High prevalence of serum immunoglobulin G antibody to *Helicobacter pylori* and raised serum gastrin and pepsinogen levels in enlarged fold gastritis

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Y Yasunaga, JJ Bonilla-Palacios, Y Shinomura, S Kanayama, Y Miyazaki, Y Matsuzawa. High prevalence of serum immunoglobulin G antibody to *Helicobacter pylori* and raised serum gastrin and pepsinogen levels in enlarged fold gastritis. Can J Gastroenterol 1997;11(5):433-436. To clarify the prevalence of *Helicobacter pylori* infection in enlarged fold gastritis, serum immunoglobulin (Ig) G antibody to *H pylori* was determined in 19 patients with severely enlarged gastric body folds (the widest fold greater than 10 mm on the radiograph), 55 patients with moderately enlarged folds (6 to 10 mm) and 44 control subjects (5 mm or less). The prevalence of serum IgG antibody to *H pylori* in the severe (100%) and moderate groups (100%) was significantly higher than that in controls (34.1%) (P<0.01). There were significant differences among the three groups in serum gastrin, pepsinogen I and pepsinogen II levels (severe had the highest levels, followed by moderate and then controls, P<0.001). *H pylori* colonization in the gastric mucosa was confirmed by culture, urease test or both, and inflammation by hematoxylin and eosin stain in the 25 *H pylori* seropositive patients who underwent endoscopy and biopsy. Results suggest that *H pylori* infection is highly prevalent in enlarged fold gastritis. Further studies on enlarged fold gastritis and *H pylori* infection are needed.

Key Words: *Antibody, Enlarged fold gastritis, Gastrin,* Helicobacter pylori, *Pepsinogen*

Forte prévalence des gammaglobulines sériques dirigées contre *Helicobacter pylori* et élévation des taux sériques de gastrine et de pepsinogène dans la gastrite avec élargissement des plis gastriques

RÉSUMÉ : Pour clarifier la prévalence de l'infection à *Helicobacter pylori* dans la gastrite avec élargissement des plis gastriques, les taux de gammaglobulines (IgG) sériques dirigées contre *H. pylori* ont été dosés chez 19 patients atteints de plis gastriques gravement élargis (les plissements les plus larges étant supérieurs à 10 mm à la radiographie), 55 patients atteints de gastrite avec élargissement modéré des plis gastriques (6 à 10 mm) et 44 témoins (5 mm ou moins). La prévalence des IgG sériques anti-*H. pylori* dans les groupes atteints sévèrement (100 %) et modérément (100 %) a été significativement plus élevée que chez les témoins (34,1 %) (P<0,01). Des différences significatives ont été décelées entre les trois groupes pour ce qui est de la gastrine, du pepsinogène I et du pepsinogène II sériques (le groupe atteint gravement présentant les taux les plus élevés, suivi des groupes atteints modérément, puis des témoins, P<0,001). La colonisation par *H. pylori* de la muqueuse gastrique a été confirmée par la culture et le test d'uréase ou par les deux et l'inflammation par la coloration à l'hématoxyline et à l'éosine chez les 25 patients *H. pylori*-positifs qui ont subi une endoscopie et une biopsie. Selon les résultats, l'infection à *H. pylori* est très prévalente dans les cas de gastrite avec élargissement des plis gastriques. D'autres études sur la gastrite avec élargissement des plis gastriques et sur l'infection à *H. pylori* sont justifiées.

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Received for publication November 6, 1996. Accepted March 3, 1997

Enlarged gastric folds are a common finding during radiographic or endoscopic examination of adults. Enlarged gastric folds may be associated with a variety of diseases, including hypertrophic gastritis, Ménétrier's disease, Zollinger-Ellison syndrome, primary gastrin cell hyperplasia, carcinoma and lymphoma (1,2). It is critical to determine the cause of this fold enlargement, especially to exclude scirrhous carcinoma. Recently it was suggested that *Helicobacter pylori* gastritis may be a cause of enlarged gastric folds (3-8). We previously reported that eradication of *H pylori* improves inflammation of the gastric mucosa and fold width in *H pylori*-positive patients with enlarged folds; these findings suggest that *H pylori* infection may cause gastritis accompanied with enlarged folds, ie, 'enlarged fold gastritis' (6). However, the relationship between the degree of fold enlargement and the prevalence of *H pylori* infection is unknown. Therefore, to clarify the prevalence of *H pylori* infection in enlarged fold gastritis, serum immunoglobulin (Ig) G antibody to *H pylori* (9,10) was determined in subjects with and without enlarged gastric folds. We also measured serum gastrin, pepsinogen I (PGI) and pepsinogen II (PGII) levels, which are known to be elevated in patients with *H pylori* infection and to decrease after eradication of the organism (10-14). In addition, *H pylori* colonization and inflammation in the gastric mucosa were confirmed in some of the *H pylori* seropositive patients.

