**Chronic Helicobacter pylori infection and migraine: a case-control study.**

# Chronic *Helicobacter Pylori* Infection and Migraine: A Case-Control Study

Lorenzo Pinessi, MD; Lidia Savi, MD; Rinaldo Pellicano, MD; Innocenzo Rainero, MD, PhD; Walter Valfrè, MD; Salvatore Gentile, MD; Donatella Cossotto, MD; Mario Rizzetto, MD; Antonio Ponzetto, MD

**Objective.—To determine whether chronic *Helicobacter pylori* infection is a risk factor for migraine.**

**Background.—Preliminary studies have shown a high prevalence of *Helicobacter pylori* infection in patients with primary headaches.**

**Methods.—One hundred three consecutive patients with migraine were enrolled in the study and compared with a group of 103 matched controls. *Helicobacter pylori* infection was diagnosed by means of both $^{13}$C-urea breath test and serology.**

**Results.—Of patients with migraine, 30.1% were positive for *Helicobacter pylori*, compared with 31.1% of controls ($P$ = NS). The odds ratio for migraine associated with chronic *Helicobacter pylori* infection was 0.96 (95% confidence interval, 0.51 to 1.80). Demographic, clinical, and psychological characteristics of *Helicobacter pylori*-positive migraineurs were compared with those of migrainous patients without infection. *Helicobacter pylori*-positive patients had a significantly ($P$<.05) lower incidence of food sensitivity than *Helicobacter pylori*-negative patients. No significant difference was found in any other feature examined.**

**Conclusions.—Our study suggests that chronic *Helicobacter pylori* infection is not more frequent in patients with migraine than in controls and that infection does not modify clinical features of the disease.**

**Key words: migraine, aura, *Helicobacter pylori*, food sensitivity**

**Abbreviations: *H. pylori Helicobacter pylori*, UBT 13C-urea breath test**

(*Headache* 2000;40:836-839)

*Helicobacter pylori* (*H. pylori*) is a gram-negative organism that causes chronic active gastric inflammation. Infection is strongly associated with duodenal ulceration, gastric ulceration, and gastric cancer.[1,2] Several case-control studies have reported a significant association between chronic *H. pylori* infection and obstructive vascular diseases such as acute myocardial infarction, primary Raynaud phenomenon, and ischemic stroke.[3-5] Several mechanisms could link chronic *H. pylori* infection and vascular diseases including a low-grade acute phase response, free radical formation, and immune-mediated mechanisms.[6-8] However, the precise mechanism by which chronic *H. pylori* infection mediates these vascular effects remains unclear.

A recent preliminary study reported that 40% of patients diagnosed as having primary headache were seropositive for *H. pylori* infection.[9] Furthermore, eradication of the bacterium resulted in a significant decrease in intensity, duration, and frequency of migraine attacks.[10]

The purpose of this study was to further investigate whether chronic *H. pylori* infection is a risk fac-

**From Neurology III–Headache Center, Department of Neuroscience (Drs. Pinessi, Savi, Rainero, Valfrè, and Gentile), and the Department of Internal Medicine (Drs. Pellicano, Cossotto, and Rizzetto), University of Turin; and the Department of Gastroenterology, Molinette Hospital (Drs. Rizzetto and Ponzetto), Turin, Italy.**

**Address all correspondence to Prof. Lorenzo Pinessi, Neurology III–Headache Center, Department of Neuroscience, University of Turin, Via Cherasco 15, 10126 Torino, Italy.**

**Accepted for publication July 4, 2000.**

tor for migraine. We compared the prevalence of the infection in a group of patients with migraine with that of healthy controls, matched for age, sex, and socioeconomic status, and we searched for clinical characteristics associated with the infection.

## PATIENTS AND METHODS

**Patients.—**One hundred three consecutive patients with migraine (25 men, 78 women; mean age, 33.5 ± 10.0 years) attending the Headache Center of the University of Turin for the first time were involved in the study. The diagnosis of migraine was made according to the International Headache Society (IHS) criteria.[11] Ninety-eight patients (24 men, 74 women) fulfilled the diagnostic criteria for migraine without aura and 5 patients (1 man, 4 women) for migraine with aura. The patients underwent an extensive physical and neurologic examination. Laboratory studies (sedimentation rate, whole blood count, and liver and renal functions) and x-rays of skull and spine were obtained. A standardized record of all the clinical and psychological characteristics of migraine, suitable for computer analysis, was also obtained. Psychological evaluation was performed using the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI X-1 and STAI X-2).

A group of 103 healthy subjects (25 men, 78 women; mean age, 33.0 ± 10.0 years) attending the Molinette Hospital's Blood Bank (Turin), matched for sex and age, served as controls. Patients and controls were from the same area of northern Italy and had similar socioeconomic status based on employment and educational status. Table 1 summarizes the demographic and clinical characteristics of patients with migraine and healthy controls.

