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Elevated Homocysteine and C-reactive Protein Levels Independently Predict Worsening Prognosis after Stroke in Chinese Patients*

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Summary

Increased plasma total homocysteine (tHcy) and high sensitivity C-reactive protein (hsCRP) levels are independent risk factors for cardiovascular disease. However, the predictive value of tHcy in combination with hsCRP in patients with stroke is not known. To determine the relationship between tHcy and hsCRP, we enrolled 291 patients with first-onset stroke (196 ischemic and 95 hemorrhagic). Plasma tHcy and hsCRP levels were measured and subsequent vascular events and deaths were determined over a 5-year period. Using the arbitrary cutoff for tHcy (<18 μmol/L and 18 μmol/L) and hsCRP (<1 mg/L, 1–3 mg/L and >3 mg/L), the patients were divided into 6 groups. Survival analysis showed that the probability of death or new vascular events during a 5-year follow-up increased according to tHcy and hsCRP levels ($P<0.01$). The relative risk (RR) of death or new vascular events was 4.67 (95% CI, 1.96 to 11.14, $P=0.001$) in patients with high tHcy (>18 μmol/L) and hsCRP (>3 mg/L) compared with those with low tHcy (<18 μmol/L) and hsCRP (<1 mg/L). The increased tHcy level (>18 μmol/L) combined with increased hsCRP level (>3 mg/L) was still significantly associated with the risk of death or new vascular events (RR, 4.10, 95% CI, 1.61 to 10.45, $P=0.003$) even when adjusted for other risk factors at inclusion. The combination of increased tHcy and hsCRP levels had a stronger predictive value than increased hsCRP alone or increased tHcy level alone. Further studies are required to evaluate the potential decrease in risks associated with lowering both Hcy and hsCRP levels in patients that present with both increased tHcy and hsCRP.

Keywords

homocysteine; C-reactive protein; inflammation; stroke

Homocysteine (Hcy) is a sulfhydryl-containing amino acid derived from the essential amino acid methionine, which is abundant in animal sources of protein^[1]. The plasma total Hcy (tHcy) level varies in the range of 5–15 μmol/L in the normal population^[2]. Either minor genetic abnormalities or nutritional deficiencies of B vitamins such as folic acid involved in metabolism of methionine could lead to increased tHcy concentration. The involvement of

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homocysteine in atherosclerosis was first promulgated by McCully on the basis of his pathological findings in infants with hyperhomocysteinemia resulting from inborn metabolism deficiency^[3]. In experimental studies, homocysteine causes oxidative stress and vascular inflammation, damages endothelial cells, inhibits endothelium-dependent relaxation, and enhances thrombogenicity^[4–6]. A large body of epidemiological studies support that increased homocysteine level is an independent risk factor for vascular diseases, including stroke^[7–11].

Inflammation is an important contributor to cardiovascular disease^[12]. Several inflammatory markers such as soluble cell adhesion molecules, cytokines, chemokines, and acute phase reactants are associated with cardiovascular events^[13, 14]. In particular, the acute phase reactant, C-reactive protein (CRP), which is a non-specific inflammatory marker, has been correlated with cardiovascular outcomes including stroke^[15–19].

Plasma tHcy level has been shown to be associated with hsCRP in cerebrovascular diseases^[20]. However, there have been no further investigative reports, and its clinical significance, especially the predictive value of the combination of elevated plasma tHcy and hsCRP levels in prognosis of patients with stroke, remains unknown. In the present study, 291 patients with first-ever stroke were investigated through a 5-year follow-up to identify the predictive role of the combination of both tHcy and hsCRP in the prognosis of stroke.

1 SUBJECTS AND METHODS

1.1 Study Population

This is a prospective, multi-center, case-cohort study for assessment of risk factors for stroke (Project 973). A total of 196 patients with first-onset ischemic stroke and 95 patients with first-onset hemorrhagic stroke were collected during the period of November 2000 to July 2001 from 5 medical centers in Hubei province in China. Diagnosis of stroke was made based on the results of strict clinical medical history, neurological examination, magnetic resonance imaging (MRI) or computerized tomography (CT) according to the International Classification of Diseases (the ninth revision). Other types of stroke, including transient ischemic attack, subarachnoid hemorrhage, embolic brain infarction, brain tumors, and cerebrovascular malformation, and severe systemic diseases such as collagen vascular disease, endocrine and metabolic disease (except diabetes mellitus), inflammation, liver, neoplastic, or renal diseases were excluded. All patients were evaluated for detailed medical history and family history, especially hypertension, diabetes and other cardiovascular risk factors such as cigarette smoking and blood pressure, fasting blood glucose, triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL) were recorded and strict physical examinations were performed and recorded by trained physicians.

