Leukoaraiosis in Relation to Prognosis for Patients with Lacunar Infarction

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Background and Purpose: Close relations between leukoaraiosis detected by computed tomography or magnetic resonance imaging and stroke, particularly lacunar infarction, have been reported. We studied whether leukoaraiosis is related to long-term prognosis for patients with lacunar infarction.

Methods: We examined monthly 215 patients with lacunar infarction after their first stroke. They comprised 95 patients with leukoaraiosis disclosed by computed tomography on admission (58 men and 37 women; mean age, 71.3±9.0 years) and 120 patients without leukoaraiosis (81 men and 39 women; mean age, 65.5±8.9 years). These patients had no previous history of either stroke or obvious dementia before their index stroke. We compared the prognosis with and without leukoaraiosis based on analysis of recurrent stroke, survival, and the prevalence of dementia and rate of dependence in activities of daily living.

Results: Life table analysis revealed that the recurrent stroke rate was significantly higher in the patients with leukoaraiosis than in those without it (p=0.004). The prevalence of dementia and rate of dependence in activities of daily living both 1 month after the index stroke and at the end of the follow-up period were significantly higher in the patients with leukoaraiosis (all parameters, p<0.001). Their survival rate was significantly lower than in those not suffering from leukoaraiosis (p=0.012). Significant differences in these comparisons were also observed after matching for age and sex.

Conclusions: The presence of leukoaraiosis as identified by computed tomography indicates a poor prognosis for patients with lacunar infarction. (Stroke 1992;23:1434-1438)

KEY WORDS • dementia • lacunar infarction • tomography, x-ray computed • white matter

Leukoaraiosis (LA) is the term proposed by Hachinski et al1 to describe patchy or diffuse abnormalities in the white matter of the periventricular regions and/or centrum semiovale, which have been identified as low-density areas on computed tomography (CT) or as areas of high signal intensity on T2-weighted magnetic resonance imaging. In elderly patients without well-defined white matter diseases such as radiation encephalopathy, LA on CT reliably indicates demyelination and loss of axons2-4 frequently associated with arteriosclerosis.2,3 The same pathological features are generally associated with subcortical arteriosclerotic encephalopathy, progressive subcortical vascular encephalopathy, orBinswanger's disease. They are thought to result from impaired cerebral blood flow or ischemia associated with arteriosclerosis.2,5-9 Thus, it is not surprising that LA is frequently observed in stroke patients.10-14 In particular, close relations between lacunar infarction and LA have been emphasized.15,16 However, the clinical relevance of LA to the prognosis of stroke patients has received little attention.

This study was designed to elucidate the relation between LA and the prognosis in lacunar infarct patients. We followed 215 lacunar infarct patients after their first stroke and compared the prognosis with and without LA based on analysis of recurrent stroke, survival, and the prevalence of dementia and rate of dependence in activities of daily living (ADL).

Subjects and Methods
From November 1, 1984 through February 28, 1990, 520 patients with acute cerebral infarction were admitted within 1 week after onset to the Kumiai Hospital in Takayama City, Japan. This group included 215 patients with lacunar infarctions who had no previous history of either stroke or obvious dementia and who were independent in ADL before the stroke. Ninety-five of these 215 patients were diagnosed as having LA (LA+) and 120 patients as not having LA (LA−). Ninety-five of the LA− patients were selected as an age- and sex-matched control for the LA+ patients (mLA−).

The presence of LA was assessed by CT at admission. Leukoaraiosis was characterized by poorly delineated hypodense areas around the frontal horn and/or around the posterior part of the lateral ventricles. The degree of LA was graded on the extent: mild, LA confined to anterior or posterior parts of the lateral ventricles; moderate, LA anteriorly and posteriorly; and severe, LA extending into centrum semiovale. Diagnosis for lacunar infarction was made by follow-up CT on days 5–10 after admission (not by "lacunar syndromes"). A lacunar infarction was defined as a deeply seated, small

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(<1.5 cm in diameter), sharply demarcated hypodense area in the basal ganglia or paraventricular white matter regions. The number of lacunes (single or multiple) was also checked on the follow-up CT. All CT scans were read by one of the authors, and scans were rechecked by the same author in 43 of the 215 patients without the information of the first assessment. Intrarater reliability in terms of determining the presence of LA and multiple lacunes was studied by comparing the first and second assessments.

