

Chronic atrophic antral gastritis and risk of metaplasia and dysplasia in an area with low prevalence of *Helicobacter pylori*

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Abstract

Introduction The Northeastern region of Peninsular Malaysia is an area with exceptionally low prevalence for *Helicobacter pylori* infection. The risk of intestinal metaplasia and dysplasia in patients with chronic atrophic gastritis (CAG) and its association with *Helicobacter pylori* is unknown in this region.

Methods This was a cross-sectional study on gastric biopsies from 234 consecutive patients (mean age 53.5 [14.8] years) who underwent upper gastrointestinal endoscopy between January 2006 and December 2006.

Results There were 137 (59%) men and 185 (79%) Malay patients. Among 234 biopsies, CAG was found in 99 and non-atrophic gastritis in 135. Intestinal metaplasia and dysplasia were detected in 8 and 6 atrophic gastritis biopsies, respectively, and in 10 and 3 of non-atrophic gastritis biopsies, respectively. *H. pylori* were detected in 16 (9 Malays, 7 non-Malays) biopsies ($p=0.024$); intestinal metaplasia was detected in 4 biopsies ($p=0.3$) and dysplasia in 5 biopsies ($p=0.3$). Of the 218 biopsies negative for *H. pylori*, intestinal metaplasia was found in 14 and dysplasia in 4. The risk of intestinal metaplasia as well as dysplasia was associated with presence of *H. pylori* infection ($p=0.029$ and $p<0.001$ respectively).

Conclusion Even in a setting of low prevalence of *H. pylori*, intestinal metaplasia and dysplasia were significantly associated with *H. pylori* infection. The frequency of intestinal metapla-

sia and dysplasia was similar different between biopsies with atrophic gastritis and non-atrophic gastritis.

Keywords Atrophic gastritis · Chronic gastritis · Dysplasia · *Helicobacter pylori* · Intestinal metaplasia

Introduction

The prevalence of chronic atrophic gastritis (CAG) varies in different geographical areas of the world with the Japanese and Chinese populations among the highest reported in literatures.¹ Chronic atrophic gastritis is associated with a 5-fold risk of gastric cancer,² and *Helicobacter pylori* infection is associated with a 2.9-fold risk for gastric cancer.³ *H. pylori* infection is closely linked with the development of CAG.^{4,5} Atrophic gastritis may progress to gastric cancer if left untreated (Correa cascade).⁶

The incidence of gastric cancer in Malaysia was 4.3/100,000 based on the National Cancer Registry in 2003.⁷ A higher incidence was seen in older age group of above 60 years, Chinese race and men. The prevalence of *H. pylori* infection in the northeastern region of Peninsular Malaysia is one of the lowest reported in literature – 4.2% among 496 blood donors and 4.8% among 921 subjects who attended health-screening clinics.⁸ The infection rate in patients who underwent endoscopy was lower in the Malays (7%) as compared to non-Malays (47%).⁹

The prevalence rate, risk of intestinal metaplasia and dysplasia in patients with CAG and its association with *H. pylori* are not known in this region of low prevalence for *H. pylori*.

Methods

This study involved the examination of gastric biopsies from 234 individuals who underwent upper gastrointestinal endoscopy between January and December 2006 in a university hospital from the Northeastern region of Peninsular Malaysia (State of Kelantan). Sample size was calculated using single-proportion formula; $N=(z/\Delta)^2 \times p(1-p)$, where $z=1.96$ (95% confidence interval), Δ (precision)=0.06 and p (proportion)=0.5 (based on global rate of chronic gastritis). The expected number of individuals needed for this study

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Received: 18 August 2008 / Revised: 20 December 2008 /

Accepted: 30 January 2009

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was $n=(1.96/0.06)^2 \times 0.5(1-0.5)=267$ patients and the actual number of individuals recruited were 234 patients. Patients who underwent upper endoscopy for dyspepsia, atypical chest discomfort and non-specific abdominal discomfort, were evaluated; those with endoscopic antral gastritis were included. At endoscopy, gastritis was defined according to the Sydney classification.¹⁰ Patients receiving proton-pump inhibitors two weeks prior to endoscopy, those who received any antibiotics prior to endoscopy and those who recently had upper gastrointestinal bleeding were excluded.

Biopsies were taken from the antrum or incisura from an area with endoscopic gastritis. *H. pylori* infection was detected using rapid urease test (CLO test) or histology or both. A minimum of 2 biopsies (range 2–4 biopsies; size 2–4 mm) were taken. Biopsies were stained with hematoxylin and eosin (H&E) stain, followed by Alcian blue-PAS stain for detection of intestinal metaplasia. Warthin-Starry stain was used in sections where *H. pylori* was not detected in H&E stained tissue. The biopsies were interpreted by 3 experienced pathologists who were unaware of the endoscopy findings; the final interpretation was made by the principal pathologist (NHO).