1.2 tHcy and hsCRP Determination

The blood samples of the subjects were drawn with anticoagulation by ethylenediaminetetraacetic acid sodium (EDTA-Na). After centrifugation at 3000 r/min for 15 min, the plasma was separated from the blood cells and stored at –80°C until used. The concentration of tHcy level was detected using high performance liquid chromatography with fluorescence detection. The hsCRP level in the plasma was measured using an enzyme-linked immunosorbent assay. This high sensitivity assay is a colorimetric competitive immunoassay that uses purified protein and polyclonal anti-CRP antibodies. All measurements were performed in duplicate with an inter-assay variation of <5%. Other plasma biochemical variables were measured with a standard automatic analyzer (Hitachi 7060, Hitachi, Japan).

1.3 Follow-up and Clinical End Points

The clinical interviews were performed by home or clinical visits and phone calls every year during the 5 years after the blood samples were collected. The investigation items in the follow-up included the presence/absence of the following: self-care ability, blood pressure control, recurrence of stroke, cardiovascular events, and drug therapy. The primary end point included the following: acute myocardial infarction, ischemic or hemorrhagic stroke and death, which were recorded.

1.4 Statistical Analysis

In this study, the analyses were performed with SPSS statistical package (version 10.0). Statistical significance for intergroup differences was analyzed by the Student *t* test for continuous variables and the χ^2 test for categorical variables. The Kaplan-Meier technique (log-rank test) was applied in survival analysis. Multivariate logistic regression analysis was used to assess the relative risk for primary end point events during the 5 years of follow-up associated with increased tHcy and hsCRP, adjusted for sex, age, body mass index (BMI), blood pressure, blood cholesterol and history of diabetes, hypertension and smoking.

2 RESULTS

2.1 The Characteristics of Population after 5 Years of Follow-up

During the 5-year follow-up, a total of 94 patients had a primary end point. Sixty-five patients died: 51 deaths were due to vascular etiology (fatal stroke in 27, failure after stroke in 15 and cardiovascular death in 9) and 14 deaths were nonvascular causes (cancer in 7, renal failure in 3, diabetes in 1, anemia in 1, trauma in 1 and emphysema in 1). Thirty-four patients experienced new vascular events: recurrent non-fatal stroke in 31 and non-fatal acute myocardial infarction in 3. A total of 21 patients were lost during the 5-year course of follow-up, with the follow-up rate being 92.8%.

2.2 Selected Baseline Characteristics of the Participants

The patients with stroke were divided into two groups on the basis of the occurrence of primary endpoint events (events group and no-events group) during the 5-year follow-up. The baseline characteristics of the study subjects are shown in table 1. The mean age and systolic blood pressure of the patients with primary endpoint events were significantly higher than those of patients without events. There was no significant difference in sex distribution, BMI, HDL, TC, TG and history of hypertension, diabetes and current cigarette usage between the group with events and the group without events. The mean plasma hsCRP level in patients with primary endpoint events was significantly higher than that in those patients without primary endpoint events (4.4 ± 4.3 vs 2.7 ± 3.2 mg/L) ($P < 0.01$). Nevertheless, there was no significant difference in mean tHcy levels between the two groups.

2.3 Prediction of End Point Events during the 5-years Follow-up by Plasma tHcy and hsCRP Level

The patients were divided into two groups based on tHcy level (<18 $\mu\text{mol/L}$ and ≥ 18 $\mu\text{mol/L}$). The relative risk of primary end point in stroke patients with different tHcy level was assessed, which showed that the relative risk of death or new vascular events was 1.97 (95% CI, 1.13 to 3.42, $P=0.017$) in patients with higher tHcy (≥ 18 $\mu\text{mol/L}$) compared with those with lower tHcy level (<18 $\mu\text{mol/L}$). The analyses of primary endpoints and the distribution of the patients in different groups based on hsCRP level showed that the relative risk of death or vascular events was 3.01 (95% CI, 1.60 to 5.64, $P=0.001$) in patients with hsCRP >3 mg/L compared to patients with hsCRP <1 mg/L during the 5-year follow-up (table 2).

Furthermore, according to the different combinations of plasma tHcy levels ($<18 \mu\text{mol/L}$ and $18 \mu\text{mol/L}$) and hsCRP concentrations ($<1 \text{ mg/L}$, $1\text{--}3 \text{ mg/L}$ and $>3 \text{ mg/L}$), the patients were divided into 6 groups. Survival analysis showed that the probability of death or new vascular events in the patients increased according to the tHcy and hsCRP level ($P<0.01$) (fig. 1).