SUBJECTS AND METHODS

Nineteen patients with severely enlarged gastric body folds (severe group; 14 males and five females, mean±SEM age 46.3±2.2 years, range 31 to 68), 55 patients with moderately enlarged folds (moderate group; 39 males and 16 females, 45.1±1.2 years, range 30 to 67) and 44 control subjects without enlarged folds (control group; 28 males and 16 females, 45.2±1.2 years, range 31 to 62) comprised the study group. Patients in the severe, moderate and control groups were assigned randomly in one year, three months and one month, respectively, from subjects who underwent upper gastrointestinal barium study as part of a mass screening for gastric carcinoma. All subjects showed gastric folds along the greater curvature in the whole body region on the radiographs. Gastric body folds were considered to be enlarged when the widest fold was greater than 5 mm (deemed severely enlarged at more than 10 mm and moderately enlarged at 6 to 10 mm) on the double contrast radiographs taken in the supine position (15,16). The fold width of the control subjects was, at most, 5 mm. Means ± SEM of the widest fold were 11.4±0.2, 7.3±0.1 and 3.7±0.1 mm in the severe, moderate and control groups, respectively. Serum creatinine concentrations were within normal limits. Hypoproteinemia (total protein concentration less than 65 g/L) was found in two patients in the severe group (63 and 64 g/L).

All subjects were free from antisecretory drugs during the study and for at least three months before. The study was performed in accordance with the principles of the local ethical committee, and informed consent was obtained from all subjects.

Fasting serum samples were taken to determine *H pylori* IgG by using enzyme-linked immunosorbent assay (9) (Pyloristat; BioWhittaker, Maryland), gastrin levels by using radioimmunoassay (17) (Gastrin RIA Kit II; Dainabot, Tokyo, Japan), and PGI and II levels by using immunoradiometric assay (18) (Pepsinogen I and II RIA Bead; Dainabot).

Twenty-five *H pylori* seropositive subjects (nine in the severe group, 10 in the moderate group and six in the control group) were randomly selected and underwent endoscopic examinations. Endoscopic examinations in the 19 patients in the severe and moderate groups demonstrated enlarged gastric body folds with and without mucosal erythema or erosions. There were no peptic ulcers or carcinomas found. Endoscopic findings in the six *H pylori* seropositive control subjects were almost normal. Biopsy specimens were taken from the prepylorus and greater curvature of the upper portion of the body. *H pylori* infection was determined by positive culture (10,19) (Fujisawa Pharmaceutical Co Ltd, Osaka, Japan) and/or urease test (CLOtest; Delta West, Bentley, Australia) (10,20). Mononuclear infiltrates (for degree of chronic inflammation) and polymorphonuclear infiltrates (for activity of inflammation) were graded into four categories (0, none; 1, mild; 2, moderate; and 3, severe) by hematoxylin and eosin stain (16).

All results are expressed as mean ± SEM. Statistical analyses used were one-way ANOVA, Scheffe's multiple comparison, χ^2 test for independence, and the one- and two-sample *t* tests. $P<0.05$ was considered statistically significant.

RESULTS

Serum *H pylori* IgG was positive in all patients with both severely and moderately enlarged gastric body folds, and in 15 of the 44 control subjects without enlarged folds. The prevalence of serum *H pylori* IgG in the severe (100%) and moder-

TABLE 1
Differences in measured variables among the three groups

	Prevalence of serum IgG antibody to *Helicobacter pylori* (%)	Serum gastrin (pg/mL)	Serum pepsinogen I (ng/mL)	Serum pepsinogen II (ng/mL)	Pepsinogen I:II ratio
Severe group (n=19)	100.0* (19/19)	195.3±24.2†‡	120.0±13.0†§	57.3±5.7†§	2.1±0.2†
Moderate group (n=55)	100.0* (55/55)	124.9±10.8*	68.8±2.8*	30.2±1.2†	2.3±0.1†
Control group (n=44)	34.1 (15/44)	72.1±4.8	47.4±2.1	9.1±0.9	6.5±0.3

*All results are expressed as mean ± SEM. Group definitions are explained in the text. *P<0.01 and †P<0.001 versus the control group; ‡P<0.01 and §P<0.001 versus the moderate group. Ig Immunoglobulin*

ate groups (100%) was significantly higher than that in the control group (34.1%) (P<0.01) (Table 1). There were significant differences among the three groups (P<0.001) in serum gastrin (severe versus moderate versus control, 195.3±24.2 versus 124.9±10.8 versus 72.1±4.8 pg/mL), PGI (120.0±13.0 versus 68.8±2.8 versus 47.4±2.1 ng/mL), PGII (57.3±5.7 versus 30.2±1.2 versus 9.1±0.9 ng/mL) and PGI:PGII ratio (2.1±0.2 versus 2.3±0.1 versus 6.5±0.3). There were no significant differences between *H pylori* seropositive and seronegative controls in serum gastrin (78.5±10.8 versus 68.7±4.7 pg/mL), PGI (45.1±2.4 versus 48.5±15.8 ng/mL) and PGII (11.0±2.2 versus 8.2±0.9 ng/mL), except in PGI:PGII ratio (5.6±0.6 versus 7.0±0.4, P<0.05).

