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Original Article

Helicobacter pylori infection, glandular atrophy, intestinal metaplasia and topography of chronic active gastritis in the Nepalese and Japanese population: The age, gender and endoscopic diagnosis matched study

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Abstract

Background: The incidence and mortality from gastric cancer is high in Japanese but extremely low in Thailand. It is different among Asian countries. The aim of this study is to investigate the difference of peptic ulcer disease, glandular atrophy, intestinal metaplasia and topography of chronic active gastritis between the Nepalese and Japanese population.

Materials and methods: Nepalese patients were paired with Japanese patients by age, gender and endoscopic diagnosis in order to compare the prevalence of *H. pylori* infection (N=309) and the difference of *H. pylori* related peptic ulcer disease (N=48). Glandular atrophy and intestinal metaplasia scores were also compared between the Nepalese and Japanese population in *H. pylori* positive cases (N=152) and negative cases (N=145) using paired cases by age, gender and endoscopic diagnosis. Paired *H. pylori*-positive Nepalese and Japanese population were also used to compare the ratio of corpus gastritis to antrum gastritis (C/A ratio) (N=152).

Results: Among peptic ulcer diseases, gastric ulcer was frequent in Japanese and duodenal ulcer was frequent in Nepalese. The prevalence of *H. pylori* infection in the Nepalese and Japanese population were similar. Glandular atrophy and intestinal metaplasia scores in the *H. pylori* positive Japanese were significantly higher than those of Nepalese in all positions according to triple site biopsy. Furthermore, there were significant differences in glandular atrophy and intestinal metaplasia scores between in the *H. pylori*-negative Nepalese and Japanese population except intestinal metaplasia score in the greater curvature of the upper corpus. Japanese C/A ratio was significantly higher than that of Nepalese. Corpus predominant gastritis (C/A ratio>1.00) was characteristic in the elderly Japanese. Nepalese was antrum predominant (C/A ratio<1.00) in every age group.

Conclusions. Gastric ulcer was a common disease in Japanese, in contrast duodenal ulcer was common in Nepalese. *H. pylori* infected Japanese patients showed severe atrophic and metaplastic gastritis in comparison with Nepalese. These results may be associated with the high incidence of gastric cancer in Japanese. Corpus predominant gastritis was found in the elderly Japanese and antrum predominant gastritis was found in every age Nepalese.

Key words: *H. pylori*, atrophy, metaplasia, corpus-predominant gastritis, Nepal

Half of the world's population is infected with *Helicobacter pylori* (*H. pylori*) and long term infection of *H. pylori* has been shown to evolve into superficial gastritis, atrophic gastritis and intestinal metaplasia[1-3]. *H. pylori* infection is also closely associated with the development of gastric cancer[4, 5]. Uemura reported that *H. pylori* infection is associated with the development of both intestinal-type and diffuse-type gastric cancer. He also reported severe atrophy accompanying intestinal metaplasia, corpus-predominant gastritis, or both among *H. pylori* infected Japanese patients are particularly high risk of gastric cancer[5]. The prevalence of *H. pylori* infection varies among races[6], and countries[7]. We have already reported a comparative study about *H. pylori* infection, mucosal atrophy, intestinal metaplasia and C/A ratio in the Chinese, Vietnamese, Thai and Japanese populations. *H. pylori* infected Japanese showed severe atrophic, metaplastic gastritis and corpus predominant gastritis in the elderly than other Asian populations[8, 9].

The aim of this study is to investigate the prevalence of *H. pylori* infection, the degree of corpus-predominant gastritis, glandular atrophy and intestinal metaplasia scores in the *H. pylori*-positive and negative Nepalese and to compare Japanese.

Materials and methods

1. Patients

From February 2004 to September 2005, 407 endoscopic examinations were performed on patients consecutively recruited with present or past abdominal complaints at Kathmandu Medical College Teaching Hospital, Kathmandu, Kingdom of Nepal. Examinations were undertaken by us with Nepalese doctors and histological findings of biopsy specimens were diagnosed by one Japanese pathologist. Results of these examinations were prospectively analyzed. Informed consent was obtained prior to examination and patients who needed medication were treated by Nepalese doctors according to our endoscopic diagnosis.