The relative risk of primary end point and the combination of tHcy level plus hsCRP level in patients with stroke was assessed. This showed that the relative risk of death or new vascular events was 4.67 (95% CI, 1.96 to 11.14, $P=0.001$) in patients with the combined higher tHcy ($18 \mu\text{mol/L}$) and higher hsCRP ($>3 \text{ mg/L}$) compared with those with lower tHcy level ($<18 \mu\text{mol/L}$) coupled to lower hsCRP ($<1 \text{ mg/L}$) (Table 3).

To investigate the relationship of tHcy and hsCRP level, the correlation analysis was performed, which demonstrated that the tHcy level was correlated with hsCRP level ($P=0.033$). In order to determine whether the combined increased hsCRP plus increased tHcy level was independently associated with death or new vascular events in patients with stroke, multiple logistic regression analyses were performed, with other risk factors including age, sex, BMI, plasma total cholesterol level, history of hypertension, diabetes and smoking also taken into account. The combination of increased tHcy level ($18 \mu\text{mol/L}$) with increased hsCRP level ($>3 \text{ mg/L}$) was still significantly associated with the risk of death or new vascular events (OR, 4.10, 95% CI, 1.61 to 10.45, $P=0.003$) even when adjusted for other risk factors at inclusion. Thus, the increased tHcy level in combination with hsCRP level was an independent risk factor for the primary end point in patients with stroke and had the stronger predictive value than increased hsCRP alone or increased tHcy alone.

3 DISCUSSION

In this study, we found that the combination of higher tHcy level ($18 \mu\text{mol/L}$) and hsCRP level ($>3 \text{ mg/L}$) was significantly associated with the risk of death or new vascular events in patients with stroke, and the association existed even after adjustment for other risk factors including BMI, age, sex, plasma cholesterol level, history of hypertension, diabetes and smoking, which suggested that the combination of higher tHcy ($18 \mu\text{mol/L}$) and hsCRP level ($>3 \text{ mg/L}$) was an independent risk factor for death or new vascular events for patients with stroke. The combination of plasma tHcy and hsCRP level had a stronger predictive value than either hsCRP alone or tHcy alone.

A large body of epidemiological studies support that increased homocysteine levels is an independent risk factor for vascular diseases, including stroke. Plasma homocysteine is a risk factor for recurrent vascular events in young patients with ischaemic stroke or TIA^[21]. This body of evidence suggests that lowering the tHcy level, such as with folic acid and vitamin B12 supplementation, could reduce the risk of cardiovascular events, including stroke. However, recently, the Heart Outcomes Prevention Evaluation (HOPE) 2, with a total of 5522 patients with vascular disease or diabetes, and the Norwegian Vitamin (NORVIT) trial in 3749 patients with acute myocardial infarction, showed that combined supplements of folic acid and vitamins B6 and B12 did not reduce the risk of major cardiovascular events in patients with vascular disease in spite of decreasing the tHcy level^[22, 23]. In both of these two studies, patients with normal plasma tHcy levels were treated with folic acid or vitamin B, which could have attenuated the impact of lowering tHcy levels in secondary prevention of cardiovascular diseases. By contrast, Guelpen's study in patients with stroke suggested a protective role of folic acid for hemorrhagic stroke, possibly in addition to its effects on homocysteine status, when used in patients with hyperhomocysteinemia^[24]. Our previous studies showed that plasma tHcy above $18 \mu\text{mol/L}$

was associated with microalbuminuria, a marker of endothelial dysfunction and a predictor of cardiovascular disease^[25]. In the present study, the relative risk of death or new vascular events was 1.97 (95% CI, 1.13 to 3.42, $P=0.017$) in stroke patients with high tHcy ($\geq 18\mu\text{mol/L}$) compared with those with lower tHcy level ($<18\mu\text{mol/L}$), although there was no significant difference in mean tHcy levels between patients with and without adverse events. All these results suggest that it is possible that stroke patients with high tHcy levels ($\geq 18\mu\text{mol/L}$) could benefit from lowering tHcy as secondary prevention.

