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Stroke. 1993;24:965-969
doi: 10.1161/01.STR.24.7.965

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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High Serum Lipoprotein(a) Levels Are an Independent Risk Factor for Cerebral Infarction

Shuzo Shintani, MD; Shuichi Kikuchi, MD; Hideo Hamaguchi, MD; Tatsuo Shiigai, MD

Background and Purpose: This study was conducted to evaluate the role of high serum lipoprotein(a) levels in a group of patients with a relatively early onset of cerebral infarction as a whole and in a subgroup with the perforating artery occlusion subtype of cerebral infarction.

Methods: Fifty-four patients with cerebral infarction, the onset of which was before age 65 years (37 men, 17 women; mean age, 61.9±7.7 years) were examined in this study. When patients with atrial fibrillation were excluded to omit cardiac embolic strokes from analysis, the group consisted of 45 patients. The patients were classified into two subtype groups, the perforating artery occlusion group and the cortical artery occlusion group, by using magnetic resonance imaging. Lipoprotein(a) levels were measured by an enzyme-linked immunosorbent assay. Four biochemical variables (serum levels of lipoprotein(a), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides) and other potential risk factors such as hypertension, diabetes mellitus, smoking habits, alcohol intake, and family history were analyzed by stepwise logistic regression to determine the independent and significant risk factors for cerebral infarction without atrial fibrillation.

Results: The incidence of subjects with serum lipoprotein(a) levels $\geq$42.6 mg/dL, which is the 95th percentile level of the control subjects, was significantly increased in the total cerebral infarction group ($P<.025$) and the perforating artery occlusion group ($P<.025$) compared with the control group. In addition, by using stepwise logistic regression analysis in the total and perforating artery occlusion patient groups we identified three independent and significant risk factors: hypertension, a low high-density lipoprotein cholesterol level, and a high serum lipoprotein(a) level. In the cortical artery occlusion group, the sample size was not large enough for the statistical analysis. Diabetes mellitus is the only known factor that correlates with serum lipoprotein(a) levels, but there were no significant correlations between serum lipoprotein(a) levels and history of diabetes mellitus or fasting blood sugar.

Conclusions: These findings indicate that high serum lipoprotein(a) levels are an independent risk factor in the development of cerebral infarction when subjects with atrial fibrillation were excluded from the total group and the perforating artery occlusion subtype group. (Stroke 1993;24:965-969)

Key Words • cerebral infarction • lipoproteins • risk factors

Lipoprotein(a) [Lp(a)] was initially detected by Berg in 1963. Lp(a) has a low-density lipoprotein (LDL)-like structure, in which apolipoprotein(a) [apo(a)] is covalently linked to apolipoprotein B. In addition, the structural similarity between apo(a) and human plasminogen has been revealed. It has also been reported that apo(a) inhibits plasminogen from binding to receptors in endothelial cells and facilitates thrombogenesis. It is rational to regard high Lp(a) levels as a potential risk factor for both atherogenesis and thrombogenesis. Indeed, in cardiology it is established that high Lp(a) levels are an independent risk factor for the development of ischemic heart disease.

Serum Lp(a) levels have been reported to be under considerable genetic control. Serum Lp(a) levels are not significantly correlated with age, sex, blood pressure, smoking habits, total cholesterol, or triglycerides, and they are relatively resistant to pharmacological and dietary restrictions. In general, environments such as food, drugs, and habits do not seem to change the value of Lp(a). It is suggested, however, that serum Lp(a) levels have a tendency to increase in subjects with diabetes mellitus (DM). The Lp(a) distribution in the normal population is highly skewed, and a clinically important Lp(a) threshold level is now being discussed.

In neurology, the role of Lp(a) in the development of cerebral infarction, including the cortical artery occlusion (CAO) type, has also been suggested. It is not clear, however, whether high serum Lp(a) levels are an independent risk factor for cerebral infarction. In previously reported studies, atrial fibrillation (AF) was not referred to and subjects with AF were not excluded in the statistical analysis. When subjects with AF are not excluded, there is a great possibility that the data include subjects with cardiac embolic strokes. In addi-
tion, two of these three reports described a negative association of a high Lp(a) level with the perforating artery occlusion (PAO) type of cerebral infarction. The aim of the present study is to elucidate the positive or negative association of a high Lp(a) level with cerebral infarction as a whole and with the PAO subtype when excluding subjects with AF.