In 24 of the 25 *H pylori* seropositive patients who were endoscoped and biopsied, *H pylori* was positive in the antrum and the body on culture, urease test or both; in one patient in the severe group it was positive only in the body. Histologic examination showed inflammatory infiltrates in both the antrum and the body (Table 2).In the severe group, polymorphonuclear infiltrates in the body were significantly more severe than those in the antrum (P<0.05); mononuclear infiltrates in both the antrum and the body, and polymorphonuclear infiltrates in the body were significantly more extensive than those in the *H pylori* seropositive control (P<0.05). In the moderate group, mononuclear infiltrates in the antrum were significantly more severe than those in the *H pylori* seropositive control (P<0.01).

TABLE 2
Inflammatory infiltrates

	Mononuclear infiltrates (grade)		Polymorphonuclear infiltrates (grade)	
	Antrum	Body	Antrum	Body
Severe group (n=9)	2.4±0.2*	2.4±0.2*	1.0±0.3	1.9±0.2*†
Moderate group (n=10)	2.6±0.2‡	2.2±0.1	1.1±0.2	1.5±0.2
Helicobacter pylori seropositive control (n=6)	1.7±0.2	1.5±0.2	0.7±0.4	0.7±0.3

**P<0.05 versus* H pylori *seropositive control; †P<0.05 versus antrum; ‡P<0.01 versus* H pylori *seropositive control*

DISCUSSION

The present study showed that serum *H pylori* IgG was positive at higher percentages in patients with severely (100%) and moderately enlarged gastric body folds (100%) than in controls without enlarged folds (34.1%). The determination of serum *H pylori* IgG has high sensitivity and specificity for *H pylori* infection in the gastric mucosa (9,10). Indeed, in this study, all *H pylori* seropositive subjects who were endoscoped and biopsied had *H pylori* colonization in the gastric mucosa on culture and/or urease test. These results suggest that *H pylori* infection is highly prevalent in enlarged fold gastritis. In agreement with our presented results, comparatively high prevalences of *H pylori* infection in patients with giant fold (fold width greater than 10 mm) were reported by Stolte et al (5) (88.4%) and Avunduk et al (8) (56.3%).

Our study also showed elevations in serum gastrin, PGI and PGII, and a fall in PGI:PGII ratio in patients with enlarged folds. These findings have frequently been reported in patients with *H pylori* infection and may predict *H pylori* infection (10-14). Our results may also support the hypothesis that enlarged folds are associated with *H pylori* infection. Moreover, serum PGI and PGII levels reportedly are elevated proportional to the degree of gastric mucosa inflammation, especially in patients with *H pylori* infection. These levels have been suggested to be indexes of severity of *H pylori* gastritis (12-14,21).

Our finding that serum PGI and PGII levels were higher in the severe group than in the moderate and control groups may suggest that inflammation caused by *H pylori* infection in the severe group is more severe than that in the moderate and control groups. Actually, in this study, inflammatory infiltrates in the body mucosa in the severe group were more extensive than those in the two other groups. Consistent with our results were those of Stolte and co-workers (5), who reported *H pylori* infection and comparatively severe chronic active inflammation of the body in patients with giant fold gastritis. Inflammation of the gastric body mucosa caused by *H pylori* infection may be associated with enlarged gastric body folds.

Enlarged gastric folds may be associated with various pathological conditions, including inflammation, hyperplasia of foveolae and/or glands, and neoplasia (1,2). Enhanced epithelial cell proliferation and mild hyperplasia of *H pylori*-infected gastric mucosa have been reported (22-24). Enlarged gastric folds in this study may be due not only to inflammatory infiltrates and edema, but also to mucosal hyperplasia. Increased serum gastrin concentrations in subjects with enlarged folds may mean that the trophic effect of gastrin on the gastric oxyntic mucosa (25) is associated with enlarged folds. Elevated serum PGI and PGII levels may reflect increases in chief cell and mucous neck cell masses (26,27). Further study is needed to clarify histopathology of enlarged gastric body folds in *H pylori* gastritis.

