Serum Homocysteine as One of the Risk Factors of Cerebral Small Vessel Disease in Chinese Patients

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Abstract

Objective: This study aimed to determine the risk factors of cerebral small vessel disease (CSVD) from different variables including serum homocysteine (Hcy) in a group of Chinese patients.

Methods: A total of 139 patients with CSVD admitted to the affiliated hospital of Xuzhou Medical University from July 2017 to July 2018 were enrolled. Fifty healthy individuals were selected as controls. According to the diagnostic criteria, the CSVD patients were divided into three groups, namely, lacunar infarction (LI) group (n=59), white matter lesion (WML) group (n=46), and LI+WML group (n=34). The serum Hcy levels of the three groups were observed and compared. Multivariate logistic regression was performed to determine whether a number of variables including serum Hcy level are the risk factors of CSVD.

Results: Hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), fasting blood glucose (FBG), and Hcy were significantly higher in CSVD group than the control group (P < 0.05). The age, gender, SBP, platelet, TG, and Hcy were significantly different between the LI group, WML group, and LI+WML group (P<0.05). The age and Hcy level of patients in LI+WML group were higher than those of the LI group and WML group, and the difference was statistically significant (P < 0.05). The level of SBP was higher in the LI group than the WML group (P < 0.05). The Hcy level of patients in the LI group was higher than that in the WML group, but there was no significant difference (P > 0.05). The platelet and TG were significantly higher in WML group than LI group and LI+WML group (P < 0.05). Controlling the influence of sex and age, multivariate logistic regression analysis revealed that the Hcy levels were correlated with the incidence of the CSVD.

Conclusion: Serum Hcy level is a risk factor for CSVD. Regular detection of serum Hcy level and timely intervention may effectively prevent and control the occurrence and development of CSVD.

Keywords: Cerebral small vessel disease; Serum homocysteine; Lacunar infarction; White matter lesion

1 Introduction

CSVD is an ischemic or hemorrhagic lesion of white matter and gray matter caused by cerebral capillaries, arterioles, and venules due to various reasons [1]. Its clinical manifestations are diverse but lack of specificity. Its diagnosis mostly relies on neuroimaging findings, which is mostly manifested as lacunar infarction, white matter lesions (WMLs), cerebral microbleeds, enlarged Virchow-Robin spaces, and brain atrophy.

Lacunar infarcts have been linked with small vessel disease, which is caused by lipohyalinosis or fibrinoid necrosis of small arteries or
arterioles supplying the deep subcortical brain structures [2]. WMLs or hyperintensities, characterized by a hyperintense signal on T2-weighted magnetic resonance imaging (MRI), are common findings in older adults. These lesions are usually located in the deep white matter and around the lateral ventricle [3].

Epidemiology of all strokes worldwide reveals that CSVD cases account for up to 25%, and the CSVD cases in China accounts for about 50% of all ischemic strokes, especially in the elderly. In recent years, with the aggravation of population aging and the high incidence of risk factors of cerebrovascular diseases, the incidence rate of CSVD is increasing. At the same time, the rapid development of neuroimaging technology enables increased detection rate of CSVD [4-6]. CSVD also increases the risk of several different types of stroke, which is an important factor in patients with cognitive decline, affective disorders, gait abnormalities, etc. [7]. According to the previous literature, about 45% of dementia is caused by the CSVD, which puts a heavy burden on families and society.

Hcy is a sulfur-containing amino acid and an important product of the methionine metabolism. The serum Hcy levels in healthy human are very low [8]. In recent years, studies found that Hcy is an independent risk factor for cardiovascular and cerebrovascular diseases [9], especially stroke. In addition, several studies suggest that high Hcy is a risk factor for cerebral infarction [10]. In this study, a total of 139 patients with CSVD admitted to the affiliated hospital of Xuzhou Medical University were enrolled for determining the risk factors of CSVD.

2 Methods

2.1 Study participants

A total of 139 participants with CSVD were recruited in the affiliated hospital of Xuzhou Medical University from July 2017 to July 2018. Among them, there were 73 male patients and 66 female patients who were aged from 38 to 88 years, with an average age of 68.07 ± 9.62 years. There were 121 patients with hypertension and 95 patients with coronary heart disease.

