THE RELATIONSHIP BETWEEN SERUM HOMOCYSTEINE LEVELS, INFLAMMATORY RESPONSE AND PLAQUE STABILITY IN PATIENTS WITH H-TYPE HYPERTENSION AND CAROTID ATHEROSCLEROSIS

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ABSTRACT

Objective: *To analyse the relationship between serum homocysteine levels, inflammatory response and plaque stability in patients with H-type hypertension and carotid atherosclerosis.*

Methods: *From February 2021 to May 2022, a total of 1,500 registered households in Baoding, China were surveyed. The results showed that 600 cases displayed high risk of H-type hypertension, of which 100 cases were directly diagnosed with H-type hypertension or transient cerebral ischemia. A questionnaire was carried out among the selected cases. According to the management methods of the pilot project of screening and intervention for groups at high risk of H-type hypertension, a questionnaire regarding multiple risk factors was developed. These factors included hypertension, real estate and heart valve disease, smoking, dyslipidemia, diabetes and so on.*

Results: *Risk factors for plasma homocysteine include smoking and diabetes, and risk factors for carotid plaque include diabetes, hypertension, LDL-C abnormalities and plasma homocysteine. Through Pearson linear analysis, serum homocysteine levels in patients with H-type hypertension were positively correlated with HCGP-39, TNF-α, Hs-CRP, IL-1β, PTX3 and Lp-PLA2 and negatively correlated with TBIL, DBIL and IBIL.*

Conclusion: *In the community medical system, it is important to implement prevention and treatment of H-type hypertension among high-risk populations, pay attention to the relationship between plasma homocysteine and blood lipid levels and practice timely prevention and early intervention regarding carotid plaque.*

Keywords: *H-type hypertension, high-risk population, homocysteine, carotid plaque, correlation, risk factors.*

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Introduction

In recent years, many studies have defined serum homocysteine levels of over 10 μmol/L as indicative of H-type hypertension. Atherosclerosis itself is a major complication of hypertensive patients; thus, many studies have suggested that the incidence of carotid artery disease in patients with H-type hypertension is higher than that of ordinary hypertensive patients, and carotid atherosclerotic lesions are relatively more serious[(1)]. Carotid atherosclerosis may lead to carotid stenosis, reduced blood supply to the brain tissue and severe stroke. Carotid angiography is a direct way to determine the severity of carotid atherosclerosis, but this examination method is invasive and not suitable for long-term follow-up. Therefore, it is very important to develop a serological index to achieve symptom judgment[(2)]. Homocysteine is categorised among sulfur-containing amino acids, which are products of methionine formed in metabolism. The concentration of homocysteine in plasma is generally less than 15 μmol/. When homocysteine levels surpass this amount, hyperhomocysteinemia occurs. There is

a direct correlation between homocysteine and vascular lesions[3-4].

In order to improve the quality of clinical diagnosis and treatment, this article summarises the correlation between homocysteine and carotid plaque as well as the corresponding risk factors by taking some patients in our hospital as an example. The specific contents are as follows.

Methods

General information

The study was conducted from February 2021 to May 2022. During this period, a total of 1,500 households registered in Baoding were selected for a questionnaire survey.

The results showed that 600 patients were at high risk for H-type hypertension, and 100 of these were directly diagnosed with H-type hypertension or transient cerebral ischemia. Physical examinations were performed on individuals selected from the high-risk group. The project involved laboratory examinations, physical examinations and carotid ultrasound examinations.

The inclusion criteria were as follows:

- No serious organ failure or mental illness;
- Agreed to this study and signed research participation agreement;
- Displayed cerebral infarction via head MRI and computed tomography;
- Met the WHO criteria for diagnosis of essential hypertension;
- Displayed high blood pressure for over six months.

The exclusion criteria included:

- Did not participate in physical examination according to regulations;
- Displayed secondary hypertension;
- Displayed type 1 or type 2 diabetes;
- Displayed severe heart, liver or kidney dysfunction;
- Displayed acute systemic infection;
- Displayed malignant disease;
- Displayed serious immune disease.

Methods

A questionnaire survey was conducted on these selected cases, and a number of risk factor questionnaires were developed in accordance with the management methods for screening and intervention pilot projects for populations at high risk of H-type hypertension. Risk factors include hypertension, real estate and valvular heart disease, smoking, dyslipidemia, diabetes and others. The physical examination primarily involved the calculation of the patient's BMI (body weight/height2). Subjects were asked to maintain a 12-hour fast, blood was taken from the external elbow vein to perform blood lipid examination and plasma homocysteine was determined by the cyclic enzyme method. Total cholesterol levels of ≥5.2mmol/L, triglyceride levels of ≥2.26mmol/L, low-density lipoprotein cholesterol levels of ≥ 3.36mmol/L and high-density lipoprotein cholesterol levels of <1.04mmol/L are considered abnormal and meet the definition of high lipemia. Homocysteine levels of ≥15 μmol/L qualify as hyperhomocysteinemia.

