High Seroprevalence of Helicobacter pylori in Chronic Bronchitis among Chinese Population

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JUN, Z.J., LEI, Y., SHIMIZU, Y., DOBASHI, K. and MORI, M. High Seroprevalence of Helicobacter pylori in Chronic Bronchitis among Chinese Population. Tohoku J. Exp. Med., 2006, 208 (4), 327-331 — An increased seroprevalence of Helicobacter pylori (H. pylori), especially high virulent cytotoxin-associated gene-A (CagA) positive strains, has been found in many extragastrointestinal disorders. Moreover, it has been reported that the risk of chronic bronchitis may be increased in H. pylori infected patients. However, until now there are no data regarding the relationship between H. pylori infection and chronic bronchitis among Chinese population. Therefore the aim of the present study was to assess the seroprevalence of H. pylori and in particular of CagA positive virulent strains in patients with chronic bronchitis among Chinese population. We evaluated 46 patients with chronic bronchitis, 48 age- and sex-matched patients with peptic ulcer and 48 healthy control subjects. All enrolled subjects underwent a serologic test for H. pylori IgG and CagA by enzyme linked-immunosorbert assay (ELISA). There was no significant difference in the seropositivity for these parameters between chronic bronchitis and peptic ulcer groups (86.9% vs 89.6% for anti- H. pylori IgG and 67.4% vs 72.9% for anti- H. pylori-CagA IgG). However, these serological parameters were significantly higher in the patients with chronic bronchitis or peptic ulcer than those in control group, who showed 60.4% for anti- H. pylori IgG seropositivity and 20.8% for anti- H. pylori-CagA IgG seropositivity. Among the patients with chronic bronchitis, no significant difference was found in these serological parameters between the current cigarette smokers and never smokers. This is the first report of a high seroprevalence of H. pylori infection in chronic bronchitis among Chinese population.

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Helicobacter pylori (H. pylori) is a microaerophilic gram-negative spiral-shaped bacterium which is causally related to chronic active gastritis, peptic ulcer disease (Marshall and Warren 1984), primary low-grade B-cell gastric lymphoma (Isaacson and Spencer 1993) and is also a risk factor for gastric cancer (Parsonnet et al. 1991). H. pylori infection is a major public health problem as it is widespread and frequent (Simsek et al. 2000). A high H. pylori seroprevalence has also been found in many extragastrointestinal disorders, including coronary heart disease (Mendall et al. 1994), rosacea (Rebora et al. 1994), growth failure in childhood (Patel et al. 1994) and active...
bronchiectasis (Tsang et al. 1998). Recently, H. pylori have been identified in the tracheobronchial aspirates in mechanically ventilated patients and the possibility that it might cause ventilator-associated pneumonia has been raised (Mitz and Farber 1993), it appears that H. pylori has a close relationship with respiratory diseases (Jun et al. 2005).

It is well known that H. pylori and particularly those strains bearing the cytotoxin-associated gene-A (CagA) positive strains, stimulate the release of a variety of proinflammatory cytokines, including interleukin-1 (IL-1), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) (Perri et al. 1999; Russo et al. 2001). The eradication of H. pylori leads to normalization of serum cytokines levels (Kountouras et al. 2000). Recent studies showed that the same cytokines might be released during the course and exacerbations of chronic bronchitis (Keatings et al. 1996; Huang et al. 1997; Nelson et al. 2000). The underlying mechanisms, which induce and control this inflammatory process in chronic bronchitis, are still unclear. Therefore, we want to further investigate the relationship between H. pylori infection and chronic bronchitis among Chinese population.

**SUBJECTS AND METHODS**

Following a predefined protocol, between March 1, 2004 and March 31, 2005, three groups of subjects, who consented to provision of venous blood, were recruited consecutively in China-Japan Union Hospital of Ji Lin University. One group consists of 46 patients with chronic bronchitis; the diagnosis was based on the criteria of the American Thoracic Society. Briefly, chronic bronchitis was diagnosed as “the presence of chronic productive cough for 3 months in each of 2 successive years, in a patient in whom other causes of chronic cough have been excluded (American Thoracic Society 1987). Exclusion criteria were: (1) an exacerbation of chronic bronchitis in the preceding month, (2) prior H. pylori eradication therapy, (3) consumption of acid-suppressive drugs or antibiotics in the preceding 6 months, (4) a known history of gastrointestinal tract pathology, and (5) a history of vagotomy or operations on the upper gastrointestinal tract. The other group consists of 48 patients who suffered from peptic ulcer (diagnosed by gastroduodenal endoscopy, 21 patients with duodenal ulcer, 27 patients with gastric ulcer) were also enrolled into this study. Exclusion criteria were (1) previous gastric surgery and gastric malignancies, (2) patients under treatment with bismuth containing drugs, proton pump inhibitors, H2 receptor antagonists and antibiotics during the last six months before the diagnosis, (3) coexistent/pre-existing systemic illness, and (4) alcoholism and nonsteroidal anti-inflammatory drug intake. 48 age- and sex-matched healthy controls were selected from subject who attended courses designed for public health education during the period of the study. Exclusion criteria for controls were: (1) a known history of chronic bronchitis, and (2) a known history of gastrointestinal tract pathology.

This study was approved by the China-Japan Union Hospital Ethics Committee, and written informed consent was obtained from each participant. All enrolled subjects underwent a serologic test for H. pylori IgG and CagA by enzyme linked-immunosorbent assay (ELISA) (Bio-Rad, Hercules, CA, USA) in accordance with the manufacturer’s guidelines. The specificity and sensitivity of the serology test, validated in our local population were 95% and 85%, respectively. Positive, borderline, and negative results were assigned when the concentration of IgG antibodies against H. pylori was greater than 20, between 12.5 and 20, and less than 12.5 U/ml, respectively. Moreover, when the concentration of IgG CagA antibody was greater than 7.5, between 5.5 and 7.5, and less than 5.5 U/ml, the result was considered as positive, border line and negative, respectively.