Both lacunar infarction (LI) and WML which are the imaging findings of CSVD are associated with high homocysteine levels [11]. In view of this, the patients were divided into three groups according to the imaging findings by two experienced chief neurologists trained in neuroimaging in the affiliated hospital of Xuzhou Medical University. There were 59 CSVD cases in the LI group, 46 cases in the WML group, and 34 cases in the LI+WML group. These patients were examined by 1.5T MRI. The diagnosis of LI is confirmed with the presence of round or oval infarcts which are 3–15 mm in diameter, distributed under the cortex, and contained same signal as cerebrospinal fluid. The T2 fluid-attenuated inversion recovery (FLAIR) manifest a low, central cerebrospinal fluid-like signal with a high signal loop around the LI. It can also be manifested as a high signal on T2-FLAIR, but as a cerebrospinal fluid-like signal at T1, T2, and other sequences, mainly distributed in the lenticular nucleus, thalamus, frontal white matter, pons, base, internal capsule, and caudate nucleus. On the other hand, the diagnosis of WML is confirmed with abnormal signal in the white matter, but the lesion can vary in a range of sizes. WML is usually located in the deep white matter and around the lateral ventricle. The imaging manifestation of WML also includes high signal on T2 or T2 FLAIR sequence and equal or low signal on T1. Depending on the sequence parameters and severity of lesion, WML would show no cavity whose signal is different from the cerebrospinal fluid.

Patients with the following conditions were excluded from the study: (1) Cardiac embolism which leads to large atherosclerosis in LI patients, (2) diseases that may cause WML including autoimmune diseases, multiple sclerosis, and tumors, (3) severe heart disease, liver, and kidney failure, (4) recent intake of vitamins and other drugs that affect serum Hcy levels, and (5) conditions that deter patients from undergoing MRI examination. Fifty healthy individuals who were aged >18 years were selected from the physical examination center of the affiliated hospital. These individuals underwent nuclear magnetic resonance examination to determine the presence of CSVD and those who do not have CSVD were referred to as healthy controls in this study.

The study was approved by the Ethics Committee of the affiliated hospital of Xuzhou Medical University (Code: 2017-079-01). Data including age, gender, height, weight, smoking history,
drinking history, history of cardiovascular and cerebrovascular disease, hypertension, diabetes, and lipid metabolism disorders were collected from the patients. This study is in line with the Declaration of Helsinki, and the informed consent was obtained from patients or their family members before enrolment.

2.2 Detection of biochemical indicators

All participants were given low-fat diet meal on the night after admission. In the next morning, 5 ml of fasting venous blood was taken from patient arm. The biochemical parameters such as blood glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and uric acid were measured using an automatic biochemical analyzer (Model 7600 Swiss Roche). The formula for calculating glomerular filtration rate (GFR) [12] was as follows:

\[
GFR \ (\text{mL/min/1.73 m}^2) = 186 \times (\text{Scr})^{-1.154} \times (\text{Age})^{0.203} \times (0.742 \text{ if female})
\]

2.3 Homocysteine detection

Fasting blood samples were centrifuged to separate the serum and clot 60 min after sample collection. The serum was separated by centrifugation at 3000 rpm for 10 min at 4°C. All the samples were tested in the hospital’s laboratory, and the Hcy special kit provided by Shenzhen Aosa Pharmaceutical Co., Ltd. was used. Hcy reference range is 0–10 µmol/L, whereby a serum Hcy level >10 µmol/L is diagnosed as hyperhomocysteinemia in the patient.

2.4 Statistical analysis

Statistical analysis was performed using SPSS19.0 statistical software. The data were expressed as mean ± standard deviation. Independent sample \(t\)-test was used for comparison between two groups. One-way ANOVA was used for multigroup comparison. Chi-square test was used to compare the count data. Multivariate logistic regression analysis was carried out to determine the risk factors of CSVD from a number of variables including serum Hcy by considering all 139 patients with CSVD in this study. \(P < 0.05\) was considered statistically significant. All data conform to normal distribution.

3 Results

3.1 Comparison of clinical data between CSVD group and control group

This study found that there was no significant difference in age, gender, platelet, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), uric acid (UA), and GFR between the

| Research factor | CSVD group (n=139) | Control group (n=50) | \(\chi^2/F\) | \(P\) |
|-----------------|-------------------|---------------------|------------|------|
| Age (years)     | 68.07±9.62        | 68.12±10.05         | 0.001      | N.S. |
| Male/female     | 73/66             | 28/22               | 0.179      | N.S. |
| Hypertension (%)| 127 (91.37)       | 15 (30.00)          | 74.119     | <0.001|
| SBP (mmHg)      | 150.15±18.98      | 125.65±17.56        | 63.675     | <0.001|
| DBP (mmHg)      | 87.62±11.57       | 78.52±10.83         | 23.511     | <0.001|
| Platelet (×10^9/L) | 231.27±60.55   | 226.51±57.49        | 0.233      | N.S. |
| TC (mmol/L)     | 4.70±1.06         | 4.51±1.03           | 1.199      | N.S. |
| LDL-C (mmol/L)  | 2.73±0.94         | 2.17±0.63           | 15.252     | <0.001|
| HDL-C (mmol/L)  | 1.25±0.30         | 1.32±0.42           | 1.600      | N.S. |
| TG (mmol/L)     | 1.75±0.82         | 1.26±0.78           | 13.467     | <0.001|
| FBG (mmol/L)    | 5.30±1.61         | 4.68±0.75           | 6.861      | <0.05 |
| Hcy (umol/L)    | 19.34±10.68       | 6.35±3.51           | 70.993     | <0.001|
| UA (umol/L)     | 264.58±65.79      | 257.25±63.85        | 0.464      | N.S. |
| GFR (ml/min)    | 117.62±33.85      | 113.56±32.59        | 0.539      | N.S. |

