Chlamydia pneumoniae Antibodies and High Lipoprotein(a) Levels Do Not Predict Ischemic Cerebral Infarctions
Results From a Nested Case-Control Study in Northern Sweden

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Background and Purpose—An association between high lipoprotein(a) [Lp(a)] levels and positive Chlamydia pneumoniae IgG titers in coronary artery disease has been described. The possibility of predicting ischemic stroke by measurements of plasma Lp(a) and C pneumoniae antibodies was investigated.

Methods—This incident case-control study included 101 case subjects (cases) who had suffered ischemic cerebral infarctions and 201 matched control subjects (controls). The study population was nested within the Västerbotten Intervention Program or the WHO MONICA project. Plasma samples were measured for C pneumoniae–specific IgG and IgA antibodies and Lp(a).

Results—A significantly higher mean Lp(a) level was found in female cases than in female controls. However, plasma Lp(a) was unable to predict ischemic cerebral infarctions in either women or men. The proportion of individuals with positive C pneumoniae–specific IgG or IgA titers did not differ between cases and controls. Antibody titers were unable to predict a future stroke. The proportion of individuals with a positive C pneumoniae IgG titer in combination with a high Lp(a) level did not differ significantly between cases and controls.

Conclusions—These data suggest that there is no association between baseline plasma Lp(a) levels, presence of C pneumoniae antibodies, and future ischemic cerebral infarctions. Furthermore, no evidence of an interactive effect between high Lp(a) levels and C pneumoniae IgG titers was found. However, selection bias and a recent C pneumoniae epidemic may have influenced the results. (Stroke. 1999;30:2013-2018.)

Key Words: lipoprotein(a) ■ ischemic cerebrovascular disease ■ Chlamydia pneumoniae

Lipoprotein(a) [Lp(a)] is a known independent risk factor for the development of coronary artery disease.1-5 Most previous studies aimed at investigating a possible connection between ischemic stroke and Lp(a) have demonstrated higher Lp(a) levels among case subjects (cases) than among control subjects (controls).6-13 However, only 1 previous study has evaluated the association between baseline plasma concentration of Lp(a) and future risk of stroke.14

In addition to the known risk factors of ischemic cerebral infarctions, eg, hypertension, smoking, diabetes mellitus, and hypercholesterolemia, infectious and immunological mechanisms has been suggested.15-17 The obligate intracellular bacterium Chlamydia pneumoniae is one of the pathogens that has been linked to atherosclerosis.18-22 The combination of high C pneumoniae IgG titers and increased Lp(a) levels has been shown to occur significantly more often in male patients with early coronary artery disease than in male controls.23 It was suggested that this finding was due to a common involvement in an autoimmune mechanism that promotes atherosclerosis.

The aim of the present study was not only to investigate whether plasma Lp(a) and C pneumoniae IgG and IgA titers can predict future stroke but also to evaluate the suggested interactive effect between high Lp(a) levels and positive C pneumoniae IgG titers in cerebrovascular atherosclerosis.

Subjects and Methods

The subjects in this study were described earlier.24 All cases and controls participated in the Västerbotten Intervention Program (VIP),25 a northern Swedish community intervention program, or in the WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project,26 which are running concurrently in northern Sweden. Blood samples were donated to the Northern Sweden Medical Research Bank (NSMRB) before the stroke. The inclusion criteria were met in 129 of 166 reported stroke subjects in the Northern Sweden MONICA incidence registry. To meet the inclusion criteria, cases could not have a cancer diagnosis according to the Swedish National Cancer Registry. In addition, they should have participated in the VIP or MONICA health surveys and donated a blood sample to the NSMRB before the stroke event. Individuals with a previous acute myocardial infarction and/or stroke were excluded. The classification of stroke events and the diagnostic
The presence of C. pneumoniae-specific IgG and IgA antibodies in plasma was determined by indirect immunofluorescence using strain IOL-207 as antigen. An IgG titer in plasma of $1/16$ were judged to be positive and were used for calculation of $P$ values for continuous variables.

