Association of *Helicobacter pylori* infection with cardiac syndrome X

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ABSTRACT

Introduction: Cardiac syndrome X (CSX) includes chest pain, positive exercise stress test and/or radionuclide test for ischaemia and normal coronary angiography. There is no obvious aetiology for this syndrome. Some mechanisms such as endothelial dysfunction and oestrogen deficiency have been invoked. In this study, we surveyed the association of *Helicobacter pylori* (HP) infection with cardiac syndrome X.

Methods: HP infection was detected by urea breath test (UBT) in patients with cardiac syndrome X, and compared with a sex- and age-matched control group. Patients with dyspepsia and coronary spasm were excluded. Statistical analysis was carried out using chi-square test.

Results: 40 patients (29 females and 11 males) with cardiac syndrome X aged between 30 and 65 years (mean 45.51 +/- 5.03 years) were compared with a control group (28 females and 12 males) aged between 31 and 64 years old (mean 44.93 +/- 5.16 years). 95 percent of patients were HP infected, while only 47.5 percent of members of the control group were infected (p-value is less than 0.001).

Conclusion: Considering the high prevalence of HP infection in patients with CSX in our sample and probable causative effect of chronic infection in vascular diseases, we believe that there is a probable role for HP infection in the pathogenesis of CSX.

Keywords: cardiac syndrome X, chest pain, coronary artery, *Helicobacter pylori*, vascular diseases

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INTRODUCTION

Cardiac syndrome X (CSX) is a condition characterised by the presence of angina pectoris and a positive response to stress or radionuclide tests (thallium scan) with a normal coronary arteriogram[1]. It was found in up to 20% of angina patients undergoing angiography[1-3]. The mechanism of this disease is not clear but microvascular and/or endothelial dysfunction has been invoked[1]. *Helicobacter pylori* (HP) is the organism most frequently associated with gastrointestinal infection[4]. This organism is also seen in other diseases such as primary biliary cirrhosis[5], functional vascular disorders (primary migraine and primary Raynaud's phenomenon)[6,7], and ischaemic heart disease[8, 9]. To study the role of inflammatory mediators in CSX, we surveyed the prevalence of HP infection in patients with CSX[10-11].

METHODS

HP infection rate was evaluated in 40 patients with CSX and 40 healthy individuals (control group) by urea breath test (UBT). All cases and control subjects were matched for age, sex and major risk factors for ischaemia, such as hypertension, hyperlipidaemia, diabetes mellitus and smoking. The control group consisted of 40 healthy persons (non-medical staff) of our hospital. They did not have any history of cardiac diseases and the results of their physical examination and electrocardiogram were normal.

Inclusion criteria for the CSX patient group were: (1) predominant effort angina; (2) ST-segment depression during exercise stress test or positive radionuclide test for ischaemia; and (3) completely smooth coronary arteries at angiography. Exclusion criteria for both groups were: (1) history of gastric symptoms, such as epigastric pain, belching, postprandial acid reflux, peptic ulcer; (2) history of using drugs such as antibiotics, H2-blockers or proton pump inhibitors during the previous month; (3) recent history of infectious and inflammatory diseases; (4) evidence of coronary artery spasm according to clinical history and electrocardiograms (angina at rest, ST-segment elevation during effort angina); and (5) other cardiac diseases (e.g. valvular heart diseases or cardiomyopathy).

UBT was performed under fasting condition, using the Isomax 2000™ (Isotechika Inc,

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Edmonton, AB, Canada) The cut-off point or threshold for the UBT test is designated 5 Delta over baseline (DOB)[12]. The study was carried out with the approval of Semnan Internal Medicine Research Center. Patients gave their written informed consent before being enrolled in the study. For statistical analysis, we used the chi-square test, and p-values below 0.05 were considered to be statistically significant.