In this study we used magnetic resonance imaging (MRI) to separate the patients into two subgroups, the PAO group and the CAO group. Since MRI can detect smaller and fainter lesions than computed tomography (CT), MRI is superior to CT scanning for detecting PAO lesions, which are usually smaller than CAO lesions.

Subjects and Methods

Subjects

Fifty-four patients with cerebral infarction, the onset ofwhich was before age 65 years (37 men, 17 women; mean age, 61.9±7.7 years; range, 25 to 73 years) and 81 normal control subjects (66 men, 15 women; mean age, 61.1±8.6 years; range, 43 to 77 years) were examined in this study. When subjects with AF were excluded to omit cardiac embolic strokes from analysis, the number of patients decreased from 54 to 45 (30 men, 15 women; mean age, 62.0±8.1 years). No normal control subjects had AF. The mean age of stroke onset in the patients without AF was 57.1±7.8 years. There was no statistical difference in age between the patient group and the normal control subjects by Student’s t test. No patients were treated with hypolipidemic drugs. Examinations of the patients by MRI (Yokogawa Resona 0.5T) revealed 38 cases of PAO, 14 cases of CAO, and 2 cases of occlusion of both arteries. The diagnosis of hypertension was determined by the patient’s history, prescribed antihypertensive medication, or systolic blood pressure greater than 150 mm Hg and/or diastolic blood pressure greater than 90 mm Hg. DM was diagnosed by the patient’s history, prescribed hypoglycemic medication, or fasting blood glucose concentrations greater than 140 mg/dL. A positive or negative family history was determined by the existence of a history of stroke in parents or siblings. AF was diagnosed by electrocardiography.

Chemical Analysis

A venous blood sample was taken from each patient at least 4 weeks after ictus following an overnight fast. Serums were also collected from control subjects after an overnight fast. The LDL cholesterol levels were calculated according to the Friedewald equation:

\[
LDL \text{ Cholesterol (mg/dL)} = \text{Total Cholesterol} - \text{HDL Cholesterol} - \frac{\text{Triglycerides}}{5}
\]

where HDL is high-density lipoprotein. The serum levels of Lp(a) were measured by enzyme-linked immunosorbent assay using a commercial kit [Tint Elize Lp(a), Biopool AB, Sweden]. Briefly, serum samples were applied on the micro test wells, which were coated with an anti-apo(a) antibody. After 2 hours of incubation, peroxidase-conjugated anti-apo(a) antibodies were added and incubated further for 1 hour (the so-called sandwich method). After washing, the substrate for the peroxidase (1,2-phenylenediamine) was reacted, and Lp(a) levels were determined by measuring the absorbance at 490 nm, which was proportional to the amount of Lp(a) present in the serum samples.

Statistical Analyses

Statistical analyses were performed using the SAS program. An unconditional logistic regression analysis was performed using the LOGIST procedure for SAS (SUGI [SAS Users Group International] supplemental library).

Results

Frequency distributions of Lp(a) levels in patients and control subjects are shown in the Figure. The Lp(a) distribution in the control subjects was highly skewed toward the lower levels. In the cerebral infarction patients, the distribution was slightly skewed and deviated to a higher range compared with the control subjects. The incidence of serum Lp(a) levels ≥42.6 mg/dL, which is the 95th percentile Lp(a) level of the control subjects, in cerebral infarction patients is summarized in Table 1. The incidence of high Lp(a) levels was significantly higher in the total cerebral infarction group (P<.01), PAO group (P<.025), and CAO group (P<.05) compared with control subjects when subjects with AF were not excluded. When the nine subjects with AF were excluded, the incidence was still significantly higher in the total cerebral infarction group (P<.025) and the PAO group (P<.025) compared with the control subjects. In the CAO group without AF, the significance was not observed, probably because of the small sample size.
TABLE 1. Incidence of High Serum Lipoprotein(a) Levels (≥42.6 mg/dL) in Patients with Cerebral Infarction

