Lipoprotein (a) and Carotid Atherosclerosis in Young Patients With Stroke

Nathalie Nasr, MD, PhD; Jean Bernard Ruidavets, MD; Ahmed Farghali, MD; Brigitte Guidolin, MD; Bertrand Perret, MD, PhD; Vincent Larrue, MD

Background and Purpose—Elevated lipoprotein (a) concentration is associated with carotid atherosclerosis in middle-aged and older patients with ischemic stroke. This association has not been explored in young patients with stroke.

Methods—A retrospective analysis of data from patients aged 16 to 54 years consecutively treated for acute ischemic stroke in a tertiary stroke unit during 4.5 years was performed. We graded carotid atherosclerosis using carotid duplex as: no atherosclerosis (A); plaque without stenosis (B); or stenosis ≥50% (C).

Results—One hundred ninety-six patients were included (male/female: 119/77; mean age±SD: 44.3±8.6 years): 115 in Group A; 67 in Group B; and 14 in Group C. Multivariate analysis using polynomial logistic regression showed a graded association of lipoprotein (a) plasma concentration with carotid atherosclerosis (P<0.001).

Conclusions—Our results showed a positive association of lipoprotein (a) plasma concentration with carotid atherosclerosis in young adults with ischemic stroke. This association was strong, graded, and independent of traditional risk factors including cholesterol. (Stroke. 2011;42:3616-3618.)

Key Words: carotid atherosclerosis ■ lipoprotein (a) ■ stroke

Elevated plasma concentration of lipoprotein (a) (Lp(a)) is a risk factor for myocardial infarction and stroke. This association does not depend on levels of cholesterol or other traditional risk factors. Potential mechanisms linking Lp(a) to cardiovascular disease include promotion of atherosclerosis and thrombosis.1

Several studies have shown a positive association of elevated Lp(a) plasma concentration with advanced carotid atherosclerosis (CA) in patients with ischemic stroke. However, these studies included mostly middle-aged and older subjects.2,3 Studies in the young have only included persons free of cerebrovascular symptoms and failed to demonstrate any association of Lp(a) concentration with early-stage CA as measured by intima-media thickness.4,5

In the present study, we sought to determine whether Lp(a) concentration was associated with CA in young adults with ischemic stroke.

Materials and Methods

This study was a retrospective analysis of data from patients aged 16 to 54 years consecutively treated for acute ischemic stroke in a tertiary stroke unit from January 2006 to June 2010.

Our institution did not require ethical review for this retrospective analysis of data that had been obtained as part of routine clinical care.

We assessed CA using duplex sonography (Philips; IU22) and classified patients into 3 groups: no atherosclerosis (Group A); plaque without stenosis (Group B); and stenosis ≥50% (Group C).6,7

Lp(a) concentration was measured by immunonephelometry using an automated assay (Immage; Beckman-Coulter). The normal value of Lp(a) in our laboratory is 0.3 g/L.

Each test (carotid duplex sonography and Lp[a] plasma concentration) was performed blinded to the results of the other.

The Cochran-Armitage trend test and a 1-way analysis of variance were used to search for an association between categorical and continuous variables, respectively, and CA grades. We used polytomous logistic regression to compare risk factors for grades subtypes and estimates ORs. Age, sex, and statin therapy were entered into the model a priori. Each other potential explicative variable was entered in the model step by step. Polynomial regression analyses were used to examine for possible nonlinear relation for each quantitative variable. The probability value <0.05 was considered significant.

Results

The initial study population was composed of 316 patients. Lp(a) plasma concentration measurement and carotid duplex sonography were performed in 225 patients. Data required for analysis were available in 196 patients. The study population included 119 men and 77 women. The mean age (±SD) was: 44.3 (±8.6) years.
Carotid duplex ultrasonography showed no atherosclerosis in 115 patients (Group A), plaque without significant stenosis in 67 patients (Group B), and carotid stenosis ≥50% in 14 patients (Group C).

Characteristics of patients and plasma levels of lipid variables according to CA grades are summarized in Table 1. Age, cigarette smoking, diabetes, hypertension, triglycerides, statin therapy, and Lp(a) concentrations were significantly associated with CA.

Multinomial logistic regression analysis showed a graded association of Lp(a) plasma concentration with CA (Table 2). All interactions of Lp(a) with age, sex, hypertension, smoking, diabetes, and statin therapy were tested. No interaction was statistically significant.