**Table 1.—Demographic and Clinical Characteristics of Patients With Migraine and Healthy Controls**

| Feature | Patients With Migraine | Controls |
|---|---|---|
| Age, y (mean ± SD) | 33.00 ± 10.0 | 33.00 ± 10.0 |
| Ratio of men to women | 25:78 | 25:78 |
| Age at onset, y (mean ± SD) | 15.35 ± 6.6 | — |
| Duration, y (mean ± SD) | 33.57 ± 22.3 | — |
| Frequency of attacks, No./y (mean ± SD) | 58.73 ± 65.4 | — |
| Coexistence of tension-type headache, No. (%) | 33 (32) | — |
| Positive family history for migraine, No. (%) | 83 (80.6) | — |
| Food sensitivity, No. (%) | 41 (39.8) | — |
| Beck Depression Inventory | 9.85 ± 7.5 | — |
| STAI X-1 | 39.63 ± 10.88 | — |
| STAI X-2 | 43.63 ± 10.22 | — |

STAI X-1 and STAI X-2 indicate State-Trait Anxiety Inventory.

**Analysis.—***H. pylori* infection was assessed by means of both the $^{13}$C-urea breath test (UBT) and the presence of antibodies (IgG) against the bacterium in serum. For the UBT protocol, we used 100 mg of $^{13}$C-labeled urea and a fat meal. The result was expressed as $^{13}CO_2/^{12}CO_2$, and an increase from baseline of more than 4% was required to diagnose infection. A commercially available enzyme immunoabsorbent assay (ELISA, Helori-test Eurospital) was used to evaluate seropositivity to the bacterium. The reported sensitivity was 94% and the specificity was 87%.[12] Calibrators, positive controls, negative controls, and diluted (1:200) serum samples were added to wells coated with purified *H. pylori* group-specific antigen. Plates were incubated for 60 minutes at 37°C. After incubation, the liquid was removed completely and three washes with 200 μL per well of washing solution were performed; the liquid was removed and 100 μL of anti-IgG conjugate was pipetted into each well. Wells were then incubated for 60 minutes at 37° C; the washing step was repeated, 100 μL of chromogenic substrate was added to each well. Wells were again incubated for 30 minutes at 37°C, and finally the reaction was stopped by adding 25 μL of stopping solution. Reactions were read at 405 nm, and the mean optical density was expressed as a percentage of the optical density of a positive-control serum assayed on the same plate.

In accordance with previously published research guidelines,[13] only patients with positive results for both tests were defined as infected by *H. pylori.*

**Statistics.—**Statistical analysis was performed using Epi Info software, version 6.04 (CDC Centers, Atlanta, Ga and WHO, Geneva, Switzerland). The clinical features of the patients with migraine who were *H. pylori*-positive and those who were *H. py-*

*lori*-negative were compared using the Student *t* test and chi-square test, as appropriate. The level of statistical significance was $P<.05$.

## RESULTS

A positive result for *H. pylori* was present in 30.1% of the patients with migraine and 31.1% of the controls ($P=$NS). The odds ratio (OR) for migraine associated with chronic *H. pylori* infection was 0.96 (95% confidence interval [95% CI], 0.51 to 1.80).

Table 2 shows the results of the comparison of the clinical features between patients diagnosed as positive or negative for infection. The following features were compared: age, sex, age at onset of the disease, duration of the disease, frequency of migraine attacks, coexistence of tension-type headache, positive family history for migraine, food sensitivity, and psychological test scores (BDI, STAI X-1, and STAI X-2). The frequency of food sensitivity was significantly lower in patients positive for *H. pylori* infection (22.6% versus 47.2%; OR = 0.33; 95% CI, 0.11 to 0.93). No significant difference in any of the remaining characteristics examined was found.

**Table 2.—Comparison of the Clinical Features Between *H. Pylori*-Positive and *H. Pylori*-Negative Patients**

| Feature | *H. Pylori*-Positive Patients | *H. Pylori*-Negative Patients |
|---|---|---|
| Age, y (mean ± SD) | 35.00 ± 8.9 | 32.79 ± 10.4 |
| Ratio of men to women | 8:23 | 17:55 |
| Age at onset, y (mean ± SD) | 16.55 ± 7.5 | 14.81 ± 6.2 |
| Duration, y (mean ± SD) | 38.06 ± 24.3 | 31.58 ± 21.2 |
| Frequency of attacks, No./y (mean ± SD) | 40.45 ± 24.8 | 66.94 ± 75.7 |
| Coexistence of tension-type headache, No. (%) | 8 (25.8) | 25 (34.7) |
| Positive family history for migraine, No. (%) | 26 (83.9) | 57 (79.2) |
| Food sensitivity, No. (%) | 7 (22.6) | 34 (57.1)* |
| Beck Depression Inventory | 11.23 ± 7.9 | 9.27 ± 7.3 |
| STAI X-1 | 40.77 ± 10.77 | 39.15 ± 10.97 |
| STAI X-2 | 42.90 ± 10.1 | 43.94 ± 10.3 |

*$P<.05$ in comparison with *H. pylori*-positive patients. STAI X-1 and STAI X-2 indicate State-Trait Anxiety Inventory.

## COMMENTS

This study shows that chronic *H. pylori* 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.