All patients underwent cervical ultrasonography, and the ultrasound diagnostic apparatus produced by GE was used to perform cervical vascular ultrasound examination on selected cases. A 6 to 12 MHz linear array probe was used, and the neck was exposed in the supine position.

The probe was placed in the neck, and lateral and longitudinal section examinations were performed at the beginning of the innominate artery, the right side and the common carotid artery.

Observation indicators

On the first day after the patient was admitted to the hospital, 2 ml of fasting venous blood was taken. Heparin was administered continuously for 30 minutes after anticoagulation and then centrifuged for 10 minutes at low speed. The supernatant was then taken, and various data indicators were measured.

Specific indicators include human cartilage glycoprotein-39 (HCGP-39), tumour necrosis factor alpha (TNF-α), hypersensitive C-reactive protein (hs-CRP), interleukin-1β (IL-1β), lipid protein-related phospholipase (LP-PLA2), total bilirubin (TBIL), direct bilirubin (DBIL) and indirect bilirubin (IBIL).

Statistical methods

The patient's basic data and observation indicators from this study were statistically analysed using SPSS software.

Quantitative and qualitative processing was performed after data entry, and data were entered as either discrete or continuous. Classification processing was not applied to qualitative data.

The data processing aspect was statistically judged using a p-value of <0.05. The percentage data were tested using x^2, and the mean data was tested using t-value data.

Results

General situation

In this study, the average age among the 600 high-risk participants was (64.2±3.5) years old. The sample contained 347 male patients and 253 female patients. 221 male patients (36.83% of total sample) were hyperhomocysteinemic, and 121 male patients (20.17% of total sample) displayed carotid plaque. 71 female patients were hyperhomocysteinemic (11.83% of total sample), and 85 (14.17% of total sample) displayed cases of carotid plaque.

Risk factors

Risk factors for plasma homocysteine include smoking and diabetes, and carotid plaque risk factors include diabetes, hypertension, LDL-C abnormalities and plasma homocysteine. See Table 1 for detailed data.

Group	Plasma homocysteine		Carotid plaque	
	High (n=292)	Normal (n=308)	Yes (n=206)	None (n=394)
Smoking	161 (55.14%)*	89 (28.90%)	81 (39.32%)	146 (37.06%)
Diabetes	165 (56.51%)*	80 (25.97%)	62 (30.10%)#	81 (20.56%)
Hypertension	251 (85.96%)	248 (80.52%)	182 (88.35%)#	321 (81.47%)
Hyperlipidemia	222 (76.03%)	221 (71.75%)	105 (50.97%)	213 (54.06%)
TC abnormality	121 (41.44%)	120 (38.96%)	121 (58.74%)	234 (59.39%)
TG anomaly	46 (15.75%)	50 (16.23%)	120 (58.25%)	230 (58.38%)
HDL-C anomaly	132 (45.21%)	136 (44.16%)	42 (20.39%)	82 (20.81%)
LDL-C anomaly	151 (51.71%)	156 (50.65%)	100 (48.54%)#	161 (40.86%)
BMI	25.84±2.46	25.94±3.40	25.46±3.33	26.14±3.23
Plasma homocysteine	17.25±6.25	5.12±2.14	17.65±8.54#	7.50±7.21

Table 1: Risk factor n (%).

*Note: *represents a significant difference between patients with hyperhomocysteinemia and normal patients, and #represents a significant difference between patients with carotid plaque lesions and normal patients. The data fulfilled statistical criteria ($p<0.05$).*

Relationship between serum homocysteine content, inflammatory factors and plaque stability in patients with H-type hypertension

Through Pearson linear analysis, serum homocysteine levels in patients with H-type hypertension were found to be positively correlated with HCGP-39, TNF-α, Hs-CRP, IL-1β, PTX3 and Lp-PLA2, while TBIL, DBIL and IBIL demonstrate negative correlation with serum homocysteine levels in patients with H-type hypertension. Detailed data is provided in Table 2.

Index	Coefficient of determination	p-value
HCGP-39	0.689	0.005
TNF-α	0.673	0.017
Hs-CRP	0.661	0.020
IL-1β	0.694	0.008
PTX3	0.673	0.015
Lp-PLA2	0.692	0.010
TBIL	-0.659	0.017
DBIL	-0.689	0.013
IBIL	-0.708	0.005

Table 2: Relationships between multiple indices.

