

Reversal of Iron Deficiency Anemia after *Helicobacter pylori* Eradication in Patients with Asymptomatic Gastritis

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Background: Iron deficiency anemia is the most common form of anemia worldwide. Recent studies have suggested an association between *Helicobacter pylori* infection and iron deficiency.

Objective: To investigate the effects of eradicating *H. pylori* with combination antibiotic therapy on iron deficiency anemia in patients with *H. pylori*-associated gastritis.

Design: Case series.

Setting: University hospital.

Patients: 30 patients with a long history of iron deficiency anemia in whom *H. pylori*-associated gastritis was the only pathologic gastrointestinal finding detected.

Intervention: Eradication therapy with two antibiotics and discontinuation of iron replacement therapy.

Measurements: Complete blood count, ferritin levels, and gastroscopy with biopsy to evaluate *H. pylori* status.

Results: At 6 months, 75% of patients had recovered from anemia ($P < 0.001$), ferritin values increased from $5.7 \pm 0.7 \mu\text{g/L}$ to $24.5 \pm 5.2 \mu\text{g/L}$ (95% CI, 8.85 to 29.97). After 12 months, 91.7% of patients had recovered from anemia.

Conclusions: Cure of *H. pylori* infection is associated with reversal of iron dependence and recovery from iron deficiency anemia.

Standard care for men and postmenopausal women with iron deficiency anemia is use of gastrointestinal evaluation to exclude gastrointestinal tract abnormality (1, 2). Nevertheless, even when the gastrointestinal tract is investigated thoroughly, a large proportion of patients (around 30%) remain without a diagnosis (2, 3).

Recent epidemiologic studies have suggested an association between *Helicobacter pylori* infection and iron deficiency (4, 5). Infection with *H. pylori* is recognized as a major risk factor in peptic ulcer disease and gastric cancer, in which lesions are likely to bleed either overtly or in an occult manner, eventually leading to iron deficiency anemia. However, most people infected with *H. pylori* only have chronic gastritis that is not associated with gastrointestinal bleeding or with any other specific disease (6). It has been suggested that infection with *H. pylori* may lead to iron deficiency or iron deficiency anemia by impairing iron uptake or increasing iron demand (4). Reversal of iron deficiency anemia after successful eradication of *H. pylori* was recently observed in children (7, 8) and in a young adult (9).

We performed a prospective open study to verify the effects of eradication of *H. pylori* infection on iron deficiency anemia in patients with *H. pylori*-associated gastritis.

Methods

Patients

Patients were observed from September 1994 to December 1997. A total of 189 consecutive adult outpatients who were older than 20 years of age and had iron deficiency anemia (158 women and 31 men; median age, 47 years [range, 20 to 79 years]) were referred to our gastroenterology department from the hematology department. Iron-deficiency anemia was defined as a hemoglobin concentration less than 14 g/L for men and less than 12 g/L for women, a mean corpuscular volume less than 80 fL, and a serum ferritin level less than 30 $\mu\text{g/L}$ (3). Outpatients with an obvious cause of blood loss, such as a heavy menstrual period (cycles > 6 days), epistaxis, active gastrointestinal hemorrhage, or evidence of fecal occult blood positivity, were excluded from the study. Other exclusion criteria were gastrointestinal or hematologic cancer at the time of

observation, chronic renal failure, severe cardiopulmonary disease, reported or suspected pica, hemolysis, aplastic anemia or thalassemia, alcoholism or liver cirrhosis, and pregnancy.

After this selection, patients who were taking nonsteroidal anti-inflammatory drugs; had had gastric surgery; or had atrophic body gastritis and celiac disease, as described elsewhere (3), were excluded from the study. An iron-poor diet as a cause of iron deficiency anemia was excluded by a hospital dietitian (3). A double-contrast barium enema or colonoscopy plus radiographic examination of the small bowel, or Meckel scintigraphy, were also carried out if indicated.

