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Beneficial effects of Helicobacter pylori eradication on migraine: a 12-month follow-up study

Abstract Helicobacter pylori (H. pylori) has been recently associated with some organic and functional vascular disorders. In particular, our group found a high prevalence of H. pylori in patients affected by migraine and a significant improvement of migraine symptoms after eradication of the bacterium, during a follow-up period of 6 months. However, seasonal variations may affect clinical manifestations of migraine, thus influencing our previous results. The present study evaluated the effect of H. pylori eradication during a 1-year follow-up period in a population of 148 consecutively enrolled migraine patients. H. pylori infection was assessed by 13C-urea breath test. Infected subjects underwent specific antibiotic treatment in order to eradicate the bacterium. Frequency, intensity and duration of attacks of migraine were assessed during a 1-year follow-up period. 42% of the patients showed H. pylori infection. 82% resulted eradicated. Interestingly, 28% of the patients reported a disappearance of migraine during the follow-up period. Moreover, a significant decrease of intensity, frequency and duration of the migraine attacks evaluated 2, 4, 6 and 12 months from H. pylori eradication was observed in the remaining patients. The beneficial effects of H. pylori eradication on migraine seem to be confirmed by this prolonged 1-year follow-up study.

Key words Helicobacter pylori • Migraine • Cytotoxins • Vasospasm

Introduction

Migraine is the most frequent kind of primary headache, affecting about 18% of females and 6% of males of the general population [1]. According to the criteria established in 1988 by the International Headache Society (IHS), migraine is defined as a periodic, commonly unilateral, throbbing headache, with or without cerebral disturbance, with intervening periods of relative freedom of headache and without evidence of primary structural abnormality [2]. However, it is often under-diagnosed and under-treated [3]. Several hypotheses have been considered in order to explain its pathogenetic background. Since all of them are supported by notable scientific evidence, the vascular involvement represents the conditio sine qua non for migraine attack [4].

Gastric infection by Helicobacter pylori (H. pylori) is extremely diffused worldwide and is actually considered to be the most relevant cause of chronic gastritis and peptic ulcer [5, 6]. It is also associated with an increased risk of MALT-lymphoma and gastric cancer [7, 8]. Since spontaneous clearance of the bacterium is extremely rare, at least in the absence of specific antibiotic treatment, the infection lasts for a long time.

In the last years, H. pylori infection has been associated with some extradigestive pathologies, and especially with organic and functional vascular disorders [9–16]. In particular,
our group [11] recently reported a high prevalence of *H. pylori* infection, with particular regard to cytotoxic strains, in patients with migraine. Moreover, we reported a complete disappearance or a significant improvement of migraine in the major part of eradicated patients, during the 6-month follow-up period. Therefore, we hypothesized that the inflammatory response caused by *H. pylori* infection may affect migraine through an immune-mediated release of cytokines and other substances endowed with both vasospastic and proalgogen properties [17–26]. However, in this study we did not take into account of the presence of some confounding factors, which may affect the clinical outcome of the migraine patients, such as some environmental factors, which also include the seasonal variations [27–29]. Since the end of the follow-up period of our previous study was in the summer, a new 1-year follow-up study was necessary to avoid possible seasonal variations of migraine, which in turn may influence our previous results.

Aim of the present study was to evaluate the effect of *H. pylori* eradication during a 1-year follow-up period in a population of patients affected by migraine, thus verifying whether the eradication of the bacterium may represent a novel, encouraging approach to the management of patients with migraine.

**Patients and methods**

This study was a open, non-randomized trial, evaluating 148 patients affected by migraine. All patients were consecutively enrolled at the Headache Center of the La Sapienza University. Migraine was defined according to the criteria of the IHS [2]. Informed consent was obtained from each patient and the study was approved by the Ethics Committee of the Catholic University of Rome. A self-evaluation test [30] was used to assess the clinical characteristics of migraine. In particular, patients were asked to record, a daily diary, the intensity (scored from 0 to 4: 0, minimum; 4, maximum), the duration (hours) and the frequency (days per months) of headache attacks, during the 3 months preceding the 1-year follow-up medical consultation. In all patients, 13C-urea breath record, a daily diary, the intensity (scored from 0 to 4: 0, minimum; 4, maximum), the duration (hours) and the frequency (days per months) of headache attacks, during the 3 months preceding the 1-year follow-up medical consultation. In all patients, a noninvasive, highly sensitive and specific method to assess *H. pylori* infection [31], was performed to assess the infection status. All *H. pylori*-positive patients underwent triple therapy with amoxicillin (500 mg qid), clarithromycin (250 mg bid) and a proton pump inhibitor (bid) for 7 days. *H. pylori* eradication was assessed 2 months after the end of the treatment. Intensity, duration and frequency of the attacks of migraine were re-evaluated 2 months (T1), 4 months (T2), 6 months (T3) and 12 months (T4) after *H. pylori* eradication.