Histological gastritis was classified into atrophic and non-atrophic gastritis based on the updated 1994 Syd-

ney system¹¹ and Atrophy Club¹² definitions. Atrophy was graded as mild, moderate or severe. The degree of activity of histological chronic gastritis was based upon the visual amount of mononuclear cells infiltration as determined by the pathologists, and graded into mild, moderate and severe. Intestinal metaplasia was identified by replacement of glandular epithelium with goblet cells¹³ and dysplasia was identified by epithelium disarray and increased nucleo-cytoplasmic ratio.¹⁴

Data were analyzed using SPSS software version 12.0.1. The correlation between endoscopic gastritis and histological gastritis was determined using kappa (κ) statistics where a κ value between 0.4 and 1.0 was considered a good agreement. Chi-square test or Fischer-exact test and independent *t* test were used to detect the association between categorical and numerical descriptive variables, respectively with CAG. The different grades of atrophy (mild, moderate and severe) were compared with each others to determine which grades of atrophy had the most significant association with the risk of intestinal metaplasia and dysplasia as determined by the p-value after Bonferroni adjustment. Multivariable analysis using logistic regression analysis was used to assess the factors significantly associated with the risk of intestinal metaplasia and dysplasia. The factors included in

Table 1 Baseline characteristics and its association with chronic atrophic and non-atrophic antral gastritis

Variables	Atrophic gastritis	Non-atrophic gastritis	Endoscopic gastritis only	p value
Total	99 (42.3)	84 (35.9)	51 (21.8)	
Age (mean [SD]) (years)	53.5 (14.8)	52.9 (16.2)	52.5 (16.1)	0.79
Men	62 (26.5)	49 (20.9)	26 (11.1)	0.55
Race				
Malays	73 (73.7)	73 (86.9)	39 (16.7)	0.11
Non-Malays	21 (21.2)	7 (8.3)	12 (5.1)	
NSAID usage	6 (2.6)	8 (3.4)		
Anti-platelet agent use	5 (2.1)	7 (3)		
Indications for endoscopy				
Dyspepsia	57 (57.5)	94 (69.6)		
Gastrointestinal bleeding	32 (32.3)	27 (20.0)		
Previous peptic ulcer	5 (5.0)	11 (8.1)		
Dysphagia	5 (5.0)	3 (2.2)		
Intestinal metaplasia	8 (3.4)	10 (4.3)		0.006
Mild	2 (0.8)			
Moderate	6 (2.6)			
Dysplasia	6 (2.6)	3 (1.3)		<0.001
Mild	1 (0.4)			
Moderate	5 (2.2)			
<i>Helicobacter pylori</i>	11 (11.1)	5 (5.9)	-	0.03

Data are as n (%). Chi-square test or Fischer-Exact test and independent *t* test

NSAID – non-steroidal anti-inflammatory drug, Anti-platelet drugs – aspirin or clopidogrel

the multivariable analysis were sex, age, race, presence of *H. pylori* and presence of atrophy. Hosmer-Lemeshow test was used to determine the model goodness of fit with p-value >0.05 implying good fit.

Results

Histology was normal in 51 (21.8%) of 234 biopsies with endoscopic gastritis. The correlation between endoscopic gastritis and histological gastritis was poor (κ value of -0.06). CAG was found in 99 (42%) biopsies and non-atrophic gastritis in 84 (35.9%) biopsies. Intestinal metaplasia and dysplasia were detected in 8 and 6 atrophic gastritis biopsies and in 10 and 3 of non-atrophic gastritis biopsies, respectively. The characteristics of the study population are shown in Table 1.

H. pylori infection was detected in 16 (6.8%) biopsies (9 [4.9%] Malays and 7 [14%] non-Malays; $p=0.024$). Similarly, the *H. pylori* infection rate in CAAG ($n=11$ [11.1%]) was higher than non-atrophic gastritis ($p=0.03$). Of 16 biopsies positive for *H. pylori*, intestinal metaplasia was detected in 4 biopsies, and dysplasia in 5 biopsies. Of the 218 biopsies negative for *H. pylori* infection, intestinal metaplasia was found in 14 biopsies and dysplasia in 4 biopsies.

The rate of metaplasia and dysplasia among Malays and non-Malays who were positive for *H. pylori* was shown in Table 2. Moderate atrophic gastritis was associated with risk of intestinal metaplasia ($p=0.006$ after Bonferroni adjustment) and risk of dysplasia ($p<0.001$ after Bonferroni adjustment). Multivariable analysis in Table 3 showed that a positive status of *H. pylori* was the only variable associated with risk of intestinal metaplasia ($p=0.03$; 95% CI 0.05–0.85) and dysplasia ($p<0.001$; 95% CI 0.007–0.152).

