Anti CagA antibody among patients with non-cardia gastric cancer in comparison with non-ulcer dyspepsia in an area with high incidence of gastric cancer

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ABSTRACT

الأهداف : تقييم العلاقة بين الأجسام المضادة للتخثر (Ab) وحضور سرطان المعدة .

الطريقة : أجريت دراسة وصفية عرضية في مركز الأمراض المعوية والمَعِدية – مستشفى الرازي – راشت – إيرآن، خلال الفترة ما بين أكتوبر 2003م وحتى أكتوبر 2005م. قمنا بتقييم مضاد التخثر هيليكوباكتر (Ab IgG) والأجسام المضادة للتخثر (Ab) بواسطة طريقة (أليسا) (معايرة الأنزيم المناعي) لـ52 مريضاً يعانون من ورم غدي معدي سرطاني، و57 مريضاً يعانون من التخمة غير التقرحية (NUD) .

النتائج : من بين 52 مريضاً يعانون من سرطان المعدة، كانت الأجسام المضادة لهيلكوباكتور بيلوري (Ab) سالبة في 13 مريضاً (25%)، وموجبة في 39 مريضاً (75%) . من بين 57 مريضاً يعانون من التخمة غير التقرحية (NUD) . كانت الأجسام المضادة لهيلكوباكتور بيلوري (Ab) سالبة لدى 5 مرضى (8.5%)، وموجبة لدى الـ52 الآخرين (91.2%) (p=0.043) . لم يبقى هذا الاختلاف الملحوظ بعد النكوص ألإمدادي لتعديل التميزات (p=0.068)، كانت الأجسام المضادة للتخثر (Ab) موجبة في 22 مريضاً (42.3%) الذين يعانون من السرطان و32 مريضاً (56.1%) من مجموعة المصابين بالتخمة غير التقرحية (NUD) . لم يكن هنالك فرقاً بالنسبة لهذه المسألة من قبل (p=0.212) وبعد تحليل النكوص ألإمدادي (p=0.131) .

خاتمة : ليس لدى الأجسام المضادة للتخثر (Ab) قيمة ذات دلالة إحصائية كما في عامل التنبؤ المستقل في الورم الغدي السرطاني المعدي .

Objective: To evaluate the correlation between anti CagA antibody (Ab) and presence of gastric cancer.

Methods: In a descriptive cross-sectional study during October 2003 to October 2005, in the Gastrointestinal Subspeciality Center in Razi Hospital, Rasht, Iran, we assessed anti-*Helicobacter* Ab immunoglobulin G (IgG) and anti CagA Ab IgG by the enzyme-linked immunosorbent assay (ELISA) method in 52 patients with gastric adenocarcinoma and 57 patients with nonulceric dyspepsia (NUD).

Results: Among 52 patients with gastric cancer, anti-*Helicobacter pylori* Ab was negative in 13 (25%) and positive in 39 persons (75%). Among 57 patients with NUD, anti-*Helicobacter pylori* Ab was negative in 5 (8.5%) and positive in 52 patients (91.2%) (p=0.043). This significant difference did not remain after logistic regression for adjustment of confounders (p=0.068). The CagA Ab was positive in 22 (42.3%) patients with cancer and 32 (56.1%) of the NUD group. There was no difference in this regard before (p=0.212) and after (p=0.131) logistic regression analysis.

Conclusion: Anti CagA Ab does not have a significant value as an independent predictive factor in gastric adenocarcinoma.

*H*elicobacter pylori is a gram-negative bacterium infecting human gastric mucosa with worldwide prevalence. This bacterium plays an important role in the pathogenesis of chronic gastritis, peptic ulcers, gastric adenocarcinomas, and gastric mucosa-associated lymphoid tissue lymphomas.[1] Chronic infection of adults with *Helicobacter pylori* is characterized by the infiltration of polymorphonuclear and mononuclear cells and the upregulation of proinflammatory cytokines and the chemokine interleukin-8 (IL-8).[2-4] Particularly, IL-8 secretion causes activation of neutrophils. Although now we know a lot on the pathogenesis of *Helicobacter pylori*, it is not clear why infected individuals develop different