Three hundred and nine pairs of the Nepalese (Kathmandu) and Japanese (Tokyo) patients were used to compare the prevalence of *H. pylori* infection based on the age (± 5 years), gender and endoscopic diagnosis. The prevalence of *H. pylori* infection between major two Nepalese races, ninety-two pairs of Aryan and Mongolian, were also compared based on the age, gender and endoscopic diagnosis. Glandular atrophy and intestinal metaplasia scores of the Nepalese were compared to those of Japanese population separately with *H. pylori*-positive or negative patients based on the age, gender and endoscopic diagnosis, respectively. One hundred and fifty-two pairs of *H. pylori* positive Nepalese and Japanese and one hundred and forty-five pairs of *H. pylori* negative Nepalese and Japanese were recruited. One hundred and fifty-two pairs of *H. pylori* positive Nepalese and Japanese were recruited to compare the ratio of corpus gastritis to antrum gastritis (C/A ratio) based on the age, gender and endoscopic diagnosis. At that time, endoscopic diagnosis was roughly classified into peptic ulcer disease, gastric cancer, normal cases including atrophic gastritis and other disease. None of these patients had been previously treated for *H. pylori* infection.

2. Diagnosis of H. pylori infection

Haematoxylin-Eosin stain, improved Toluidine-Blue stain and *H. pylori* specific antibody immune stain (Dako, Denmark) in selected cases were used for the histological diagnosis of *H. pylori* infection. Biopsy specimens for the histological diagnosis were sampled from the greater curvature of the lower antrum (Figure 1, #1), the greater curvature of the upper corpus (#2) and the lesser curvature of the lower corpus (#3) in accordance with the triple sites gastric biopsy method in all cases[8,9].

3. Histological diagnosis of neutrophil activity, glandular atrophy and intestinal metaplasia

Biopsy specimens taken from triple sites (#1～#3) were used for the histological diagnosis of glandular atrophy and intestinal metaplasia. Neutrophil activity score specimen #1 and specimen #2 were used to determine the C/A ratio. Neutrophile activity, glandular atrophy and intestinal metaplasia scores were classified into four grades according to the Updated Sydney system (0: none, 1: mild, 2: moderate and 3: severe)[10].

4. Statistical analyses

The prevalence of *H. pylori* infection was compared between Nepal and Japan using McNemar's test. An unpaired two groups *t*-test was used to compare items of peptic ulcer diseases. Mann-Whitney's test was used to compare differences in neutrophile activity, glandular atrophy and intestinal metaplasia with a PC (SPSS Version 10.01J, SPSS Inc., USA). For the purposes of this study, P values smaller than 0.05 were considered statistically significant.

Results

1. The frequency of peptic ulcer disease

Table 1 shows subjects matched by the age, gender and endoscopic diagnosis between the Nepalese and Japanese population. Among 48 peptic ulcer disease, duodenal ulcer was the most frequent disease in the Nepalese (75.0%) (Figure 2) and showed significantly higher frequency than Japanese population (P<0.0001). The frequency of gastric ulcer in the Japanese was higher than Nepalese population (P<0.0001).

2. The prevalence of H. pylori infection

The overall prevalence of *H. pylori* infection was the same in the Nepalese (167/309, 54.0%) and Japanese population (171/309, 55.3%) (P=0.8059). There was no difference in the prevalence of *H. pylori* infection between the Aryan (48/92, 52.2%) and Mongolian races(50/92, 54.3%)(P=0.7773).

3. Glandular atrophy and intestinal metaplasia

Glandular atrophy scores in the greater curvature of the lower antrum (Figure 1, #1), in the greater curvature of the upper corpus (#2) and in the lesser curvature of the lower corpus (#3) in the *H. pylori*-positive Nepalese were all significantly lower than those of Japanese (#1: P<0.0001, #2: P=0.0145, #3: P=0.0027, respectively) (Table 2). Intestinal metaplasia scores in all positions (#1, #2 and #3) in the *H. pylori*-positive Nepalese were also

significantly lower than Japanese (#1: P<0.0001, #2: P=0.0145, #3: P=0.0027, respectively) (Table 2). Glandular atrophy score in all positions (#1, #2 and #3) in the *H. pylori*-negative Nepalese were significantly lower than those of Japanese (#1: P=0.0041, #2: P=0.0298, #3: P=0.0027, respectively) (Table 2). Intestinal metaplasia score in the lesser curvature of the lower corpus (#3) in the *H. pylori*-negative Nepalese was lower than that of Japanese (P=0.0040) (Table 2).

