The Cardiology 1 (2): 126-131, 2005

Chronic Helicobacter Pylori Infections and Carotid Intima- Media Thickness: Is There a Link

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Abstract: Chronic infections are related with cardiovascular diseases. The thickness of carotid intima-media is an indicator of atherosclerosis. Helicobacter pylori induced chronic active gastritis is resulted with atrophic gastritis. This study was done to studied the thickness of carotid intima-media in patients with atrophic gastritis and without it. One hundred and twenty three patients who were performed esophagogastroduodenoscopy for various reasons. Biopsy samples have been taken from antrum and corpus for histologic evaluation and rapid urease test. Helicobacter pylori was accepted as positive in patients in whom both histologic evaluation and rapid urease test result had been positive. Histopathologic evaluation has been performed according to to the Sydney classification. Helicobacter pylori positive casess were diveded into two groups as atrophic gastritis and non-atrophic gastritis. In 92 of 123 patients, helicobacter pylori positive non-atrophic gastritis and in 31 of them, helicobacter pylori positive atrophic gastritis was observed. In both groups. The mean age was 46 years. There were not differences between the two groups according to age, sex, body mass index, blood lipids, ferritin, platelet count, fibrinogen, vitamin B-12, C-reactive protein and the thickness of carotid intima media. The thickness of carotid intima media was not found as related with the chronic helicobacter pylori infection.

Key words: Helicobacter pylori, atrophic gastritis, carotid intima-media thickness

INTRODUCTION

Multiple factors contribute to the pathogenesis of atherosclerosis, including abnormalities in lipid metabolism, endothelial dysfunction, inflammatory and immunologic factors, plaque rupture and smoking[1]. It has also been proposed that infectious factors may play an important role in the pathogenesis of atherosclerosis by producing chronic infection of the vessels with persisting low-grade inflammation leading to endothelial dysfunction[1,2]. Bacterial endotoxin exhibits a variety of proatherogenic properties, including endothelial dysfunction[3] and it has been suggested that exposure to sustained high levels of endotoxin constitutes a risk factor for atherosclerosis in animal models and, likely, in humans[4,5].

The organisms proposed to have a role in the pathogenesis of atherosclerosis are C. pneumoniae, cytomegalovirus, Helicobacter Pylori (Hp), hepatitis A virus and herpes simplex virus types 1 and 2[6]. Furthermore, an association between vascular pathology and peptic ulcer disease was reported before Hp was considered the major cause of peptic ulcer. For example in 1976, Sternby *et al.*[7] reported the results of a large autopsy study performed in five European cities, involving over 50,000 patients. In people ages 40 to 59 years, obstruction of the left coronary artery was associated with prior duodenal or gastric ulcer fivefold more frequently than in those without peptic ulcer disease[7]. Pasceri *et al.*[8] compared patients with coronary heart disease with age and sex matched controls with similar social status and reported that the prevalence of Hp infection was significantly higher than among controls (62 vs 40%, p=0:004). This difference was also associated with higher prevalence of more potentially virulent strains (cytotoxin-associated gene-A positive strains) (43 vs 17%, p= 0:0002)[8]. In 1122 young patients (ages 30 to 49) with a myocardial infarction, Danesh *et al.*[9] found a higher prevalence of Hp seropositivity among those with myocardial infarction compared to 1122 matched controls without infarction (42 vs 24%, respectively). The odds ratio (OR) yielded by this difference was of 2.28 (99% CI, 1.80-2.90), which fell to 1.75 after adjusting for other risk factors and socioeconomic status[9]. That study also

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evaluated 510 age-and sex-matched pairs of siblings and found that those with a myocardial infarction were more likely to be seropositive (99% CI, 0.86-2.05; OR D 1.33)[9]. These data suggest a moderate association between coronary heart disease and Hp, independent of other risk factors[9]. In addition, it was hypothesized that antigenic mimicry between Hp antigens and structural elements of blood vessels cross-reacted with antigensof normal and atherosclerotic arteries, providing a possible pathogenic link with atherosclerosis[10]. Franceschi *et al.*[10] in a recent elegant study, demonstrated that anti-Hp cagA antibodies cross-react with antigens of both normal and atherosclerotic blood vessels and speculated that the binding of anti*cagA* antibodies to those antigens in injured arteries could influence the progression of atherosclerosis in patients positive for Hp infeotion.