**TABLE 1. Distribution of Risk Factors for Stroke in Cases and Controls at Baseline**

<table>
<thead>
<tr>
<th></th>
<th>All Cases</th>
<th>All Controls</th>
<th>$P$</th>
<th>Male Cases</th>
<th>Male Controls</th>
<th>$P$</th>
<th>Female Cases</th>
<th>Female Controls</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>($n=101$)</td>
<td>55.6 (6.9)</td>
<td>55.6 (6.8)</td>
<td>0.965</td>
<td>55.7 (6.8)</td>
<td>55.6 (6.8)</td>
<td>0.974</td>
<td>55.6 (7.1)</td>
<td>55.5 (7.0)</td>
<td>0.976</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.9 (4.1)</td>
<td>26.5 (4.0)</td>
<td>0.507</td>
<td>26.2 (3.4)</td>
<td>26.1 (2.9)</td>
<td>0.894</td>
<td>27.8 (4.9)</td>
<td>27.1 (5.2)</td>
<td>0.444</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.4 (1.3)</td>
<td>6.3 (1.4)</td>
<td>0.456</td>
<td>6.3 (1.2)</td>
<td>6.2 (1.3)</td>
<td>0.915</td>
<td>6.7 (1.4)</td>
<td>6.5 (1.4)</td>
<td>0.310</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10/98 (10)</td>
<td>1/196 (0.5)</td>
<td>&lt;0.005</td>
<td>9/58 (16)</td>
<td>1/118 (1)</td>
<td>&lt;0.005</td>
<td>1/40 (3)</td>
<td>0/78 (0)</td>
<td>0.733</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42/100 (42)</td>
<td>63/201 (31)</td>
<td>0.089</td>
<td>25/60 (42)</td>
<td>36/119 (30)</td>
<td>0.176</td>
<td>17/40 (43)</td>
<td>27/82 (33)</td>
<td>0.405</td>
</tr>
<tr>
<td>Present smokers</td>
<td>25/99 (25)</td>
<td>32/199 (16)</td>
<td>0.082</td>
<td>16/59 (27)</td>
<td>24/118 (20)</td>
<td>0.409</td>
<td>9/40 (23)</td>
<td>8/81 (10)</td>
<td>0.109</td>
</tr>
</tbody>
</table>

Values are mean (SD) or number (%). For categorical variables, $P$ values were calculated by use of continuity-corrected $\chi^2$ analyses. Independent-sample $t$ tests were used for calculation of $P$ values for continuous variables.

**Results**

The distribution of risk factors for stroke in cases and controls at baseline is presented in Table 1.

The proportion of individuals with $Lp(a) \geq 300$ mg/L in plasma did not differ significantly between cases and controls (Table 2). A similar result was found when men and women were analyzed separately. However, a significantly higher mean $Lp(a)$ level was found in female cases than in female controls. When men were analyzed separately, no difference was found. The results from the conditional logistic regression analyses did not show any association between the risk of ischemic cerebral infarction and $Lp(a)$ either in the total population or in men or women (Table 3).

Adjustment for smoking, hypertension, diabetes mellitus, BMI, and total cholesterol was performed for the total population but not in women and men separately, because there were too few subjects. The adjustment did not change the result for the total population (Table 3).

The distribution of IgG and IgA titers among cases and controls is presented in Table 4. No significant difference in proportion of individuals with a positive C. pneumoniae-specific IgG or IgA titer was found when cases and controls were compared (Table 2). Similar results were found when men and women were analyzed separately. The risk of cerebral infarction was not found to be associated with a positive C. pneumoniae-specific IgG or IgA titer in plasma (Table 3). Surprisingly, when adjustment was made for smoking, hypertension, diabetes mellitus, BMI, and total cholesterol, a decreased risk of cerebral infarction was found to be associated with a positive C. pneumoniae IgG titer in the total population (Table 3). Adjustment was not performed in women and men separately.

The proportion of individuals with a positive C. pneumoniae IgG titer and $\geq 300$ mg/L $Lp(a)$ in plasma did not differ significantly between cases and controls (Table 2). A
combination or only 1 of the characteristics did not seem to have any influence on the risk of developing ischemic cerebral infarction in this population (Table 3).

The prevalence rate of \textit{C pneumoniae} IgG seropositivity in smokers was 89% and in nonsmokers 83% (\textit{P}=0.400). Daily smoking was reported in 25% of the cases and in 16% of the controls (\textit{P}=0.082) (Table 1).