The results of this study are at variance with those of Gasbarrini et al.[9] Several methodological discrepancies may explain the observed differences. First, we studied only patients with migraine and not patients with "primary headaches" (ie, tension-type headache, cluster headache, and migraine with or without aura). Second, in our study, the diagnosis of *H. pylori* infection was based on both a positive $^{13}$C-urea breath test and a positive serological study, according to the European guidelines for clinical trials.[10] Finally, it is necessary to emphasize that there is a significant age effect in the prevalence of *H. pylori* infection: in the United Kingdom, about 30% of 30-year-olds are infected, while the proportion increases to 60% in those aged 45 years.[14] An inadequate selection of the control group may explain the differences observed in the two studies. Our study, on the contrary, is in accord with the results of a recent study performed in children showing that *H. pylori* infection is not significantly different in patients with migraine than in controls.[15]

We have extensively compared the clinical and psychological features of the migraineurs with chronic *H. pylori* infection with those without infection. Food sensitivity was the unique clinical feature differentiating the two groups of migraine sufferers. Food sensitivity in migraine is a well-known but still unexplained phenomenon.[16] Several authors have suggested that allergy to foods might be the basis of this phenomenon, but additional mechanisms cannot be ruled out.[17,18] In our study, patients with chronic *H. pylori* infection reported a significantly lower food sensitivity than those unaffected by infection. In experimental animals, *H. pylori* infection alters antigen absorption and processing in the digestive tract.[19] A reduced absorption of food antigens might explain this finding.

*Acknowledgments: This work was supported by a 1996 grant from the European Community and by a 1998 grant from Ministero dell'Università e della Ricerca Scientifica (MURST) Italy.*

## REFERENCES


1. Graham DY. *Helicobacter pylori* infection in the pathogenesis of duodenal ulcer and gastric cancer: a model. *Gastroenterology.* 1997;113:1983-1991.
2. Alexander GA, Brawley OW. Association of *Helicobacter pylori* infection with gastric cancer. *Mil Med.* 2000;165:21-27.
3. Martin-de-Angila C, Boixeda D, Canton D, Gisbert JP, Fuertes A. High seroprevalence of *Helicobacter pylori* infection in coronary heart disease. *Lancet.* 1995;346:310.
4. Gasbarrini A, Serricchio M, Tondi P, Gasbarrini G, Pola P. Association of *Helicobacter pylori* infection with Raynaud phenomenon. *Lancet.* 1996;348:966-967.
5. Markus HS, Mendall MA. *Helicobacter pylori* infection: a risk factor for ischaemic cerebrovascular disease and carotid atheroma. *J Neurol Neurosurg Psychiatry.* 1998;64:104-107.
6. Patel P, Carrington D, Strachan D. Fibrinogen: a link between chronic infection and coronary artery disease. *Lancet.* 1994;343:1634-1635.
7. Phull PS, Gower JD, Price AB, Green CJ, Jacyna MR. Alpha-tocopherol levels in chronic gastritis: correlation with mucosal neutrophil infiltration. *Gut.* 1993;34(suppl 1):T133.
8. Madalinski K, Dzierzanowska D, Januszewicz P. Immunology of *Helicobacter pylori* infection. *J Physiol Pharmacol.* 1993;50:807-815.
9. Gasbarrini A, De Luca A, Fiore G, Giacovazzo M. Primary headache and *Helicobacter pylori. Intl J Angiol.* 1998;7:310-312.
10. Gasbarrini A, De Luca A, Fiore G. Beneficial effects of *Helicobacter pylori* eradication on migraine. *Hepatogastroenterology.* 1998;45:765-770.
11. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia.* 1998;8(suppl 7):1-96.
12. Danielli E. A fluorometric enzyme-linked immunosorbent assay for serological diagnosis of *Helicobacter pylori* infection. *Eur J Gastroenterol Hepatol.* 1993;5(suppl 2):S57-S59.
13. Guidelines for clinical trials in *Helicobacter pylori* infection. Working party of the European *Helicobacter pylori* study group. *Gut.* 1997;41(suppl 2):S57-S59.
14. Sitas F, Forman D, Yarnell JW. *Helicobacter pylori* infection rates in relation to age and social class in a population of Welsh men. *Gut.* 1991;32:25-28.
15. Caselli M, Chiamenti CM, Soriani S, Fanaro S. Migraine in children and *Helicobacter pylori. Am J Gastroenterol.* 1999;94:1116-1118.
16. Peatfield RC, Sandler M, Rose FC. The prevalence and inheritance of dietary migraine. In: Rose FC, ed. Migraine: Chemical and Therapeutic Advances. Basel: Karger; 1985:218-224.
17. Clifford Rose F. Food and headache. *Headache Q.* 1997;8:319-329.
18. Moffett AM, Swash M, Scott DF. Effect of chocolate in migraine: a double-blind study. *J Neurol Neurosurg Psychiatry.* 1974;37:445-448.
19. Matysiak-Budnik T, Terpend K, Alain S. *Helicobacter pylori* alters exogenous antigen absorption and processing in a digestive tract epithelial cell line model. *Infect Immun.* 1998;66:5785-5791.