Incidence of Silent Lacunar Lesion in Normal Adults and Its Relation to Cerebral Blood Flow and Risk Factors

Shotai Kobayashi, MD, PhD; Kazunori Okada, MD, PhD; and Kazuya Yamashita, MD, PhD

Background and Purpose: There are few reports comparing incidence of silent lacunar lesions detected by magnetic resonance imaging and cerebral blood flow in neurologically normal adults.

Methods: We studied the incidence of such lesions and its relation to cerebral blood flow and risk factors in 246 neurologically normal adults (145 men, mean age 62 years; 101 women, mean age 60 years) who received health screening examinations of the brain.

Results: Thirty-two subjects (13%) had possible silent lacunar lesions (66% of these were recognized by both T1- and T2-weighted image). The regional cerebral blood flow measured by the xenon-133 inhalation method was significantly lower in subjects with silent lacunes than in those without (p<0.02). Cerebral blood flow was mildly but significantly decreased in those with silent lacunes (p<0.05). Periventricular hyperintensity was closely related to silent lacune (p<0.01). However, there was no significant difference in cerebral blood flow between subjects with and without apparent periventricular hyperintensity.

Conclusions: Silent lacunar lesion was closely related to decrease of cerebral circulation and may be an important risk factor for symptomatic cerebrovascular disease. (Stroke 1991;22:1379-1383)

Magnetic resonance signal abnormalities in the white matter have been recognized as incidental findings in neurologically normal elderly patients. The incidence of these hyperintense white matter lesions on T2-weighted images (T2WI) increases with advancing age and with an increase in risk factors for stroke. It has been suggested that white matter lesions are closely related to cerebrovascular disease. Meyer et al. reported that progressive decline in cerebral blood flow preceded symptomatic stroke by 2 years. However, there are few reports comparing incidence of abnormalities detected by magnetic resonance imaging (MRI) and cerebral blood flow in neurologically normal adults. We started health screening examinations of the brain in 1988 at the Institute of Shimane Health Science to prevent cerebrovascular diseases. In this investigation, we studied the incidence of silent lacune and its relation to regional cerebral blood flow (rCBF) and risk factors in normal adults.

Subjects and Methods

Among subjects registered for health screening of the brain, we selected 246 who had no history of cerebral disease and who were socially active and neurologically normal. The subjects consisted of 145 men (mean age 62±8.9 years) and 101 women (mean age 60±7.1 years) whose age distribution was 37–81 years. All subjects received a neurological examination by the same neurologist on the same day as MRI examination. Informed consent was obtained according to institutional guidelines.

Magnetic resonance imaging was performed by using 0.15-T MRI (MRI-T15, Toshiba Co., Japan). We used T2WI (repetition time [TR] 2,000 msec; echo time [TE] 50 msec) at the transverse plane parallel to the orbitomeatal line and T1-weighted images (T1WI) (inversion-recovery, TR 2,000 msec/TE 40 msec; inversion time 400 msec) at coronal slices at 1-cm intervals. We used the “moderate T2WI” because this technique showed the cerebrospinal fluid as a dark gray or black signal intensity and helped delineate periventricular foci of increased signal intensity from the cerebrospinal fluid in the adjacent space. We considered the lesion to be a silent lacune when the high-intensity area of the T2WI coincided with the low-intensity area of the T1WI (Figure 1). We also considered the lesion showing only a high-intensity area except for the rim of the ventricle on the T2WI to be a possible lacunar lesion. These two types of lesions were considered to be silent lacunes in this study.

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Received February 28, 1991; accepted June 11, 1991.
Periventricular hyperintensity (PVH) was evaluated on the T2WI and classified as grade 0–4 as follows: grade 0, no PVH; grade 1, a small localized area of PVH at the frontal horn; grade 2, thin PVH surrounding the lateral ventricle; grade 3, thick PVH surrounding the lateral ventricle; and grade 4, marked diffuse PVH. Evaluation of the lesions on MRI was made by two of the authors independently and in a blinded fashion. Regional cerebral blood flow was measured by the xenon-133 inhalation method, using a Novo-16ch-cerebrograph (Denmark), and calculated gray matter flow by the method of Obrist et al. Blood pressure was measured by the standard sphygmometric method during rCBF measurement. Hemoglobin, hematocrit, serum lipids (total cholesterol and high density lipoprotein cholesterol [HDL]), fasting blood sugar, and electrocardiogram were measured on the same day. Retinal arteries were also examined for arteriosclerotic changes with an ophthalmoscopic camera. We defined a smoker as any subject whose smoking index (number of cigarettes/day \times years) was more than 200, and an alcohol drinker as any subject consuming more than 48 g of alcohol per day. Statistical analysis was performed by Student’s $t$ test and the $\chi^2$ test. Data are presented as mean±SD.