Results are expressed as mean±SEM. Statistically significant differences between groups were assessed using either Student’s *t* test, when appropriate. A *p* value <0.05 was considered to be significant. A 50% of symptoms improvement was expected with a power of 0.8.

Ricerca in Medicina (Bologna, Italy), which partly supported the study, did not have any role in the collection of data, its analysis and interpretation, nor did it approve or disapprove of the manuscript for publication.

**Table 1** Intensity of migraine attacks assessed in the 3 months preceding admission (T0), and every 2 months for 12 months (T1, T2, T3, T4) after *H. pylori* eradication. Intensity is scored from 0 to 4: 0, minimum; 4, maximum. Intensity of migraine is compared between treated and eradicated, treated but not eradicated by *H. pylori* infection, and *H. pylori*-negative patients. Values are means (95% CI)

| Times | Negatives | Not eradicated | Eradicated | *p* value |
|-------|-----------|---------------|-----------|-----------|
| T0    | 2.9 (2.5–3.5) | 3 (2.5–3.4) | 3 (2.7–3.2) | NS        |
| T1    | 2.8 (2.3–3.2) | 2.7 (2.3–3.0) | 2 (1.8–2.2) | <0.01     |
| T2    | 3 (2.5–3.5) | 2.8 (2.4–3.1) | 1.5 (1.3–1.7) | <0.01     |
| T3    | 3 (2.5–3.5) | 2.9 (2.6–3.1) | 1.4 (1.2–1.6) | <0.01     |
| T4    | 2.9 (2.7–3.1) | 3 (2.5–3.5) | 1.2 (1.0–1.3) | <0.01     |

NS, not significant
Before discussing the results of this study, it appears important to assume that patients presenting to a Headache Center (University Department) are not representative sample of migraine sufferers in the general population. Several studies, in fact, showed that migraine patients consulting headache centers are clinically different from those of general population [32].

In the previous study [11], we reported the results of administering of \textit{H. pylori} eradicating treatment to a group of infected patients affected by migraine. In particular, we observed a disappearance of migraine in about 25% of the patients, as well as a significant improvement of intensity, duration and frequency of the migraine attacks, 6 months after \textit{H. pylori} eradication. Since those results strongly suggested a role of \textit{H. pylori} infection in the pathogenesis of migraine, a new study with a prolonged follow-up period appeared to be necessary in order to avoid possible confounding factors able to influence migraine. Some studies, in particular, proposed a seasonal variation of migraine, even though there are still conflicting results in this field [27–29], whereas the end of the follow-up period during the summer was one possible bias of our previous study.

Results from the present study confirm our previous findings. In particular, no recurrence of migraine has been observed in the majority of the patients who previously reported a disappearance of the attacks after \textit{H. pylori} eradication, whereas more than 90% of the patients maintained a significant improvement of intensity, duration and frequency of migraine.

Since these findings suggest a possible link between presence of a long-lasting infectious disease and dismotility of cerebral arterial districts, no definitive data are available to explain such association. Nevertheless, we hypothesize that the chronic immuno-inflammatory response evoked by the infection is one of the possible mechanisms by which \textit{H. pylori} affects migraine. Human inflammatory response to \textit{H. pylori}, in particular, is characterized by recruitment and activation of neutrophils, monocytes, and lymphocytes into the gastric mucosa [20], which is followed by the release of a large variety of cytokines (in particular interleukins 1, 6, 8 and interferon \(\gamma\)) and other molecules endowed with proinflammatory, vasospastic, and proalgogen properties [17–26]. Interestingly, CagA-positive strains, which are predominant in patients affected by migraine [11], are able to produce significantly higher amounts of such cytokines than CagA-negative ones [33, 34]. Moreover, \textit{H. pylori} eradication leads to a gradual decrease of the gastric infiltrate, which is followed by a decrease of cytokines, during the following 3–12 months [35, 36]. Therefore, we hypothesize that cytokines and other proinflammatory substances released by the infection may flow into the systemic circulation, thus inducing a