The progression of atrophic gastritis is a result of chronic active gastritis caused by Hp infection[11]. Annibale *et al.*[12] have suggested that atrophic gastritis of the corpus is a spectrum of damage where Hp was a key agent able to induce gastric atrophic damage and also gastric autoimmunity. According to these results; long term Hp infection which caused atrophic gastritis may be related atherosclerosis.

Carotid artery Intima-media Thickness (CIMT) measured by ultrasound has been shown to be correlated with existing Cardiovascular Disease (CVD) and predictive of CVD in individuals without clinically evident disease[13]. CIMT is now widely used as a surrogate marker for atherosclerotic disease.

In this prospective study, we investigated to assess whether the CIMT of patients with Hp infection related atrophic gastritis is thicker than that of individuals without atrophic gastritis.

MATERIALS AND METHODS

A total of 123 patients, treated at our department of gastroenterology (university clinic), were recruited into the study between October 2002 and July 2003. Patients were randomly chosen every day. All patients had referred to the endoscopy unit for esophagogastroduodenoscopic examination. The patients with gastroduodenal cancer were excluded. Informed consent was obtained from all participants before examination. Participants attended for a single visit. The following data were obtained either with an interview or through the analysis of the medical record: name, age (years), address, telephone, sex, smoking habit, presence of dyslipidemia, familial history, systemic arterial hypertension, hormone replacement, use of drugs with cardiovascular or lipid-lowering effects, previous cardiac surgery, previous coronary angiography, previous coronary angioplasty and previous acute myocardial infarction. Measurements, such as weight (kg) and height (m), were taken at the time of the ultrasound examination. Body mass index was calculated as [body weight (kg)/ height $(m)^2$].

Smoking was defined based on its active presence in the last 6 months; an ex-smoker was someone who quit the habit 6 months before; and a nonsmoker was someone who did not smoke in the last 15 years. Dyslipidemia was defined as the presence of cholesterol levels=240 mg dL^{-1} and LDL=160 mg dL^{-1} (or=130 mg dL^{-1} in the group with coronary artery disease) in a random measurement, or only the use of a lipid-lowering drug, or the presence of HDL<35 mg dL^{-1}. The presence of systemic arterial hypertension was considered when the use of antihypertensive drugs was reported, when a clinical history of hypertension existed, or when it was reported in the medical record. Myocardial infarction was considered when reported in the medical records with electrocardiographic and enzymatic documentation. Diabetes mellitus was diagnosed in patients with a history of dietary treatment or additional oral antidiabetic or insulin medication.

Venous blood was drawn in the study morning under standardized conditions and a complete blood cell count was done by automated cell counters. We measured plasma fasting blood glucose, fibrinogen, vitamin B12, C-Reactive Protein (CRP), Total Cholesterol (TC), Triglycerides (TG) and high Density Lipoprotein (HDL-C) cholesterol and calculated Low Density Lipoprotein (LDL-C) cholesterol. Biochemical assays were performed with blinding to clinical details and the results of ultrasound examinations.

Endoscopic examination: During the endoscopic procedure, two biopsies from the antrum and two biopsies from the corpus were taken for pathology and a biopsy from the antrum for urease test was taken. The gastric biopsy samples have been evaluated according to the Sydney Classification for gastritis. The patients have been accepted as Hp- positive if they had been found as positive both histologically and rapid urease test results. Two groups were constituted by being based on histopathology; Hp-Positive Atrophic Gastritis Group (HPAGG) and Hp-Positive nonatrophic Gastritis Group (HPnAGG).

Ultrasound imaging: B-mode ultrasonographic images of the carotid artery were obtained with a 7.5-15 MHz brandband lineer transducer (Toshiba Powervision 8000, Tokyo, Japan). Common carotid artery IMT was measured

in accordance with previous reports, 1 cm before the carotid bifurcation at the far wall of the carotid artery[14,15]. The distance between the echoes arising from the blood-intima interface and the media-adventitia interface was taken as the measure of IMT. Multiple longitudinal and cross-sectional measurements of both common carotid arteries were summarized and the mean carotid IMT was calculated for each individual. Ultrasound imaging was performed by the same experienced radiologist, who was unaware of the subjects' clinical and laboratory characteristics.

