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Association between *Helicobacter pylori* infection and carotid atherosclerosis in patients with vascular dementia

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ABSTRACT

Background and purpose: Accumulating evidence indicates that various infections contribute to the pathogenesis of atherosclerosis. *Helicobacter pylori* (Hp) has been implicated as a risk factor of atherosclerosis for stroke and other cardiovascular disease, but limited data exist regarding vascular dementia (VD). This study aimed to investigate the relationship between Hp infection and carotid atherosclerosis in patients with VD.

Methods: A total of 354 patients who were diagnosed with VD were enrolled. Patients were divided into Hp positive VD group (n = 208) and Hp negative VD group (n = 156) using the ^{13}C-urea breath test (^{13}C-UBT). Serum YKL-40, a marker for inflammation, were analyzed by ELISA. Traditional atherosclerotic risk factors including age, gender, body mass index (BMI), total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides (TG), systolic blood pressure (SBP), diastolic blood pressure (DBP) and fasting blood glucose (FBG) were collected or detected. Carotid intima-media thickness (CIMT) was determined by color Doppler ultrasound.

Results: CIMT values and serum YKL-40 significantly increased in Hp positive VD group in comparison with Hp negative VD group ($p < 0.05$). In Hp positive VD group, serum YKL-40 was positively correlated with CIMT ($r = 0.412$, $p < 0.05$), and the association was independent of traditional atherosclerotic risk factors ($\beta = 0.381$, $p < 0.001$).

Conclusions: CIMT and serum YKL-4 were significantly higher in Hp positive patients than Hp negative patients. Hp-induced inflammation may be a risk factor for atherosclerosis in patients with VD.

1. Introduction

The rising prevalence of vascular dementia (VD) is of great public health concern. VD is the second most common type of dementia accounting for about 20% of all dementia patients [1]. The World Health Organization estimates that 35.6 million people live with dementia, which is anticipated to triple by 2050. Due to the continuous population aging, VD has become one of the leading chronic diseases imposing a tremendous burden on families and social economy [2]. Thus, searching for potential risk factors and developing preventative and curative treatments are top priorities.

Atherosclerosis is a major cause of VD and the most important cause of morbidity and mortality worldwide [3]. Inflammation plays an important role in the progression of atherosclerosis and has attracted much attention. A variety of infections including *Helicobacter pylori* (Hp) infection can stimulate the production of pro-inflammatory cytokines and may be a critical risk factor of atherosclerosis [4]. Hp was first discovered in 1982 in Australia by Marshall, found in a large proportion of humans worldwide (>50%) [5]. Evidence has shown that Hp infection might contribute to carotid atherosclerosis in stroke and other cardiovascular disease [6], but limited data exist regarding VD.

YKL-40, also called as human cartilage glycoprotein-39, is a novel biomarker of inflammation. The serum YKL-40 is up-regulated in various inflammatory conditions [7]. Recent studies have showed that YKL-40 is closely associated with atherosclerotic progression [8]. Nevertheless, few reports exist on the relation between Hp infection and YKL-40 in the process of atherosclerosis in patients with VD.

In our previous study, we found that Hp infection might partly contribute to the cognitive decline in patients with VD through increasing expression of IL-1α, IL-6 and TNF-β (traditional inflammation factors) [9]. In the present study, we wonder whether there exist other mechanisms linking Hp infection to VD through carotid atherosclerosis and

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YKL-40 (a novel biomarker of inflammation). We hypothesized that Hp infection is involved in the process of carotid atherosclerosis by increasing serum YKL-40 in patients with VD.

2. Methods

2.1. Patients

From January 2013 to June 2015, a total of 364 patients who were diagnosed with VD were enrolled in this study. The patients were recruited consecutively and prospectively from the Department of Neurology in the Central Hospital of Tai'an, Tai'an, Shandong Province, China. The patients were diagnosed with VD based on the criteria in Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV) and National Institute for Neurological Disorders and Stroke (NINDS-AIREN) [10, 11]. Patients with a known history of a major psychiatric disorder, smoking, gastrointestinal disease, tumor, lobar hemorrhages, autoimmune disease, substance abuse, HIV infection and chronic inflammatory disorder were excluded. Data were collected on demographic and clinical characteristics including age, sex and body mass index (BMI). This study was carried out in accordance with the Helsinki Declaration and approved by the Human Ethics Committees of Tai'an City Central Hospital. All patients provided written informed consent.

2.2. ^{13}C-urea breathe test

All patients recruited into this study underwent the ^{13}C urea breath test (^{13}C-UBT). The ^{13}C-UBT was performed according to the manufacturer's instructions. Briefly all patients performed fasting and a baseline breath sample was collected. After 10 min, patients drank 50 mL of water dissolved with 75 mg of ^{13}C isotope-labeled urea and a second breath sample was taken 30 min later. The $^{12}CO2/^{13}CO2$ ratio was then measured using an infrared spectrophotometer. The results of ^{13}C-UBT were considered positive if ^{13}C concentration rose in the exhaled air greater than 5%. According to the ^{13}C-UBT, patients were divided into two groups: Hp positive VD group and Hp negative VD group.

