

## Gastric Histopathology, Iron Status and Iron Deficiency Anemia in Children with *Helicobacter pylori* Infection

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### ABSTRACT

**Objectives:** *Helicobacter pylori* has been established as a major cause of gastritis and peptic ulcer disease in adults and children. *H. pylori* infection may also have a role in the development of some extragastrointestinal diseases, including iron deficiency anemia. The aim of this study is to investigate *H. pylori*-related changes in gastric physiology and histology and the relationship of these changes to iron deficiency anemia in children.

**Methods:** Fifty-two patients with gastrointestinal complaints were studied. Hematologic parameters, 3-day vitamin C and iron consumption, serum gastrin levels, and gastric juice ascorbic acid levels were compared in patients with and without *H. pylori* infection. Dietary intake of vitamin C and iron, serum gastrin, gastric juice ascorbic acid content, and gastric histology were compared in patients with *H. pylori* infection and anemia and in patients with *H. pylori* infection and no anemia. The CagA status of the *H. pylori* organisms was evaluated.

**Results:** Twenty-eight of 52 patients had *H. pylori*. Thirty-one patients had iron deficiency anemia. *H. pylori* infection was associated with low serum iron levels. *H. pylori* gastritis was associated with a decrease in the gastric juice ascorbic acid level. Infection with CagA-positive strains was associated with a greater decrease in gastric juice ascorbic acid than infection with CagA-negative strains. However, the gastric juice ascorbic acid levels of patients with *H. pylori* and anemia were not different from those of non-anemic patients with *H. pylori*. Among patients with *H. pylori* infection, pangastritis was twice as common in those with anemia than in those without anemia.

**Conclusions:** *H. pylori* infection was associated with a decrease in gastric juice ascorbic acid concentration, and this effect was more pronounced in patients with the CagA-positive strain. Pangastritis was more common in patients whose *H. pylori* infection was accompanied by anemia. **JPGN 38:146–151, 2004. Key Words:** Ascorbic acid—CagA—Children—*Helicobacter pylori*—Iron deficiency anemia.

The role of *Helicobacter pylori* infection in the development of extragastrointestinal diseases, including iron deficiency anemia (IDA), has been the focus of attention during the last decade (1,2). Epidemiologic studies have indicated that *H. pylori* seropositivity is associated with low serum ferritin and hemoglobin levels compared with seronegative controls in adults and children (3–5). These findings have been supported by a few case reports in which eradication of *H. pylori* resulted in improvement of iron deficiency anemia (IDA) in patients resistant to iron replacement therapy (6–11). It has also been reported that eradication of *H. pylori* may result in im-

provement of anemia even without iron supplementation (12–14).

Confirmation of the relationship between *H. pylori* infection and IDA has not confirmed the pathophysiologic mechanisms involved in the phenomenon. Two main hypotheses have been proposed to explain the association between *H. pylori* infection and IDA. The first hypothesis is sequestration of iron by antral *H. pylori* infection (8,15). Barabino et al. (8) showed that iron was diverted away from the bone marrow in patients with *H. pylori* infection and IDA. The second hypothesis is that *H. pylori*-related changes in the gastric physiology result in IDA (16). It has been shown that *H. pylori* gastritis decreases gastric acidity and the ascorbic acid content of gastric juice (GAA), both of which may decrease non-heme iron absorption (17–22). Capurso et al. (23) demonstrated that both pangastritis and pangastritis-induced hypochlorhydria were more prevalent in adult patients with *H. pylori* who had anemia than in those who did not have anemia.

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It has been claimed that the virulence of *H. pylori* may be responsible for various physiological and histologic changes (24,25). The role of virulence factors in the development of IDA has not been clarified. In the current study, we investigated *H. pylori*-related changes in gastric physiology and histology, and the role of the virulence of *H. pylori*. These changes were compared in *H. pylori* positive pediatric patients with and without anemia to evaluate the possible role of bacteria in IDA.

## PATIENTS AND METHODS

### Patients

Fifty-two patients were eligible for the study (29 female and 23 male; mean age [ $\pm$ SD],  $8.9 \pm 4.7$  years). Indications for esophagogastroduodenoscopy were recurrent abdominal pain, refractory IDA, and other gastrointestinal complaints, such as vomiting. Patients with an obvious cause of blood loss, such as active or recent gastrointestinal hemorrhage, epistaxis or menorrhagia were excluded. Other exclusion criteria were the presence of chronic diseases, hematologic diseases other than iron deficiency causing anemia, motor-mental retardation, celiac disease, recent antibiotic or antacid use, and malabsorption syndromes.

