Silent Cerebrovascular Disease and Ambulatory Blood Pressure in the Elderly

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Silent cerebrovascular disease can be frequently revealed by magnetic resonance imaging (MRI) in asymptomatic elderly subjects. These incidental lesions include lacunae and periventricular hyperintensity (PVH), and are associated with several vascular risk factors including age and blood pressure. The relationship between diurnal blood pressure variations and hypertensive cerebrovascular disease, however, has not been fully understood. We found that ambulatory blood pressure monitoring is superior to casual pressure measurements in predicting these lesions. Furthermore, the absence of a nocturnal blood pressure reduction is associated with greater abnormalities of these MRI lesions. Other factors such as high predicted blood viscosity and low HDL-cholesterol levels were associated with advanced multiple (defined as more than four) lacunar lesions. In particular, left ventricular hypertrophy on ECG had high positive and negative predictive values for the advanced multi-lacunar lesions in the asymptomatic elderly patients with hypertension. The most important questions which remain to be answered, however, is the prognosis of the subjects with these silent cerebrovascular disease. (Hypertens Res 1994; 17 Suppl. I: S55-S58)

Key Words: ambulatory blood pressure, silent cerebral infarct, elderly

Silent Cerebrovascular Disease in the Elderly

The pattern of cardiovascular disease in Japan is quite different from that in the West (1). Japan is at the bottom of the international league table for ischemic coronary heart disease and, until lately was at the top of the stroke table. Despite a precipitous fall in stroke rates over the past two decades, mortality rates for stroke is still substantially higher in this country than many other countries including United States (2).

The prevention of cerebrovascular disease may be effectively achieved by the earliest possible detection of the brain vascular damage. With the advent of new technology such as magnetic resonance imaging (MRI), there is increasing evidence that “asymptomatic” intracranial morphological changes are fairly common in apparently normal elderly subjects (3). Table 1 summarizes the possible underlying pathological processes of the lesions of a vascular etiology incidentally seen in the brain MRI. Lacunar are small, deep infarcts from penetrating arteriolar occlusive disease (4). Leukoaraiosis are also often incidental findings in the elderly. Subcortical hypertensive small vessel disease is suggested to play an etiological role in this type of lesion (5). This process, in some case, may account for the development of intellectual impairment in the elderly, ultimately leading to Binswanger-type of vascular dementia. The condition named état criblé is not a true infarct, but reflect dilated perivascular spaces, and vascular ectasia, resulting from chronic, low grade vascular insufficiency (6). These changes are related with age, and can be accelerated by hypertension.

A number of questions exist regarding silent cerebrovascular disease in the elderly. How frequent are they? In the Framingham study, the CT evidence of prior lacunar stroke without a history of such an event was reported to be found in approximately 10% of middle-aged subjects who presented acute stroke symptoms (7). Then, what is a true prevalence of silent brain vascular damage in entirely asymptomatic elderly subjects? The prevalence rate may depend on the population studied. Factors such as age, physical, mental and social activity, as well as selection criteria (e.g., voluntary or ambulatory patient basis) of the study population can influence the results. Secondly, what factors are associated with these conditions? Cerebrovascular risk factors other than age and blood pressure may be related

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to this silent as well as symptomatic cerebrovascular disease. From a clinical point of view, are these advanced hypertensive cerebral injuries clinically predictable before the MRI study is undertaken in asymptomatic elderly hypertensive patients: and most importantly are they related to the future development of ischemic strokes or multi-infarct vascular dementia? All these issues should be addressed in the future investigation.

