CORRELATION ANALYSIS OF CAROTID ATHEROSCLEROTIC PLAQUES AND SERUM MARKERS IN ELDERLY PATIENTS WITH ESSENTIAL HYPERTENSION

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ABSTRACT

In this paper, the relationship between carotid atherosclerosis (CAS) and serum markers in elderly patients with essential hypertension (EH) was examined via in-depth research. In this study, 318 elderly EH patients in either our hospital or clinic were selected as the research subjects and were classified as the EH group. All EH patients underwent carotid color ultrasonography and blood biochemical examination and were divided into three groups by their carotid artery plaques (123 cases in the without plaque group, 104 cases in the stable plaque group and 91 cases in the unstable plaque group). Meanwhile, patients who had physical examinations and who were healthy during the same time period comprised the placebo-controlled group (116 cases). The relationships between CAS and serum parameters including fasting plasma glucose (FPG), Hcy, total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), uric acid, ferritin, fibrinogen (Fib) and C-reactive protein (CRP) were investigated. The results showed that the levels of CAS and Hcy in the EH group were significantly higher than those in the control group [61.32% (10.83±2.44 μmol/L) vs 28.45% (7.21±1.16 μmol/L), respectively]; this result showed statistical significance(P value less than 0.01). The incidence of CAS in patients with EH was 61.32%. Compared with the nonplaque group, the parameter values (FPG, TC, TG, LDL-C, Hcy, uric acid, ferritin, Fib, and CRP) were significantly higher in the stable plaque group and the unstable plaque group (P value less than 0.05), and the values of TBIL, DBIL and IBIL were significantly lower than those in the without plaque group (P value less than 0.01). The logistic regression analysis showed that CAS plaques were negatively correlated with TBIL levels and were positively correlated with FPG, TC, LDL-C, Hcy, uric acid, ferritin, Fib, CRP, smoking, diabetes and hypertension (P value less than 0.05). In summary, TBIL and IBIL in serum are protective factors for CAS in elderly EH patients; however, FPG, Hcy, uric acid, ferritin, Fib and CRP are adverse factors.

Keywords*: hypertension, carotid artery disease, atherosclerosis, bilirubin.*

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Introduction

In recent years, cardiovascular diseases (CVD) have been the leading cause of death in humans. More than 17 million people had died every year by 2013 and it is estimated that more than 23 million people will die each year by 2030[(1)]. With increases in age, the cardiovascular vessels tend to harden and the blood pressure tends to rise, and the risks of disease and death gradually increase in the elderly population. Coronary heart disease, one of the typical cardiovascular diseases, is identified by coronary angiography and the extent of coronary artery disease can be predicted by coronary CT angiography. Both of these imaging techniques need contrast agents, which brings certain limitations to examining elderly patients, who have different degrees of decline in renal function. It is well known that atherosclerosis (AS) is the main cause of CVD, which greatly threatens the health and survival of human beings. Feigin et al. found that there were more than 17 million ischemic strokes reported worldwide in 2013[(2)], and the World Heart Federation estimated that there were approximately 15 million people worldwide who suffered from strokes per year[(3)]. According to a recent population study, many factors can cause a stroke, with approximately 16.6% of ischemic strokes being caused by macrovascular atherosclerosis[(4)]. Carotid artery position is superficial and is easily detected by using a surface ultrasound, and carotid atherosclerosis (CAS) is an early manifestation of

atherosclerosis that is an important "window" for systemic arteriosclerosis ultrasonography, which can predict the severity of coronary atherosclerosis that is increasingly valued by clinicians[5].

Recently, studies on atherosclerosis and serum markers, including homocysteine (Hcy), uric acid, bilirubin, ferritin, fibrinogen (Fib), and C-reactive protein (CRP), have been reported in-depth; of these, Hcy is an independent risk factor that accelerates AS development. Serum Hcy is a sulfur-containing amino acid, which is an important intermediate of cysteine and methionine in the metabolic process. Under normal bodily conditions, blood Hcy can be catabolized in the body and maintained at a relatively low level. However, both primary and secondary causes of atherosclerosis may affect the metabolism of serum Hcy in daily life, thus resulting in an increase in serum Hcy concentrations. An increased serum Hcy concentration will significantly increase the risk of coronary heart disease, cerebrovascular disease and peripheral vascular disease, which are risk factors for stroke and cardiovascular disease and can cause a variety of diseases[6], such as an acceleration of vascular endothelial injuries, the oxidation of low-density lipoproteins and the proliferation of vascular smooth muscle cells[7]. Studies have shown that the carotid plaque volume will increase with increasing Hcy concentrations in men and can also be associated with carotid intima-media thickness and hemodynamics[8-10].

