The Relation Between Plasma Homocysteine Level and Cardiovascular Risk Factors in Cerebral Ischemia

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Abstract-

Purpose: Hyperhomocysteinemia (HHcy) is associated with a higher risk of cerebral ischemia and other vascular thrombosis. Homocysteine is greatly influenced by a broad spectrum of physiological and pathological conditions but the confounding factor for HHcy is unknown in our population, especially in normocreatininemic individuals. It is our aim in this study to elucidate the relation between homocysteine and cardiovascular risk factors, and also describe the distribution of plasma homocysteine level in cerebral ischemia patients with normal serum creatinine level.

Methods: A retrospective study was conducted to understand the frequency of HHcy in cerebral ischemia patients, and the confounding cardiovascular risk factors in HHcy. Patients were classified into two groups by their plasma homocysteine levels; group I patients were those whose level was ≥ 12 µM/L whereas group II < 12 µM/L.

Results: A total of 218 patients were enrolled. Their plasma homocysteine level ranged from 3.57 to 46.37 µM/L (mean: 10.01 ± 5.03 µM/L). Group I included 45 patients whereas group II 173 patients. The frequency of hypertension, diabetes mellitus and cardiac disease, as well as age, aminotransferases, total cholesterol, triglyceride, albumin, hematocrit, hemoglobin and leucocyte count did not differ between group I and II patients, except serum creatinine level was higher in group I patients (p<0.01). Serum creatinine level correlated directly to and was an independent predictor for the plasma homocysteine level.

Conclusions: HHcy is common in our cerebral ischemia patients. Since renal function is a determinant for HHcy even in normocreatininemic patients, as a cardiovascular risk factor which detriments the renal function, it should be regularly monitored as HHcy is amenable for treatment.

Key Words: Homocysteine, Hyperhomocysteinemia, Cerebral ischemia, Creatinine

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INTRODUCTION

Stroke is a worldwide disease carrying a high morbidity and mortality regardless of ethnicity. The prevalence of ischemia ranges from 70% in Taiwan or Japan to 90% in industrial countries. Recently it was reported that at least 30% of cerebral ischemia patients did not have any definite traditional risk factors found for their stroke and this factor is a problem worthy of exploration of other risk factors being previously unidentified or underestimated. Homocysteine is an intermediate, sulphydryl-containing amino acid that is derived from the demethylation of methionine. It was discovered in 1902 and identified a prothrombotic risk factor in 1969. However, it was not until the last decade when the cellular effects of homocysteine were consequently elucidated and epidemiological studies have revealed hyperhomocysteinemia (HHcy) as a potent risk factor for thrombosis in different vascular beds, including the brain. The odds ratio of HHcy for cerebral ischemia in the general population cohort is 1.10; 1.24 in nested-controls and 1.36 in case-control studies. Although HHcy has been recognized as an emerging risk factor for stroke in Caucasians, and for coronary artery disease or deep vein thrombosis in Taiwanese, its role in cerebral ischemia has not been described in our society. As far as any racial differences in stroke risk factors is concerned, we attempt to reveal the frequency of HHcy in patients with cerebral ischemia, as well as the distribution of plasma homocysteine level in patients with normal creatinine level in this study.

PATIENTS AND METHODS

Cerebral ischemia patients admitted to the Department of Neurology, Koahsiung Medical Center of Chang Gung Memorial Hospital, between January and November, 2005, were reviewed. Cerebral ischemia was defined as a patient with acute onset of focal neurological deficits, with corresponding infarct on neuroimage study and an exclusion of nonvascular etiologies. The exclusion criteria were: (1) transient ischemic attack; (2) serum creatinine level > 1.5 mg%; (3) recent vitamin supplement and (4) no complete routine study. In addition, no patient had nutritional deficiency, megaloblastosis, gastrectomy or religious vegetarianism. Cardiac echogram and electrocardiogram were done to investigate the cardiac function.

After an overnight fasting of 8 hours, antecubital venous blood was collected for determining serum fasting glucose, creatinine, aspartate aminotransferases, glutamate aminotransferases, albumin, total cholesterol, triglyceride, leucocyte count, hemoglobin, hematocrit, and plasma homocysteine levels. The serum folate and cobalamin levels were not examined in our patients because we did not find a significant decrease of either one in HHcy patients before (personal data). The laboratory procedures had been clearly mentioned in our previous studies. Patients were then classified into two groups according to their plasma homocysteine level, in that ≥ 12 µM/L as group I and < 12 µM/L as group II.

