Frequency of *Helicobacter pylori* and cytotoxine associated gene A antibodies in patients with cardiac syndrome X

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ABSTRACT

Background: Cardiac syndrome X (CSX) is a condition in which patients have the pain of angina despite normal coronary angiogram. Recently, *Helicobacter pylori (H. pylori)* bacteria has been associated with CSX. However, there is no obvious data about the frequency of its virulent strain (cytotoxine associated gene A: CagA) in patients with CSX. We surveyed the frequency of *H. pylori* and CagA antibodies in patients with cardiac syndrome X and healthy controls. **Materials and Methods:** Plasma samples from 100 CSX patients (61 females and 39 males; mean age: 51.8 ± 12.3 years) and 100 healthy controls (61 females and 39 males; mean age: 48.9 ± 6.3 years) were tested for the presence of IgG antibody to *H. pylori* using enzyme linked immunosorbent assay (ELISA) method. Also, infected patients were determined by the presence of IgG antibody to CagA by ELISA method. Statistical analysis was carried out using chi-square test and independent samples T-test. **Results:** Ninety two percent (92/100) of patients were anti-*H. pylori* positive (anti-*H. pylori*+), while only 56.0% (56/100) of control group were anti-*H. pylori*+ (P<0.01). However, prevalence of anti-CagA positive (anti- CagA+) in *H. pylori* infected- CSX patients and control groups were 59.8% (55/92) and 60.7% (34/56), respectively (P >0.05). **Conclusion:** Thus, due to the high frequency of anti-*H. pylori* in CSX patients, and the probable causative effect of chronic infection in vascular diseases, it is suggested that *H. pylori* has a probable role in the pathogenesis of CSX.

Key words: Cardiac syndrome X, CagA, chest pain, *Helicobacter pylori*

INTRODUCTION

Cardiac syndrome X (CSX) is defined by a typical angina like chest pain without flow-limiting stenoses on coronary angiography and exclusion of noncardiac chest pain.[1] There is no obvious etiology for this syndrome.[2] One to 12% of individuals with myocardial infarction who undergo coronary angiography are found to have normal coronary arteries.[3] The pathogenesis of this syndrome is not well known despite of the extensive studies.[4] Previous studies had shown an association between viral and bacterial infections with vascular diseases, such as ischemic heart disease and CSX.[5]

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium that causes various extra-digestive diseases, including functional vascular disorders such as primary migraine and primary Raynaud's phenomenon, as well as ischemic heart disease.[5,6] An inflammatory response possibly due to *H. pylori* has been proposed as a mechanism in patients with coronary artery disease (CAD). In addition, *H. pylori* has been recently also associated with ischemic heart disease and CSX.[2,3,7,8] *H. pylori* strains may be divided into at least two subgroups based on the expression or nonexpression of cytotoxin-associated gene A (CagA) and the vacuolating cytotoxin.[9,10] The CagA has been identified as a possible marker of *H. pylori* virulence.[11,12]

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Our literature review did not bring up any obvious data about the frequency of CagA in patients with CSX. Hence, this study was designed to determine the frequency of anti-*H. pylori* and anti-CagA status in CSX patients.

MATERIALS AND METHODS

Study design

Patients with CSX and apparently healthy controls were studied. The CSX group consisted of 100 consecutive patients. Entry criteria were typical anginal chest pain, normal 12-lead electrocardiography (ECGs) at rest, a positive exercise ECG stress test response and normal coronary angiogram. Non-cardiac causes of chest pain such as gastrointestinal and musculoskeletal disorders were also investigated and ruled out as appropriate. Patients with diabetes mellitus were not included, as inflammatory marker levels increase in diabetes mellitus. A questionnaire was administrated to obtain general information regarding age, sex, body mass index (BMI), systolic and diastolic blood pressures. The control group consisted of 100 apparently healthy subjects. None of the control individuals had a previous history of chest pain or acute/chronic diseases. Also, none of these subjects were taking cardiac or non-cardiac medications. The study was approved by Medical Ethics Committee at Urmia University of Medical Sciences, Urmia, Iran; and all subjects gave written informed consent.

Laboratory assays

A 5-ml tri_sodium citrated blood sample was obtained from each subject and centrifuged at 2000 *g* for 15 minutes. Plasma was aliquoted and stored at -80°C until analysis. Specific anti-*H. pylori* immunoglobulin-G (IgG) positivity was determined with a commercial enzyme-linked immunosorbent assay (ELISA) kit (Glob anti-*H. pylori*/IgG, Milan, Italy) according to the manufacturer's instructions (sensitivity 96.5% and specificity 98.6%). Also, plasma positivity to the antigen CagA was assessed by ELISA (Dia.Pro, Milan, Italy; sensitivity and specificity >98%) in anti-*H. pylori* positive (anti-*H. pylori*+) samples.