Complete blood count, serum iron, and ferritin levels were determined in all patients. IDA was diagnosed when serum ferritin level was lower than  $12 \mu\text{g/L}$ , serum iron level was lower than  $50 \mu\text{g/dL}$ , and the hemoglobin level was more than 2SD below age- and gender-adjusted normal values. Patients were divided into four groups: those with *H. pylori* and anemia ( $n = 12$ ), those with *H. pylori* but no anemia ( $n = 16$ ), those without *H. pylori* but with anemia ( $n = 12$ ), and those without *H. pylori* or anemia ( $n = 12$ ).

### Collection of Specimens

All endoscopic examinations were performed under deep intravenous sedation. Five milliliters of venous blood was drawn during intravenous catheter placement. The blood samples were centrifuged and stored at  $-70^\circ\text{C}$  until analysis. During endoscopy, 5 mL of gastric juice was aspirated into a sterile container before biopsy specimens were obtained. The gastric juice sample was centrifuged for 5 minutes immediately after collection, and a 2 mL aliquot of the supernatant was added to 2 mL of 5% trichloroacetic acid. The gastric juice samples were stored at  $-70^\circ\text{C}$  until the analysis.

Several biopsy specimens were obtained from the upper gastrointestinal tract (2 from esophagus, 3 from corpus, 3 from antrum, and 3 from distal duodenum). Two biopsy specimens, one from the antrum and one from the corpus, were used for rapid urease test (Pyloritek Test Kit, Bard Interventional Products, U.S.A.). Duodenal aspirates were collected from the second part of duodenum before duodenal biopsy specimens were obtained. This material was examined immediately for the presence of *Giardia lamblia* and other intestinal parasites by light microscopy.

### Endoscopic Evaluation and Histopathologic Examination

Upper gastrointestinal endoscopies were performed by an experienced endoscopist using an Olympus GIF XP-20 and

Fujinon videoendoscope (Fujinon EG-200HR). Gastric biopsy specimens were stained with hematoxylin and eosin and modified Giemsa and were examined for the presence of *H. pylori*. The patients were considered to have *H. pylori* infection if both the rapid urease test and the histologic examination of the gastric specimens revealed were positive. Gastritis was graded according to the updated Sydney histologic scoring system (26). Patients were classified as having antrum-dominant or corpus-dominant gastritis, according to the location of the most severe inflammation. Patients were considered to have pangastritis when both antrum and corpus were inflamed to the same degree.

### Dietary Analysis

All parents were asked to record on a standard questionnaire the amount and type of all foods consumed on 3 consecutive days. The dietitian confirmed the accuracy of the questionnaire after reviewing it with the parents. The same dietitian calculated the mean intake of iron and vitamin C expressed as milligram per day (mg/day).

### Biochemical and Microbiologic Analysis

Ascorbic acid in gastric juice was measured spectrophotometrically using the 2,4-dinitrophenylhydrazine method (27). Gastric juice (0.5 mL) was mixed with 1.5 mL of 5% trichloroacetic acid and then at 1,500 rpm for 10 minutes. Then 0.5 mL supernatant was mixed with 0.5 mL of DTC solution (2,4-dinitrophenylhydrazine solution in  $\text{H}_2\text{SO}_4$ ,  $\text{CuSO}_4$  and thiourea mixture). Samples were incubated at  $37^\circ\text{C}$  for 4 hours and then 65% cold  $\text{H}_2\text{SO}_4$  was added, and absorbance at 520 nm was measured.

Fasting serum gastrin concentrations were determined using a commercial gastrin radioimmunoassay kit (Double Antibody Gastrin, Diagnostic Products Corporation, Los Angeles, CA). A commercial Western-blot kit (Euroimmun, Medizinische Labordiagnostika, Germany) was used to determine the CagA status of the *H. pylori*.

### Statistical Analysis

All statistical analysis was performed with SPSS 9.0 for Windows. Data were expressed as the mean ( $\pm$ SD) or median (range) as appropriate. Mann-Whitney *U* test was used to compare the differences in physiological variables between *H. pylori*-positive and *H. pylori*-negative groups. Anemic patients with *H. pylori* were compared with non-anemic patients with *H. pylori* by  $\chi^2$  or Fisher exact tests and Mann-Whitney *U* test as necessary.

### Ethics

This study was approved by The Research Ethical Committee of Marmara University Medical School, and informed parental consent was obtained in each case.