\section*{Discussion}

In addition to traditional risk factors, an infectious pathogenesis for atherosclerosis has been proposed and a number of different pathogens have been investigated. The first serological evidence of an association between the obligate intracellular bacterium \textit{C pneumoniae} and atherosclerosis in coronary arteries was provided in 1988.\footnote{Glader et al. \textit{C pneumoniae} and Lp(a) for Cerebral Infarctions 2015} Seropositivity for \textit{C pneumoniae} was found to be significantly more common among individuals with chronic coronary artery disease and acute myocardial infarction than among controls. The issue of a connection between \textit{C pneumoniae} and atherosclerosis in cerebral arteries has also been addressed. An association between \textit{C pneumoniae} and stroke has been demonstrated in a few studies.\footnote{Glader et al. \textit{C pneumoniae} and Lp(a) for Cerebral Infarctions 2015} We could not confirm this association in the present study, however, because no significant difference was found between patients and controls regarding \textit{C pneumoniae}–specific antibodies. Seropositivity for \textit{C pneumoniae} was found not to be associated with an increased risk of

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|l|l|}
\hline
 & \textbf{All Cases} & \textbf{All Controls} & \textbf{P} & \textbf{Male Cases} & \textbf{Male Controls} & \textbf{P} & \textbf{Female Cases} & \textbf{Female Controls} & \textbf{P} \\
\hline
\textbf{Lp(a) in plasma, mg/L} & 184.5 (207.5) & 167.6 (224.0) & 0.243 & 155.6 (198.3) & 160.5 (193.8) & 0.868 & 224.9 (237.0) & 178.1 (257.7) & 0.049 \\
\hline
& n=96 & n=196 & & n=56 & n=116 & & n=40 & n=80 & \\
\hline
\textbf{Lp(a) in plasma} \geq 300 mg/L & 23/96 (24) & 33/196 (17) & 0.196 & 11/56 (20) & 18/116 (16) & 0.646 & 12/40 (30) & 15/80 (19) & 0.246 \\
\hline
\textbf{C.p.-IgG in plasma} = 1/32 & 77/97 (79) & 170/197 (86) & 0.177 & 48/57 (84) & 100/117 (86) & 1.000 & 29/40 (73) & 70/80 (88) & 0.074 \\
\hline
\textbf{C.p.-IgA in plasma} = 1/16 & 44/97 (45) & 85/197 (43) & 0.814 & 31/57 (54) & 58/117 (50) & 0.664 & 13/40 (33) & 27/80 (34) & 1.000 \\
\hline
\textbf{Lp(a) in plasma} < 300 mg/L and \textbf{C.p.-IgG in plasma} < 1/32 (I) & 14 (15) & 20 (10) & 8 (14) & 12 (10) & 6 (15) & 8 (10) & & & \\
\hline
\textbf{Lp(a) in plasma} < 300 mg/L and \textbf{C.p.-IgG in plasma} \geq 1/32 (II) & 59 (62) & 141 (73) & 37 (66) & 85 (74) & 22 (56) & 56 (71) & & & \\
\hline
\textbf{Lp(a) in plasma} \geq 300 mg/L and \textbf{C.p.-IgG in plasma} < 1/32 (III) & 6 (6) & 6 (3) & 1 (2) & 4 (4) & 5 (13) & 2 (3) & & & \\
\hline
\textbf{Lp(a) in plasma} \geq 300 mg/L and \textbf{C.p.-IgG in plasma} \geq 1/32 (IV) & 16 (17) & 27 (14) & 10 (18) & 14 (12) & 6 (15) & 13 (16) & & & \\
\hline
\textbf{Total} & 95 & 194 & 0.256 & 56 & 115 & 0.565 & 39 & 79 & 0.106 \\
\hline
\end{tabular}
\caption{Values are mean (SD) or number (%). C.p. indicates \textit{C pneumoniae}. For categorical variables, \textit{P} values were calculated by use of continuity-corrected $\chi^2$ analysis or Fisher’s exact test. Independent-sample $t$ tests were used for calculation of \textit{P} values for continuous variables.}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|l|}
\hline
 & \textbf{All Cases} & \textbf{All Controls} & \textbf{Male Cases} & \textbf{Male Controls} & \textbf{Female Cases} & \textbf{Female Controls} \\
\hline
\textbf{Lp(a) in plasma per 200 mg/L} & 1.1 & 0.8–1.4 & 1.1 & 0.9–1.5 & 0.9 & 0.7–1.3 \\
\hline
& 1.0 & 1.0 & & & & 1.2 & 0.9–1.7 \\
\hline
\textbf{Lp(a) in plasma} \geq 300 mg/L & 1.6 & 0.8–2.9 & 1.8 & 0.9–3.7 & 1.2 & 0.5–2.9 \\
\hline
& 1.0 & 1.0 & & & & 2.2 & 0.8–5.9 \\
\hline
\textbf{C.p.-IgG in plasma} \geq 1/32 & 0.6 & 0.3–1.0 & 0.4 & 0.2–0.9 & 0.7 & 0.3–1.7 \\
\hline
& 1.0 & 1.0 & & & & 0.4 & 0.2–1.1 \\
\hline
\textbf{C.p.-IgA in plasma} \geq 1/16 & 1.1 & 0.6–1.8 & 0.9 & 0.5–1.6 & 1.2 & 0.6–2.4 \\
\hline
& 1.0 & 1.0 & & & & 0.9 & 0.4–2.1 \\
\hline
\textbf{Lp(a) in plasma} \geq 300 mg/L and \textbf{C.p.-IgG in plasma} \geq 1/32 (I) & 0.6 & 0.3–1.3 & 0.4 & 0.2–1.0 & 0.5 & 0.2–1.4 \\
\hline
& 1.6 & 0.4–5.6 & 1.3 & 0.4–5.0 & 0.3 & 0.0–3.2 \\
\hline
\textbf{Lp(a) in plasma} \geq 300 mg/L and \textbf{C.p.-IgG in plasma} \geq 1/32 (II) & 0.9 & 0.3–2.3 & 0.8 & 0.3–2.2 & 0.8 & 0.2–2.8 \\
\hline
& 0.9 & 0.3–2.3 & 0.8 & 0.3–2.2 & 0.8 & 0.2–2.8 \\
\hline
\end{tabular}
\caption{Conditional Logistic Regression Analyses Expressing ORs and 95\% CIs for Different Lp(a) and Positive \textit{C pneumoniae}–Specific IgG and IgA Antibody Contents in Plasma}
\end{table}
TABLE 4. Comparison of C pneumoniae IgG and IgA Levels in Cases and Controls with Various Cutoff Points