N.S., not significant; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FBG, fasting blood glucose; Hcy, serum homocysteine; UA, uric acid; GFR, glomerular filtration rate.
CSVD group and the control group \((P > 0.05)\). Hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein cholesterol (LDL-C), TG, fasting blood glucose (FBG), and Hcy were significantly higher in CSVD group than in the control group \((P < 0.05)\) (Table 1).

3.2 Comparison of observational indicators of three groups of patients

The present study found that the age, gender, SBP, platelet, TG, and Hcy were significantly different between LI group, WML group, and LI+WML group \((P < 0.05)\). The age and Hcy level of patients in the LI+WML group were significantly higher than those in the LI group and WML group \((P < 0.05)\). SBP was higher in the LI group than WML group \((P < 0.05)\). The Hcy level of patients was higher in the LI group than WML group, but there was no significant difference \((P > 0.05)\). The platelet and TG in WML group were significantly higher than those in LI group and LI+WML group \((P < 0.05)\) (Table 2).

3.3 Multivariate logistic regression analysis of CSVD

In this study, multivariate logistic regression analysis was performed using a number of variables such as hypertension, Hcy, TG, and LDL-C as independent variables, and CSVD as the dependent variables, controlling the influence of sex and age. We found that hypertension (OR=5.27, 95% CI=2.26–10.59, \(P < 0.01\)), Hcy level (OR=1.14, 95% CI=1.07–1.21, \(P < 0.01\)), TG (OR=1.05, 95% CI: 1.02–1.08, \(P < 0.01\)), and LDL-C (OR=1.06, 95% CI=1.03–1.10, \(P < 0.01\)) were correlated with the occurrence of CSVD (Table 3). These results were consistent with those in Table 1.

4 Discussion

CSVD is an insidious cerebrovascular disease. The pathological changes of blood vessels including the arterioles with a diameter of 30–300 μm, namely, cerebellar vessels, including those capillaries supplying gray matter nuclei and deep white matter, and small brain stems. The wall of these small arteries is mainly composed of endothelial cells and a small number of smooth muscle cells and is in direct contact with astrocyte synapses, but these capillaries generally have no collateral anastomosis \([13,14]\). The incidence of CSVD is largely unknown and has various clinical manifestations. Its diagnosis mainly depends on imaging changes.

The common hazard factors for CSVD are old age, hypertension, diabetes, and hyperhomocysteinemia, such as hypertension, Hcy, TG, and LDL-C as independent variables, and CSVD as the dependent variables, controlling the influence of sex and age. We found that hypertension (OR=5.27, 95% CI=2.26–10.59, \(P < 0.01\)), Hcy level (OR=1.14, 95% CI=1.07–1.21, \(P < 0.01\)), TG (OR=1.05, 95% CI: 1.02–1.08, \(P < 0.01\)), and LDL-C (OR=1.06, 95% CI=1.03–1.10, \(P < 0.01\)) were correlated with the occurrence of CSVD (Table 3). These results were consistent with those in Table 1.

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among which hyperhomocysteinemia is currently considered to be one of the important independent risk factors for cognitive impairment [15,16]. Hcy levels are affected by age, nutritional status, heredity, and renal function.

In this study, univariate analysis showed that there were no significant differences in gender, age, platelet, TC, HDL-C, UA, and GFR between CSVD group and control group (P > 0.05). Hypertension, SBP, DBP, LDL-C, TG, FBG, and Hcy were significantly higher in CSVD group than those in the control group (P < 0.05). Then, CSVD patients were divided into three groups: LI, WML, and LI+WML. We found that the age, gender, SBP, platelet, TG, and Hcy were significantly different between LI group, WML group, and LI+WML groups (P < 0.05). The age and Hcy level of patients with LI+WML group were higher than those of the LI group and WML group, and the difference was statistically significant (P < 0.05). The level of systolic blood pressure in the LI group was higher than that in the WML group (P < 0.05). The Hcy level of patients in the LI group was higher than that in the WML group, but there was no significant difference (P > 0.05). The platelet and TG in WML group were higher than that in the LI group, and LI+WML group, the difference was statistically significant (P < 0.05). Furthermore, multivariate logistic regression analysis showed that hypertension, Hcy level, TG, and LDL-C were all risk factors for CSVD.