Discussion

H-type hypertension has been confirmed to be an independent influencing factor for coronary heart disease by many studies. It has also been found to be a susceptibility factor for stroke incidence in patients with H-type hypertension in recent years, and the incidence of malformation cerebral infarction in patients with H-type hypertension is much higher than that of ordinary hypertensive patients, which proves that serum cysteine is an important influencing health factor[5]. Cerebral infarction is mainly caused by the occlusion of intracranial and extracranial vessels. Most current research focuses on the relationship between serum cysteine and intracranial arteries, basilar arteries and other forms of intracranial large vessel atherosclerosis.

There are few studies on arteries and other extracranial blood vessels[6]. The carotid artery is one of the main arteries that supply blood to the brain. Severe carotid intima thickening and stenosis can cause cerebral infarction in patients. At this time, many studies have proved that serum cysteine levels contribute to the development of carotid atherosclerosis. However, there is currently not much research on the role of H-type hypertension in the development of carotid atherosclerosis[7].

Carotid plaque is an independent predictor of cardiovascular disease, and it has several common risk factors[8]. Three risk factors were included in this study. Additionally, studies have shown that patients with H-type hypertension display significantly higher plasma homocysteine levels than normal, which also indirectly demonstrates that hyperhomocysteinemia and the occurrence and development of H-type hypertension are closely related[9]. In this regard, the timely implementation of plasma homocysteine monitoring and intervention in patients at high risk of H-type hypertension is of great significance and

value. In terms of the inflammatory mechanism of the pathogenesis of atherosclerosis, many studies on the subject have reached a general consensus. Bioinflammation, immune inflammation and chemical inflammation are all factors that directly influence the progression of atherosclerosis, among which chemical inflammation is the most closely related. The most in-depth study involves inflammatory cytokines, inflammatory mediators, adhesion media and channelisation factors[10]. HCGP-39, TNF-α, hs-CRP and IL-1β are all common inflammatory cytokines. In recent years, studies have suggested that inflammatory cytokines are risk factors for atherosclerosis and important prognostic indicators. The results of the test can be directly applied to the objective evaluation of atherosclerosis and long-term cardiovascular events. Plaque stability is an effective objective indicator of the severity of atherosclerosis. Unstable plaque in the carotid artery is prone to rupture, and acute cerebral infarction is also a possibility. Therefore, the plaque stability test is one of the most reliable ways to identify atherosclerosis and attain a prognosis[11].

The results of this study show that risk factors for plasma homocysteine include smoking and diabetes, and carotid plaque risk factors include diabetes, hypertension, HLD-C abnormalities and plasma homocysteine. The results of this study essentially confirm that the risk factors for hyperhomocysteinemia include smoking and diabetes, and the formation of carotid plaque is directly related to diabetes, hyperlipidemia and LDL-C abnormalities. In clinical settings, it is imperative to detect high-risk individuals in a timely manner, minimise cardiovascular risk factors, control the lipid and homocysteine levels in patients, slow the formation of carotid plaque and improve clinical intervention levels[12]. Another study using Pearson linear analysis shows that serum homocysteine levels in patients with H-type hypertension were positively correlated with HCGP-39, TNF-α, Hs-CRP, IL-1β, PTX3 and Lp-PLA2. TBIL and negatively correlated with DBIL and IBIL. This result indicates that inflammatory cytokines are directly involved in the development of atherosclerosis, and systemic inflammatory responses in H-type hypertensive patients are more severe than in ordinary hypertensive patients, which may lead to the aggravation of carotid atherosclerosis due to plaque instability. Some studies have found many acute response proteins and lipoproteins in ruptured plaques, among which PTX3 and LP-PLA2 are important indicators of plaque instability[13]. In addition, some studies also believe that a low concentration of red protein is an independent risk factor for coronary heart disease. The serum bilirubin level can be directly used as an objective indicator of coronary plaque stability. From the above results, it is clear that high levels of PTX3 and LP-PLA2, as well as low levels of TBIL, DBIL and IBIL, are important indicators of patients with H-type hypertension[14].

Both inflammatory factors and plaque stability indicators can directly influence the severity of atherosclerosis. Some scholars believe that the mechanism of plasma homocysteine promoting atherosclerosis is similar[15]. Correlation analysis shows that plasma homocysteine content, inflammatory factors and plaque stability indicators are directly related to H-type hypertensive patients, and high levels of plasma homocysteine may be caused by inflammatory factors. The regulation of the plaque stability index can influence the progression of atherosclerosis, which is a major factor in the aggravation of carotid atherosclerosis in patients with H-type hypertension[16].