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Serum Lp(a) level (mean±SD [mg/dL])</th>
<th>Subjects with Lp(a) ≥42.6 mg/dL</th>
<th>Excluding subjects with AF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Control</td>
<td>81</td>
<td>15.2±12.1</td>
<td>6.2</td>
<td>5</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>26.1±21.4</td>
<td>22.2</td>
<td>12*</td>
</tr>
<tr>
<td>PAO</td>
<td>38</td>
<td>26.0±20.6</td>
<td>21.1</td>
<td>8†</td>
</tr>
<tr>
<td>CAO</td>
<td>14</td>
<td>27.4±24.6</td>
<td>28.6</td>
<td>4‡</td>
</tr>
</tbody>
</table>

Lp(a), lipoprotein(a); AF, atrial fibrillation; PAO, perforating artery occlusion; CAO, cortical artery occlusion.

*χ²=7.6, P<.01; †χ²=5.9, P<.025; ‡χ²=4.6, P<.05; §χ²=5.6, P<.025; ||χ²=5.3, P<.025 compared with control subjects by χ² test with Yates’ correction.

The serum levels of lipids and fasting blood sugar in patients without AF and control subjects are shown in Table 2. No statistical differences between the patients and control subjects were observed in the levels of total cholesterol, LDL cholesterol, triglycerides, and fasting blood sugar. The levels of HDL cholesterol were significantly lower in the total cerebral infarction group (P<.01), PAO group (P<.05), and CAO group (P<.05).

The incidence of hypertension, DM, smoking habits, alcohol intake, and positive family history in patients without AF and in control subjects is shown in Table 3. The incidence of hypertension was significantly higher in the total cerebral infarction group (P<.001) and the PAO group (P<.001) compared with control subjects.

Four biochemical variables (serum levels of Lp(a), LDL cholesterol, HDL cholesterol, and triglycerides) and other potential risk factors listed in Table 3 were analyzed by stepwise logistic regression to determine the independent and significant risk factor for the group with cerebral infarction without AF as a whole and for the PAO subtype group (Table 4). We identified three significant risk factors in the total and PAO subtype groups of cerebral infarction patients: hypertension, a low HDL cholesterol level, and a high serum Lp(a) level. We did not perform a multivariate analysis of the CAO subtype group because of an insufficient number of subjects.

The history of DM is the only known factor that correlates with serum Lp(a) levels. There was no significant difference in serum Lp(a) levels between patients with DM (n=4) and patients without DM (n=41) (P>.9 by Mann-Whitney U test). In addition, there was no significant correlation between levels of fasting blood sugar and serum Lp(a) levels (r=.03, P>.5 by Spearman’s rank correlation coefficient).

**Discussion**

Murai et al\(^{20}\) first observed a positive association of high Lp(a) levels and the CAO subtype of cerebral infarction in Japanese patients. In their study, however, high Lp(a) levels were not significantly increased in the cerebral infarction group as a whole or in the PAO subtype group. Subsequently, Zenker et al\(^{21}\) reported that the median values of serum Lp(a) levels were significantly higher in white patients with cerebrovascular disease than in control subjects. More recently, Woo et al\(^{22}\) reported that a high Lp(a) level increased the overall risk of stroke, especially cerebral infarction and intracerebral hemorrhage, in Chinese patients. Although we excluded the subjects with AF to omit cardiac embolic strokes from the statistical analysis in the present study, Murai et al\(^{20}\) and Zenker et al\(^{21}\) did not refer to subjects with AF in their studies. On the other hand, Woo et al\(^{22}\) evaluated the risk factors including AF but did not exclude subjects with AF in their multivariate analysis. In addition, in the three studies reported above, brain CT was used for the neuroradiological examinations. In the present study, MRI, which can detect smaller and fainter lesions than CT, was used for the diagnostic examinations.

Table 2. Age, Serum Lipids, and Fasting Blood Sugar Levels in Cerebral Infarction Patients Without Atrial Fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=81)</th>
<th>Cerebral infarction patients without AF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=45)</td>
<td>PAO (n=34)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.1±8.6</td>
<td>62.0±8.1</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>188.3±32.0</td>
<td>193.3±38.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>112.8±60.7</td>
<td>118.0±45.6</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>53.4±14.4</td>
<td>46.4±14.4*</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>107.9±29.3</td>
<td>115.8±36.3</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>106.2±30.2</td>
<td>105.8±29.8</td>
</tr>
</tbody>
</table>

Values are mean±SD. AF, atrial fibrillation; PAO, perforating artery occlusion; CAO, cortical artery occlusion.