However, few studies have focused on the association between CAS plaques and serum markers in elderly patients with essential hypertension (EH). This study attempted to find the relationship between them, aiming at the early identification of high-risk subgroups of hypertensive patients with carotid plaques, thus reducing the incidence of acute events, such as coronary heart disease.

Materials and methods

Materials

Approximately 318 elderly patients (the EH group) who were admitted to the hospital from January 2017 to January 2018, including 162 women and 156 men aged 60 to 88 (65.21±6.43) years, were followed. The carotid ultrasound results were used to divide cases into 3 groups: 123 cases were in the without plaque group, 104 cases were in the stable plaque group and 91 cases were in the unstable plaque group. The selected patients were referred to the 2010 Chinese hypertension guidelines[11]. The following exclusion criteria were used: secondary hypertension, acute cardiovascular and cerebrovascular diseases, liver and kidney dysfunction, hematological diseases, hepatobiliary diseases, acute infection, gout, folic acid and taking vitamin B6 and B12 in 2 weeks. The healthy control group included 116 patients who had healthy physical examinations and , including 67 men and 49 women aged 60 to 85 (64.38±6.88) years.

Methods

All patients were tested for serum parameters, including fasting blood glucose (FPG), serum total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), TC, TG, LDL-C, HDL-C, Hcy, uric acid, ferritin, Fib, CRP and other indicators. These parameters were measured by using an automatic biochemical analyzer and subjected to carotid ultrasound. The following serum index determination conditions were used: all patients fasted for 10 hours and had 3 ml of elbow venous blood taken at rest in the morning and centrifuged at 3000 r/min for 15 min. A color Doppler ultrasound system with a peripheral blood vessel probe frequency of 7.5 MHz was used for carotid ultrasound. Each subject was placed in the supine position with the head slightly reclined, and the common carotid bifurcation, the inner diameter of the internal carotid artery and the intima-media thickness (IMT) were examined, and plaque formations and plaque properties were observed. The distal wall of the bilateral common carotid artery and the proximal segment of the internal carotid artery were selected from the vessel wall at a distance of 1.0 to 1.5 cm. The vertical distance between the anterior and posterior intimae of the artery and the endocardial interface was measured. The endometrial interface of the lumen is the carotid IMT; accordingly, thickening of the irregular wall of the tube wall, IMT≥1.2 cm and the local structural changes of the convex lumen, are regarded as indicating the formation of atherosclerotic plaques; the absence of these featured is considered the absence of plaques. According to the nature of each plaque, it is categorized as an unstable plaque (a hypoechoic plaque, a rough echogenic plaque, a heterogeneous echogenic plaque or an ulcer plaque) or a stable

plaque (a strong echo plaque, a smooth surface and other echo plaques or mixed echogenic plaques with strong echoes)[12].

Statistical method

Statistical analysis was performed by the SPSS 11.5 software, and the measurement data were consistent with a normal distribution (x±s). The comparison between the groups was analyzed by ANOVA, and the count data were analyzed by using a χ^2-test. The correlation analysis was performed by logistic regression analysis and, if the P value was less than 0.05, the difference was statistically significant.

Result

Group baseline data comparison

The results of the comparisons of age, diabetes, FPG, TBIL, DBIL, IBIL, TC, TG, LDL-C, HDL-C, uric acid, ferritin, Fib and CRP levels between the control group and the EH group are shown in Table 1, and the differences were not statistically significant. However, the CAS and Hcy levels of the EH group were significantly higher than those of the control group and showed significant differences (P value less than 0.01 (Table 1).