Diabetes mellitus was defined as increased blood glucose and glycohemoglobin (> 6.2%) measured twice. Hypertension was defined according to the criteria of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JCN-7). Cardiac disease was considered when potential embolization, including atrial fibrillation or flutter, sick sinus syndrome, sinus bradycardia (< 50 beats/min), prolonged pause, mitral stenosis, aortic stenosis, mitral valve prolapse, ventricular aneurysm, hypertrophy of septum or left ventricle, congestive heart failure, patent foramina ovale, myocardial infarction or myxoma, was present.

Continuous variables (age, plasma homocysteine level, creatinine, aspartate aminotransferases, glutamate aminotransferases, albumin, total cholesterol, triglyceride, leucocyte count, hemoglobin, hematocrit) were expressed as a mean ± 1 SD. The Student’s unpaired t-test and Chi-Square test were used for statistical analysis. Simple regression tests were used to illustrate the correlation between the plasma homocysteine level and metabolic determinants. Multiple variables regression tests were used to test the independent determinants for HHcy. A probability less than 0.05 was accepted as significance.
RESULTS

A total of 218 patients were enrolled in this study. There were 133 men and 85 women and their age ranged from 24 to 90 years; average being 66.28 years. Hypertension was found in 159 patients (72.93%), diabetes mellitus in 83 patients (38.07%) and cardiac disease in 35 patients (16.05%), respectively.

The plasma homocysteine level was 3.57-46.37 µM/L (mean: 10.01 ± 5.03 µM/L) in our cerebral ischemia patients. When assigned to groups, group I included 45 patients whereas group II ended up with 173 patients. The mean plasma homocysteine level was 16.92 µM/L (range: 12.05-46.37 µM/L) in group I patients, whereas it was 8.22 µM/L (range: 3.57-11.80 µM/L) in group II patients. The gender and age did not differ between group I and II patients (Table).

The frequency of hypertension, diabetes mellitus and cardiac disease was 77.8%, 35.5%, and 17.8% in group I patients, and 71.7%, 38.7% and 15.6% in group II patients. There was no difference between them (Table). The aspartate aminotransferases, glutamate aminotransferases, albumin, total cholesterol, triglyceride, leucocyte count, hemoglobin and hematocrit did not differ between group I and II patients. On the other hand, the serum creatinine level was higher in group I (1.142 ± 0.235 mg%) than group II (0.929 ± 0.239 mg%) patients (t=5.33, p<0.01, 95% confidence interval: 0.1340-0.2914). A positive correlation between plasma homocysteine level and serum creatinine level, but not other risk factors, was disclosed (R²=0.1517, F=38.630, p<0.001) (Fig.). Multiple variables regression tests also showed the serum creatinine level as an independent factor for plasma homocysteine level (beta coefficient=0.396, t=6.254, p<0.001).

Table. The laboratory data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n=45)</th>
<th>Group II (n=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.24±11.86</td>
<td>65.50±10.49</td>
</tr>
<tr>
<td>Male gender (case, %)</td>
<td>35, 77.8%</td>
<td>98, 56.7%</td>
</tr>
<tr>
<td>Hypertension (case, %)</td>
<td>35, 77.8%</td>
<td>124, 71.7%</td>
</tr>
<tr>
<td>Diabetes mellitus (case, %)</td>
<td>16, 35.6%</td>
<td>67, 38.7%</td>
</tr>
<tr>
<td>Cardiac disease (case, %)</td>
<td>8, 17.8%</td>
<td>27, 15.6%</td>
</tr>
<tr>
<td>Homocysteine (µM/L)</td>
<td>16.92±7.00</td>
<td>8.22±1.92</td>
</tr>
<tr>
<td>Creatinine (mg%)*</td>
<td>1.142±0.235</td>
<td>0.929±0.239</td>
</tr>
<tr>
<td>Total cholesterol (mg%)</td>
<td>206.07±51.32</td>
<td>197.43±41.31</td>
</tr>
<tr>
<td>Triglyceride (mg%)</td>
<td>134.76±85.58</td>
<td>141.93±83.05</td>
</tr>
<tr>
<td>Albumin (mg%)</td>
<td>3.39±0.42</td>
<td>3.40±0.42</td>
</tr>
<tr>
<td>Aspartate transferase (IU/L)</td>
<td>26.98±13.72</td>
<td>26.83±13.67</td>
</tr>
<tr>
<td>Glutamate transferase (IU/L)</td>
<td>24.20±12.46</td>
<td>27.12±19.81</td>
</tr>
<tr>
<td>Leucocyte count (/cmm)</td>
<td>7.72±2.53</td>
<td>7.40±2.29</td>
</tr>
<tr>
<td>Hemoglobin (gm%)</td>
<td>14.01±2.23</td>
<td>13.78±1.75</td>
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<tr>
<td>Hematocrit (%)</td>
<td>41.98±5.98</td>
<td>41.48±4.66</td>
</tr>
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</table>