diseases. This can be because of different factors such as genetic susceptibility of the host, differences in the host response to the bacteria, differences in host-microbe interactions, and variety among bacterial strains.[5-8] Two major important virulence markers of *Helicobacter pylori*, cytotoxin-associated protein (CagA) and vacuolating cytotoxin (VacA) encoded by cagA and vacA genes, have been well described. It has been reported that the CagA gene was present in approximately 60% of *Helicobacter pylori* strains from Western populations but over 90% of the strains from southeast Asian populations. In contrast to CagA, the VacA gene was present in nearly all the *Helicobacter pylori* strains informed around the world, as only half of the isolates expressed VacA with vacuolating cytotoxity.[9] The *Helicobacter pylori* virulence factors CagA and VacA are implicated in the development of gastroduodenal diseases. Most strains possessing CagA also possess the more virulent vacuolating form of VacA.[10] Epidemiological studies have established a strong association between Cag pathogenicity island (CagPAI) + *Helicobacter pylori* and gastric disease based on either polymerase chain reaction (PCR) data or the high seroprevalence for CagA,[11-24] although according to some studies, CagA and VacA are not related to the ability of invasion and adhesion of *Helicobacter pylori* in different cell lines in vitro.[25] As there are diverse results on the correlation between anti CagA antibody (Ab) and presence of gastric adenocarcinoma, we tried to evaluate this relation in the Gastrointestinal and Liver Diseases Research Center (GLDRC) of Guilan University of Medical Sciences in north province of Iran, an area with a high incidence of gastric cancer.

Methods. This descriptive study was conducted during October 2003-2005 in the Gastrointestinal Subspeciality Center in Razi Hospital, Rasht, Iran. The cases of this study consisted of 52 patients with gastric adenocarcinoma, and 57 patients with nonulceric dyspepsia (NUD) who were matched for age and gender with the cancer group. Including criteria of our study were suffering from non-cardia gastric adenocarcinoma confirmed by endoscopy and pathology report (cancer group). Exclusion criteria were history of chemotherapy, negative history of any surgery on the stomach (cancer group). Suffering from NUD without any ulcer or other pathologies based on endoscopy report (NUD group). Negative ultrasonography report on existence of any stone or other gallbladder diseases (in NUD group). Negative history of blood products transfusion and not taking bismuth, proton pump inhibitors, or any antibiotics during last 4 weeks. Considering the including criteria, the cases were chosen. Ethical approval form was accepted from research ethics committee of GLDRC of Guilan, Iran. One blood sample was taken from each of

them to check anti *Helicobacter pylori* Ab IgG and anti CagA Ab IgG by enzyme-linked immunosorbent assay (ELISA) method.

All statistical analyses were carried out using Statistical Package for Social Science version 11.5. The test was based on informed consent and the data were collected and kept confidential. A *p* value <0.05 was considered statistical significant.

Results. Totally, 109 patients with gastric cancer and NUD had our inclusion criteria and were enrolled in this study. In the gastric cancer group, the patients age was between 19-85 with the mean of 46.06±14.21 (Kolmofgrov Smirnov *p*=0.228) and in the NUD group, the patients' age was ranged between 25-82 with mean of 43.64±12.05 (Kolmogrov Smirnov *p*=0.199). The age of patients suffering from cancer was significantly higher than the one with NUD (T-test *p*=0.009). Age should be considered as a confounding factor in final analysis of this study. Among 109 cases of the study, 59 cases were males (54.1%) and 50 patients were females (45.9%). Among patients with NUD, 24 patients (42.1%) were males and 33 patients (57.9%) were females (**Table 1**). Since the ratio of female/male between NUD cases and cancer cases is significantly different (Yate's corrected chi-square *p*=0.014), gender as a confounding factor was considered as a result of this study.