Conclusion

In summary, plasma homocysteine elevation is a major contributor to the severity of hypertensive carotid atherosclerosis and plaque instability in patients with H-type hypertension. In the community medical system, it is imperative to raise awareness for the timely prevention and treatment of populations at high risk of H-type hypertension, with a focus on the examination of plasma homocysteine and blood lipid levels, as well as timely prevention and early intervention regarding carotid plaque.

References

1) Cainzos-Achirica M, Acquah I, Dardari Z, Mszar R, Greenland P, et al. Long-Term Prognostic Implications and Role of Further Testing in Adults Aged ≤55 Years with a Coronary Calcium Score of Zero (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol 2021; 161: 26-35.

2) Liu M, Zhang H, Wang G. Hyperhomocysteinemia Promotes Carotid Artery Damage in Newly Diagnosed Type 2 Diabetic Patients without Hypercholesterolemia. Metab Syndr Relat Disord 2021; 19(10): 575-80.

3) Ye J, Wang Y, Wang Z, Lin Y, Liu L, et al. Circulating IL-37 Levels Are Elevated in Patients with Hypertension. Exp Ther Med 2021; 21(6): 558.
4) Tan Y, Nie F, Wu G, Guo F, Wang Y, et al. Impact of H-Type Hypertension on Intraplaque Neovascularization Assessed by Contrast-Enhanced Ultrasound. J Atheroscler Thromb 2021 Apr.
5) Wang Y, Li B, Jiang Y, Zhang R, Meng X, et al. YKL-40 Is Associated With Ultrasound-Determined Carotid Atherosclerotic Plaque Instability. Front Neurol 2021; 12: 622869.
6) Guo J, OuYang L, Wang X, Liao W, Huang Q, et al. Preliminary Study of Subclinical Brain Alterations in Patients with Asymptomatic Carotid Vulnerable Plaques Using Intravoxel Incoherent Motion Imaging by Voxelwise Comparison: A Study of Whole-Brain Imaging Measures. Front Neurosci 2020; 14: 562830.
7) Zhou F, Hua Y, Ji X, Jia L. A Systemic Review into Carotid Plaque Features as Predictors of Restenosis after Carotid Endarterectomy. J Vasc Surg 2021; 73(6): 2179-88.e4.
8) Spence JD. Management of Asymptomatic Carotid Stenosis. Ann Transl Med 2020; 8(19): 1262.
9) Jing-Hui H, Di Z, Ke X, Hai-Yan Y. [Effect of Xiaoji Recipe on Stability of Carotid Artery Vulnerable Plaque in Elderly Patients with Type 2 Diabetes Mellitus and Type H Hypertension]. Zhongguo Zhong Yao Za Zhi 2020; 45(17): 4246-53. Chinese.
10) Li L, Ma X, Zeng L, Pandey S, Wan R, et al. Impact of Homocysteine Levels on Clinical Outcome in Patients with Acute Ischemic Stroke Receiving Intravenous Thrombolysis therapy. PeerJ 2020; 8: e9474.
11) Azarpazhooh MR, Andalibi MSS, Hackam DG, Spence JD. Interaction of Smoking, Hyperhomocysteinemia, and Metabolic Syndrome with Carotid Atherosclerosis: A Cross-Sectional Study in 972 Non-Diabetic Patients. Nutrition 2020; 79-80: 110874.
12) Ben Z, Wang J, Zhan J, Li X, Ruan H, et al. Characteristics of the Carotid Plaque in Hypertensive Patients with Hyperhomocysteinemia Using Multimode Ultrasound. J Stroke Cerebrovasc Dis 2020; 29(8): 104925.
13) Song Y, Dang Y, Cai H, Wang J, Liu B, et al. Carotid Intraplaque Neovascularization Predicts Atherosclerotic Renal Artery Stenosis in Patients with Carotid Artery Stenosis. Nutr Metab Cardiovasc Dis 2020; 30(9): 1492-9.
14) Bosevski M, Zlatanovikj N, Petkoska D, Gjorgievski A, Lazarova E, et al. Plasma Homocysteine in Patients with Coronary and Carotid Artery Disease: A Case Control Study. Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2020; 41(1): 15-22.
15) Spence JD. Stroke Prevention: A Lifetime of Lessons. Stroke 2020; 51(7): 2255-62.
16) Kozakova M, Morizzo C, Penno G, Shore AC, Nilsson J, et al. Plasma Homocysteine and Cardiovascular Organ Damage in a Population with a High Prevalence of Risk Factors. J Clin Endocrinol Metab 2020; 105(8): dgaa289.

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