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\hline
Times & Negatives & Not eradicated & Eradicated & \(p\) value \\
\hline
T0 & 15.2 (11.0–18.8) & 15 (10.1–19.9) & 16 (12.1–19.9) & NS \\
T1 & 15 (10.3–19.1) & 14.6 (9.7–19.5) & 13 (9.6–16.4) & NS \\
T2 & 15.5 (11.1–20.2) & 16.4 (10.6–22.2) & 10 (6.9–13.0) & <0.05 \\
T3 & 15.2 (9.8–19.8) & 15 (10.1–19.9) & 9 (6.3–11.7) & <0.05 \\
T4 & 15.5 (10.9–19.9) & 15.4 (10.4–20.4) & 8 (5.8–10.2) & <0.01 \\
\hline
\end{tabular}
\caption{Duration (hours) of migraine attacks assessed in the 3 months preceding admission (T0) and every 2 months for 12 months after \textit{H. pylori} eradication (T1, T2, T3, T4). Duration of migraine attacks is compared between treated and eradicated and treated but not eradicated by \textit{H. pylori} infection, and \textit{H. pylori}-negative patients. Values are means (95\% CI).}
\end{table}

\begin{table}
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Times & Negatives & Not eradicated & Eradicated & \(p\) value \\
\hline
T0 & 7.8 (5.9–9.9) & 7.2 (4.5–9.9) & 8.3 (7.1–9.4) & NS \\
T1 & 7.9 (5.8–10.2) & 7.5 (5.3–9.7) & 6.7 (5.6–7.8) & NS \\
T2 & 7.5 (5.6–10.0) & 7.0 (4.5–9.5) & 4.5 (3.8–5.2) & <0.05 \\
T3 & 7.4 (5.7–9.8) & 7.1 (4.7–9.5) & 4.0 (3.4–4.6) & <0.01 \\
T4 & 7.9 (5.9–10.2) & 7.0 (4.5–9.5) & 3.8 (3.3–4.3) & <0.01 \\
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\end{tabular}
\caption{Frequency (days per month) of migraine attacks assessed in the 3 months preceding admission (T0) and every 2 months for 12 months (T1, T2, T3, T4) after \textit{H. pylori} eradication. It is compared to the frequency after finishing the eradication treatment (T1, T2, T3) in treated and eradicated and treated but not eradicated by \textit{H. pylori} infection, and \textit{H. pylori}-negative patients. Values are means (95\% CI).}
\end{table}
dismotility of peculiar arterial districts. *H. pylori* eradication would decrease the production of such substances, thus inducing the disappearance or the improvement of migraine. However, it is known that not all the patients infected by *H. pylori* are affected by migraine. The most convincing explanation for this observation can be found in the complex interaction between host and bacterium. In particular, the presence of particular factors, such as infection with CagA-positive strains in subjects with a genetic susceptibility to develop migraine, may explain the different clinical outcomes of the infection in different patients.

In conclusion, as previously reported, this study showed that standard antibiotic therapy used to eradicate *H. pylori* infection appears to significantly improve migraine symptoms in the subgroup of infected migraine patients. The anti-*H. pylori* therapy effects could be either nonantibiotic or a consequence on other chronic infections, unknown at present to be associated with migraine. Moreover, a double-blind cross-sectional eradication trial, which should also include the evaluation of vasoactive and proallogenic cytokines as well as the HLA genotype of the patients, remains at present necessary to verify the presence of a possible infectious origin of migraine.