The present study, together with our previous report that eradication of *H pylori* improves inflammation of the gastric mucosa and fold width in *H pylori*-positive patients with enlarged folds (6), suggests that *H pylori* infection is a main cause of enlarged fold gastritis. Recently it was suggested that *H pylori* infection is associated with Ménétrier's disease and hypertrophic lymphocytic gastritis (28-31), both of which cause enlarged gastric folds. Enlarged fold gastritis may resemble Ménétrier's disease if the former is accompanied with hypoproteinemia, which was found in this study in two patients with severely enlarged gastric folds. Hypertrophic lymphocytic gastritis is considered a rare type of enlarged fold gastritis that is accompanied by a marked increase in lymphocytes in the surface epithelium and gastric pits (29-31). In this study intra-epithelial infiltration of polymorphonuclear cells, rather than lymphocytes, was found in enlarged fold gastritis. We previously suggested that *H pylori* infection is one of the causes of 'primary' gastrin cell hyperplasia (4), which also is a type of enlarged fold gastritis. Thus, there

likely are several special forms of enlarged fold gastritis. It remains unknown what causes the differences between enlarged fold gastritis and *H pylori* gastritis without enlarged folds, and between enlarged fold gastritis with and without additional characteristics. The present report encourages further studies on enlarged fold gastritis and *H pylori* infection.

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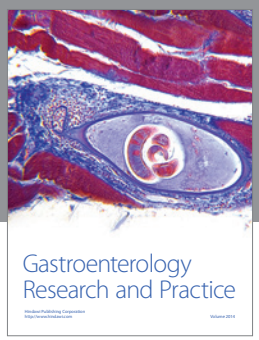

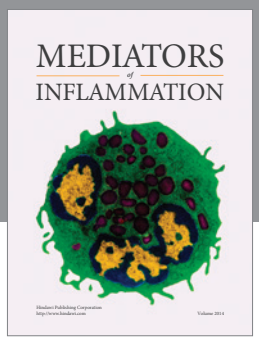

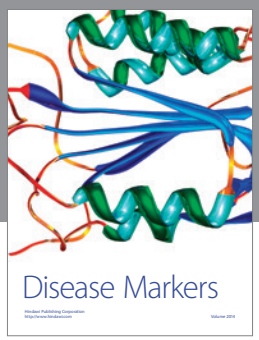

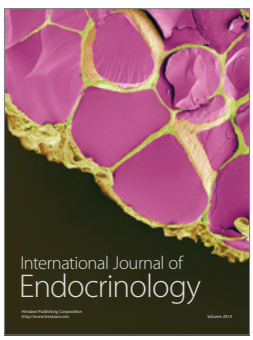

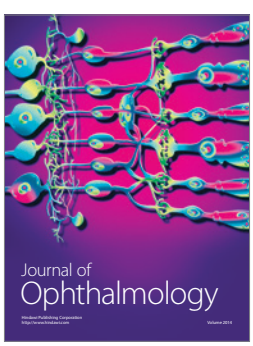

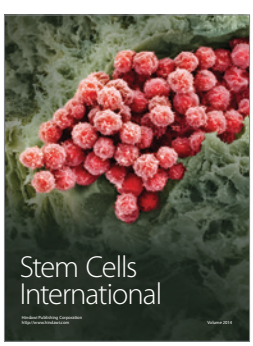

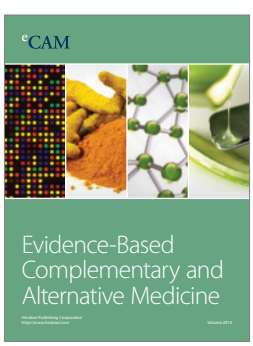

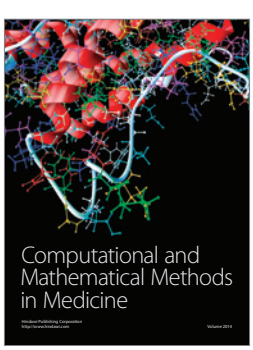

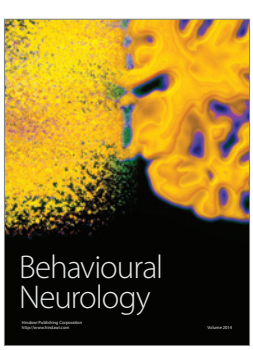

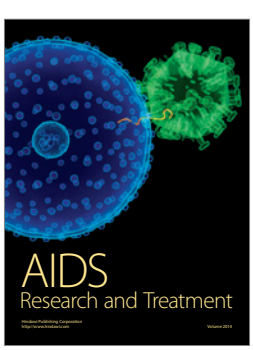

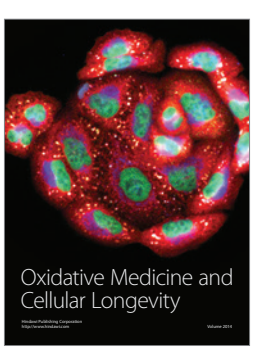

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