RESULTS

40 patients (29 females and 11 males) with a mean age of 45.51 ± 5.03 years were compared with 40 healthy individuals (28 females and 12 males) with a mean age of 44.93 ± 5.16 years in the control group. The results indicated that 95% of patients were positive for HP infection, while only 47.5% of the control group were found to have HP infection ($p<0.001$). The prevalence of major risk factors for coronary artery diseases in both groups is depicted in Table I. In the CSX patient group, 76.2% of females (22 cases) were post-menopausal, and did not receive any hormone replacement therapy.

Table I. Major risk factors in CSX patients and control group.

Risk factors	CSX patients	Control	p-value
Mean age (years)	45 ± 5	44 ± 4	NS*
Sex (female/male)	29/11	28/12	NS*
Hypertension	40%	39.5%	NS*
Diabetes mellitus	2.5%	2.5%	NS*
Hyperlipidaemia	17.5%	15%	NS*
Smoker	7.5%	7.5%	NS*

* NS: not significant

DISCUSSION

We have shown that patients with CSX have a higher prevalence of HP infection compared to the control group, indicating an association between CSX and HP infection. The main causes of CSX are microvascular dysfunction and abnormal response to vasoconstrictor and vasodilator stimuli[1,13]. Endothelial dysfunction and sub-angiographical atheroma have been reported in patients with CSX[14]. The association between endothelial dysfunction in microcirculation and high prevalence of HP occurrence in the setting of early atherosclerosis or CSX is not clear. HP infection can be a trigger or the probable mechanism of inflammation in this setting. It has recently been suggested that inflammation is also involved in coronary microcirculation abnormalities observed in patients with CSX[15].

Previous studies had shown an association between viral and bacterial infections with vascular diseases, such as ischaemic heart disease and CSX[2]. It was also shown, in an earlier study, that HP and *Chlamydia pneumoniae* infection in ApoE(-/-) mice may exert a synergistic effect in the development of arteriosclerosis, which may induce increased expression of cell adhesion molecules ICAM-1 and VCAM-1[16].Chronic infection may be accompanied by persistently-increased production of various inflammatory metabolites, such as cytokines (IL-1-IL-6-TNF-α), which may affect vessel motility and induce endothelial dysfunction and microvascular hyperconstriction[2,17].

The concentrations of these cytokines will increase in the gastric mucosa in HP positive patients[18]. Interleukin-6 can increase hepatic gluconeogenesis and triglyceride synthesis. TNF-α also inhibits lipoprotein lipase activity and stimulates hepatic lipogenesis, altering the lipid levels. HP has been shown to influence fibrinogen concentration and total leukocyte count[16]. Chronic inflammation can contribute to the risk of vascular disease by increasing some acute phase reactants and inflammatory mediators, leading to endothelial cell damage, altered lipid oxidation and blood coagulation[18].

The host immune response against HP can determine the occurrence of extraintestinal manifestations. In particular, the virulent CagA-positive strain may evoke a more consistent release of cytokines with vasoactive properties, and such effect might be the basis of systemic effects[2]. It can be speculated that the gastric infection caused by virulent CagA-positive strain in a subject having a particular genetic susceptibility could trigger cardiac microvascular alteration[2].

Contrary to our results, another study showed a difference in HP infection rate that was not significant between CSX patients and the control group[11]. Reasons for this discrepancy are not clear. However, there are differences between the two studies. Firstly, Lanza et al included patients taking anti-ischaemic drugs, which can influence the stress test results; and also patients on proton pump inhibitors, which could influence UBT results[11]. We excluded such patients in our study. Secondly, Lanza et al selected CSX patients based on positive exercise stress test and negative coronary angiography[11]. In our study, 85% of our CSX patients had positive thallium scans in addition to positive exercise stress test, decreasing the likelihood of false positive exercise stress test results.

In our study, there is a high prevalence of HP

infection in CSX. Given the probable causative role of inflammation in vascular diseases[3,4,6-18], it is possible that HP infection also plays a role in the pathogenesis of CSX. Further prospective clinical trials with longer follow-up may be necessary to clarify this association.

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