Silent Cerebral Infarcts in Basal Ganglia Are Advanced in Congenital Protein C–Deficient Heterozygotes With Hypertension

Kazuomi Kario, Toshiyuki Sakata, Masahito Higashikawa, Yoshiaki Katayama, Satoshi Hoshide, Kazuyuki Shimada, and Toshiyuki Miyata

Congenital protein C deficiency is now widely recognized as a genetic risk for venous thrombosis. However, it remains uncertain whether this condition also confers risk for arterial thrombosis. We evaluated the association of congenital protein C deficiency with hypertension and silent cerebrovascular disease using brain magnetic resonance imaging (MRI) (T1- and T2-weighted and proton density images) in a large family pedigree of protein C deficiency diagnosed by gene analysis, compared with 46 non–pedigree related control subjects with normal protein C levels (75%) who were selected from among 55 asymptomatic hypertensive subjects matched for age and cardiovascular risk factors. Of the 58 living subjects in this pedigree, we measured plasma protein C levels in 45 subjects, and found 2 cerebral infarctions in the 24 heterozygotic subjects, whereas there was no stroke in the 21 normal homozygotic subjects. We performed brain MRI in 14 asymptomatic hypertensive subjects without any cardiovascular disease and in two patients with cerebral infarction, and found 28 cerebral infarcts (two corresponded to the patients’ neurologic deficits and 26 were silent). All were lacunar infarcts <10 cm in size. A total of 25 silent lacunar infarcts were found in nine heterozygotic subjects, whereas only one was found in the seven normal homozygotic subjects (2.8 v 0.14 lacunes per person, P = .002). No advanced white matter hyperintense lesions in T2-weighted images were found in either group. The prevalence of silent lacunar infarcts in the heterozygotic subjects was also significantly higher than that in normal control subjects (1.0 per person, P = .01). Concerning the distribution of silent infarcts, the number of lacunes located in the basal ganglia was higher in the heterozygotic subjects (2.3 per person, P < .001) than in the seven normal homozygotic subjects (0.14 per person) or in the control group (0.28 per person), whereas the number of lacunes in the white matter was not different among the groups. In conclusion, congenital protein C deficiency may accelerate the progression of silent cerebral infarct formation in hypertension, particularly in the basal ganglia, and may be a potential risk for stroke or vasculally induced dementia. Am J Hypertens 2001;14:818–822 © 2001 American Journal of Hypertension, Ltd.

Key Words: Silent cerebral infarcts, protein C deficiency, hypertension, basal ganglia.

Hypertension is one of the greatest risk factors for stroke. However, other risk factors for stroke in hypertensive subjects have not been fully investigated. Silent cerebral infarct, which is frequently detected in elderly or hypertensive subjects, is considered to be a predisposing condition for clinically overt stroke.1 We have recently found that coagulation activation increases along with silent cerebral infarct formation in the high-risk elderly population.2

Protein C, a vitamin K–dependent serine protease, serves as an anticoagulant through degradation of the procoagulant cofactors Va and VIIIa by its active form, activated protein C. Protein C is activated by thrombin in the presence of an endothelial cell cofactor, thrombomodulin, and endothelial cell protein C.3 The deficiency of this coagulation inhibitor leads to hypercoagulability. Congenital protein C deficiency is a well known risk factor for venous thrombosis.4 However, it is still controversial...
as to whether protein C deficiency confers potential risk for arterial thrombotic diseases (myocardial infarction and cerebral infarction). This is especially relevant to cerebral infarction, in which thrombomodulin is less commonly expressed in cerebral arteries compared with elsewhere in the circulation. Thus, the effect of protein C deficiency may be enhanced to reduce its coagulant inhibitory activity in the cerebral vessels, leading to atherosclerosis in the brain.

A persistent decrease in coagulation inhibitory activity in congenital protein C deficiency may result in silent cerebral infarcts through enhanced microthrombus formation. In this study, we therefore investigated silent cerebral infarcts in hypertensive subjects within a large family pedigree of protein C deficiency diagnosed by gene analysis.

**Subjects and Methods**

**Subjects**

The study populations are summarized in Fig. 1. We studied 58 subjects in the same family pedigree of congenital protein C deficiency diagnosed by gene analysis (protein C Asp359Asn). First we studied the incidence of stroke by telephone interviews. Then we recruited 16 hypertensive volunteers (two with previous strokes and 14 asymptomatic subjects), who agreed to further examination with brain magnetic resonance imaging (MRI), among the 45 subjects (78% of total subjects) in whom we had identified as heterozygotic for protein C deficiency (n = 24) or normal homozygotic subjects (n = 21). We also examined brain MRI in 55 asymptomatic hypertensive patients with or without diabetes mellitus, who were matched for age (between 48 and 71 years). We considered 46 (84%) subjects with protein C levels ≥ 75% among these 55 hypertensive patients as the control group (Fig. 1). Plasma protein C levels were measured using the amidolytic assay or coagulation assay as previously described. This study was approved by the Institutional Review Board at the Department of Cardiology, Jichi Medical School, and all subjects studied gave informed consent.