## RESULTS

### Virulence and Frequency of *H. pylori* Infection in Relation to Iron Deficiency Anemia

Twenty-eight of 52 (53.8%) patients had *H. pylori*. IDA was found in 24 (46.2%) patients. The frequency of

*H. pylori* infection in patients with anemia and those without was similar (12/24 v 16/28, respectively;  $P = 0.7$ ). Serum iron levels were lower in patients with *H. pylori* than in those without *H. pylori* ( $63.3 \pm 31.0 \mu\text{g/dL}$  v  $81.1 \pm 30.3 \mu\text{g/dL}$ , respectively,  $P < 0.05$ ). Mean serum ferritin and hemoglobin levels were similar in these two groups.

Among patients with *H. pylori*, 11 (39.3%) were infected with the CagA positive strain. The frequency of infection with the CagA-positive strain was not different in patients with *H. pylori* and anemia and those with *H. pylori* but no anemia (4/12 v 7/16,  $P = 0.7$ ).

### Dietary analysis

Mean daily intake of vitamin C and iron was not different in patients with *H. pylori* and those without *H. pylori*. The daily intake of vitamin C and iron in patients with and without anemia and patients with *H. pylori* and anemia or no anemia are shown in Table 1.

### *H. pylori* Infection, Gastroduodenal Histology and Iron Deficiency Anemia

Twenty-six of 28 patients with *H. pylori* had gastritis. The severity of gastritis, grouped according to the updated Sydney scoring system, is shown in Table 2. The frequency of infection with the CagA-positive strain was not related to severity of gastritis (Table 2). Among patients with *H. pylori*, the difference between the severity of gastritis in those with anemia and those without anemia was not statistically significant (Table 2).

The localization of gastritis in patients with *H. pylori*, both those with anemia and those with no anemia, is shown in Table 3. Pangastritis was more common in patients with *H. pylori* and anemia than in those with *H. pylori* and no anemia, but the difference was not statistically significant. There was no association between infection with the CagA-positive strain and the localization of gastritis (Table 3).

Serum hemoglobin and ferritin were lower in patients with pangastritis than in those with antral gastritis (Table 4). Patients with corpus gastritis and those with no gastritis were omitted from the statistical analysis because these groups had so few patients. Serum iron was significantly lower in patients with pangastritis than in those

**TABLE 1.** Comparison of daily intake of vitamin C and iron between different patient groups

Patients (n)	Vitam in C intake (mg/d)	Iron intake (mg/d)
Anemic (n = 24)	66.0 ± 28.9	8.9 ± 2.9
Nonanemic (n = 28)	56.9 ± 40.0	10.5 ± 4.4
<i>P</i> value	0.5	0.3
<i>H. pylori</i> infected anemic (n = 12)	66.0 ± 28.9	8.9 ± 2.9
<i>H. pylori</i> infected nonanemic (n = 16)	51.8 ± 40.0	9.8 ± 6.0
<i>P</i> value	0.3	0.6
<i>H. pylori</i> gastritis (n = 26)	59.6 ± 35.4	9.6 ± 4.8
No gastritis (n = 26)*	55.2 ± 37.5	9.5 ± 4.5
<i>P</i> value	0.6	0.9

Vitamin C and iron intakes were given as mean ± SD.

\* Including two patients infected with *H. pylori* but without gastritis.

with antral gastritis (median, 38.5  $\mu\text{g/dL}$  v 68.0  $\mu\text{g/dL}$ , respectively;  $P < 0.05$ ).

No patient in the study had duodenitis and duodenal ulcer. None of the patients had *Giardia lamblia* or other intestinal parasites.

### *H. pylori* Infection, Gastric Physiology and Iron Deficiency Anemia

Gastric juice ascorbic acid (GAA) levels were significantly lower in patients with *H. pylori* gastritis than in those without gastritis (median, 5.6 mg/dL; range, 2.3–14.6 mg/dL v 9.0 mg/dL, range, 2.8–24 mg/dL, respectively;  $P < 0.05$ ). Patients with the CagA-positive strain had even lower GAA levels than did patients with the CagA-negative strain (median, 3.8 mg/dL; range, 2.3–9.3 mg/dL v 6.7 mg/dL, range, 3–17 mg/dL, respectively;  $P < 0.05$ ). The severity of gastritis was inversely related to GAA levels, but the differences did not reach statistical significance ( $6.2 \pm 3.3$  mg/dL,  $6.0 \pm 1.9$  mg/dL and  $5.7 \pm 2.6$  mg/dL for mild, moderate, and severe gastritis, respectively). The localization of gastritis was not related to GAA concentrations. GAA levels were similar in patients with *H. pylori* and anemia and patient with *H. pylori* but no anemia ( $6.5 \pm 3.5$  mg/dL v  $6.3 \pm 3.8$  mg/dL).

