Further Evidence of Interrelation between Homocysteine and Hypertension in Stroke Patients: A Cross-Sectional Study

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Abstract

Background: A high total plasma homocysteine level is an independent risk factor for cardiovascular and cerebrovascular disease, but the evidence connecting plasma tHcy level with hypertension is inconsistent.

Objective: To determine the association between plasma tHcy level and some common risk factors for cerebrovascular disease (recurrent stroke, diabetes mellitus, hypertension, ischemic heart disease and hyperlipidemia) in patients presenting with primary or recurrent acute ischemic strokes.

Methods: This retrospective cross-sectional chart analysis was conducted in a university-affiliated referral hospital. During an 18 month period we identified 113 acute ischemic stroke patients (mean age 71.2), 25 of whom had a recurrent stroke. Plasma tHcy level, obtained 2–10 days after stroke onset, was determined by the high performance liquid chromatography method with fluorescence detection. A multi-variate logistic regression model was used to determine the independent relationship between each potential risk factor and tHcy level above or below the 75th percentile.

Results: Hypertension was more frequent among patients with plasma tHcy level above than below the 75th percentile (51.7% vs. 80.8%, respectively, $P = 0.012$). After adjusting for demographic and clinical variables, the odds ratio for recurrent stroke and hypertension, with tHcy above or below the 75th percentile, was 3.4 (95% confidence interval 1.01–10.4, $P = 0.037$) and 4.02 (95% CI 1.2–13.9, $P = 0.028$), respectively.

Conclusions: A high plasma tHcy level is associated with history of hypertension and recurrent stroke among patients presenting with acute ischemic stroke. These results were independent of other risk factors such as atrial fibrillation, diabetes and hyperlipidemia. Hypertensive stroke patients with hyperhomocysteinemia should be identified as high risk patients as compared to non-hypertensive stroke patients, and more vigorous measures for secondary prevention may be warranted.

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Stroke is a major cause of global disability [1] and the second most leading cause of death in the world [2]. Elevated total plasma homocysteine level is common in the elderly [3] and is a well-established risk factor for cardiovascular disease [4] and stroke [5]. This is assumed to involve several pathophysiologic mechanisms that interfere with blood coagulation systems and damage arterial walls [6,7]. Prospective studies have shown increased plasma tHcy level to be an independent risk factor for secondary vascular events

in stroke patients [8] as well as for new atherothrombotic brain infarction [9,10]. It has been suggested that high plasma homocysteine levels may predict the severity of cerebral atherosclerosis in patients with cerebral infarction [11].

However, there is still controversy [12] regarding the possible role of high plasma tHcy level – as well as other well-known risk factors such as hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia and history of recurrent stroke – in patients with acute ischemic stroke [9,10]. However, hypertensive and/or hyperhomocysteinemic stroke patients, as compared to others, may represent a high risk group for the development of recurrent stroke.

The present study investigated the possible associations between plasma tHcy level, stroke (primary or recurrent) and the presence of some prevalent vascular diseases. Such interrelations may have future therapeutic implications on prevention strategies.

Patients and Methods

Our study group comprised consecutive patients admitted to our ward during an 18 month period. Patients with a primary diagnosis of acute ischemic stroke were admitted either from departments of internal medicine or directly from the emergency medicine ward. The diagnosis was based on the clinical presentation of acute onset of focal neurologic signs. Computerized tomography scan was performed in all patients to confirm the ischemic nature of the stroke. Exclusion criteria included non-ischemic strokes, cardioembolic strokes, patients with residual brain damage due to infection, trauma or surgery, and patients with space-occupying lesions or any hemorrhagic strokes.

Eleven patients, despite their atrial fibrillation, had suffered strokes that were considered clinically to be of ischemic non-embolic origin. Determination of the non-cardioembolic nature of such strokes was based on previously published criteria by Hart et al. [13]. The presence of hypertension, ischemic heart disease, atrial fibrillation, diabetes mellitus and hyperlipidemia, and a history of recurrent stroke were established by medical history obtained by interview and a complete physical examination. Data were cross-examined and confirmed by ICD-9 codes.

Plasma tHcy level was measured 2–10 days after stroke onset. Venous blood samples from patients after an 8–10 hour fast were collected in tubes containing EDTA and centrifuged immediately. The obtained plasma was kept at -20°C. Plasma tHcy level was determined by the high performance liquid chromatography method using fluorescence detection [14]. Patients were dichot-

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tHcy = total plasma homocysteine
CI = confidence interval

omized according to the serum homocysteine level. The cutoff point was established at the 75th percentile (15 mole/L) in accordance with previous studies [5,15].