**Brain MRI**

Brain MRI was performed with a 1.5-T MR system (VISART, Toshiba, Tokyo, Japan). T1-weighted images (repetition time, 500 msec; echo time, 15 msec), T2-weighted images (repetition time, 3800 msec; echo time, 100 msec), and proton density images (repetition time, 2800 msec; echo time, 12 msec) were obtained in the transverse plane with sections 6 mm thick. A silent cerebral infarct was defined as a focal lesion ≥ 3 mm in diameter that was both of low intensity in the T1-weighted image and high intensity in the T2-weighted and proton density images. The location of silent cerebral infarct was coded separately as basal ganglia or white matter.

**Statistical Analysis**

Data are expressed as the mean ± SE or as percentages. One-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA) (controlling for age, gender, smoking status, hyperlipidemia, and diabetes) were performed to detect differences among groups, and Bonferroni’s test was used for multiple pairwise comparisons of means among groups. The χ²-test was used to evaluate differences in proportions among groups. Statistical calculations were performed using SPSS version 8.0J (SPSS

**FIG. 1.** The study populations. Study groups were obtained from a family pedigree of congenital protein C deficiency and hypertensive control subjects.
Results
In the 58 subjects within this family pedigree, there were two cases of cerebral infarction. One subtype was atherothrombotic infarction, and the other was lacunar infarction. Both subjects were heterozygotic for protein C deficiency. In the 16 hypertensive volunteers who agreed to the brain MRI study, we detected 28 cerebral infarcts (two corresponded to the patients’ neurological deficits and 26 were silent infarcts). All of these cerebral infarcts were lacunar infarcts, 10 mm. A total of 25 silent lacunar infarcts were found in nine heterozygotic subjects, whereas only one was found in the seven normal homozygotic subjects, (2.8 ± 0.11 lacunes per person, \( P < .001 \)) vs. 1.0 ± 0.23 (Table 1). No advanced white matter hyperintense lesions (visible only in T2-weighted images) were found in either group. The number of silent lacunar infarcts in the heterozygotes was significantly higher than in the 46 control subjects with a normal protein C level (\( \geq 75\% \)), who were matched for age and cardiovascular risk factors (1.0 per person, \( P = .01 \)).

Concerning the distribution of silent lacunar infarcts, the number of lacunes in the basal ganglia was higher in nine heterozygotic subjects (2.8 ± 0.90 lacunes per person, \( P < .001 \)) vs. 0.14 ± 0.14 (Table 2). In the seven normal homozygotic subjects (0.76 ± 0.19 per person) or in the control group (0.28 per person), whereas the number of lacunes in the white matter was not different among the groups. After controlling for age, gender, smoking status, hyperlipidemia, and diabetes, the results were essentially the same (Table 2).

Discussion
In this study, we found that silent cerebral infarcts were much more advanced in the hypertensive heterozygotic subjects with protein C deficiency than in the hypertensive normal homozygotic subjects within the same family pedi-

---

**Table 1.** Silent cerebrovascular disease in protein C deficient subjects with hypertension and hypertensive control subjects

<table>
<thead>
<tr>
<th>Protein C Deficiency Pedigree</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 9 )</td>
</tr>
<tr>
<td>Age, years</td>
<td>63 ± 2.2</td>
</tr>
<tr>
<td>Male (%)</td>
<td>44</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>11</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>44</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>44*</td>
</tr>
<tr>
<td>Clinical stroke (%)</td>
<td>22</td>
</tr>
<tr>
<td>Protein C activity level (%)</td>
<td>59 ± 4.0\†§</td>
</tr>
<tr>
<td>Silent lacunae (number/person)\¶</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>2.3 ± 0.90\†§</td>
</tr>
<tr>
<td>Deep white matter</td>
<td>0.33 ± 0.50</td>
</tr>
<tr>
<td>Total</td>
<td>2.8 ± 1.0\†‖</td>
</tr>
<tr>
<td>Advanced deep white matter lesion (%)#</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are mean ± SE for age, plasma protein C activity, and silent lacunae, or percentage for the prevalence of male, smoking, hyperlipidemia, diabetes, stroke, and advanced deep white matter lesion in each group.

* \( P < .05 \), \( \dagger P < .001 \), \( \ddagger P < .01 \) v normal homozygotes; \( § P < .001 \), \( \| P < .02 \) v control group.

¶ Detected by brain magnetic resonance imaging (MRI).