Statistical methods: The ststistical evaluation has been done with the SPPS version 11.0 software.The comparison for, sex, disease status, drug and alcohol usage and smoking status of patients between the groups has been done according to the Chi-square test test and for the other properties of the groups according to the oneway ANOVA test. The value of $p<0.05$ was accepted as significance. Quantitative data were expressed as Means±SD or as medians

RESULTS

There were totally 31 patients, fourteen males and 17 females, in HPAGG. The mean age was 46.9±10.5. There were totally 92, 35 males and 57 females in HPnAGG . The mean age was 46.2±12.1 (Table 1). There was any difference between the groups according to the age, sex, BMI, diabetes mellitus, hypertension, coronary heart disease, NSAIIDs usage and smoking status of the patients.

With recpect to blood lipids; in HPAGG the mean value of TC was 194.8±44.3 mg dL^{-1}, HDL-C was 51.3±13.4 mg dL^{-1}, LDL-C was 118.4±35.5 mg dL^{-1} and TG; 127.1±86.5 mg dL^{-1}. In HPnAGG the mean value of TC was 199.5±41.4 mg dL^{-1}, HDL-C was 52.0±14.0 mg dL^{-1}, LDL-C was 120.5±37.0 mg dL^{-1} and, TG was 134.0±75.2 mg dL^{-1}. There were not differences between two groups according to the levels of blood levels; p values were 0.595, 0.803, 0.788 and 0.676, respectively (Table 2).

In comparison with inflammation marker; the level of CRP has been measured as higher in HPnAGG; but the difference between the groups was not statistically significant. The mean value of CRP was 2.1±1.5 mg dL^{-1} in HPAGG, whereas 4.5±11.7 mg dL^{-1} in HPnAGG (p=0.292), teh mean value of fibrinogen was 345.8±100.7 mg dL^{-1} in HPAGG, whereas 329.8±91.9 mg dL^{-1} in HPnAGG (p=0.487) and the mean platelet count was 228833±58494.9/mm^3 in HPAGG, 236200±71535.9 /mm^3 in HPnAGG (p=0.611).

The mean level of ferritin was 36.1±34.6 ng mL^{-1} in HPAGG, whereas 45.6±40.5 ng mL^{-1} in HpnAGG

Table. 1: The characteristics of study population

Characteristic	HPAGG	HPnAGG
Number	31	92
Sex (F/M)	17/14	57/35
Age (±SD)	46.9±10.5	46.2±12.1
Diabetes mellitus (n)	02	04
Coronary heart disease (n)	02	02
Hypertension (n)	06	16
Hyperlipidemia (n)	03	04
Smoking (n)	07	29
Alcohol	01	01
NSAIDs	15	33

Table. 2: The comparison of groups

Parameter	HPAGG	HPnAGG	Statistical significans
Age (Year)	46.9±10.5	46.2±12.1	ns
BMI (kg/m^2)	25.78±4.3	26.21±3.8	ns
Total Cholesterol (mg dL^{-1})	194.8±44.3	199.5±41.4	ns
LDL- Cholesterol (mg dL^{-1})	118.4±35.5	120.5±37.0	ns
HDL- Cholesterol (mg dL^{-1})	51.3±13.4	52.0±14.0	ns
Triglyceride (mg dL^{-1})	127.1±86.5	134.0±75.2	ns
Ferritin (ng mL^{-1})	36.1±34.6	45.6±40.5	ns
Platelet count (mm^3)	228833±58494.9	236200±71535.9	ns
C-reactive protein (mg dL^{-1})	2.1±1.5	4.5±11.7	ns
Fibrinogen (mg dL^{-1})	345.8±100.7	329.8±91.9	ns
Vitamin B_{12} (mg dL^{-1})	252.9±114.8	303.8±121.7	ns
CIMT (mm)	0.65±0.16	0.65±0.13	ns

Performed statistical method was the oneway ANOVA test. The value of $p<0.05$ was accepted as significance. Quantitative data were expressed as Means±SD. Abbreviations: CIMT; Carotid Intima-Media Thickness, ns; not significans

(p=0.259). Although the mean value of vitamin B-12 has been measured as lower in HPAGG relatively to the HPnAGG as expected, but this difference was not statistically significant (252.9±114.8 mg dL^{-1} vs 303.8±121.7 mg dL^{-1}, p=0.088).

CIMT has been measured as 0.65±0.16 mm in HPAGG and in 0.65±0.13 mm HPnAGG and no difference between the groups has been found (p=0.911).

DISCUSSION

In this prospective study that investigated to assess whether the CIMT of patients with Hp infection related atrophic gastritis is thicker than that of individuals without atrophic gastritis it wasn't found an association between chronic Hp related atrophic gastritis and CIMT.