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**References**

1. Ferrari MD (1998) Migraine. Lancet 351:1043–1051
2. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8[Suppl 7]:19–34
3. Lipton RB, Stewart WF, Von Korff M (1995) Migraine impact and functional disability. Cephalalgia 15 [Suppl]:4–9
4. Blau JN (1992) Migraine: theories of pathogenesis. Lancet 339:1202–1209
5. Calam J (1994) *H. pylori*. Eur J Clin Invest 24:501–510
6. Gasbarrini G, Pretolani S, Bonvicini F, Gatto MRA, Tonelli E, Megraud F et al (1995) A population based study of *H. pylori* infection in a European country: the San Marino Study. Relations with gastrointestinal diseases. Gut 36:838–844
7. Bouzourene H, Hafleriger T, Delacretaz F, Saraga E (1999) The role of *Helicobacter pylori* in primary gastric MALT lymphoma. Histopathology 34(2):118–123
8. Danesh J (1999) *Helicobacter pylori* infection and gastric cancer: systematic review of the epidemiological studies. Aliment Pharmacol Ther 13(7):851–856
9. Gasbarrini A, Serricchio M, Tondi P, Gasbarrini G, Pola P (1996) Association of *H. pylori* infection with Raynaud phenomenon. Lancet 348:966–967
10. Gasbarrini A, De Luca A, Fiore G, Franceschi F, Ojeti V, Torre ES et al (1998) Primary headache and *Helicobacter pylori*. Int J Angiol 7(4):310–314
11. Gasbarrini A, De Luca A, Fiore G, Gabrielli M, Franceschi F, Ojeti V et al (1998) Beneficial effects of *Helicobacter pylori* eradication on migraine. Hepatogastroenterology 45(21):765–770
12. Mendall MA, Moggin PM, Molineaux N, Levy J, Toosy T, Strachan D et al (1994) Relation of *H. pylori* infection and coronary heart disease. Br Heart J 71:437–439
13. Mendall MA, Patel P, Carrington D, Strachan D, Leatham E, Molineaux N et al (1995) Association of *H. pylori* and *Chlamydia pneumoniae* infection with coronary heart disease and cardiovascular risk factors. Br Med J 311:711–714
14. Pasceri V, Cammarota G, Patti G, Cuoco L, Gasbarrini A, Grillo RL et al (1998) Association of virulent *Helicobacter pylori* strains with ischaemic heart disease. Circulation 97:1675–1679
15. Gasbarrini A, Serricchio M, Tondi P, Franceschi F, Ojeti V, Sanz Torre ES et al (1998) *Helicobacter pylori* infection and vascular diseases. Ital J Gastroenterol Hepatol 30[Suppl 3]:S307–S309
16. Gasbarrini A, Serricchio M, Tondi P, Franceschi F, Ojeti V, Sanz Torre ES et al (1998) Beneficial effects of *Helicobacter pylori* eradication on migraine. Scand J Gastroenterol Suppl 215:3–10
17. Bodger K, Crabtree JE (1998) *Helicobacter pylori* and gastric inflammation. Br Med Bull 54(1):139–150
18. Yoshida N, Granger DN, Evans DJ, Graham DY, Anderson DC (1993) Mechanism involved in *H. pylori*-induced inflammation. Gastroenterology 105:1431–1440
19. Kurose I, Granger DN, Evans DJ, Evand DG, Graham DY, Miyasaka M et al (1994) *H. pylori*-induced microvascular protein leakage in rats: role of neutrophils, mast cells and platelets. Gastroenterology 107:70–79
20. Yamaoka Y, Kita M, Kodama T, Sawai N, Tanahashi T, Kashima K et al (1998) Chemokines in the gastric mucosa in *H. pylori* infection. Gut 42(5):609–617
21. De Koster E (1993) Microbiological aspects of *H. pylori*. Eur J Gastroenterol Hepat 5:S33–S35
22. Ahmed A, Holton J, Vaira D, Smith SK, Hoult JRS (1992) Eicosanoid synthesis and *H. pylori* associated gastritis: Increase in leukotriene C4 generation associated with *H. pylori* colonization. Prostaglandins 44:75–86
23. Maseri A, Biasucci LM, Liuzzo G (1996) Inflammation in ischaemic heart disease. Br Med J 312:1049–1050
25. Maseri A, Biasucci LM, Liuzzo G (1996) Inflammation in ischaemic heart disease. Br Med J 312:1049–1050
26. Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC (1996) C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. Br Med J 312:1061–1065
27. Fox AW, Davis RL (1998) Migraine chronobiology. Headache 38(6):436–441
28. Robbins L (1994) Precipitating factors in migraine: a retrospective review of 494 patients. Headache 34(4):214–216
29. Brewerton TD, George MS (1990) A study of the seasonal variation of migraine. Headache 30(8):511–513
30. Logan RPH (1996) The 13C urea breath test. In: Lee A, Megraud F (eds) *H. pylori*. Techniques for clinical diagnosis and basic research. WB Saunders, London, pp 74–81
31. Colucci D’Amato C, Alfano V, Giordano E, Marmolo T, Pizza V (1997) Le cefalee. Idelson, Naples, p 258
32. Ziegler DK, Paolo AM (1995) Headache symptoms and psychological profile of headache-prone individuals. A comparison of clinic patients and controls. Arch Neurol 52:602–606
33. Covacci A, Censini S, Bugnoli M, Petracca R, Burrone D, Macchia G et al (1993) Molecular characterization of the 128-kDa immunodominant antigen of *Helicobacter pylori* associated with cytotoxicity and duodenal ulcer. Proc Natl Acad Sci USA 90:5791–5795
34. Blaser MJ, Perez-Perez G, Kleanthous H, Cover TL, Peek RM, Chyou PH et al (1995) Infection with *Helicobacter pylori* strains possessing CagA is associated with an increased risk of developing adenocarcinoma of the stomach. Cancer Res 55:2111–2115
35. Russo F, Messa C, Amati L, Caradonna L, Leoci C, Di Matteo G et al (1998) 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 33(3):271–275
36. Lynch DA, Mapstone NP, Clarke AM, Sobala GM, Jackson P, Morrison L et al (1995) Cell proliferation in *Helicobacter pylori* associated gastritis and the effect of eradication therapy. Gut 36(3):346–350