Interventions

Patients were treated for 2 weeks with omeprazole, 40 mg, in the morning; amoxicillin, 1 g; and metronidazole, 250 mg three times daily after meals, for the first week. Patients were also instructed to discontinue any iron replacement therapy, including over-the-counter iron-containing medication. A clinical evaluation was performed 3 months after eradication therapy to check for clinical signs of anemia. Two follow-up visits at 6 and 12 months were planned. At each visit, a complete blood count was done and ferritin levels were measured. Baseline and 12-month transferrin saturation indexes were also calculated. The 6-month follow-up examination included endoscopy with biopsy to evaluate *H. pylori* eradication. Patients were considered cured of *H. pylori* infection if both rapid urease testing and histologic examination of the gastric antral and body biopsy samples were negative.

Successful eradication therapy for iron deficiency anemia was defined as no need for iron replacement therapy, recovery from anemia, or both. All patients gave full informed consent to participate the study, which was approved by the local ethical committee.

Measurements

History of anemia, expressed as length of time from first laboratory diagnosis of iron deficiency anemia to referral to the gastroenterology department, was assessed.

Serum ferritin levels were measured by using commercial kits (Ciba-Corning Diagnostic Corp., Milan, Italy) (3). Hemoglobin concentrations and mean corpuscular volume were determined by an automated Coulter counter (Technicon H1, Bayer Corp., Tarrytown, New York) (3). Serum transferrin levels were measured by using a commercial kit (Beckman Analytical, Milan, Italy) (10). Serum iron levels were measured and the transferrin saturation index (normal value, 16% to 45%) was calculated as described elsewhere (10).

Patients underwent gastroscopy with gastric antral ($n = 3$) or body ($n = 3$) biopsy. One sample was tested by using a rapid urease test, and the others were examined by conventional histology (3, 9). Duodenal biopsy specimens were also obtained to exclude celiac disease. The pathologist was unaware of clinical and endoscopic data. Gastritis status was described according to the Updated Sydney System classification (8). *Helicobacter pylori* status was considered positive when the organism was detected on histologic examination, by rapid urease testing, or both.

Statistical Analysis

Data are expressed as the mean (\pm SE) or median (range) as appropriate and were analyzed by using the *t*-test for paired data. Subgroups (percentages of patients) were compared by using the McNemar test. A *P* value less than 0.05 was considered statistically significant.

Role of the Funding Sources

Our funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the paper for publication.

Results

Of the 189 patients referred to our gastroenterology department, 30 (15.9%) had iron deficiency anemia: 4 men and 26 women (of whom 3 were postmenopausal) with a median age of 35.5 years (range, 20 to 65 years). In these patients, *H. pylori*-associated gastritis was the only pathologic finding. Gastroscopy did not reveal any sign of current or past mucosal erosion or ulcer disease. All patients had a suboptimal response to oral iron therapy; they needed continuous or intermittent oral iron treatment to prevent the decrease of hemoglobin levels. All patients denied having any specific gastrointestinal symptom or having used antisecretory drugs. Occasional, nonpersistent, mild dyspeptic symptoms were considered nonspecific. Anamnestic interview and evaluation of previous medical records documented moderate to severe iron deficiency anemia in all patients (hemoglobin level, 9.5 ± 0.25 g/L; mean corpuscular volume, 69 ± 1.15 fL; and serum ferritin level, 6.2 ± 0.8 μ g/L) associated with clear clinical signs of anemia, such as fatigue, pallor, and decreased exercise capacity. Median history of anemia and of oral iron therapy in these patients was 4.8 years (range, 2 to 20 years).