<table>
<thead>
<tr>
<th>C.p.-IgG</th>
<th>All Cases (n=97)</th>
<th>All Controls (n=197)</th>
<th>P</th>
<th>OR</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1/16</td>
<td>14 (14)</td>
<td>17 (9)</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1/16</td>
<td>83 (86)</td>
<td>180 (91)</td>
<td>0.186</td>
<td>0.5</td>
<td>0.2–1.0</td>
</tr>
<tr>
<td>&lt;1/32</td>
<td>20 (21)</td>
<td>27 (14)</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1/32</td>
<td>77 (79)</td>
<td>170 (86)</td>
<td>0.177</td>
<td>0.6</td>
<td>0.3–1.0</td>
</tr>
<tr>
<td>&lt;1/64</td>
<td>33 (34)</td>
<td>67 (34)</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1/64</td>
<td>64 (66)</td>
<td>130 (66)</td>
<td>1.000</td>
<td>0.9</td>
<td>0.6–1.5</td>
</tr>
<tr>
<td>&lt;1/128</td>
<td>48 (49)</td>
<td>95 (48)</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1/128</td>
<td>49 (51)</td>
<td>102 (52)</td>
<td>0.937</td>
<td>0.9</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>&lt;1/256</td>
<td>66 (68)</td>
<td>136 (69)</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1/256</td>
<td>31 (32)</td>
<td>61 (31)</td>
<td>0.969</td>
<td>1.0</td>
<td>0.6–1.8</td>
</tr>
<tr>
<td>&lt;1/512</td>
<td>76 (78)</td>
<td>167 (85)</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1/512</td>
<td>21 (22)</td>
<td>30 (15)</td>
<td>0.229</td>
<td>1.6</td>
<td>0.8–3.0</td>
</tr>
<tr>
<td>C.p.-IgA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1/8</td>
<td>44 (45)</td>
<td>92 (47)</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1/8</td>
<td>53 (55)</td>
<td>105 (53)</td>
<td>0.927</td>
<td>1.0</td>
<td>0.6–1.7</td>
</tr>
<tr>
<td>&lt;1/16</td>
<td>53 (55)</td>
<td>112 (57)</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1/16</td>
<td>44 (45)</td>
<td>85 (43)</td>
<td>0.814</td>
<td>1.1</td>
<td>0.6–1.8</td>
</tr>
<tr>
<td>&lt;1/32</td>
<td>72 (74)</td>
<td>145 (74)</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1/32</td>
<td>25 (26)</td>
<td>52 (26)</td>
<td>1.000</td>
<td>0.9</td>
<td>0.5–1.7</td>
</tr>
<tr>
<td>&lt;1/64</td>
<td>78 (80)</td>
<td>160 (81)</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1/64</td>
<td>19 (20)</td>
<td>37 (19)</td>
<td>0.994</td>
<td>1.0</td>
<td>0.5–2.0</td>
</tr>
</tbody>
</table>