**Results**

We found no silent lacunar lesions in the 13 subjects under age 49, in five of 82 (6%) subjects in their 40s, in 20 of 117 (17%) in their 50s, and in seven of 34 (21%) in their 60s. Twenty-one of these 32 subjects (66%) had high-intensity spots not only on the T2WI but also on the T1WI, and 11 of them (34%) showed them only on T2WI. The regional distribution of these abnormal high-intensity spots was as follows: 14 subjects had multiple silent lesions in the subcortical white matter of the anterior half of the brain (this was considered a watershed area between the corticomedullary arteries and the perforating arteries) and the basal ganglia, 11 in the subcortical white matter only, five in the basal ganglia only, and two in the cortex. This incidence increased with age. Men showed a significantly higher incidence of silent lacunar lesions than women.
The overall incidence of silent lacunar lesions was 13%. Mean age was significantly higher in subjects with silent lesions than in those without them ($p<0.01$).

Mean rCBF was significantly lower in subjects with silent lacunar lesions than in those without them ($60.6\pm16.6$ versus $67.5\pm13.6$ ml/100 g/min, $p<0.02$). Subjects with silent lesions showed significantly lower rCBF in the bilateral frontotemporal regions than those without the lesions (Figure 2). Six of eight detectors in the right hemisphere and four of eight in the left hemisphere showed a significant difference between the two groups ($p<0.05$).

Table 1 shows the incidence of risk factors in our study population. A history of hypertension was observed in 72% of subjects with silent lesions and in 28% of those without them. There was a significant difference between the two groups ($p<0.01$). The average systolic, diastolic, and mean arterial blood pressures at the time rCBF was measured were significantly higher in subjects with lesions than in those without them ($p<0.01$).

Hypercholesterolemia ($\geq 220$ mg/dl) was observed in 22% of subjects with lesions and 41% of those without. There was no significant difference in the percentage of subjects with both hypertension and hypercholesterolemia between the two groups (19% versus 20%), and there were no significant differences in percentage of subjects with hypo-HDL ($\leq 35$ mg/dl) or hyperglycemia (fasting blood sugar $\geq 110$ mg/dl) or in the subjects who showed a hematocrit $\geq 50$% between the two groups. An arteriosclerotic change in the optic fundi (more than Keith-Wegener IIa) was significantly more often observed in subjects with lesions than in those without them ($p<0.01$). Ischemic changes in electrocardiogram were observed in almost the same percentage in the two groups. No subject with lacunar lesions showed atrial fibrillation, whereas two of those without lesions did. Smoking and habitual alcohol drinking were not significant risk factors.

The incidence of apparent PVH (more than grade 3) was 11.4% in all subjects (26 in grade 3 and two in grade 4). This incidence also increased with age as follows: no subjects under age 40 years, three subjects in their 40s (3.8%), 16 in their 50s (15.8%), and nine in their 60s (36%). Apparent PVH was significantly more often observed in subjects with silent lacunar lesions than in those without (49.6% versus 6%) ($p<0.01$). In subjects with silent lacunar lesions associated with apparent PVH, silent lacunes revealed by both T1WI and T2WI were observed in 76.5%, as opposed to 53.3% in those without. There was no significant difference in mean rCBF between subjects with and without apparent PVH ($66.1\pm16.9$ versus $66.6\pm13.8$ ml/100 g/min). We examined the same risk factors for stroke as compared to PVH.

### Table 1. Statistical Analysis of Risk Factors for Silent Lacunar Lesions

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Silent lacune</th>
<th>No silent lacune</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>25/7</td>
<td>120/94</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>66±6.1</td>
<td>61±8.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension (history)</td>
<td>23 (72%)</td>
<td>60 (28%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>95.1±15.1</td>
<td>86.8±13.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TC ≥220 mg/dl</td>
<td>7 (22%)</td>
<td>87 (41%)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL ≤35 mg/dl</td>
<td>3 (9.4%)</td>
<td>11 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>FBS ≥110 mg/dl</td>
<td>9 (28%)</td>
<td>39 (18%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit ≥50%</td>
<td>3 (9.4%)</td>
<td>18 (8.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Retinal artery sclerosis</td>
<td>12 (38.7%)</td>
<td>27 (12.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ECG ischemic change</td>
<td>6 (18.8%)</td>
<td>30 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (40.6%)</td>
<td>50 (23.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Habitual alcohol</td>
<td>8 (25%)</td>
<td>28 (13%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

MABP, mean arterial blood pressure; TC, total serum cholesterol; HDL, high density lipoprotein; FBS, fasting blood sugar; ECG, electrocardiogram.
Age and a history of hypertension were the only significant risk factors for PVH. The mean age of those with apparent PVH was also significantly higher than that of those without (67±6.1 versus 60±8.2 years, p<0.001). Hypertension was observed in 61% of subjects with apparent PVH compared to 30% of those without (p<0.01).

