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

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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 proallogenic 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 test, 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 amox-

icillin (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.

Results

We studied 148 patients affected by migraine (102 without aura and 46 with aura; 95 women and 53 men, mean age 38±10 years).

Overall, 42% of the patients showed *H. pylori* infection (62 of 148 patients). Infected patients showed a mean age significantly higher than not-infected patients (45±8 vs. 31±12 years; *p*<0.001). Neither gender nor migraine type affected the infection status. In particular, *H. pylori* infection was detected in 38% of patients affected by migraine with aura and in 44% of subjects affected by migraine without aura.

82% (47/57; per protocol analysis) and 76% (47/62; intention to treat) of the patients showed *H. pylori* eradication 2 months after the end of the treatment. The infected patients who did not complete the eradication study (5 of 62; 8%) were considered to be drop outs. Interestingly, 28% (16 of 57 patients) reported a disappearance of migraine during the follow-up period. Moreover, there was a significant decrease in intensity, frequency and duration of the migraine attacks at 2 months (T1), 4 months (T2), 6 months (T3) and 12 months (T4) after *H. pylori* eradication in the remaining patients. No significant correlation was found between clinical improvement after *H. pylori* eradication and kind of migraine. Interestingly, migraine symptoms did not change significantly during the follow-up period in treated but not eradicated patients, as well as in *H. pylori*-negative subjects (Tables 1–3).

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	<i>p</i> 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

Table 2 Duration (hours) of migraine attacks assessed in the 3 months preceding admission (T0) and every 2 months for 12 months after *H. pylori* eradication (T1, T2, T3, T4). Duration of migraine attacks is compared between treated and eradicated and treated but not eradicated by *H. pylori* infection, and *H. pylori*-negative patients. Values are means (95% CI)

Times	Negatives	Not eradicated	Eradicated	<i>p</i> value
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

NS, not significant

Table 3 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 *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 *H. pylori* infection, and *H. pylori*-negative patients. Values are means (95% CI)

Times	Negatives	Not eradicated	Eradicated	<i>p</i> value
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

NS, not significant

Discussion

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 *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 *H. pylori* eradication. Since those results strongly suggested a role of *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 *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 *H. pylori* affects migraine. Human inflammatory response to *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 γ) and other molecules endowed with proinflammatory, vasospastic, and proallogenic 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, *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

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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