Values are number (%). C.p. indicates C pneumoniae. P values were calculated by use of continuity-corrected χ² analyses. Odds ratios and 95% CIs were calculated by use of conditional logistic regression analyses.

ischemic cerebral infarction. Surprisingly, when controlled for other risk factors, such as smoking, hypertension, BMI, diabetes mellitus, and total cholesterol, a decreased risk of ischemic cerebral infarction was found to be associated with a positive C pneumoniae–specific IgG titer at baseline.

Smoking is associated with the development of atherosclerotic disease. In this study, the proportion of smokers was larger among cases than controls, even though the difference was statistically nonsignificant. An association between smoking and C pneumoniae seropositivity has been described previously. Smoking may increase the risk of being infected with C pneumoniae and should perhaps be regarded as a confounder of the association between C pneumoniae infections and the development of atherosclerosis. However, in the present study, no association was found between C pneumoniae IgG seropositivity and daily smoking.

The prevalence of positive C pneumoniae IgG titer has been shown to increase with increasing age. More than 50% of middle-aged adults have C pneumoniae–specific IgG antibodies. In our study population, with a mean age of ≈56 years, 79% of the cases and 86% of the controls had positive C pneumoniae IgG antibody titers. This high prevalence of seropositivity in both cases and controls may be explained in part by a recent large C pneumoniae epidemic in northern Sweden. The possibility of finding an association between chronic C pneumoniae infections and ischemic cerebral infarctions may have been prevented by this epidemic, especially because serology cannot distinguish between an ongoing and an earlier infection. If the sampling had been repeated in time, the proportion of controls with positive titers might have been lower.

Serology has been shown to be an unsatisfactory marker of the C pneumoniae–associated arterial disease status. The bacterium has even been found to a larger extent in tissues from individuals with a low C pneumoniae–specific IgG titer than in individuals with a high IgG titer. These findings may also be valid for cerebral arterial fatty streaks and fibrolipid plaques.

High levels of Lp(a) are a known independent risk factor for the development of coronary artery disease and acute myocardial infarctions. Results have also been presented linking high Lp(a) levels and cerebrovascular disease. However, other studies have failed to confirm such an association. Comparison of results from different studies is difficult because of methodological variations. For example, the method for defining cases differs among studies. In the ARIC study, no distinction was made between ischemic cerebral infarctions and hemorrhagic strokes, and the diagnoses were based on self-reported events. In the present study, the diagnosis of ischemic cerebral infarction was verified by CT examinations, and cases with hemorrhagic strokes were excluded. In most studies, cases were sampled after the ictus. Because Lp(a) has been shown to react as an acute-phase protein, the observed differences between cases and controls might have been exaggerated because of the time chosen for sampling.

To the best of our knowledge, only 1 study before the present one has directly evaluated the risk of future stroke and baseline levels of plasma Lp(a) concentration. In that study, by Ridker et al, no association was found between baseline plasma concentration of Lp(a) and future risk of stroke, a result that is in agreement with our findings. However, factors that may influence the data need to be considered. For example, atrial fibrillation is a strong independent risk factor for stroke. Shintani et al found a significant difference in Lp(a) levels between cases with cerebral infarction and controls only when cases with atrial fibrillation were excluded. In the present study, the number of cases with atrial fibrillation is unknown, and therefore, the possibility exists that subjects with cardiac embolic strokes were included. The impact of this confounding factor is unknown.

Another methodological factor that is probably of importance is the fact that individuals who had previously suffered acute myocardial infarctions were excluded. As previously stated, high Lp(a) levels are known to increase the risk of developing early acute myocardial infarctions. In the present study, the population mean age is quite high. The possibility therefore exists that individuals at risk of suffering acute myocardial infarction as a result of high Lp(a) levels had already suffered the consequences of this risk factor and were therefore excluded. Accordingly, our negative findings may be partly due to the unintentional rejection of cases with high Lp(a) levels.