Statistical analysis

Univariate analysis was used to determine the relationship between each explanatory variable and the plasma tHcy as the dependent variable. Comparisons between upper and lower quartiles of plasma tHcy level with regard to demographic and clinical factors were performed using t-tests, Mann-Whitney and Fisher's exact tests as applicable. Spearman correlation coefficients were calculated for all continuous parameters and plasma tHcy levels. A multivariate logistic regression model was applied to the data to simultaneously study the independent relationship between each risk factor and plasma tHcy level of the upper quartile. The model predicts the probability of a high level of plasma tHcy levels as a function of the explanatory variables. All variables correlating with the plasma tHcy level (in the univariate analysis) at a significance level below 0.25 were entered into the model. Using this level, as a criterion for selection of variables to the model, serves to identify important variables failing to enter the model at the more traditional level, such as <0.05 [16]. We also performed a multiple linear regression analysis to evaluate the effect of each factor simultaneously on plasma tHcy levels as continuous variables. The statistical significance level was set at 0.05. SPSS software, Version 10.0, was used for the analysis

Results

The data of 137 consecutive patients admitted with acute stroke were available. We excluded 24 patients due to the non-ischemic nature of their stroke and the lack of tHcy data. Thus the final analysis involved 113 patients with acute ischemic stroke.

Table 1 presents the clinical and demographic characteristics of patients with high and low plasma tHcy percentiles. The mean age was 71.2 $\pm$ 10.0 years (range 48–95) and most of the patients were male (77/113). Mean plasma tHcy level of the total study sample was 12.9 $\pm$ 7.2 µmole/L. Eighty-eight patients had a primary stroke (mean age 71.2 $\pm$ 10.4, mean plasma tHcy level 12.19 $\pm$ 5.33 µmole/L) and 25 had a recurrent stroke (mean age 76.9 $\pm$ 9.8, mean plasma tHcy level 15.81 $\pm$ 11.22 µmole/L). The difference in plasma tHcy level between patients with primary stroke and patients with recurrent stroke was statistically significant ($P < 0.01$ and $P = 0.032$ respectively, t-test). A linear regression analysis with stroke being the dependent factor versus all other variables (hypertension, gender, age, ischemic heart disease, plasma tHcy level, diabetes and hyperlipidemia) showed that only plasma tHcy level was an independent risk factor for stroke ($P = 0.026$).

There was no statistically significant difference between patients whose plasma tHcy level was above the 75th percentile (>15 µmole/L, n=26) and the remaining patients (n=87) by age, gender, diabetes, ischemic heart disease, atrial fibrillation, hyperlipidemia, or history of recurrent stroke. We found no significant correlation between severity of stroke (defined as hemiparesis versus hemiplegia) and homocysteine level (Fisher's exact test, $P = 0.78$). Hypertension emerged as the only statistically significant para-

Table 1. Ischemic stroke patients below and above tHcy 75% percentile

	Plasma tHcy ⩽75th percentile	Plasma tHcy >75th percentile	P
Demographic			
No. (%)	87 (77)	26 (23)	
Age (mean ± SD)	72.4 ± 9.7	73 ± (13.1)	0.8*
Gender, females	29 (33.3)	7 (26.9)	0.6**
Previous diseases			
Diabetes	21 (24.1)	10 (38.5)	0.2**
Arterial hypertension	45 (51.7)	21 (80.8)	0.012**
Ischemic heart disease	20 (25.3)	7 (28)	0.8**
Atrial fibrillation	9 (11.4)	2 (8.0)	1**
Hyperlipidemia	17 (19.5)	5 (19.2)	1**
Previous stroke	16 (18.4)	9 (34.6)	0.1**

Values presented are No. (%)

* Student's t-test of difference between means.

** Fisher's exact test

Table 2. Odds ratios of tHcy levels above 75% percentile (x > 15 µmol/L)*

Variable	OR	95%CI	p
Arterial hypertension	4.02	1.2–13.9	0.028
Previous stroke	3.4	1.01–10.4	0.037
Atrial fibrillation	0.7	0.13–3.9	0.7
Diabetes	1.7	0.6–4.8	0.3
Hyperlipidemia	0.8	0.2–2.7	0.7
Age	0.5	0.2–1.5	0.2
Gender	1.2	0.4–3.8	0.7

* Multiple logistic regression analysis.