Table 1. Characteristics of Patients According to Carotid Atherosclerosis Grades

<table>
<thead>
<tr>
<th></th>
<th>Grade A (n=115)</th>
<th>Grade B (n=67)</th>
<th>Grade C (n=14)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.3 (9.7)</td>
<td>48.6 (4.3)</td>
<td>47.5 (3.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>54.8</td>
<td>68.7</td>
<td>71.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>16.5</td>
<td>47.8</td>
<td>28.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>39.1</td>
<td>76.1</td>
<td>85.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>2.6</td>
<td>17.9</td>
<td>21.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Statin therapy before stroke, %</td>
<td>7.0</td>
<td>16.4</td>
<td>21.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Total cholesterol, g/L</td>
<td>1.90 (0.37)</td>
<td>2.05 (0.44)</td>
<td>1.95 (0.64)</td>
<td>0.07*</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, g/L</td>
<td>0.51 (0.15)</td>
<td>0.48 (0.14)</td>
<td>0.45 (0.13)</td>
<td>0.18*</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, g/L</td>
<td>1.15 (0.34)</td>
<td>1.28 (0.37)</td>
<td>1.23 (0.55)</td>
<td>0.08*</td>
</tr>
<tr>
<td>Triglycerides, g/L</td>
<td>1.22 (0.59)</td>
<td>1.34 (0.58)</td>
<td>1.85 (1.15)</td>
<td>0.008†</td>
</tr>
<tr>
<td>Lipoprotein (a), g/L</td>
<td>0.26 (0.33)</td>
<td>0.44 (0.43)</td>
<td>0.73 (0.69)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise indicated.
*Welch analysis of variance.
†Analysis performed after log-transformed data.

Carotid duplex ultrasonography showed no atherosclerosis in 115 patients (Group A), plaque without significant stenosis in 67 patients (Group B), and carotid stenosis ≥50% in 14 patients (Group C).

Characteristics of patients and plasma levels of lipid variables according to CA grades are summarized in Table 1. Age, cigarette smoking, diabetes, hypertension, triglycerides, statin therapy, and Lp(a) concentrations were significantly associated with CA.

Multinomial logistic regression analysis showed a graded association of Lp(a) plasma concentration with CA (Table 2). All interactions of Lp(a) with age, sex, hypertension, smoking, diabetes, and statin therapy were tested. No interaction was statistically significant.

Table 2. Variables Associated With Carotid Atherosclerosis in Multivariate Analysis Using Stepwise Polynomial Logistic Regression With Grade A (N=115) as a Reference

<table>
<thead>
<tr>
<th></th>
<th>Grade B (N=67)</th>
<th>Grade C (N=14)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* (≥47 y)</td>
<td>4.36 (1.94–9.82)</td>
<td>4.24 (1.04–17.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.90 (0.41–2.01)</td>
<td>0.95 (0.24–3.79)</td>
<td>0.95</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.27 (1.81–10.8)</td>
<td>1.61 (0.34–7.49)</td>
<td>0.13</td>
</tr>
<tr>
<td>Smoking</td>
<td>6.67 (2.87–15.5)</td>
<td>11.5 (2.07–64.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11.3 (2.26–56.4)</td>
<td>25.3 (2.88–222.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>0.68 (0.19–2.41)</td>
<td>1.37 (0.21–8.89)</td>
<td>0.84</td>
</tr>
<tr>
<td>Lipoprotein (a) for 1 SD</td>
<td>1.89 (1.26–2.85)</td>
<td>2.96 (1.68–5.21)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; OR, odds ratio; CI, confidence interval.
*For age, 47 y is the median. In each cell, odds ratio (95% confidence interval).

The graded association of Lp(a) plasma concentration with CA was still highly significant using cutoff values commonly used in clinical practice (Table 3).

**Discussion**

The present study shows a positive association of Lp(a) plasma concentration with CA in young adults with ischemic stroke. This association was strong and independent of traditional risk factors including cholesterol. There was a graded relationship between Lp(a) concentration and severity of CA. Age and diabetes were, however, more strongly associated with CA than Lp(a).

Our findings are consistent with the results of studies in older patients. On the other hand, they contrast with previous studies in young adults that could not demonstrate any significant relationship of Lp(a) with early-stage atherosclerosis as defined by the intima-media thickness. These studies were population-based or included volunteers free of cerebrovascular symptoms and advanced atherosclerotic lesions. The apparent discrepancy between our results and previous findings in young subjects might be explained by a variable effect of Lp(a) on the progression of atherosclerosis depending on the lesion stage. In keeping with this interpretation, a previous study in older patients showed that Lp(a) concentration was associated with carotid stenosis or occlusion but not with total plaque area.

There are some potential limitations to our study. The retrospective design might have caused some selection bias because required data were not available in all patients.

There is some heterogeneity in the size of Lp(a) related to a variable size of apolipoprotein (a) isoforms. Smaller apolipoprotein (a) isoforms have been associated with cardiovascular risk and CA. However, it is uncertain whether these associations are independent of Lp(a) concentration because apolipoprotein (a) size is inversely correlated with Lp(a) concentration.

In conclusion, our results suggest a graded relationship between Lp(a) concentration and CA in young patients with ischemic stroke. These findings underscore the need for well-characterized longitudinal studies to confirm such a relationship.

**Disclosures**

None.
References


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