*The serum creatinine level, p<0.001.
DISCUSSION

The frequency of HHcy is higher in patients with coronary artery disease\(^7\), symptomatic atherosclerotic disease\(^8\) or deep vein thrombosis\(^9\), and HHcy carries a higher risk to develop these occlusive vascular disorders\(^10\). In our series, we find the frequency of HHcy to be 20.64\% in cerebral ischemia patients, which is higher than the 5\% in general population\(^11\). This result is similar to the 18.5\% to 42.0\% in Caucasians with cerebral ischemia\(^11\-\(^12\). HHcy seems to be a universal risk factor for cerebral ischemia regardless of ethnicity.

Increased plasma homocysteine levels have been reported in a broad spectrum of pathological conditions. In our series, the HHcy patients were not associated with a higher frequency of hypertension, diabetes mellitus or cardiac disease. Nevertheless, we found a higher serum creatinine level in HHcy patients. HHcy is present in 98\% of hemodialysed patients\(^8\), and it is very common in cases of nondialized chronic renal function insufficiency or end-stage renal disease\(^13\). Since the serum creatinine level in our patients is within the reference range, that is < 1.5 mg\%, the pathogenesis of HHcy may be different from that in renal failure patients.

The human kidney handles the hemostasis of plasma and intracellular sulphur-containing amino acids, such as methionine, cysteine, serine and arginine. Generally, about 75\% of circulatory homocysteine is bound to serum proteins. The free form of homocysteine is freely filtered at the glomerulus similar to creatinine but it is nearly totally reabsorbed in tubular region\(^14\-\(^15\). Accordingly, a deterioration of renal function is expected to enhance glomerular filtration or reduce tubular reabsorption of homocysteine\(^14\-\(^15\), and thus theoretically decreases the circulating homocysteine. However, this proposed mechanism is in opposition to previous observations that plasma homocysteine level increases in cases of renal insufficiency or uremia. Some investigators have suggested that an inhibition of extrarenal homocysteine metabolism by uremic substances might render as HHcy in uremic patients but it is not confirmed yet.

Homocysteine is metabolized via remethylation or trans-sulfuration\(^14\). Homocysteine is remethylated back to methionine by cyanocobamide-dependent methionine synthase. The N5-methyltetrahydrofolate acts as a donor in the remethylation cycle, and is replenished with N5, N10-methylenetetrahydrofolate reductase. Homocysteine is also converted to methionine catalysed by betaine homocysteine methyltransferase. In trans-sulfuration, homocysteine is converted to cysteine and glutathione by pyridoxine-dependent cystathionase and cystathionine \(\beta\) synthase. Compared with the liver, the kidney contains more betaine homocysteine methyltransferase and less cystathinase and methionine synthase. Therefore, an accumulation of homocysteine might likely occur in renal impairment when both remethylation and trans-sulfuration cycles are blocked.

Our findings show a direct correlation between plasma homocysteine level and serum creatinine level. However, there are four shortcomings in this study. First, creatinine is a marker for glomerular filtration rate which represents actual renal function\(^16\). Numerous factors, such as body mass, diet, advanced age or diseases, can lead to erroneous estimation of the glomerular filtration rate using serum creatinine level alone\(^16\). Second, homocysteine metabolism is influenced by a variety of cofactors (such as pyridoxine, magnesium), enzymes and gene expression (such as N5, N10-methylenetetrahydrofolate reductase). A normal blood cyanocobalamin and folate level was found in cerebral ischemia patients with HHcy before (personal data); however, these were not examined in our patients in this study. Third, the effect of diet and life style could not be controlled. Fourth, plasma homocysteine level was previously reported to have decreased at initial onset and escalated progressively until convalescent stage after stroke\(^17\-\(^19\). Although many doubt this change in initial suppression of homocystine after stroke, some authors interpret HHcy as a consequence rather than a cause of the stroke\(^17\-\(^18\). Our aim is to investigate the relation between plasma homocysteine level and other metabolic parameters. Nevertheless, our results point out the risk of HHcy for cerebral ischemia and suggest a tight control of cardiovascular risk factors is warranted.

Dietary supplementation with folic acid, cyanocobal-
amin and pyridoxine lowers the plasma homocysteine level by 25% to 30%. In observational studies, a 25% decrease of homocysteine is associated with a 10% reduction of coronary heart disease or 20% of stroke. Since HHcy is common in cerebral ischemia patients and amenable to treatment at a very low medical cost, a further recognition of homocysteine could benefit in stroke reduction.

REFERENCES