OR = odds ratio

meter that differed between the groups (80.8% and 51.7% among patients above and below the 75th percentile respectively, $P = 0.012$) [Table 1].

A stepwise multiple logistic regression analysis showed that odds ratios for hypertension and recurrent stroke, among patients with plasma homocysteine level above the 75th percentile compared to patients below the 75th percentile, were 4.02 (95% confidence interval 1.2–13.9, $P = 0.028$) and 3.4 (95%CI 1.01–0.4, $P = 0.037$) respectively [Table 2]. Age, gender, diabetes, ischemic heart disease, atrial fibrillation and hyperlipidemia had no association whatsoever with lowest or highest homocysteine percentiles.

Discussion

Stroke patients typically have underlying diseases. Some of them will suffer a recurrent stroke later on. Identifying patients who may be more prone than others to have a second stroke is crucial and may affect the policy of secondary prevention, e.g., the reduction of plasma tHcy to lower level, such as low density lipoprotein reduction in patients who suffered myocardial infarction.

The present analysis revealed a significant association of high plasma tHcy level with hypertension and recurrent stroke after controlling for other variables. These results support an earlier published study that found an increased rate of hypertension

(odds ratio 3, 95%CI 1.0–12.6) among stroke patients with hyperhomocysteinemia [17]. The National Health and Nutrition Examination Survey [18] also found an association between higher plasma tHcy levels and greater risk for hypertension. Another recently published longitudinal study [18] found a significantly higher frequency of hypertension among patients with plasma homocysteine levels above the 75th percentile. However, these authors could not show any difference between the two groups regarding a history of recurrent stroke, as well as atrial fibrillation, heart disease, diabetes or hypercholesterolemia. Our cross-sectional study showing that patients with plasma tHcy level above the 75th percentile may be at greater risk for hypertension, and previous stroke is therefore complementary and supports the findings of the above mentioned studies. This is in contrast with Brattstrom et al. [19] who found no association between plasma homocysteine level, hypertension, hypercholesterolemia and blood glucose concentrations in stroke patients. Eikelboom et al. [20] came to similar conclusions in a case-control study, while results of the UK National Diet and Nutrition Survey [21] and the Hordaland Study [22] supported only a weak association between high blood pressure and serum homocysteine level. The difference in results regarding the possible association between homocysteine and hypertensive stroke patients may be explained by the methodology of the various studies, i.e., case-control studies (like previous studies) and a cross-sectional study like ours.

Since the association between a primary stroke and high plasma tHcy level is well established, our finding of the association with a history of recurrent stroke is not surprising. In contrast, the possible relation between tHcy and hypertension is not completely understood, though it would seem reasonable to predict such an association in the general population [12]. However, we are unaware of well-designed studies addressing the issue, though an association of high plasma tHcy level with renal impairment is well known [23], which could, at least theoretically, be the common pathway resulting in hypertension. This may be explained by mechanisms linking homocysteine with impaired lipid peroxidation, vascular endothelial toxicity and abnormal proliferation of smooth muscle cells, ultimately contributing to early onset of hypertension and atherothrombosis [6].

Possible limitations of our study are the relatively small number of patients and the nature of its cross-sectional design, which included hypertensive strokes patients who cannot be compared with non-normotensive non-stroke controls. This study is retrospective and therefore lacks data on tHcy values at the primary stroke in patients from the group with recurrent stroke. Also, we did not consider data on current or previous smoking, dietary consumption, and serum levels of folate, vitamin B6 and vitamin B12. These vitamins are important co-factors in the metabolic pathway of plasma tHcy and may affect plasma tHcy level. However, it seems improbable that the measured plasma homocysteine levels were influenced by these factors since the blood samples were taken 2–7 days after stroke onset.

Mangoni and colleagues [24] showed that the administration of folic acid for a short period not only reduced plasma tHcy levels but also reduced blood pressure in young healthy smokers. This finding may support the use of folate for primary and secondary prevention of stroke among patients with high blood pressure.

In conclusion, the present study demonstrates significant interrelations of high plasma tHcy levels with hypertension and recurrent stroke. This might have therapeutic implications for public health, reducing the risk of recurrent stroke. Although the efficacy of stroke prevention by lowering high plasma homocysteine levels is still unproven, secondary prevention studies are in progress. Once such interventions prove efficient, routine detection of plasma tHcy levels in stroke patients may be advised and appropriate measures taken to prevent recurrent stroke.

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