2.3. Risk factors assessment

Peripheral venous blood samples were collected from all patients and stored at −80 °C until analysis. Enzyme-linked immunosorbent assays (ELISA) were used to measure concentrations of YKL-40 (R&D systems, Minneapolis, MN) according to the manufacturer's instructions. Levels of traditional atherosclerotic risk factors including total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides (TG) and fasting blood glucose (FBG) were also determined from the same sample. Blood pressure was measured with Omron electronic sphygmomanometer (HEM-7223-E; Omron Healthcare Co., Ltd., Kyoto, Japan).

2.4. Measurement of carotid intima-media thickness

The carotid intima-media thickness (CIMT) was measured using a Toshiba 790 A color Doppler system (Toshiba Medical Systems Corporation, Ottawa, Tochigi, Japan) with a 10 MHz transducer. All the measurements were performed by the same trained operators (YL Liu and RT Cui) who were blinded to patients' clinical information. In a quiet room, patients were examined in the supine position with the neck rotated away from imaging transducer. CIMT was defined as the distance between the leading edge of the media adventitia interface of the far wall and the leading edge of the lumen intimal interface. CIMT measurements were performed at two points: 10 and 20 mm away from the bifurcation, and the average of the two measurements was recorded as the IMT. Both common carotid arteries were scanned. The mean value between the right and left common carotid artery IMT was taken into the study.

2.5. Statistical analyses

Data analysis was done with a statistical software package SPSS (SPSS Inc., Chicago, IL) version 20. Subjects were identified using the total numbers (proportions) of categorical variables and the mean ± standard deviation (SD) of continuous variables. Normality of the continuous variables was examined by the Kolmogorov–Smirnov test. For the comparison between two groups, the Student's t-test (or Mann–Whitney U-test) was used for continuous variables and the chi-square test for categorical variables. The degrees of associations between continuous variables were calculated by Pearson correlation coefficient and multiple linear regression analysis was used to examine the associations between serum atherosclerotic risk factors and CIMT. All the tests were 2-tailed and differences were considered statistically significant when $p < 0.05$.

3. Results

A total of 364 VD patients were included in the study. According to ^{13}C-UBT, 208 patients (57.1%) were Hp positive VD patients and 156 patients (42.9%) were Hp negative VD patients. Patients' characteristics are shown in Table 1. CIMT values and serum YKL-40 levels increased significantly in subjects with Hp positive VD group in comparison with those with Hp negative VD group ($p < 0.05$). No differences were observed with respect to age, sex, BMI, TC, LDL-C, HDL-C, TG, SBP, DBP and FBG ($p > 0.05$).

Univariate correlation analysis between CIMT values and characteristics of Hp positive VD group are summarized in Table 2. CIMT values were higher in men than in women, though the difference was not statistically significant ($p > 0.05$). By univariate analysis, CIMT values was positively correlated with serum YKL-40 levels ($r = 0.412$, $p < 0.05$). However, there was no statistically significant correlation between CIMT values and traditional atherosclerotic risk factors including age, BMI, TC, LDL-C, HDL-C, TG, SBP, DBP and FBG ($p > 0.05$).

Multiple regression analysis of relationships between CIMT values and characteristics of Hp positive VD group are summarized in Table 3. By multiple regression analyses, the association between CIMT values and serum YKL-40 in Hp positive VD group remained significant ($\beta = 0.381$, $p < 0.05$). Nevertheless, there was also no statistically significance between CIMT values and traditional atherosclerotic risk factors including age, sex, BMI, TC, LDL-C, HDL-C, TG, SBP, DBP and FBG ($p > 0.05$).

4. Discussion

In this study, we examined the association between Hp infection and carotid atherosclerosis in patients with vascular dementia. The results

Table 1
Subject characteristics (n = 364).

Features	Hp (−) group (n = 156)	Hp (+) group (n = 208)	p value
Age, years	62.8 ± 11.7	63.2 ± 10.4	0.744
Men, n (%)	81 (51.9)	112 (53.8)	0.797
BMI, kg/m^2	23.1 ± 2.8	23.3 ± 2.0	0.349
TC, mmol/L	4.24 ± 1.13	4.31 ± 0.98	0.776
LDL-C, mmol/L	2.65 ± 0.76	2.63 ± 0.81	0.865
HDL-C, mmol/L	1.30 ± 0.24	1.27 ± 0.28	0.331
TG, mmol/L	1.66 ± 0.56	1.65 ± 0.48	0.928
SBP, mm Hg	133.6 ± 21.1	135.6 ± 19.4	0.366
DBP, mm Hg	78.4 ± 8.4	78.1 ± 8.3	0.720
FBG, mmol/L	5.11 ± 0.96	5.13 ± 1.08	0.807
YKL-40, ng/mL	6.9 ± 0.5	18.7 ± 1.6	<0.001
CIMT, mm	0.93 ± 0.15	1.12 ± 0.18	<0.001

Hp, *Helicobacter pylori*; BMI, body mass index; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; CIMT, carotid intima-media thickness.