# High-intense lesion in the T2-weighted images of brain MRI.

---

**Table 2.** Association between silent lacunar infarcts and protein C deficiency in hypertension after controlling for cardiovascular risk factors

<table>
<thead>
<tr>
<th>Silent Lacunae, Number/Person</th>
<th>Protein C Deficiency Pedigree</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 9 )</td>
<td>( n = 7 )</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>2.4 ± 0.39\†</td>
<td>0.17 ± 0.48</td>
</tr>
<tr>
<td>Deep white matter</td>
<td>0.41 ± 0.40</td>
<td>0.09 ± 0.48</td>
</tr>
<tr>
<td>Total</td>
<td>2.9 ± 0.60\†§</td>
<td>0.26 ± 0.72</td>
</tr>
</tbody>
</table>

Data are mean ± SE after controlling for age, gender, smoking status, hyperlipidemia, and diabetes.

* \( P < .01 \); \( \ddagger P < .05 \) v normal homozygotic subjects; \( \ddagger P < .001 \); \( § P < .02 \) v control group.
igree, and in the hypertensive control group matched for age and other cardiovascular risk factors.

Lacunar Infarcts

In most previous reports on stroke occurring in patients with congenital protein C deficiency, major cerebral vessels were involved. However, in this study population, all of the silent cerebral infarcts were lacunar infarcts, which occurred in the small cerebral vessels. Hypertension is a well-known risk factor for lacunar stroke and accelerates the progression of silent lacunar infarcts. Thus, hypertension may have augmented the difference in the progression of silent cerebral infarction between the protein C–deficient heterozygotic and normal homozygotic subjects within this family. This speculation is consistent with the previous findings of a case report showing that, in two congenital protein C–deficient patients who developed ischemic stroke, advanced multiple lacunar infarctions were detected by brain MRI. Both patients also had hypertension.

Distribution of Silent Cerebral Infarcts

The silent lacunar infarcts found in heterozygotic subjects with congenital protein C deficiency are mainly distributed in the basal ganglia, whereas the white matter lacunes or high intensity lesions (visible only in the T2-weighted image) in the white matter were not increased when compared with normal homozygotic subjects within the same family pedigree or the control group with normal protein C levels, matched for age and cardiovascular risk factors. The pathogenesis of lacunar formation is different between the basal ganglia infarcts and the white matter infarcts. Sclerotic changes of the medullary arteries supplying the white matter are predominantly fibrohyaline thickenings of the wall, whereas the perforating arteries in the basal ganglia were of various forms. A recent study using brain MRI disclosed that even in the same silent lacunar infarcts, the related risk factors are different between the basal ganglia infarcts and the white matter infarcts. In that study, hypertension was a predominant risk factor for the white matter infarct, whereas carotid artery stenosis and coronary artery disease were associated with basal ganglia infarcts. Thus, that study indicated that the silent basal ganglia infarcts may partly be associated with systemic atherosclerosis when the protein C level is within normal range.

Pathogenesis

Basal ganglia infarcts found in the hypertensive heterozygotes of congenital protein C deficiency may be predominantly determined by the distribution of the protein C cofactor thrombomodulin. Thrombomodulin is distributed less in basal ganglia compared with the cerebral cortex. Thus, the impaired anticoagulant effect of persistent low protein C levels in the hypertensive heterozygotic subjects with congenital protein C deficiency may be augmented in the basal ganglia and may lead to the progression of silent lacunar infarction in the small vessels.

Clinical Significance

This study suggests the possibility that persistent lower protein C activity might predict stroke risk in hypertensive patients. Antithrombotic therapy including antiplatelet therapy might have greater benefit for high-risk hypertensive patients who also have lower protein C levels.

Study Limitations

The prevalence of diabetes and hyperlipidemia was higher in the heterozygotic subjects than in the normal homozygotic subjects within this pedigree. Both of these factors increase the risk for stroke, particularly atherothrombotic stroke, which occurs in larger cerebral arteries than does lacunar stroke. Thus, we could not completely exclude the two potentially confounding factors within this pedigree. However, when compared with the control group in which the prevalence of diabetes and hyperlipidemia was similar to that in heterozygotic subjects, the number of silent cerebral infarcts (particularly those located in the basal ganglia) was significantly higher in the heterozygotic subjects. In addition, even after controlling for these cardiovascular risk factors, heterozygosity remained an increased risk factor for silent lacunar infarction, particularly when located in the basal ganglia. Another study limitation is the small number of study subjects, who all come from one family. Further studies are necessary to confirm our findings.

In conclusion, our preliminary study indicates that congenital protein C deficiency may accelerate the progression of silent lacunar infarct formation in hypertension, particularly in the basal ganglia, and may be a potential risk factor for stroke.

Acknowledgment

We thank Ms. Beth Harre, BS (Integrative and Behavioral Cardiology Program, Zena and Michael A. Wiener Cardiovascular Institute Mount Sinai School of Medicine) for discussing this paper.

References