Serum gastrin levels were significantly higher in patients with *H. pylori* gastritis than in patients without gastritis (median, 10.5 pg/mL; range, 0.3–258 pg/mL v median, 2.2 pg/mL, range, 0.1–61.1 pg/mL, respectively;

**TABLE 2.** Severity of *H. pylori* gastritis, CagA positivity, and relationship with iron deficiency anemia

	Mild gastritis	Moderate gastritis	Severe gastritis	No gastritis
<i>H. pylori</i> infection (n = 28)	12 (42.9)	9 (32.1)	5 (17.9)	2 (7.1)
CagA positivity (n = 11)	3 (25.0)	5 (55.5)	3 (60.0)	0 (0.0)
<i>H. pylori</i> infected anemic (n = 12)	6 (50.0)	4 (33.3)	2 (16.7)	0 (0.0)
<i>H. pylori</i> infected non-anemic (n = 16)	6 (37.5)	5 (31.3)	3 (18.7)	2 (12.5)

Values are given as number (and percentages).

**TABLE 3.** Localization of *H. pylori* gastritis, CagA status, and relationship with iron deficiency anemia

	Antral gastritis	Corpus gastritis	Pangastritis	No gastritis
<i>H. pylori</i> infection (n = 28)	15 (53.6)	3 (10.7)	8 (28.6)	2 (7.1)
CagA positivity (n = 11)	6 (40.0)	2 (66.7)	3 (37.5)	0 (0.0)
<i>H. pylori</i> infected anemic (n = 12)	6 (50.0)	1 (8.3)	5 (41.7)	0 (0.0)
<i>H. pylori</i> infected nonanemic (n = 16)	9 (56.3)	2 (12.5)	3 (18.7)	2 (12.5)

Values are given as number (and percentages).

$P = 0.013$ ). There was a trend towards higher serum gastrin levels in patients with pangastritis than in those with antral and corpus gastritis (median, 24.2 pg/mL; range, 1.7–257 pg/mL; median, 10.0 pg/mL, range, 0.3–66.8 pg/mL  $\nu$  median, 4.9 pg/mL; range, 1.9–202.9 pg/mL, respectively). CagA positivity was also associated with higher serum gastrin levels (median, 26.2 pg/mL in CagA positivity  $\nu$  4.3 pg/mL in CagA negativity, respectively,  $P = 0.09$ ). Among patients with *H. pylori*, serum gastrin levels were not statistically different between those with anemia and those with no anemia.

## DISCUSSION

We found that *H. pylori* gastritis was closely related to lower gastric ascorbic acid levels in our pediatric patients. *H. pylori*-related pangastritis was more common in patients with anemia than in those with no anemia.

IDA is an important problem in developing countries. The most common causes of IDA in children are inadequate dietary intake of iron, rapid growth, and gastrointestinal disorders producing either malabsorption or gastrointestinal blood loss (28). IDA without a history of blood loss is recognized as an indication for gastrointestinal evaluation in adults (29). In recent years, *H. pylori* infection has been recognized as a contributing factor to IDA in both adults and children. In some epidemiologic studies, it has been suggested that *H. pylori* seropositivity is related to lower serum ferritin and hemoglobin levels than those found in adult and pediatric seronegative controls (3–5).

Gastric acidity and ascorbic acid are important promoters of iron absorption. Ascorbic acid chelates iron, protects its stability at the duodenum, and increases its

absorption (16). Gastric acidity maintains ferric iron in its soluble form and enhances its absorption (30). In adults, it has been demonstrated that *H. pylori* gastritis causes hypochlorhydria and decreased GAA levels (20–22,31). *H. pylori*-related hypochlorhydria might also adversely affect the bioavailability of vitamin C by inactivating, consuming, or decreasing the secretion of vitamin C into the gastric juice (20,32). Processes resulting in hypochlorhydria or decreased GAA levels may impair the bioavailability of iron (16). In our study, we found that patients with *H. pylori* gastritis had lower GAA concentration than patients without gastritis, although dietary intake of vitamin C was the same in both groups. The GAA concentration seemed to be inversely related to the severity of gastritis, but this relationship was not statistically significant. The localization of gastritis was not related to GAA concentration in our study group. Patients with *H. pylori* gastritis had significantly lower GAA concentrations, and this difference was more pronounced when patients with CagA positivity were compared with those with CagA negativity. Our study clearly indicated that GAA concentration was lower in children with *H. pylori* gastritis, and this effect was significantly related to the CagA status of *H. pylori*. To our knowledge, this is the first study in children that investigates the effects of *H. pylori* infection and virulence on gastric physiology. The GAA concentrations were not different between patients with *H. pylori* and anemia and those with *H. pylori* and no anemia. Moreover, these two groups were not different in terms of CagA positivity.