4. C/A ratio

The C/A ratio of the *H. pylori*-positive Japanese increased with age and exceeded 1.00, corpus dominant gastritis, in the over 50 age group (Figure 3). We found a significant difference compare with the Nepalese in 30's (P=0.0094), 40's (P=0.0018) and 50's (P=0.0015). Conversely, the C/A ratio of the *H. pylori*-positive Nepalese remained less than 1.00, antrum dominant gastritis, in every age groups (Figure 3).

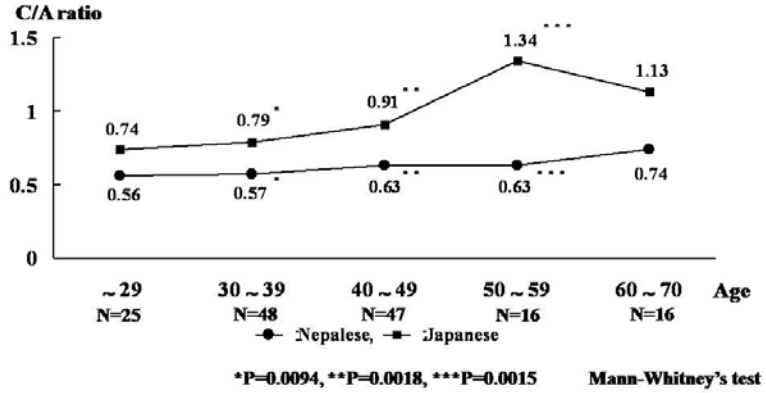

Fig 1: A schematic illustration of triple sites gastric biopsy procedure
#1 indicates the greater curvature of the lower antrum. Specimen #2 indicates the greater curvature of the upper corpus. #3 indicates the lesser curvature of the lower body. Biopsy specimens were also taken from the ulcer or cancer lesions (#4 or more).

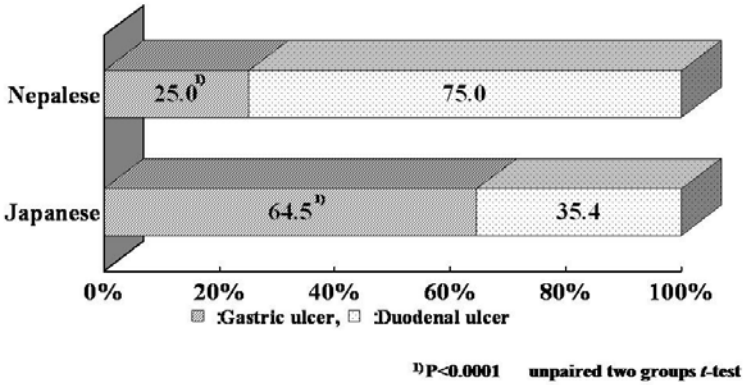

Fig 2: Comparison of peptic ulcer disease between the Nepalese and Japanese population.
Among 48 pairs of peptic ulcer disease, duodenal ulcer was frequent in the Nepalese and gastric ulcer was frequent in Japanese population. Gastroduodenal ulcer was included in gastric ulcer.