All patients underwent an eradication regimen. At the 3-month clinical evaluation, no patients reported anemia-related symptoms. Twenty-eight patients underwent endoscopy at 6 months to verify *H. pylori* eradication. Two female patients (27 and

Table. Hematologic Data from 24 Patients with Iron Deficiency Anemia*

Measurement	Baseline†	At 6 Months	At 12 Months
Hemoglobin level, g/L‡	10.2 ± 0.2	13.0 ± 0.3§	13.3 ± 0.03§
Increase over baseline hemoglobin level, %		20.6 ± 2.5§	23.4 ± 2.6§
Mean corpuscular volume, fL	72.9 ± 1.2	86.25 ± 1.1§	85.4 ± 1.3§
Ferritin level, µg/L¶	5.7 ± 0.7	24.5 ± 5.2**	24.1 ± 5.0††

* Data are expressed as the mean ± SE.

† Patients were receiving oral iron treatment.

‡ Reference values are 12 to 16 g/L for women and 14 to 18 g/L for men.

§ $P < 0.001$ compared with baseline.

|| Reference range, 80 to 100 fL.

¶ Reference range, 30 to 180 µg/L.

** $P = 0.0011$ compared with baseline.

†† $P = 0.0018$ compared with baseline.

36 years of age) declined further follow-up because they were in good general health. *Helicobacter pylori* infection was cured in 25 patients (89.3% [95% CI, 72% to 98%]); at this point, one female 31-year-old patient was excluded from further follow-up because she had developed heavy menstrual periods due to a uterine myoma that was not present at the initial diagnosis. Thus, 24 patients (3 men and 21 women; median age, 35.7 years [range, 20 to 65 years]) in whom *H. pylori* infection was cured and 3 patients (1 man 21 years of age and 2 women 22 and 37 years of age) in whom *H. pylori* infection was not cured were eligible for evaluation.

Effects of *Helicobacter pylori* Eradication on Iron Deficiency Anemia

At 6 months of follow-up, 18 of 24 (75%) patients recovered from anemia ($P < 0.001$) and had a significant increase in the hemoglobin concentration, mean corpuscular volume, and ferritin level (Table).

At 12 months of follow-up, 4 more patients (22 of 24 [91.7%]) showed recovery from anemia without resuming iron supplementation. The mean values of all measurements obtained were similar to those seen at the 6-month evaluation (Table). Even though ferritin levels returned to normal in only 4 patients at the 12-month follow-up visit, we observed a significant increase of more than 300% over baseline values (5.7 ± 0.7 µg/L compared with 24.1 ± 5.0 µg/L [$P = 0.0018$]; mean increase, 18.4 µg/L [CI, 8.08 to 29.44 µg/L]). Mean transferrin saturation index also significantly increased from baseline (from $5.5\% \pm 0.8\%$ to $18.7\% \pm 1.8\%$ [$P < 0.001$]; mean increase, 13.2 percentage points [CI, 8.92 to 17.46 percentage points]), even though values in 5 patients were still below the normal range.

Eight patients were followed for 1 more year. Hemoglobin levels returned to normal in the two patients who were still anemic at the previous 12-

month examination. In these patients, ferritin levels further increased from those measured at the 12-month follow-up (23.9 ± 6.7 µg/L and 30.5 ± 7.4 µg/L [$P = 0.047$]; mean increase, 6.6 µg/L [CI, 0.5 to 12.6 µg/L]).

In the three patients who were not cured, the hemoglobin level at 6 months of follow-up was stable in the male patient and was slightly decreased in the two female patients. These three patients experienced mild fatigue. However, in all patients, a clear decrease in ferritin levels was observed (data not shown).

Helicobacter pylori Gastritis

At diagnosis, 7 patients had mild antral atrophic gastritis, of whom 4 had associated chronic, body nonatrophic gastritis; 1 patient had only body nonatrophic gastritis; and 22 patients had chronic antral nonatrophic gastritis, 20 of whom had a similar pattern in the gastric body mucosa. Thus, considering the involvement of both gastric compartments, 24 of 30 (80%) patients with iron deficiency anemia had chronic pangastritis. Overall, the chronic inflammation score was mild and did not differ between the antrum and the gastric body (0.95 ± 0.13 and 1.1 ± 0.14 , respectively; $P > 0.2$). The *H. pylori* density score did not differ for the antrum or body of the anemic patients and was mild to moderate in both compartments (1.5 ± 0.13 and 1.75 ± 0.15 , respectively; $P > 0.2$).