Project	Control group (116 case)	EH group (318 cases)	P value	t
Age (years) a	64.38±6.88	65.21±6.43	0.244	-1.17
Male [number of cases (%)]	67(57.76)	156(49.06)	0.109	2.58
Smoking [number of cases (%)]	72(62.07)	168(52.83)	0.087	2.93
Diabetes [number of cases (%)]	62(53.45)	162(50.94)	0.214	0.64
CAS [number of cases (%)]	33(28.45)	195(61.32)	Below 0.001	36.83
FPG (mmol/L) [a]	5.97±1.38	6.32±1.82	0.060	-1.88
TBIL (μmol/L) [a]	10.89±2.06	11.15±1.51	0.153	-1.43
DBIL (μmol/L) [a]	4.48±1.87	4.73±2.03	0.247	-1.16
IBIL (μmol/L) [a]	9.37±2.18	9.66±1.94	0.184	-1.33
TC (mmol/L) [a]	3.78±1.37	4.02±1.51	0.134	-1.50
TG (mmol/L) [a]	2.16±0.79	2.24±0.66	0.291	-1.06
LDL-C (mmol/L) [a]	2.91±0.85	3.07±1.04	0.138	-1.49
HDL-C(mmol/L) [a]	1.26±0.82	1.18±0.74	0.334	0.97
HCY (μmol/L) [a]	7.21±1.16	10.83±2.44	Below 0.001	-15.35
Uric acid (μmol/L) [a]	289.44±26.75	293.48±28.62	0.186	-1.32
Ferritin (μg/L) [a]	214.66±20.38	218.18±21.53	0.125	-1.54
Fib (g/l) [a]	4.41±1.38	4.64±1.14	0.080	-1.75
CRP (mg/L) [a]	7.33±2.06	7.84±2.54	0.053	-1.94

Table 1: Comparison of the baseline data of the two groups.
Note: a is expressed as x±s

Comparison of the basic data between the CAS group and the non-CAS group in patients with EH

The incidence of CAS in patients with EH was 61.32%. There were significant differences between the CAS group and the non-CAS group in smoking, diabetes, age, EH grade and EH duration, in which the p values were more than 0.05. The comparison of data of men in the CAS group and in the non-CAS group showed no significant differences (P>0.05). When compared with the same group (the CAS group age greater than 70 years, an EH grade more than 2, and an EH duration more than 5 years), the differences were statistically significant (P<0.05, shown in Table 2).

Project	group CAS (195 case)	No CAS group (123 case)	P value	t
Male	99(50.77)	58(47.15)	0.530	0.39
smoke	161(82.56)	56(45.53)	Below 0.001	47.73
Diabetes	127(65.13)	36(29.27)	Below 0.001	38.82
Age			0.018	8.07
60~69 years	51(26.51)	48(39.02) [b]		
70~79 years	63(32.31) [a]	41(33.33) [a]		
Over 80 years	81(41.54) [b]	34(27.64)		
EH classification			Below 0.001	14.67
1 level	52(26.67)	51(41.46) [b]		
2 level	57(29.23) [a]	43(34.96) [a]		
3 level	86(44.10) [b]	29(23.58)		
EH course of disease			Below 0.001	37.16
Less than 5 years	31(15.90)	56(45.53) [b]		
5~9 years	46(23.59) [a]	27(21.95) [b]		
10~15 years	53(27.18) [b]	22(17.89) [a]		
Over 15 years	65(33.33) [b]	18(14.63)		

Table 2: The comparison of the basic data between the CAS group and the non-CAS group in EH patients [(figure)%].
Note: compared with the same group, [a]P less than 0.05, [b]P less than 0.01

Relationship between CAS plaques and serum markers in 3 groups of patients

Compared with the nonplaque group, the levels of FPG, TC, TG, LDL-C, Hcy, uric acid, ferritin, fib and CRP were significantly increased in the stable plaque and the unstable plaque groups, while the levels of TBIL, DBIL and IBIL were significantly decreased (P less than 0.05, P less than 0.01, shown in Table 3).