*P<.01, †P<.05 compared with control subjects by Student’s t test.
study, the frequency distribution of serum Lp(a) levels was remarkably shifted to a higher range in patients with cerebral infarction compared with control subjects, and the incidence of subjects with Lp(a) levels of ≥42.6 mg/dL or above, which is the 95th percentile of the control subjects, was significantly higher in patients than in control subjects. Stepwise logistic regression analysis also revealed three independent risk factors, one of which was high serum Lp(a) levels. These findings indicate that high serum Lp(a) levels are an independent risk factor for cerebral infarction as a whole.

Murai et al.20 reported a positive association between high Lp(a) levels and the CAO type of cerebral infarction. Woo et al.22 divided strokes into three subtypes: intracerebral hemorrhage, lacunar infarction, and cerebral infarction. The cerebral infarction subtype in the study of Woo et al very likely corresponds to the CAO subtype. In the present study, a positive association with high Lp(a) levels was also observed in the CAO group \((P<.05)\) when subjects with AF were not excluded. When subjects with AF were excluded to omit cardiac embolic strokes from the analysis, a statistically significant positive association was not observed in the CAO group, probably because of the small sample size. The stepwise logistic regression procedure also could not be performed because of the small sample size. We could not draw a conclusion about the independent contribution of high serum Lp(a) levels in the development of the CAO subtype in this study.

In the present study, a positive association between high serum Lp(a) levels and the PAO subtype of cerebral infarction was observed. Stepwise logistic regression analysis also revealed three independent risk factors, including high serum Lp(a) levels in the PAO subtype of cerebral infarction. In the study of Woo et al., lacunar infarction, which very likely corresponds to the PAO subtype, did not seem to be associated with high Lp(a) levels. Therefore, there is a discrepancy between the results of our study and the studies reported by Murai et al.20 and Woo et al.22 Because we selected patients by the onset age of younger than 65 years and the mean age of our patients was younger than in the two aforementioned studies, the discrepancy may be due to the difference in ages. In addition, because MRI can detect smaller and fainter lesions than CT, the difference in methods of examination may also be related to this discrepancy.

Although it has been suggested that serum Lp(a) levels are increased in patients with DM, Lp(a) levels were not related to the history of DM or fasting blood sugar in the present study. The data obtained in this study suggest that high Lp(a) levels are an independent risk factor for cerebral infarction as a whole as well as for the PAO subtype. Since Lp(a) levels are to a great extent controlled by the apo(a) locus,11,12 an association study on cerebral infarction and the apo(a) phenotypes is under way in our laboratories.

### References


### Table 3. Prevalence of Potential Risk Factors in Control Group and Cerebral Infarction Patients Without Atrial Fibrillation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n=81)</th>
<th>Cerebral infarction patients without AF (n=45)</th>
<th>PAO (n=34)</th>
<th>CAO (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25.9</td>
<td>21</td>
<td>60.0</td>
<td>27*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4.9</td>
<td>4</td>
<td>8.9</td>
<td>4</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>35.8</td>
<td>29</td>
<td>53.3</td>
<td>24</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>51.9</td>
<td>42</td>
<td>42.2</td>
<td>19</td>
</tr>
<tr>
<td>Family history</td>
<td>32.1</td>
<td>26</td>
<td>44.4</td>
<td>20</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; PAO, perforating artery occlusion; CAO, cortical artery occlusion.

\[\chi^2=12.8, P<.001; \chi^2=13.8, P<.001.\]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>(\chi^2)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.47</td>
<td>0.428</td>
<td>11.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>0.0402</td>
<td>0.0144</td>
<td>7.82</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.0434</td>
<td>0.0164</td>
<td>6.97</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>PAO group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.65</td>
<td>0.475</td>
<td>12.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>0.0463</td>
<td>0.0158</td>
<td>8.54</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.0174</td>
<td>0.0173</td>
<td>4.52</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Lp(a), lipoprotein(a); HDL, high-density lipoprotein; PAO, perforating artery occlusion.