The previous studies have shown that Hcy is significantly associated with age, indicating a sharp increase in Hcy levels with age, and Hcy levels are also significantly higher in men than in women [17,18]. These findings are consistent with the results of our study. Besides, Hcy is strongly associated with CSVD than other types of stroke [14], and LI is independently associated with the increase in Hcy levels [19]. The 2011 SMART-MA study found that Hcy levels were associated with the volume of white matter lesions [20]. Patients with both LI and WML exhibited higher levels of Hcy [21]. This is parallel to our results as shown in Table 2 that the Hcy level of patients in LI + WML group is significantly higher than that of LI group and WML group. Furthermore, it also implies a positive correlation between the level of Hcy and the severity of lesions in patients with CSVD. The present study found that the level of Hcy is correlated with the incidence of CSVD. However, the mechanism of hyperhomocysteinemia causing cardiovascular and cerebrovascular diseases remains to be elucidated [22]. The previous study showed that the increased levels of Hcy reduce the ratio of S-adenosylmethionine to S-adenosylhomocysteine during metabolism, resulting in hypomethylation of DNA, which prevents cell cycle G1/S phase conversion, leading to endothelial dysfunction and inhibition of vascular endothelial cell growth [23].

Apart from those findings, many articles in recent years have explained that dyslipidemia, especially low-density lipoprotein elevation, is considered to be one of the major risk factors for aortic atherosclerosis [24], which exacerbate the occlusion of various arterioles. Furthermore, LI is mainly caused by the occlusion of cerebral arterioles, overtime, which can be transformed into vascular-derived lacunar or ischemic white matter hyperintensity. The presence of LI indicates an increased risk of a severe stroke. Yet, another study shows that LI is closely related to atherosclerosis [25]. However, the outcomes of our study disclosed that TG in the WML group was higher than LI group and LI+WML group, the difference was statistically significant, while the differences in total cholesterol, low-density lipoprotein, and high-density lipoprotein were not statistically significant among the three groups.

### Table 3. Logistic multivariate regression analysis of CSVD

| Variable factor | β    | SE   | Wald | OR    | 95% CI       | P     |
|-----------------|------|------|------|-------|--------------|-------|
| Hypertension    | 1.67 | 0.38 | 16.28| 5.27  | 2.26–10.59   | <0.01 |
| Hcy level       | 0.13 | 0.07 | 13.23| 1.14  | 1.07–1.21    | <0.01 |
| TG              | 0.05 | 0.02 | 10.56| 1.05  | 1.02–1.08    | <0.01 |
| LDL-C           | 0.06 | 0.02 | 14.21| 1.06  | 1.03–1.10    | <0.01 |

Hcy, serum homocysteine; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol.
and these parameters were not relevant to the incidence of CSVD. This study helped determine the risk factors of CSVD, and with that, create patient’s awareness toward secondary prevention and long-term use of lipid-lowering drugs such as statin, and studies have shown that low-dose statins can prevent the onset of CSVD and delay its progression [26].

Consuming high-fat foods, excessive alcohol intake, and low intake of vegetables and fruit not only cause abnormal blood lipids but also cause an increase in Hcy levels. Therefore, a well-balanced diet is the basis for the prevention of CSVD. Supplementation of Vitamin B and folic acid as well as regular monitoring of serum Hcy levels were considered to be helpful in preventing CSVD, and thus, controlling these factors can effectively delay the disease progression [27]. In the present study, we found that the level of Hcy is correlated with the incidence of CSVD. Therefore, our study recommends that clinicians should prescribe folic acid, Vitamin B, and rational diet to reduce Hcy levels in patients with CSVD, in addition to regular monitoring of Hcy levels to observe the effect of said prescription in the patients.

In summary, hyperhomocysteinemia is an independent risk factor for CSVD. Therefore, the hazard of hyperhomocysteinemia should be given much attention in clinical practice, and timely intervention, pharmacologically and/or non-pharmacologically, might prevent the onset and progression of CSVD.

Lacunar infarction and white matter lesions were considered inpatient categorization in this study. However, other imaging findings that are common in CSVD patients, such as cerebral microbleeds and perivascular space expansion, have not been studied. It is necessary to conduct further multicenter, large sample, and long-term studies to draw further conclusions.

5 Conclusion

The level of serum Hcy is the relevant risk factor of CSVD. Regular detection of serum Hcy level and timely intervention can effectively prevent and control the occurrence and development of CSVD.

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Conflicts of interest

The authors declared that they have no conflicts of interest in this work.

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Author Contributions

YT and DG conceived and designed experiments; YT collected data; YT, SY, and BM carried out experiments; HD, BD, and YM helped to analyze the data results; and YT drafted the manuscript. All the authors read and approved the publication of the final manuscript.

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