Hp is one of the most frequent causes of gastroduodenal infection worldwide, resulting in the release of various bacterial and host dependent cytotoxic

substances including ammonia, platelet activating factor, cytotoxins and lipopolysaccharides as well as cytokines such as interleukins 1-12, tumor necrosis factor alpha, interferon gamma and reactive oxygen species[16,17] Recently, several extradigestive pathologies have been linked to Hp infection including vascular (atherosclerosis and ischaemic heart disease, primary Raynaud phenomenon, primary headache), autoimmune (Sjogren's syndrome, Henoch-Schonlein purpura, autoimmune thyroiditis, idiopathic arrythmias, Parkinson's disease, nonarterial anterior optic ischemic neuropathy) and skin diseases (chronic idiopathic urticaria, rosacea, alopecia areata), sideropenic anemia, growth retardation, late menarche, extragastric MALT lymphoma, diabetes mellitus, hepatic encephalopathy, sudden infant death syndrome and anorexia of aging[18,19]. A high Hp seroprevalence has been found in many extragastrointestinal disorders.

Hp infection is postulated to have an effect on clotting mechanisms[20]. A further hypothesis suggests that exposure to Hp may lead to an increased risk of arteriosclerosis by an autoimmune process to Heat shock Proteins (Hsps)[21]. Seroepidemiological studies about the role of Hp in the development of coronary and cerebrovascular arteriosclerosis yielded controversial results. Several authors found an association[21-24], whereas others did not[20,25-28]. Further studies found an association, adequately explained by the much stronger association of Hp infection with age, male gender and social class, which are linked with coronary heart disease[29-31].

In a study of socioeconomically homogeneous men, controlled for age and smoking, limited evidence of association between Hp exposure and risk for future myocardial infarction was found[32]. A population-based study did not find an association of elevated Hp antibodies with ischemic stroke; however, Hp infection was associated with strokes caused by small artery occlusion[33]. To explain the contradictory results regarding the association of Hp with arteriosclerosis, it was suggested that strains expressing the virulent Cytotoxin-associated gene product A (CagA) are more strongly related to coronary heart disease than are other strains of Hp[34]. A study in late-middle-aged men, however, showed that CagA positive strains appear to be no more strongly related to the disease than other strains[35].

Advanced atrophic corpus gastritis is an important and common cause of low serum vitamin B_{12} and increased serum homocysteine[36]. Consequently, it is possible that advanced atrophic corpus gastritis is a common risk factor for low vitamin B_{12} and high homocysteine related extragastric diseases, such as atherosclerosis, thromboembolic disease, stroke, anemias and degenerative neurological diseases. But, in this study, although the level of vitamin B_{12} has been measured as lower in HPAGG, this difference between two groups has not been found as statistically significant.

We have not found any statistically significant difference between the levels of CRP, fibrinogen and platelet count as the inflammation markers in our study. Inflammation represents an important feature of CHD and several authors have discussed the role of an increased inflammatory response to various infectious stimuli that might represent the pathophysiological link between infection and CHD[37-39]. In a large case-control study, Koenig *et al.*[40] have found no consistent increase in CRP, fibrinogen, plasma viscosity or leukocyte count related to seropositivity to Hp as assessed by IgG antibody or, more specifically to infection by the more virulent CagA-positive strains. This held true in patients and control subjects.

Induction of changes in lipoproteins by cytokines, which indirectly predisposes patients to atherosclerosis[41]. For instance, a secondary increase in Low-Density Lipoprotein (LDL) levels and a decrease in High-Density Lipoprotein (HDL) levels may be induced, resulting in pre-atherosclerotic conditions. Infection and inflammation are associated with a decrease in HDL cholesterol levels[41]. The mechanism for the decrease in HDL cholesterol levels during infection and inflammation has not been firmly established. Nevertheless, a persistently low level of HDL cholesterol in chronic infection and inflammation suggests that this change may be undesirable, since data from epidemiologic studies have shown a greater risk of CAD in subjects with low HDL cholesterol levels[41]. We have not found any difference HPAGG and HPnAGG according to the blood lipids.

CONCLUSIONS

Although many currently consider atherosclerosis an inflammatory process, these data do not support a role for Hp infection as a contributor to the development of this common disease. We found no association between Hp and carotid artery disease. Evidence for a moderate association between Hp and atherosclerosis is difficult to interpret even in population-based studies.

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