The age span in the present study is positively skewed. Only 6.9% of the cases are ≤45 years of age. Results have been presented indicating that Lp(a) plays an important role...
in the development of early cerebrovascular atherosclerosis. In a study population consisting of individuals with atherothrombotic stroke, Lp(a) levels were shown to be significantly increased in cases <45 years compared with cases >45 years old. It is not possible to address this issue in our study, because the number of young cases was limited. In the present study, female cases were found to have a significantly higher mean Lp(a) level than female controls. However, as in men, the logistic regression analysis did not show any association between high Lp(a) levels and an increased risk of ischemic cerebral infarction. A similar result has been described in a previous, not prospectively designed, study in which a nonsignificant trend toward higher mean Lp(a) levels among female cases compared with female controls was observed. Cardiovascular disease in premenopausal women is rare. After menopause, its occurrence increases, but it is still less frequent in women than in men of the same age. A relation between Lp(a) levels and female sex hormones has been suggested, and higher Lp(a) concentrations in postmenopausal women than in premenopausal women have been reported. Hormone replacement therapy has been shown to lower Lp(a) levels in postmenopausal women. In the present study, the difference in Lp(a) levels between cases and controls found in women but not in men may perhaps be explained by the fact that women are usually older than men when they suffer their first myocardial infarction. Because there was no significant age difference between men and women in the present study, the selection bias due to rejection of individuals with previous myocardial infarction is probably greater among men than women.

The pathogenic mechanisms linking high Lp(a) levels and atherosclerotic disorders have still not been fully explained. Numerous different hypotheses have been proposed. One important discovery was the striking homology between structures in apo(a) and plasminogen. This finding presented a structural basis for in vivo competition with plasminogen receptors on endothelial cells and with fibrin, which could damage the endothelial cells or inhibit fibrinolysis on the arterial wall because Lp(a) resists activation by tissue plasminogen activator. A hypothesis linking immunological mechanisms, high Lp(a) levels, C pneumoniae, and atherosclerosis has previously been presented. The serine protease domain in apo(a) has a structural resemblance to the trypsin unit of the nonpathogenic bacterium Streptomyces griseus. It has been suggested that cross-reactivity between antibodies against pathogenic bacterial epitopes and apo(a) in Lp(a) could occur if structural similarities exist. In a similar way, C pneumoniae–specific antibodies may form circulating immune complexes with apo(a) in Lp(a).

Certain HLA class II DR genotypes have been found to be significantly more common in male patients with early coronary artery disease than in controls, especially in patients with high Lp(a) levels. These results indicate that an immune response to Lp(a) antigenic sites might occur, restricted to the HLA class II system. The high Lp(a) level may be related to HLA class II DR genotypes. T cells cannot be activated by an HLA-presented antigen alone. Therefore, secondary simultaneous costimulatory signals are needed. Furthermore, the B7 surface molecules expressed by antigen-presenting cells are strong costimulatory signal carriers. These molecules can also be expressed by macrophages separately from the cell that presents the HLA antigen complex. Macrophages express B7 molecules when they are infected. C pneumoniae is capable of multiplying in monocytes-macrophages and has moreover been found in macrophages in atherosclerotic lesions. Lp(a) is known to be taken up by macrophages. If C pneumoniae is present in macrophages in the arterial wall and epitopes from apo(a) are presented at the same time, the T cells may be activated, resulting in T-cell proliferation and release of interferon-γ. This process would result in further activation of macrophages, induction of HLA class II antigens, and the formation of circulating immune complexes containing apo(a) immunoreactive epitopes. The harmful effects of a high Lp(a) level could be further aggravated by the presence of a chronic C pneumoniae infection leading to the formation of circulating immune complexes, possibly causing faster progression of the atherosclerotic process. It is not known whether the suggested interactive effect between high Lp(a) levels and positive C pneumoniae IgG titers is also relevant in cerebrovascular atherosclerosis, but our results fail to demonstrate any such association. Further studies to investigate interactions between Lp(a) and C pneumoniae are needed. Regarding C pneumoniae, detection of C pneumoniae DNA in peripheral blood mononuclear cells may be a better tool than serology for identifying subjects with a persistent C pneumoniae infection.

Acknowledgments

This study was supported by grants from the Swedish Medical Research Council (grant 27P-12314 to B.S.), the Stroke Fund, the Joint Committee of the Northern Sweden Care Region, the Swedish Heart-Lung Foundation, King Gustaf V’s 80th Anniversary Fund, and the Kempe Foundations. We wish to thank research assistant Åsa Ågren, Department of Public Health and Clinical Medicine, Umeå University, for her assistance in organizing data collection for the study and Mrs Karin Andersson for skillful technical assistance.

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Stroke, 1999;30:2013-2018
doi: 10.1161/01.STR.30.10.2013

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