**Incidental Brain MRI Abnormalities in the Elderly**

We performed brain MRI studies in the group of nearly 100 active community-dwelling healthy elderly subjects who voluntarily participated in the program (8). Here, lacunae were strictly defined as low signal intensity areas of less than 1 cm in size on T1-weighted images, which were visible as hyperintense lesions on T2-weighted images. Periventricular hyperintensities (PVH) in T2-weighted images correspond to leuko-araioisis, and were classified into four groups, from Grade I, defined as no abnormality or minimal periventricular signal hyperintensities to Grade IV, defined as multiple high signal intensity areas which reached confluency in the periventricular region. Since few subjects showed PVH grade IV, these subjects were included in III grade for the following analysis. On the other hand, the hyperintense spots visible only in T2-weighted images were classified as unidentified bright object (UBO). Lacunae as defined above may also include other lesions such as état crible, especially if their size is small (i.e. less than 5mm).

### 24-Hour Blood Pressure Monitoring

The relationship between 24-hour blood pressure and silent cerebrovascular disease defined as above on brain MRI has not been fully investigated. Does the average daily blood pressure correlate with hypertensive cerebrovascular disease better than the casual pressure as has been reported in other target organ involvements? Is the extent of cerebrovascular disease in the group of subjects defined as “white coat or office hypertension” similar to that in normotensive subjects as has been reported in cardiac hypertrophy? Finally is there any relationship between a nocturnal reduction in blood pressure and hypertensive brain damage? These questions were investigated as follows.

**Relationship between Silent Cerebrovascular Disease and the Average of 24-Hour Blood Pressure**

A half of the normotensive subjects had at least one lacune. The number of lacunae greater than the mean plus two standard deviations in the normotensive group, which turned out to be more than 4 lacunae, was considered to represent advanced cerebrovascular damages in the following analysis (9). There was a weak, but significant, correlation between the number of lacunae and age (8). The localization of these lacunar lesions were essentially the basal ganglia and deep white matter. The difference in age among three different PVH groups was also significant. Twenty six % of the subjects had PVH of the grade greater than III. On the other hand, there was no significant relationship between UBO and age. Thus, lacunae and PVH are increased with advancing age even in the elderly population.

Table 2 shows the correlation coefficient of the relationship between lacunae and various blood pressure parameters. The number of lacunae was significantly correlated with the means of ambulatory blood pressure readings during the total 24-hour and the asleep periods. The relation with casual office blood pressure or awake systolic blood pressure was only marginal.

The relationship between PVH and various blood pressure was then examined. There were significant differences among three PVH groups in the means of systolic blood pressures during the 24-hour and asleep periods, but not in the mean of ambulatory measurements during the awake period or in casual office systolic blood pressure.

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<th>Table 2. Correlation Coefficients of the Relationship between the Number of Lacunae per Subject and Blood Pressure Values</th>
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<td><strong>Correlation coefficients</strong></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
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<td>24-hour average</td>
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<td>Asleep average</td>
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On the other hand, UBO was not significantly correlated with office or any ambulatory blood pressure parameters.

**Silent Cerebrovascular Disease in “Office Hypertension”**

MRI findings were then compared among three defined blood pressure-groups; normotensives, office and persistent hypertensives (8). The mean age was not significantly different between the groups, and office blood pressure levels were quite similar between office and persistent hypertensive patients. The number of lacunae as well as the grade of PVH in “office hypertensives” were not significantly different from those in “normotensives” but significantly less than in “hypertensives”. Thus, all these data suggest that MRI abnormalities are more appropriate to the level of 24-hour blood pressure than to that of the clinic blood pressure, indicating that the adverse effects of blood pressure on the brain depend on the average level of blood pressure over time as has been reported in the heart (10).

**Silent Cerebrovascular Disease and Cardiac Complication**

Hypertensive cardiac complications are related with brain MRI lesions (11). Hypertensive patients were divided into two groups by the presence or absence of ECG evidence of LVH. The two groups did not differ either for age or for the status of anti-hypertensive treatment. The known duration of hypertension as well as systolic and diastolic blood pressures were greater in patients with ECG evidence of LVH. The number of lacunae was significantly greater in patients with LVH. The grade of PVH also tended to be greater in the LVH group, although this did not reach a statistical significance (p=0.12).