Discussion

Our data show that in a group of patients with iron deficiency anemia in whom *H. pylori*-positive chronic pangastritis was the only gastrointestinal pathologic finding, cure of the infection determines prolonged reversal of iron dependence and recovery from anemia.

In our patients, 12 to 24 months were needed to achieve an increase in iron deposits, even if recovery from anemia was followed by a significant increase in ferritin levels (>300% over baseline), indicating a progressive build-up of body iron deposits after effective eradication. This delay may reflect the fact that most of our patients were premenopausal women, who have a predictable and stable cause of blood loss. The presence of a factor that can further impair iron absorption, as was recently suggested for *H. pylori* (5), can easily unbalance an already unstable equilibrium and lead to the development of iron deficiency anemia. Similarly, premenopausal women who have undergone gastrectomy, a procedure well known to impair iron absorption, develop iron deficiency anemia after surgery at a faster rate than do men and postmeno-

pausal women (11). A similar process has also been observed in premenopausal woman with atrophic body gastritis (3). Thus, in premenopausal women, even a normal menstrual flow is an additional factor that unbalances iron status when *H. pylori* is present.

Our results must be interpreted in the context of our study's limitations. First, we have no firm data on the medications that patients took before and after eradication therapy. Second, our sample size was small. Our findings must be considered preliminary; further studies with larger groups of patients and controlled clinical trials are needed to prove the efficacy of our results.

Another interesting finding of our study is the high prevalence of pangastritis. Equally distributed pangastritis with a tendency to involve the gastric body to a greater extent was present in 80% of patients. This prevalence is higher than that reported elsewhere (12, 13–15), especially considering the relatively young mean age of our patients. It is known that most persons who develop chronic *H. pylori* gastritis will exhibit more prominent gastritis in the antrum than in the body (6). A mild, diffuse form of chronic gastritis involving both gastric compartments has no clear disease association, and most affected persons do not manifest any clinical symptoms (6). Therefore, the form of gastritis observed in our study should represent a distinctive characteristic of patients with iron deficiency anemia. How the infection may induce the development of anemia remains to be explained. Possible mechanisms may correlate *H. pylori* infection to the development of disturbed iron absorption. Ascorbic acid, the reduced form of vitamin C, is present in the gastric juice of healthy persons (16) is known to be the most potent enhancer of nonheme iron absorption (17). It has been shown that *H. pylori* causes a considerable decrease in the concentration of ascorbic acid in the gastric juice and that this can be reversed by cure of the infection (16). In addition, it has been observed that gastric juice concentrations of ascorbic acid are significantly reduced when gastritis extends from the antrum to the gastric body (18). Thus, the diffuse *H. pylori*-related chronic inflammation could exert a negative effect by reducing the amount of ascorbic acid available for iron absorption.

Helicobacter pylori infection may lead to an imbalance of body iron homeostasis by increasing iron demand (4). As it is for many other bacteria, iron is an essential growth factor for *H. pylori*. The bacterium has been shown to contain an iron-binding protein resembling ferritin with a binding activity for heme iron in erythrocytes (19). Moreover, *H. pylori* can use iron bound to human lactoferrin, an iron-binding glycoprotein produced by neutrophils

located on the human mucosal surface (20). It has been speculated that if the bacteria in the stomach are diffuse and numerous, this affinity for iron binding and uptake may increase the need for iron (4). Our finding of diffuse, mild to moderate *H. pylori* colonization in both gastric compartments in our patients may support this hypothesis.

In conclusion, our study indicates that in patients with iron deficiency anemia and chronic *H. pylori*-related gastritis, cure of the infection leads to the reversal of the need of iron treatment, to normalization of hemoglobin levels after 6 months, and to long-lasting recovery from iron deficiency anemia.

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