Serum gastrin levels are related to gastric acidity in patients with *H. pylori* (19,33). In our study group, serum gastrin levels were significantly increased in children with *H. pylori*; however, among patients with *H. pylori*, serum gastrin levels were not different in those with anemia and those with no anemia. The increase in serum gastrin level was more pronounced in children with pangastritis, which was two times more common in patients with *H. pylori* and anemia. Capurso et al. (23) demonstrated that patients with *H. pylori* and anemia predominantly had pangastritis and corpus-dominant gastritis when compared with control subjects with no anemia. Those authors also found that patients with pangastritis had increased serum gastrin levels, which might be the result of decreased parietal cell activity in corpus. It has not been clearly established whether similar histopatho-

**TABLE 4.** Serum hemoglobin, ferritin, and iron levels with respect to localization of *H. pylori* gastritis

	Pangastritis (n = 8)	Antral gastritis (n = 15)	<i>P</i>
Hemoglobin (g/dL)	11.9 (9.3–11.8)	12.6 (10.3–15.2)	0.1
Ferritin ( $\mu$ g/L)	14.7 (4.0–67.0)	23.2 (8.1–67.6)	0.2
Iron ( $\mu$ g/dl)	38.5 (11–60)	68.0 (42–126)	<0.05

Values were given as median (range).

Patients with corpus gastritis and patients without gastritis were excluded because these groups have few patients (3 and 2, respectively).

logic presentations in adults and children have similar associations with gastric physiology. In our study, we found that pangastritis was more common, although statistically not significant, in pediatric patients with *H. pylori* and anemia than in patients with *H. pylori* and no anemia. It has also been demonstrated that serum iron levels were statistically lower in patients with pangastritis than in patients with antral gastritis.

It has been reported that infection with virulent *H. pylori* strains may be associated with more severe gastritis, higher risk of peptic ulcer disease, and increased incidence of gastric cancer compared with infection with nonvirulent strains (25). However, this association has not been consistently found throughout the world (34). In our study, we did not find an association between CagA status and the severity of gastritis. However, infection with the CagA-positive strain was associated with more pronounced changes in gastric physiology, specifically decreased GAA levels and increased serum gastrin concentrations.

Our findings suggest that GAA is decreased in pediatric patients with the virulent *H. pylori* strain. However, decreased GAA could not be linked to *H. pylori*-related IDA in this study. It was demonstrated that pangastritis was associated with low serum iron levels, and that pangastritis tended to be more common in pediatric patients with *H. pylori* and anemia than in those with *H. pylori* and no anemia. Pangastritis-associated hypochlorhydria might contribute to IDA in children by impairing the bioavailability of iron. The contribution of *H. pylori*-associated pangastritis to IDA needs to be confirmed by additional studies designed to reveal whether pangastritis-associated hypochlorhydria decreases iron absorption or not. The growing body of evidence suggesting that *H. pylori* gastritis truly does predispose to anemia should expand the scope of investigations to include a study of the possible mechanisms by which *H. pylori* might affect iron absorption.

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## Clinical Quiz

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From the first month of life, white plaques had been observed on the oral cavity mucous, the buccae, and the tongue of a 6 year old girl. The plaques did not disappear after antifungal treatment. The development of the girl in the first years of life was normal, and she had good appetite. There was no history of abdominal pain, diarrhea, chronic constipation, or weight loss. Family history was not significant. At the age of 6 years, she was admitted to determine if a diagnosis could be made regarding the persistent changes on the oral cavity mucosa. At admission, the child's general condition was good. On the buccal mucosa of the buccae and the tongue, white plaques were observed that could not be scraped off with a spatula. Moreover, softened gingivae and advanced caries of the teeth were noticed. Endoscopy of the upper part of the digestive tract revealed an esophagus covered with linear white plaque and fragile mucosa which bled when touched. The cardia and subcardial region of the stomach were normal. In the smear from the oral cavity and in the culture of stool, strains *Candida albicans* were detected. Two weeks after treatment, direct microbiologic examination by superficial exfoliation of the oral mucosa was repeated. Other than some desquamative elements, the test results were negative. Urine culture was sterile, and urine culture for fungi was negative. Results of laboratory evaluations, including cytomegalovirus and human immunodeficiency virus infection, were normal. Serum IgG and IgA were slightly elevated. Cellular immunity was undisturbed.

Question: What is the etiology of the white plaques on the mucosa?

ANSWER: See page 226.