Values for results are expressed as means ± s.d. The significance of differences between groups was assessed by unpaired Student’s t-test for continuous variables and the χ² test for proportions. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program (SPSS, Los Angeles, IL, USA), and p values were two-tailed analyzed. P values of less than 0.05 were considered statistically significant.

**RESULTS**

The demographic data of the patients and control subjects is shown in Table 1. There was no significant difference in age and sex distribution among the three groups.

As cigarette smoking may be a risk factor for both H. pylori infection and development of chronic bronchitis, we compared the H. pylori infectious status between the current cigarette smokers and never smokers in patients with
chronic bronchitis. However, there was no significant difference in both anti-\textit{H. pylori} IgG seropositivity and anti-\textit{H. pylori}-CagA IgG seropositivity between the two groups (Table 2).

Table 3 shows the analysis of the serologic parameters. There was no statistical difference in parameters between men and women. Both anti-\textit{H. pylori} IgG seropositivity and anti-\textit{H. pylori}-CagA IgG seropositivity were significantly higher in patients with chronic bronchitis or with peptic ulcer than those in control subjects ($p < 0.01$), however, there was no significant difference between the chronic bronchitis group and peptic ulcer group ($p > 0.05$).

**DISCUSSION**

The present study is the first study that focuses on the seroprevalence of \textit{H. pylori} and in particular of CagA positive virulent strains in the population of Chinese with chronic bronchitis. Earlier data about the relationship between \textit{H. pylori} infection and chronic bronchitis are limited. In 1999, Caselli et al. (1999) found an 81.6% seroprevalence of antibodies against \textit{H. pylori} in 60 consecutive patients with chronic bronchitis and a 57.9% seroprevalence in 69 control subjects ($p = 0.008$). In another study in Danish women, Rosenstock et al. (2000) found that the presence of antibodies against \textit{H. pylori} was associated with chronic bronchitis. These studies suggest an association between chronic bronchitis and \textit{H. pylori} infection, but the potential pathogenetic mechanism remains unclear.

Chronic activation of inflammatory mediators induced by \textit{H. pylori} infection might lead to the development of chronic bronchitis. The increased prevalence of CagA positive strains in our study population further supports this hypothesis. It is well known that these virulent stains and particular those CagA positive strains, stimulate the release of a variety of proinflammatory cytokines, including IL-1, IL-8 and TNF-\textit{\alpha} (Perri et al. 1999; Russo et al. 2001). Moreover, eradication of \textit{H. pylori} leads to normalization of serum cytokines levels (Kountouras et al. 2000). These cytokines are also thought to be involved in the pathogenesis of chronic bronchitis (Keatings et al. 1996; Huang et al. 1997; Nelson et al. 2000). Therefore, \textit{H. pylori} infection in general and CagA positive strains in particular might play a proinflammatory role in co-triggering chronic bronchitis with other more specific environmen-

| Table 1. Demographic data of patients and control subjects |
|-------------------|-------------------|-------------------|
| Parameters        | Chronic bronchitis (\(n = 46\)) | Peptic ulcer (\(n = 48\)) | Controls (\(n = 48\)) |
| Age               | 50.5 ± 12.4        | 52.8 ± 11.5        | 51.5 ± 11.8 |
| Male sex (%)      | 60.9               | 62.5               | 58.3 |

| Table 2. Serological parameters in different smoking status in patients with chronic bronchitis |
|-----------------------------------------------|-------------------|-------------------|
| Chronic bronchitis                           | Anti-\textit{H. pylori} IgG (+)(%) | Anti-\textit{H. pylori}-CagA IgG (+)(%) |
| Current smoker (31)                          | 27/31 (87.1)      | 20/31 (64.5)      |
| Never smoker (5)                             | 4/5 (80)          | 3/5 (60)          |

| Table 3. Serological parameters in patients and control subjects |
|-------------------|-------------------|-------------------|
| n                 | Anti-\textit{H. pylori} IgG (+)(%) | Anti-\textit{H. pylori}-CagA IgG (+)(%) |
| Chronic bronchitis | 46                | 40 (86.9)         | 31 (67.4)         |
| Peptic ulcer      | 48                | 43 (89.6)         | 35 (72.9)         |
| Controls          | 48                | 29 (60.4)         | 10 (20.8)         |
tal, genetic and some unknown factors.

The reported association between these two diseases was previously attributed to cigarette smoking that was known as an independent factor in both chronic bronchitis and development of ulcerogenesis (Stemmermann et al. 1989), however, the data on the relationship between *H. pylori* infection and smoking habits are controversial. The prevalence of *H. pylori* infection in smokers has been reported as low (Ogihara et al. 2000), normal (Brenner et al. 1997), or high (Parasher and Eastwood 2000). The influence of smoking on the prevalence of chronic bronchitis has also been little understood (Takemura et al. 2005). Therefore, in the present study, we also compared the *H. pylori* infectious status between the current cigarette smokers and never smokers in patients with chronic bronchitis, showing no impact of cigarette smoking on *H. pylori* infection.

In conclusion, the present study has shown that patients with chronic bronchitis have an increased seroprevalence of *H. pylori* infection. However due to limitation of small size in this study, future studies should be large enough and randomized control methods should be undertaken, not only in *H. pylori* seropositivity study but also in *H. pylori* eradication study. The pathogenetic mechanisms underlying this association also need further evaluation; focus should be on the prevalence of CagA positive *H. pylori* strains and the effect of *H. pylori* eradication on the natural history of chronic bronchitis.

**References**