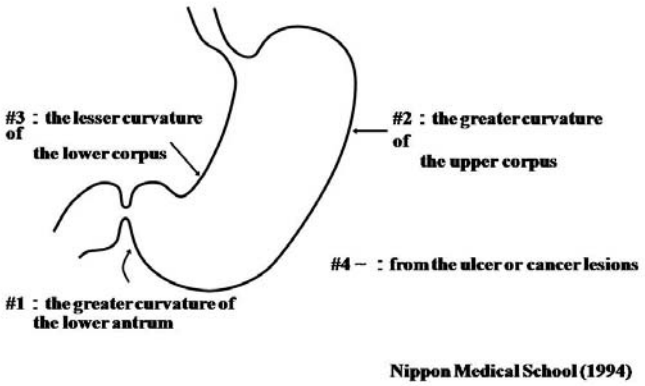

Fig 3: The C/A ratio in the *H. pylori*-positive Nepalese and Japanese population: matched the age, gender and endoscopic diagnosis.
The Japanese C/A ratio increased gradually with age. There was no increase in the C/A ratio in the Nepalese and less than 1.00 in every age group, antrum prdominant gastritis. The Japanese C/A ratios were significantly higher than Nepalese population in 30's (P=0.0094), 40's (P=0.0018) and 50's (P=0.0015) by Mann-Whitney test. The Japanese C/A ratio exceeded 1.00, corpus predominant gastritis, in over 50 age group

Discussion

Epidemiological evidence indicates that *H. pylori* infections are much more prevalent in developing countries than in developed nations[11]. Previous studies have shown the prevalence of *H. pylori* infections is influenced by several factors including: living conditions[11], income[6, 11], ethnicity[6], socioeconomic status[12] especially in childhood[12], availability of public water supplies and sewers, the number of family support organizations[13], and the number of rooms in the home[13]. *H. pylori* infection is closely associated with the development of gastric cancer[4,5]. Past studies have reported high incidences of gastric cancer in the Japanese and Chinese and very low incidences in Thai and Vietnamese populations[14]. *H. pylori* infection is high in the Thai but gastric cancer incidence is very low in this population and was named this situation as "Asian Paradox"[15]. Taking into consideration these reports and the differing prevalence rates of *H. pylori* infections among ethnic groups, we conducted an age, gender and disease matched study to compare the prevalence of *H. pylori* infection, the difference of peptic ulcer diseases, gastric glandular atrophy, intestinal metaplasia and C/A ratio as precursory lesions of gastric cancer.

We began this comparative study in 1994 and visited China, Thailand, Vietnam, Myanmar, Congo (Africa) and Nepal a total of twenty-four times and performed approximately 2,300 endoscopic examinations[8, 9]. These examinations were all performed by the same Japanese endoscopists and one Japanese pathologist. To our knowledge there are no previous studies that compare these clinicopathological characteristics between the Japanese and other Asian populations that utilize the same endoscopic and pathological criteria in each country.

Japanese has a high frequency of gastroduodenal disease compare with other Asian populations. Among peptic ulcer disease, the prevalence of gastric ulcer in the Japanese is significantly higher than other Asian populations including Nepalese and that of duodenal ulcer in the Japanese is significantly lower than in other Asian populations including Nepalese. Many papers have showed that incidence of gastric cancer was associated positively with that of gastric ulcers and reversely with duodenal ulcers[16]. High frequency of gastric ulcer among peptic ulcer disease seems to be one of the reasons of high incidence of gastric cancer in Japan.

As mentioned above, there are many factors that may influence the incidence of *H. pylori* infection. The prevalence of *H. pylori* infection between the Nepalese and Japanese population at a university hospital were similar by means of the age, gender and endoscopic diagnosis match method. The number of cases in this study is 309 pairs and not enough for the epidemiological survey. However, we tried to maintain the same conditions to the maximum extent possible. We could not find any reports by the same endoscopist and pathologist

using the same criteria. It will be impossible to compare the differences among many countries using another method.

It has been suggested that there are differences in the prevalence of *H. pylori* infection among races living in Malaysia[17]. The prevalence of *H. pylori* infection in Malays (11.9%) has been reported to be lower than that in the Chinese (26.7%, P<0.001) or Indian (49.4%, P<0.001) population in West Malaysia as determined in blood samples[17]. A similar trend was reported for East Malaysia[17]. Therefore, we tried to compare the prevalence of *H. pylori* infection among different races in Nepal, but found no significant differences in the prevalence between the Aryan and Mongolian races.