Logistic regression analysis

The stability of the CAS plaque acts as as dependent variable and the levels of FPG, TBIL, DBIL, IBIL, ALT, AST, TC, TG, LDL-C, HDL-C, Hcy, uric acid, ferritin, Fib, CRP, smoking and

age act as independent variables for the logistic regression analysis. The analysis results showed that CAS plaques were negatively correlated with serum levels of TBIL and IBIL and were positively correlated to levels of FPG, TC, LDL-C, Hcy, uric acid, ferritin, Fib, CRP, smoking, diabetes and hypertension (P<0.05, shown in Table 4)

project	No plaque group	stable plaque group	Unstable plaque group	F	P
	(123 cases)	(104 cases)	(91 cases)		
FPG (mmol/L)	5.72±2.15	6.41±2.24[a]	6.76±2.63[b]	5.62	0.004
TBIL (mol/L)	14.31±3.74	12.94±2.76[a]	10.62±3.01[b]	26.28	<0.001
DBIL (mol/L)	5.36±1.98	4.83±1.21[a]	4.36±1.03[b]	11.54	<0.001
IBIL (mol/L)	12.17±2.64	11.03±2.72[a]	9.47±1.98[b]	30.56	<0.001
ALT (U/L)	20.13±6.63	22.36±7.03	24.39±7.37	9.87	<0.001
AST (U/L)	20.97±8.24	22.03±7.85	22.98±6.95	1.78	0.171
TC (mmol/L)	4.73±1.86	5.24±2.01[a]	5.82±1.76[b]	8.78	<0.001
TG (mmol/L)	1.82±1.54	2.36±1.33[a]	3.51±1.82[b]	31.03	<0.001
LDL-C (mmol/L)	2.56±1.13	3.28±1.69[a]	3.94±2.03[b]	19.35	<0.001
HDL-C (mmol/L)	1.48±0.57	1.24±0.61[a]	1.03±0.46[a]	17.47	<0.001
Hcy (mol/L)	8.04±2.47	15.26±3.31[b]	18.91±3.98[b]	256.98	<0.001
Uric acid (mu mol/L)	267.24±38.33	311.28±37.27[a]	243.45±46.29[b]	71.81	<0.001
Ferritin (mu g/L)	201.29±21.62	237.81±35.77b	314.83±41.29[b]	314.74	<0.001
Fib (g/L)	4.07±2.44	5.91±2.36a	6.84±2.13[b]	39.83	<0.001
CRP (mg/L)	7.04±1.95	8.25±2.18a	10.43±2.62[b]	60.63	<0.001

Table 3: The CAS plaques and the serum markers were compared between the three groups (x±s).
Note: compared with the nonplaque group, [a]P less than 0.05, [b]P less than 0.05

Independent variable	B value	SE	OR value	95% CI	P
TBIL	-0.158	0.031	0.71	0.54~0.92	0.034
IBIL	-0.176	0.037	0.62	0.35~0.96	0.023
FPG	0.058	0.071	1.43	1.18~2.25	0.041
TC	0.086	0.052	1.32	1.07~1.96	0.033
LDL-C	0.045	0.056	1.48	1.06~2.64	0.037
Hcy	0.039	0.064	1.52	1.03~3.83	0.021
uric acid	0.043	0.041	1.12	1.04~1.96	0.042
Ferritin	0.031	0.058	1.38	1.14~2.11	0.046
Fib	0.046	0.053	1.42	1.18~2.06	0.037
CRP	0.042	0.042	1.24	1.06~1.57	0.039
smoke	0.032	0.051	1.36	1.03~1.94	0.047
Diabetes	0.063	0.082	1.23	1.11~1.65	0.041
Hypertension	0.062	0.074	1.18	1.01~1.46	0.043

Table 4: The CAS plaques and the serum markers were compared between the three groups (x±s).
Note: compared with the nonplaque group, [a]P less than 0.05, [b]P less than 0.05

Discussion

The formation of CAS is related to many factors that may be predictors of its occurrence, such as blood pressure, blood lipids, blood sugar and other factors[13].

In this study, the incidence of CAS in elderly EH patients was 63.40%. The incidence of CAS was related to age, EH grade, EH duration, smoking, FPG, and blood lipids, among other factors. As age and the duration of hypertension increased, the grade of hypertension increased and the proportion of CAS occurrence gradually increased, with the differences being statistically significant. Early detection of high blood pressure and active control of blood pressure, blood lipids and blood sugar as well as a light diet, reasonable exercise, smoking cessation and other lifestyle interventions can help delay the progression of atherosclerosis. Atherosclerosis is also closely related to a variety of serum markers. Hcy has a stimulating effect on a variety of active cellular substances, such as cytokines and proteins, which can aggravate damage by these substances to the blood vessel wall and can promote the deposition of Fib and thrombi in the blood vessel wall. It stimulates the damaged smooth muscle to overgrow, undergo fibrosis and harden, and promotes the formation of foam cells and aggravation of atherosclerosis. Hcy can also cause the release of free radicals, which then cause the degradation of elastic fibers, the thickening of blood vessel walls, and the narrowing of lumens[14].