Inflammation plays a key role in the pathogenesis of atherosclerosis^[12] and is correlated with increased incidence of cardiovascular disease, including stroke^[26, 27]. Several inflammatory markers have been studied, but the most widely studied is hsCRP. Elevated hsCRP level is associated with increased risk of cardiovascular disease, and in some cases, is associated with cardiovascular outcomes^[8, 27–29]. In particular, higher CRP levels were correlated with a poorer prognosis after ischemic stroke in Caucasian patients^[30, 31]. The present study shows that the relative risk of death or vascular events was 3.01 (95% CI, 1.60 to 5.64, $P=0.001$) in patients with hsCRP $>3\text{ mg/L}$ compared to that in patients with hsCRP $<1\text{ mg/L}$ during the 5 year follow-up. Although homocysteine causes oxidative stress and vascular inflammation, damages endothelial cells, inhibits endothelium-dependent relaxation, and enhances thrombogenicity^[4–6], lowering tHcy by $3.7\mu\text{mol/L}$ with folic acid-based multivitamin therapy does not significantly reduce blood concentrations of these biomarkers of inflammation, endothelial dysfunction or hypercoagulability in DUSITANOND's study^[32]. In their study, not all patients in the treatment group had hyperhomocysteinemia (especially not higher than $18\mu\text{mol/L}$) or increased hsCRP level, but all patients received treatment with folic acid, i.e., the treatment was not hyperhomocysteinemia-selective or high hsCRP-selective. Youssef's study recently demonstrated that high plasma tHcy level was associated with increases in hsCRP levels in an association analysis of a small sample^[20]. We also observed this linear association between plasma tHcy and hsCRP levels in this larger sample study. However, its clinical significance, especially its predictive value in the prognosis of stroke, remains unknown. Interestingly, in the present 5-year follow-up study, we were excited to find that the relative risk of death or new vascular events was 4.67 (95% CI, 1.96 to 11.14, $P=0.001$) in stroke patients that presented with the combination of higher tHcy ($\geq 18\mu\text{mol/L}$) and higher hsCRP ($>3\text{ mg/L}$), as compared with those with lower tHcy concentration ($<18\mu\text{mol/L}$) or hsCRP ($<1\text{ mg/L}$) levels alone, and the combination was an independent risk factor and predictive factor, although the elevated tHcy concentration and high hsCRP level alone are associated independently with adverse cerebrovascular events.

In summary, this study showed that plasma tHcy levels are linearly associated with hsCRP levels, and more importantly, the higher tHcy level ($\geq 18\mu\text{mol/L}$) combined with higher hsCRP level ($>3\text{ mg/L}$) has much more predictive value for the risk of death or new vascular events in first-onset stroke patients during long-term follow-up period. Indeed, plasma tHcy level combined with hsCRP level had a much stronger predictive value and was a more precise risk factor than hsCRP or tHcy alone. Further studies are required to evaluate the potential decrease in risks associated with lowering both Hcy and hsCRP levels in patients that present with both increased tHcy and hsCRP.

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Fig. 1. Survival study showing the probability of free primary endpoint events in patients with different tHcy concentrations in combination with hsCRP levels during follow-up period

Table 1

Baseline characteristics of subjects

Parameters	Groups		<i>P</i>
	Events (<i>n</i> =94)	No events (<i>n</i> =176)	
Age (year)	66±9	60±10	<0.01
Sex (female), [<i>n</i> (%)]	29 (30.8)	69 (39.2)	>0.05
BMI (kg/m ²)	23.7±4.1	24.4±4.6	>0.05
Hypertension [<i>n</i> (%)]	60 (63.8)	110 (62.5)	>0.05
SBP (mmHg)	151.4±25.4	141.7±27.5	<0.01
DBP (mmHg)	89.7±14.4	86.7±17.1	>0.05
Diabetes [<i>n</i> (%)]	14 (14.9)	18 (10.2)	>0.05
Current smokers [<i>n</i> (%)]	25 (26.6)	40 (22.7)	>0.05
HDL (mmol/L)	0.9±0.3	0.9±0.3	>0.05
TC (mmol/L)	4.6±1.0	4.6±1.0	>0.05
TG (mmol/L)	1.8±0.7	2.1±1.4	>0.05
Plasma hsCRP (mg/L)	4.4±4.3	2.7±3.2	<0.01
Plasma tHcy (μmol/L)	17.4±10.7	16.2±12.7	>0.05

Table 2

Relative Risk of primary endpoints and different hsCRP levels

hsCRP level	Relative Risk	95% CI	P
<1	1	–	–
1–3	1.64	0.84–3.20	0.15
>3	3.01	1.60–5.64	0.001

Table 3

Relative risk of primary end point and tHcy levels in combination with hsCRP levels

hsCRP levels (mg/L)	tHcy levels (μmol/L)	Relative risk	95% CI	P
<1	<18	1	–	–
	18	1.25	0.391–3.997	0.707
1–3	<18	1.446	0.668–3.125	0.349
	18	3.111	1.033–9.371	0.044
>3	<18	2.528	1.194–5.354	0.015
	18	4.667	1.955–11.139	0.001