Statistical analysis

The data were analyzed by Statistical Package for Social Sciences (SPSS) 16.0 software. Age, systolic blood pressure, diastolic blood pressure and BMI were shown as mean ± standard deviation (SD). Statistical analysis was carried out using chi-square test and independent samples *T*-test. *P* value of < 0.05 was considered statistically significant.

RESULTS

One hundred CSX patients (61 females and 39 males) were compared with 100 age and sex matched healthy controls (61 females and 39 males). Demographic and clinical characteristics of both groups are depicted in Table 1.

As shown in Table 2, anti- *H. pylori*+ was diagnosed in 92 (92.0%) patients with CSX and 56 (56.0%) individuals in control group ($P < 0.01$). Also, among CSX group, 55 patients were positive for anti- CagA (anti- CagA+) (55/92: 59.8% of anti- *H. pylori*+) while only 34 individuals in control group were anti- CagA+ (34/56: 60.7% of anti- *H. pylori*+ samples, $P > 0.05$).

DISCUSSION

Coronary endothelial dysfunction has been proposed as pathogenetic mechanism in CSX.[1,13,14]

The mechanisms responsible for endothelial dysfunction in CSX patients are not well understood;[15] however, some risk factors of CAD such as obesity, hypertension, hypercholesterolaemia and smoking, are frequently present in

Table 1: Demographic and clinical characteristics of cardiac syndrome X patients and control group

	CSX	Control	*P* value
Age (years)	51.8 ± 12.3	48.9 ± 6.3	> 0.05
Sex (female/male)	61/39	61/39	> 0.05
Systolic BP (mmHg)	122.5 ± 9.3	120.2 ± 7.0	> 0.05
Diastolic BP (mmHg)	77.6 ± 8.5	75.8 ± 6.9	> 0.05
BMI (kg/m^2)	26.7 ± 4.6	26.2 ± 3.2	> 0.05

BP: Blood pressure, BMI: Body mass index, CSX: Cardiac syndrome X

Table 2: Frequency of anti- *H. pylori* and anti-CagA status in cardiac syndrome X patients and control group

Infection Status	CSX	Control	*P* value
Anti-*H. pylori*+ /Total	92/100 (92.0)	56/100 (56.0)	< 0.01
Anti-CagA+/anti-*H. pylori*+	55/92 (59.8)	34/56 (60.7)	> 0.05

H. pylori: Helicobacter pylori; CagA: Cytotoxin-associated gene A, Figures in parentheses are in percentage, CSX: Cardiac syndrome X

these patients and may have roles.[16] Also, previous studies have suggested that chronic inflammation may contribute to endothelial dysfunction in CSX. Lanza *et al.*, showed that two indexes of systemic inflammation, C-reactive protein and interleukin-1 receptor antagonist, increased in patients with CSX compared with well-matched healthy control subjects. Thus, this result suggested that low-grade inflammation may play a pathogenetic role in CSX patients.[7]

Recent studies have suggested a possible association of viral and bacterial infections such as *H. pylori* infection in the etiology of acute coronary syndromes in patients with CAD.[17] Endothelial injury due to circulating endotoxin, autoimmunity with cross-reactivity of bacterial antigens and endothelial cells are discussed as possible underlying mechanisms.[3] In addition, *H. pylori* has been recently associated with CSX.[2] We speculated that *H. pylori* may also cause endothelial dysfunction directly by affecting the structure and function of vascular endothelial cells via inflammation.[18]

H. pylori may cause chronic inflammation and enhanced immune response due to the release of some cytotoxic substances which are responsible for the systemic manifestations of *H. pylori*.[19] Chronic infection of *H. pylori* most probably causes increased production of various inflammatory metabolites, and this could also affect blood vessel motility and induce endothelial dysfunction.[20] Epithelial cell act as the most probable target in *H. pylori* infection, and also as major interfaces between the host and pathogens. Thus, this interaction initiates acute mucosal inflammation, and interacts with the other mucosal cell proliferation via a cytokine network.[21] These two responses may be regulated differentially following induction of cytokines in the inflammatory cascade, including tumor necrosis factor-alpha and interleukin-6.[22,23]

Thus, with the results of our study, the possible role of *H. pylori* infection in the pathogenesis of CSX is suggested. This is the first study that shows anti- CagA status of *H. pylori* in CSX, however well designed clinical trial studies are needed to further confirm these results.

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