**Prediction of Silent Cerebrovascular Disease**

We have selected three variables; age over 70 years, LVH on ECG, and hypertension on ambulatory blood pressure criteria for the prediction of multiple lacunar lesions (9). Among these three variables, LVH on ECG had relatively high predictive values for the presence or absence of multi-lacunar lesions (0.70 and 0.91 respectively).

**Factors Associated with Silent Cerebrovascular Disease**

Factors associated with advanced multi-“lacunar” lesions defined as more than 4 lacunar lesions were investigated in elderly hypertensive subjects (9). Several cerebrovascular risk factors were compared between two hypertensive groups with or without multi-lacunar lesions. The predicted whole blood viscosity from both hematocrit and total plasma protein concentration was significantly higher in the group of subjects with multiple lacunae. Although total cholesterol and triglyceride were not different between two groups, the group with advanced lesions showed a significantly lower HDL-cholesterol than the group without multi-lacunar lesions. Thus, silent cerebrovascular disease is associated with several risk factor parameters in addition to age and high blood pressure.

**Nocturnal Blood Pressure and Cerebrovascular Disease**

We then examined the effect of diurnal blood pressure changes on cerebrovascular damages in elderly patients with hypertension (11). Diurnal variations were defined as a difference of mean awake and asleep systolic blood pressures equal to or greater than 10 mmHg. Hypertensives were thus classified as “dippers” (n = 39) or “nondippers” (n = 15). In contrast with a clearcut difference in blood pressure at night between two groups, a comparable reduction in night-time heart rate was observed in both groups.

In comparisons between two hypertensive subgroups, the averages of both 24-hour and asleep blood pressures were significantly higher in the “nondipper” group than in the “dipper” group. The average blood pressure during awake, however, was similar in these two groups. Other risk factors did not differ between these two hypertensive subgroups. In other words, the only difference in the two hypertensive groups is the level of blood pressure at night.

Brain and cardiac complications were then compared among these groups and shown in Fig. 1. The number of lacunae per subject was significantly greater in the “nondipper” hypertensive group than in the dipper hypertensive group. Furthermore, a significantly, greater portion of the subjects showed advanced PVH (i.e., PVH-III) as well as electrocardiographic evidence of left ventricular hypertrophy in the “nondipper” hypertensive group than in the “dipper” group. On the other hand, no
differences were observed in these indexes between the normotensive and the “dipper” hypertensive groups.

The present study showed that “nondippers” showed a higher frequency of echocardiographic evidence of left ventricular hypertrophy than “dippers”. Previously reported data demonstrated that echocardiographic left ventricular hypertrophy was associated only with the absence of nocturnal blood pressure reduction (12). Thus, target-organ damages in both brain and heart of hypertensive patients might have a closer relation to sleep blood pressure than to awake pressure. The interpretation of these findings, in particular, a cause-effect relation, however, is not known at present time.

Clinical Implication

Silent cerebrovascular disease is not uncommon in apparently normal elderly subjects. Age, high blood pressure, and other vascular risk factors including blood viscosity and lipids are associated with this condition. At present, it is not known whether these incidental damages are a predictor of future cerebrovascular events including ischemic strokes and vascular dementia. We have recently shown that neurobehavioral functions are already depressed in the “asymptomatic” elderly subjects with advanced PVH on MRI (13). Thus, it appears to be imperative to prevent the progression of these silent lesions before symptoms develop. Antihypertensive treatment may play a central role in the preventive strategy. Several large clinical trials clearly demonstrated the benefit of blood pressure reduction for preventing stroke in elderly patients with hypertension (14). Our data showing the adverse effects of nocturnal high blood pressure on hypertensive brain damages may imply that blood pressure should be controlled through the day and the night. Caution should be exercised, however, when we treat blood pressure. Since the lower limit of blood pressure in the autoregulation of cerebral blood flow is shifted upward in hypertensive patients with brain damages (15), in order to maintain cerebral perfusion, blood pressure should be lowered gradually and mildly.

References