The important coagulation factor and inflammatory factor Fib is cleaved into fibrin monomers, which are then aggregated into the thrombus, greatly influencing platelet aggregation, vascular endothelial cells, coagulation, etc. Meanwhile, Fib elevation can activate coagulation factor (VII), leading to increases in blood coagulability and platelet aggregation. Elevated Fib levels also produce fibrin degradation products, which are constantly deposited in the vascular wall. On one hand, elevated levels of Fib directly destroy vascular endothelial cells, thus promoting the proliferation and migration of smooth muscle cells, which is conducive to the infiltration and accumulation of lipids. Conversely, it can regulate the adhesion and migration of inflammatory cells and can stimulate endothelial cells and inflammatory cells to secrete various inflammatory factors and active substances to induce the body's inflammatory and immune responses. These processes aggravate the processes of atherosclerosis and promote plaque formation, growth and rupture, leading to increased vulnerability. The levels of Fib are inversely proportional to the thickness of the fibrous cap, and an abnormal thickness of fibrous cap can lead

to plaque rupture and thrombosis. Therefore, Fib is a sensitive indicator for predicting subclinical atherosclerosis and may act as an independent severity predictor of coronary atherosclerosis. It is evident that inflammation and oxidative stress are involved in the atherosclerotic process[15-17].

In this paper, the serum parameters (FPG, TC, TG, LDL-C, Hcy, uric acid, ferritin, Fib and CRP) in the stable plaque group were significantly higher than those in the nonplaque group, and the same result is true for the unstable plaque groups. Logistic regression analysis showed that CAS plaques were positively correlated with FPG, TC, LDL-C, Hcy, uric acid, ferritin, Fib, CRP, smoking, diabetes, and hypertension, which is consistent with related studies[13]. This indicates that there is high inflammation and oxidative stress in the unstable plaque population. Plaques can easily lead to rupture and acute cardiovascular events. In clinical work, serum marker analysis should be emphasized to identify the risk of atherosclerosis. Early intervention and active control of blood pressure, blood sugar and blood lipids can reduce the incidence of acute events. In this study, the uric acid contents of the stable plaque group and the unstable plaque group were higher than those of the nonplaque group, and the unstable plaque group had the highest uric acid content, which is consistent with the results of Zhang Yandi et al[18].

Bilirubin is an effective antioxidant with endogenous reducing abilities, and can effectively scavenge oxygen free radicals, prevent low-density lipoprotein oxidative modification, facilitate cholesterol dissolution and discharge, inhibit inflammatory reactions, protect endothelial cells, and gather antiplatelets. It can also weaken the immune responses involved in complement pathways by reducing the complement activity and effectively preventing the occurrence of atherosclerosis, which is a protective factor for cardiovascular and atherosclerotic diseases[19-20].

This study showed that patients with unstable plaques had lower serum TBIL and IBIL. A logistic regression analysis showed that the levels of TBIL and IBIL were negatively correlated with CAS plaques. It is speculated that serum bilirubin may have protective effects for atherosclerosis, which is consistent with results from Kawamoto[21]). Approximately 80% of arteriosclerotic thromboses are caused by ruptures of arterial plaques in mild to moderate stenosis and secondary thrombosis situations.

Thus, the early detections of unstable plaques and early interventions can prevent heart disease (such as coronary heart disease)[22]. This article aimed to study the relationship between CAS and serum markers in elderly EH patients. Clinically, the serum marker and carotid color ultrasound results can be used to comprehensively determine the occurrence and development of CAS plaques and to identify high-risk groups early. By using lifestyle interventions, by actively controlling blood pressure, blood sugar, blood lipids and uric acid, as well as strengthening smoking cessation techniques in high-risk groups, the incidences of acute cardiac events (such as coronary heart disease) can be reduced. Limitations were present in this study, including the low sample size and the retrospective nature of this case analysis. Therefore, a larger sample and a prospective observational study are needed in the future.

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