Totally, 18 samples (16.3%), including 5 patients (8.8%) with NUD and 13 patients (25%) with gastric adenocarcinoma, were negative for anti *Helicobacter pylori* Ab and 91 samples (83.5%), including 52 patients (91.2%) with NUD and 39 patients (75%) with gastric adenocarcinoma, were positive for it. This means that if we do not consider factors of gender and age, anti *Helicobacter pylori* Ab in the NUD group is significantly higher than the gastric cancer group. Totally, 55 patients (50.5%), including 25 patients (43.9%) with NUD and 30 cases (57.7%) with gastric cancer, were nonreactive for anti CagA Ab, and 54 patients (49.5%), including 32 cases (56.1%) with NUD and 22 cases (42.3%) with gastric cancer, were positive. Therefore, not considering the factors of gender and age, anti CagA Ab was not significantly different between our 2 groups. Among 18 patients with negative samples of anti *Helicobacter pylori* Ab, 12 patients (66.7%) were nonreactive for anti CagA Ab, and 6 cases (33.3%) were positive for it. Among 91 cases with positive anti *Helicobacter pylori* Ab, 43 patients (47.3%) were nonreactive for anti CagA Ab and 48 patients (52.7%) were positive for it (**Table 2**). So, we did not find a significant relation between the presence of anti *Helicobacter pylori* Ab and anti CagA Ab (Yate's corrected chi-square *p*=0.212). Finally, to eliminate the probable effect of confounding factors, age and gender, we used logistic regression module. Age was known as the only effective variant to distinguish between these

Table 1 - Demographic characteristics of patients.

Characteristics	Nonulceric dyspepsia	Gastric cancer
Age (years)	25-82	19-85
Mean±SD	43.64±12.05	46.06±14.21
Gender		
Male	24 (42.1)	59 (54.1)
Female	33 (57.9)	50 (45.9)

Table 2 - Reactive and non-reactive anti Cag-A Ab among patients with positive or negative results of anti Hp.

Anti *Helicobacter pylori* Ab (IgG)	Negative	Positive
Anti-Cag-A Ab (IgG)		
Reactive	6 (33.3)	48 (52.7)
Non-reactive	12 (66.7)	43 (47.3)
Ab - antibody, IgG - immunoglobulin G		

2 diseases. According to this module, gender, anti *Helicobacter pylori* Ab titer and anti CagA Ab titer were not known as significant influential factors.

Discussion. In this study, we did not find a significant difference in anti CagA Ab between 2 studied groups; NUD and Gastric adenocarcinoma. Limitation of this study was small sample size of it. This result is not in concordance with some studies' results. Shimoyama et al[26] in Japan, assessed 2 groups, 81 cases with gastric cancer and 81 patients with normal endoscopy. Anti CagA Ab, by ELISA, was measured. Anti CagA Ab was positive in 60% of the case group, but just in 44% of the control group. Indicating that incidence of anti CagA Ab would increase the risk of gastric cancer.

In Siavoshi et al's[27] findings, CagA was present in 44% of the patients. Nonulceric dyspepsia patients had a frequency of cagA positivity similar to that of the overall population (46%). Siavoshi et al's,[27] the CagA was present frequently more than CagA-negative in patients with gastric carcinoma (20%) than cagA-negative in patients with gastric carcinoma (8%). Talebkhan et al[28] determined the frequency of cagA in Iranian *Helicobacter pylori* strains and showed that antibodies against the CagA protein were present in 90.7% of patients. Ghoshal et al's[29] studies in India indicated that CagA IgG was more common in gastric neoplasm than in non-ulcer dyspepsia patients (124/163 [76%] versus 64/101 [63%]) however, comparable to that in healthy volunteers patients (87/98 [89%], *p*=NS). Parssonet et al[30] in California showed that when compared with the uninfected subjects, patients infected with CagA positive *Helicobacter pylori* are at considerably increased risk of gastric cancer. The CagA negative *Helicobacter pylori* are less strongly linked to malignancy and may only be associated with diffuse type disease. Held et

al[31] in Sweden showed that odds ratio was 7.4 (95% confidence interval [CI] 3.3-16.6) for CagA-positive relative to CagA-negative subjects. Among antibodies to *Helicobacter pylori* ELISA-positive subjects, the presence of CagA antibodies increased the risk 3.6 times (95% CI 1.2-11.1). Enzyme-linked immunosorbent assay-positive CagA-negative infections were associated with a 4 fold increased risk (OR=4.2, 95% CI 1.0-17.0) compared to no infection (ELISA-negative and CagA-negative). According to this study, Although patients with antibodies to CagA have the greatest risk of developing gastric cancer, those with CagA-negative infections run a significantly greater risk than uninfected persons.

