfre W, Gentile S, et al. *Helicobacter pylori* Eradication and Migraine. Cephalalgia 2000;20:346-7.
15. Mervat M El-Eshmawy, Amany K El-Hawary, Soma S Abdel Gawad, Azza A El-Baiomy. *Helicobacter pylori* Infection Might

be Responsible for the Interconnection between Type 1 Diabetes and Autoimmune Thyroiditis. Diabetol Metab Syndr 2011; 3: 28.

16. Nagata K, Yu H, Nishikawa M, Kashiba M, Nakamura A, Sato EF,et al. *Helicobacter pylori* Generates Superoxide Radicals and Modulates Nitric Oxide Metabolism. J Biol Chem 1998; 273: 14071-3.
17. Russo F, Messa C, Amati L, Caradonna L, Leoci C, Di Matteo G, et al. The influence of *Helicobacter pylori* eradication on the gastric mucosal content of epidermal growth factor, transforming growth factor-alpha and their common receptor. Scand J Gastroenterol 1998; 33(3): 271-5.
18. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current Concepts in the Management of *Helicobacter pylori* Infection: the Maastricht III Consensus Report. Gut 2007; 56(6):772-81.
19. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders. 2nd ed; Cephalalgia 2004; 24(Suppl 1): 1-150.
20. Yiannopoulou K, 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.
21. Tunca A, Türkay C, Tekin O, Kargili A, Erbayrak M. Is *Helicobacter pylori* Infection a Risk Factor for Migraine? A Case-Control Study. Acta Neurol Belg 2004;104:161-4.
22. Bodger K, Crabtree JE. *Helicobacter pylori* and Gastric Inflammation. Br Med Bull 1998;54:139-50.
23. Cutrer FM, Sorensen AG, Weisskoff RM, Ostergaard L, Sanchez del Rio M, Lee EJ, et al. Perfusion-Weighted Imaging Defects During Spontaneous Migrainous Aura. Ann Neurol 1998;43:25-31.
24. Woods RP, Iacoboni M, Mazziotta JC. Brief Report: Bilateral Spreading Cerebral Hypoperfusion During Spontaneous Migraine Headache. N Engl J Med 1994;331:1689-92.
25. Mavromichalis I, Zaramboukas T, Giala MM. Migraine of Gastrointestinal Origin. Eur J Pediatr 1995;154:406-10.
26. Hosseinzadeh M, Khosravi A, Saki K, Ranjbar R. Evaluation of *Helicobacter pylori* Infection in Patients with Common Migraine Headache. Arch Med Sci 2011;7:844-9.