Association of Plasma Homocysteine Concentration With Atherosclerotic Carotid Plaques and Lacunar Infarction

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Background and Purpose—Higher plasma total homocysteine (tHcy) levels have been associated with carotid atherosclerosis and cerebral infarction in whites. However, data regarding such associations are limited for Asians. This study examined associations between tHcy levels and severity of carotid atherosclerosis in Japanese subjects. Additionally, because lacunar infarction is the most prevalent type of ischemic stroke in Japan, we also investigated its associations with tHcy levels.

Methods—The subjects were 152 Japanese patients (age, 66.2±11.0 years) at our hospital. Using ultrasound, we evaluated severity of carotid atherosclerosis by plaque score, which is defined by the sum of all plaque (intima-media thickness ≥1.1 mm) height in bilateral carotid arteries. In 112 of 152 patients, the existence of lacunar infarction was evaluated on brain MRI scans.

Results—A moderate linear association was found between tHcy levels and plaque score (r=0.48, P<0.0001). Moreover, tHcy level was associated with plaque score (β=0.26, P<0.001) independently of traditional atherosclerotic risk factors. In logistic regression analyses, each 1-μmol/L-higher tHcy level was associated with a 1.37-fold-higher [95% confidence interval (CI), 1.19 to 1.58] likelihood for lacunar infarction, increasing the likelihood by 1.22-fold (95% CI, 1.04 to 1.43) independently of traditional atherosclerotic risk factors.

Conclusions—Higher tHcy levels appear to have associations with increased severity of carotid atherosclerotic plaques and prevalent lacunar infarction in the Japanese. Larger prospective studies are necessary to establish whether higher tHcy levels serve as a harbinger for insidious carotid and cerebrovascular diseases. (Stroke. 2002;33:1493-1496.)

Key Words: carotid arteries • homocyst(e)ine • lacunar infarction • risk factors

Subjects and Methods

Subjects
Subjects for this investigation were enrolled from 184 patients consecutively admitted to the National Osaka (Japan) Minami Hospital. All patients had at least 1 of the following diseases: hypertension, diabetes mellitus, hyperlipidemia, ischemic stroke, or arteriosclerosis obliterans. Stroke was diagnosed in 77 of the 184 patients, including 34 lacunar infarction, 21 atherothrombotic infarction, 11 cardioembolic infarction, and 11 unclassified stroke.

The exclusion criteria for the current study were malignant diseases, hypothyroidism, chronic renal failure (serum creatinine concentration >0.26 mmol/L), recent myocardial infarction, major surgery, and the use of anticonvulsants, multivitamins, methotrexate, or nitrous oxide. Additionally, because the implication of atherosclerosis is not clear for cardioembolic infarction and unclassified stroke, patients with these conditions were also excluded.

Among the 184 patients, 32 patients met either of the above criteria and were excluded. Consequently, a total of 152 Japanese patients (age, 66.2±11.0 years), 81 women and 71 men, were...
TABLE 1. Demographic and Clinical Characteristics of 152 Subjects

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine (μmol/L)</td>
<td>0.370</td>
<td>0.260</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.177</td>
<td>0.372</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male=1)</td>
<td>2.369</td>
<td>0.226</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.037</td>
<td>0.090</td>
<td>0.18</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.712</td>
<td>0.063</td>
<td>0.51</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.576</td>
<td>0.044</td>
<td>0.37</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>−0.127</td>
<td>−0.011</td>
<td>0.86</td>
</tr>
</tbody>
</table>

No significant interactions were observed between significant regressors.
TABLE 3. Logistic Regression Analysis for Predicting Lacunar Infarction

<table>
<thead>
<tr>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine (μmol/L)</td>
<td>1.22</td>
<td>1.04–1.43</td>
</tr>
<tr>
<td>Age (/10 yr)</td>
<td>1.61</td>
<td>1.02–2.53</td>
</tr>
<tr>
<td>Sex (male=1)</td>
<td>4.58</td>
<td>1.84–11.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.01</td>
<td>0.74–5.44</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.85</td>
<td>0.29–2.49</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.15</td>
<td>0.85–5.48</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.01</td>
<td>0.41–2.53</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

Subsequently, the ability of tHcy levels to stratify the likelihood for lacunar infarction was examined by logistic regression analyses. Each 1-μmol/L-higher tHcy level was associated with a 1.37-fold-higher [95% confidence interval (CI), 1.19 to 1.58] likelihood for lacunar infarction, increasing the likelihood by 1.22-fold (95% CI, 1.04 to 1.43) independently of traditional atherosclerotic risk factors (Table 3).

Discussion

Elevated tHcy levels have attracted much attention in recent years as a potential risk factor for cardiovascular diseases. Also, higher tHcy levels have been linked to carotid atherosclerosis as assessed by IMT. However, controversies still exist regarding whether a slight increase in IMT represents focal atherosclerosis. Namely, IMT below certain levels could merely represent an adaptive response to the changes in shear stress, lumen diameter, tensile stress, and pressure. Given such controversies, we focused on atheromatous plaques as defined by focal increases in IMT and tHcy levels, multiple regression analysis was performed to further examine the link between carotid atherosclerosis and tHcy levels, multiple regression analysis was performed (Table 2). When traditional atherosclerotic risk factors were controlled for, tHcy was found to be significantly associated with plaque score, suggesting a potential effect of higher tHcy in the evolution of carotid atherosclerosis. This finding is consistent with a previous study showing associations between tHcy and carotid plaque area. Additionally, age and male sex were associated with plaque score independently of other risk factors, supporting previous studies. In the present study, hypertension, diabetes, hyperlipidemia, and smoking habits did not have independent associations with plaque score. Although we realize that duration and severity of such risk factors are important for the initiation and progression of atherosclerosis, we defined them as binary variables, which could have diluted their associations with plaque score. Also, the prevalence of diabetes and hyperlipidemia was relatively low, limiting our statistical power to examine their link with the plaque score.

As a manifestation of cerebral small-artery diseases, lacunar infarction is the most prevalent type of ischemic stroke in Japanese people. Although hypertension and diabetes mellitus are often found in such patients, no established atherosclerotic risk factors are present in 18% of them. In contrast to the well-defined association between tHcy and large artery atherosclerosis, the relationships between tHcy levels and small artery diseases are still controversial. FathBender et al have reported that homocysteine injures small perforating arteries rather than major cerebral arteries. Also, Evers et al reported that tHcy levels are higher in patients with lacunar infarction than in those with other stroke subtypes. In the present study, each 1-μmol/L-higher tHcy level was associated with a 1.37-fold-higher likelihood of lacunar infarction. Moreover, the association was modified little when age, sex, and other traditional atherosclerotic risk factors were controlled for. These results provide evidence for the association between higher tHcy level and prevalent lacunar infarction in Japanese people.

The present study has certain limitations. First, dietary habits such as meat, alcohol, and coffee consumption, which were not considered in this study, have been shown to affect tHcy levels. Second, tHcy levels in lacunar infarction patients could be underestimated because of lifestyle improvements after the infarction was diagnosed, potentially diluting the association between lacunar infarction and tHcy. Taken together, they indicate that larger prospective studies are necessary to establish whether higher tHcy levels serve as a harbinger for insidious carotid and cerebrovascular diseases.

In summary, plasma tHcy levels appear to be associated with carotid atherosclerotic plaques and lacunar infarction in the Japanese. Because tHcy levels are modifiable by lifestyle improvement, the modifications could have a potential therapeutic value for the prevention of carotid plaque formation and lacunar infarction.

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