In a study conducted by Gurbuz et al's[32] in Turkey, 32 patients with gastric adenocarcinoma (cases) and 46 patients with NUD (control) were assessed. *Helicobacter pylori* was positive in 56% and 71.7% of cases and controls. Anti CagA Ab was positive in 100% of cases and 56.5% of control group. It means that incidence of anti CagA Ab was significantly higher among patients with gastric cancer and incidence of *Helicobacter pylori* was higher among those with NUD. Hussein et al[33] in a comparative study of dyspeptic patients of Iran and Iraq showed that cagA was found in similar proportions of strains from both countries (76% in Iran versus 71% in Iraq) and was significantly associated with peptic ulcer disease in Iraq (*p*≤0.01) but not in Iran.

Our results were in concordance with some other studies. In the study by Yang et al,[34] anti CagA Ab was evaluated among 808 Chinese with chronic superficial gastritis, chronic atrophic gastritis, peptic ulcer, duodenal ulcer, or gastric cancer. According to this survey, being infected by CagA+ strains had more severe injuries in upper gastrointestinal, but no significant difference was found in anti CagA Ab among different disease groups. In another study by Grimley et al[35] in England, anti CagA, anti VacA, and anti *Helicobacter pylori* Abs among 148 patients including 4 different groups: 1) duodenal ulcer, 2) gastric cancer, 3) esophageal cancer, 4) control groups were assessed. This study confirmed that no significant difference was found between gastric cancer and duodenal ulcer.

In the study conducted by Lawinczak and Starzynaska[36] in Poland, on the prevalence of anti CagA Ab presence between 2 groups, 270 cases with gastric cancer and 205 patients as control group, showed no difference totally (54.4 versus 42.5). However, according to this study, being infected by CagA+ strains would increase the risk of cancer among the young. In a study conducted by Mitchell et al[37] in Australia, 136 Australians and 83 Chinese were included. Ninety-six Australians suffered from NUD; 29 patients from duodenal ulcer and 19 patients were symptom free. Among the Chinese, 48 patients suffered from gastric

cancer and 35 patients were symptom free. Results showed a meaningful relation between anti CagA Ab and duodenal ulcer in Australians, but no significant correlation between anti CagA Ab and gastric cancer among Chinese. They suggested that anti CagA Ab cannot be considered as a predictive factor in developing countries.

Some other studies confirmed this suggestion. In a study by Abasiyanic et al[38] in Turkey, 66 patients with gastrointestinal complaints and 119 ones without any problems were tested for *Helicobacter pylori* by ELISA. Eighty-two percent of patients with symptoms and 64% of symptom free ones were *Helicobacter pylori+*. The *Helicobacter pylori+* ones were tested for anti CagA Ab by immunoblot. Anti CagA Ab was positive in chronic gastritis was 79%, duodenal ulcer was 92%, gastric cancer was 100%, and symptom free ones was 83%. Meaning that anti CagA Ab was prevalent among both groups, with or without gastrointestinal problems. In another study in Japan by Nishiya et al,[39] 39 patients with gastric cancer (case) and 39 *Helicobacter pylori+* with chronic gastritis (control) were included. The CagPAI, by PCR, was reported positive in 92.3% of the cases and 89.7% of the control group; that means, there was not a significant difference between case and control groups for the CagA. According to a study on genetic diversity of CagA in China by Zhou et al,[40] CagA, by PCR, was evaluated in 82 *Helicobacter pylori+* patients. One hundred percent of patients with peptic ulcer, 100% of the ones with gastric cancer, 91.4% of patients with chronic gastritis, and 94.4% of healthy volunteers had positive CagA reports. Meaning that presence of CagA cannot be solely considered as an indicator for *Helicobacter pylori* related gastrointestinal disorders among Chinese population.

In conclusion, based on the results of research developed in different countries especially Asia, we should not contemplate CagA solely as a risk factor of gastric cancer, and more research is necessary on genetic diversity or deletions of CagPAI and possible effects of it on serum anti CagA Ab presentation in our country. In the future, performance of this study with a larger sample size, in the places with high prevalence of *Helicobacter pylori* and compare its findings with neighborhood countries is necessary.

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