Discussion

Our results show a 13% incidence of possible lacunar lesions in 246 normal adults. This rate is lower than that of other reports studying white matter lesions on MRI in neurologically normal subjects1-4,7 because we calculated the incidence of silent lacunar lesions and that of apparent PVH (grades 3 and 4) separately. A retrospective clinicopathological study of a large number of autopsied cases showed lacunar lesions in 6% of 2,859 patients, with as many as 81% of them asymptomatic.9

An MRI and pathological study in neurologically normal subjects revealed that most of the patchy small white matter lesions in the T2WI corresponded to état crible, whereas only a small number corresponded to lacunar infarction.10,11 However, 66% of our subjects with silent lesions showed abnormalities in both the T1WI and T2WI. Based on earlier findings,12 these lesions are probably the result of lacunar infarction.

In our study, the watershed zone between the long medullary branch and the perforating branch of the middle or anterior cerebral artery, especially in the anterior part of the brain, was the most vulnerable region, followed by the basal ganglion. Lechner et al4 reported that 65.4% of silent white matter lesions in normal adults are located in the middle cerebral artery watershed area. These areas may easily become ischemic from advanced cerebral arteriosclerosis, especially when a hemodynamic effect is added. McQuinn and O'Leary13 reported that a hemodynamic effect was important in causing changes similar toBinswanger's disease on MRI. Kinkel et al14 discussed reversible developments of white matter changes after endarterectomies confined to the boundary zones of their arterial supply. However, the contribution of the extracranial arterial disease to white matter lesions is controversial.7,15 In our previous study, severity of PVH was correlated to persistent high blood pressure in patients with multiple lacunar infarcts but no major arterial stenosis.15

Our results demonstrate that mean cerebral blood flow in subjects with possible lacunes is significantly lower than in those without lacunes, whereas there is no difference between those with and without apparent PVH. This result suggests that lacunes may be more related to severe cerebral arteriosclerosis than to PVH.

The effect of age on rCBF should also be considered because the subjects with silent lacunes were significantly older than those without. We reported previously that the mean rCBF at 6 years before MRI was significantly lower in subjects with silent lacunes than in those without them in a 6-year follow-up study on normal aging.17 Moreover, there was no difference in mean rCBF between subjects with and without apparent PVH despite the significant difference in age. Thus, a decrease in rCBF may be more closely related to silent lacunes than to aging.

Meguro et al10 reported that rCBF was significantly lower in neurologically normal subjects with severe PVH than in those with mild or no PVH. But there was no significant difference in rCBF between the mild and moderate PVH groups. The grade of PVH in our subjects was milder than that in Meguro's subjects. Kobari et al18 reported that rCBF only in subcortical white matter correlated to leukoaraiosis on computed tomography in normal volunteers. These reports focused on leukoaraiosis alone and did not discuss the relation between rCBF and silent lacunes. Fazekas et al7 studied rCBF in normal subjects, who had punctate foci of hyperintensity, and demonstrated a tendency toward decrease in mean gray matter blood flow.

Awad et al19 concluded that the MRI signal did not differentiate between the mild form of histological changes (enlarged perivascular spaces and vascular ectasia) and the more severe form (myelinated fiber loss and gliosis). The mild form has long been known to affect the aging brain as état crible, but we believe that the PVH alone in our subjects may be more related to aging. Our results indicate that possible silent lacunes may be a more important risk factor for symptomatic ischemic stroke in normal adults than PVH.

Although the relation between a silent lacune with PVH and multilacunar dementia has not been fully elucidated, it is important to prevent subjects with silent lesions from progressing to multilacunar dementia. Better understanding of this relation will require long-term prospective study.

Acknowledgments

We thank Mr. Akira Besho for conducting MRI; Mr. Mitsuyoshi Murao (Shimane Institute Health Science), Dr. Mitsuhiro Kitani, Dr. Hitoshi Fukuda, and Dr. Hiromi Koide for assistance in rCBF measurement and other examinations; and Miss Yuki Sano for arranging the data.

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**KEY WORDS** • cerebral blood flow • hypertension • lacunar infarction • magnetic resonance imaging
Incidence of silent lacunar lesion in normal adults and its relation to cerebral blood flow and risk factors.
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Stroke. 1991;22:1379-1383
doi: 10.1161/01.STR.22.11.1379

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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