Table 2. Rate of intestinal metaplasia and dysplasia among the Malays and non-Malays positive for *Helicobacter pylori*

	Race		p value
	Malays (n=146)	Non-Malays (n=28)	
<i>H. pylori</i>	9 (4.9)	7 (14.3)	0.024
Metaplasia	2 (1)	2 (4)	0.3
Dysplasia	2 (1)	3 (6)	0.3

Values are as n (%)

Table 3. Multiple logistic regression analysis showing association between various factors (including age, sex, race, *Helicobacter pylori* and atrophy) and the risk of intestinal metaplasia and dysplasia

Factors	Standard error	Wald statistics	p-Value	Odds ratio	95% confidence interval	Hosmer-Lemeshow test (p-value)
Intestinal metaplasia <i>Helicobacter pylori</i>	0.735	4.764	0.029	0.201	0.048–0.849	0.159
Dysplasia <i>Helicobacter pylori</i>	0.782	19.083	<0.001	0.03	0.007–0.152	0.277

Discussion

The prevalence rate in this study for chronic antral atrophic gastritis (CAAG) in the Northeastern region of Peninsular Malaysia was 42.3%, though *H. pylori* infection was seen in only 6.8%.

Most population studies have reported a prevalence of CAG above 50%; higher prevalence up to 80% has been reported amongst Japanese and Chinese, largely due to a higher prevalence of *H. pylori* in these regions.¹⁵ The prevalence in our study was lower compared to the other populations in Asia.

Patients with chronic gastritis were older. Chronic gastritis progresses with age; and the “birth cohort effect” of Sipponen¹⁶. The non-Malays population had a higher frequency of CAAG compared to Malays. This is probably related to a higher *H. pylori* infection rate amongst the Chinese.

The *H. pylori* prevalence rate in our study was in concordance with the other reported studies^{8,9} from this area in Malaysia. The risks of intestinal metaplasia and dysplasia in CAAG were higher if *H. pylori* infection was present. This suggests that though *H. pylori* infection rate is exceptionally low, the effects on risk factors of gastric cancer progression (metaplasia and dysplasia) are significant. This further supports the notion – No *Helicobacter pylori*, No gastric cancer. Dysplasia was seen in 4 cases of *H. pylori*-negative patients. It is known that urease test and histology can miss *H. pylori* especially in areas of atrophic gastritis. In addition, dysplasia may be misinterpreted in the presence of severe inflammation. We took a minimum of two biopsies (instead of recommended four in Sydney system); this may have led to low rate of *H. pylori* detection in the 4 cases of dysplasia.

Data from areas with high prevalence rate of *H. pylori* in Malaysia have shown that Chinese and Indians have the highest rate of infection, and Malays have lower rate.¹⁷ There are no published data on chronic gastritis, metaplasia and dysplasia from this region with high prevalence for *H. pylori*. A recent paper by Goh *et al.* demonstrated that gastric cancer rate amongst *H. pylori*-positive individuals was highest in Chinese and the lowest in Indians, with the Malays in between.¹⁸ This finding seems consistent when extrapolated to our data, which showed that the rate for intestinal metaplasia and dysplasia were almost similar in the Malays and non-Malay patients who were *H. pylori*

positive, even though the number of Malays were much higher than the non-Malays.

The risks of intestinal metaplasia and dysplasia were higher if moderate atrophy was present compared to no or mild atrophy. This finding suggests that treatment of gastritis and eradication of *H. pylori* may be useful to stop the progression of gastric cancer at the stage of mild or no atrophy.¹⁹

In conclusion, even in a setting of low prevalence of *H. pylori*, intestinal metaplasia and dysplasia were associated with *H. pylori* infection. The frequency of intestinal metaplasia and dysplasia were similar amongst biopsies with atrophic gastritis and non-atrophic gastritis.

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News and notices

Workshops on Biostatistics and Research Ethics will be organized at Sanjay Gandhi Post Graduate Institute of Medical Sciences between July and September 2009 at Lucknow. Travel support may be available. For further details, Please contact: Dr. Rakesh Aggarwal, Department of Gastroenterology, SGPGI, Lucknow E-mail: spggi.courses@gmail.com

The 18th Annual Meeting of the Indian National Association for Study of Liver will be held at Bhubaneswar on March 12–14, 2010. For further details, please contact: Prof. S. P. Singh, Organizing Secretary. E-mail: scb_gastro_dept@hotmail.com