We developed the method of triple site gastric biopsy for the histological diagnosis of *H. pylori* infection in 1994[8, 9]. According to the Updated Sydney system revised in 1996[10], gastric specimens should be taken from five points in the stomach. In the triple site gastric biopsy technique, specimens #1 and #2 correspond to A2 (the greater curvature of the antrum within 2 to 3cm from the pyloric ring) and B2 (middle portion of the greater curvature of the corpus approximately 8cm from the cardia), respectively. Specimen #3 is located near the middle of IA (the incisura angularis) and B1 (the lesser curvature of the corpus about 4cm proximal to the angulus). This position is very important for endoscopic diagnosis of gastric mucosal atrophy[18] and histological diagnosis of glandular atrophy.

In this study all of the atrophic gastritis was type B gastritis[19], which spreads from the lesser curvature of the antrum and angulus to the lesser curvature of the corpus. *H pylori* infections tend to begin in the antrum and extend proximally into the corpus along the lesser curvature[20]. Glandular atrophy scores and intestinal metaplasia scores in all positions (#1, #2 and #3) in *H. pylori* infected Japanese was significantly higher compared to Nepalese population. The C/A ratio of Japanese was significantly higher than Nepalese population with the increase of age. The C/A ratio increased to over 1.00 in the over 50 Japanese age groups, indicating corpus predominant gastritis. Nepalese showed corpus predominant gastritis. It was same in other Asian countries: China, Vietnam, Thailand[9], and Myanmar. In Japanese, *H. pylori* infection and chronic active gastritis progress to the corpus with advancing age, resulting in corpus predominant gastritis. In constant, antrum gastritis will not develop into corpus gastritis in the Nepalese like other Asian populations.
The difference of mucosal changes induced by *H. pylori* infection between the Japanese and other Asian populations may be correlated with the different incidences of gastric cancer in the Japanese and other Asian populations. Uemura reported that among *H. pylori* infected Japanese patients, those with severe atrophy accompanying intestinal metaplasia, corpus-predominant gastritis, or both, are particularly high risk[5]. Our data corresponds to his report.

Although the scores were very low as compared with those in the *H. pylori*-positive cases, the glandular atrophy scores (#1, #2 and #3) and intestinal metaplasia scores (#3) were significantly higher in the *H. pylori*-negative Japanese than in the *H. pylori*-negative Nepalese population. In our experience, we have never found any differences in the glandular atrophy or intestinal metaplasia scores in *H. pylori* negative cases between Japan and other Asian countries, e. g., China, Vietnam, Thailand and Myanmar. This is our first experience in Asian countries. In general, *H. pylori* infection is considered as the major factor causing glandular atrophy and intestinal metaplasia[3]. However, other factors may also be involved in the development of these changes. For example, environmental factors, such as salt intake, have been reported to be important in the development of glandular atrophy and intestinal metaplasia[21, 22, 23]. Japanese consume much more salt as compared with populations in other countries and about twice as much salt as compared to Americans. This factor may be responsible for the difference in the glandular atrophy and intestinal metaplasia scores between the *H. pylori*-negative Nepalese and Japanese populations in our study.

The prevalence of *H. pylori* infection in Thai is higher than Japan[8]. The reasons why infection rate of *H. pylori* is higher but atrophy and intestinal metaplasia is significantly lower in Thai than Japanese are not clear. Differences of strain of *H. pylori*, host factors, and food habits are assumed. *CagA* gene which causes cell damage was positive in more than 90% of *H. pylori* in both Japanese and Thai[24, 25]. It was reported that there were high Asian type and low Western type of cell growth activity of CagA which depended on a physical complex with SRC homology 2 domain (SH-2) tyrosine phosphatase as an intercellular target of *H. pylori* CagA protein[26], and Southeast Asia was low Western type (personal communication). Differences of this CagA protein may participate in glandular atrophy, and a future study is necessary to clarify this possibility. In conclusion, the gastric mucosa in *H. pylori* infected Japanese patients showed significant and severe atrophic change accompanying intestinal metaplasia. In contrast, significantly lower incidences of atrophy and

intestinal metaplasia were found in *H. pylori* infected Nepalese patients. These results may be correlated with the high and the low incidence of gastric cancer in the Japanese and Nepalese population, respectively.

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