Demographic data and vascular risk factors were recorded for each patient at admission. Thereafter, each patient was neurologically examined at least once a month until May 31, 1990 or death. At each follow-up visit, we checked recurrent stroke or death. The date of any such event was duly recorded. When the patients were suspected to be demented at the visit, we examined them for the presence or absence of cognitive impairment (in memory, abstract thinking, and judgment), personality change and any interference with work, usual social activities, or relations with others, based on interviews with the patients and their families; and we performed the Mini-Mental State Examination. The patients were considered demented when they met the criteria for dementia listed in the revised version of the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III-R) and showed a Mini-Mental State Examination score lower than 20. The Hachinski Ischemic Score was used to diagnose the type of dementia. At the same time, we checked whether the patients were dependent in the four basic ADLs (eating, dressing, bathing, and walking indoors) on the basis of bedside examinations and information from patients’ families. Information on the clinical status of patients unable to come in on a monthly basis after discharge was obtained from public nurses who made regular home visitations. From these data the cumulative recurrent stroke rate and survival rate were calculated. The prevalence of dementia and rate of dependence in ADL were checked 1 month after the index stroke and at the end of the follow-up study.

We used \( \chi^2 \) analysis to compare sex ratio, frequency of the vascular risk factors and multiple lacunes, and percentage of patients with dementia and those dependent in ADL. Mean ages were compared using Student’s \( t \) test. Using generalized Wilcoxon methods we compared the curves of the recurrent stroke rate and the survival rate. We evaluated intrarater reliability in terms of determining the presence of LA and multiple lacunes using the kappa statistic. Differences were considered significant at \( p<0.05 \).

**Results**

Table 1 shows that LA+ and LA− patients were significantly different in terms of age, history of heart failure, ischemic ST-T patterns and atrial fibrillation in the electrocardiograms, and multiple lacunes. However, only a history of heart failure was observed significantly more often in LA+ patients than in mLAA patients (\( p<0.05 \)).

In the comparison of the first and second assessments of the presence of LA and multiple lacunes on CT, high levels of intrarater agreement were obtained. The \( \kappa \) value for the presence of LA was 0.90 (almost perfect agreement) and for multiple lacunes 0.79 (substantial agreement).

The average follow-up was 25 months for LA+ patients and 29 months for LA− patients (28 months for mLAA patients). Figure 1 shows the recurrent stroke curves in LA+ and LA− patients. New episodes of complete stroke (recurrent stroke) occurred in 18 LA+ patients but in only seven LA− patients during follow-up. Among the episodes in LA+ patients, 13 were lacunar infarctions, three were nonlacunar cere-

| TABLE 1. Clinical Characteristics of Lacunar Infarct Patients With and Without Leukoaraiosis |
|-----------------|---------|---------|---------|
|                 | LA+ (n=95) | LA− (n=120) | mLAA (n=95) |
| Demographic factors |         |         |         |
| Age (mean±SD) (years) | 71±3.9 | 65.5±8.9§ | 69.9±8.0 |
| Range | 51−91 | 42−86 | 50−86 |
| Sex (men/women) | 58/37 | 81/39 | 58/37 |
| Risk factors |         |         |         |
| Hypertension* | 62 (65.3) | 66 (55.0) | 55 (57.9) |
| Diabetes mellitus* | 14 (14.7) | 11 (9.2) | 10 (10.5) |
| Coronary heart disease* | 6 (6.3) | 3 (2.5) | 2 (2.1) |
| Heart failure* | 11 (11.6) | 2 (1.7)§ | 2 (2.1)§ |
| Hypercholesterolemia† | 7 (7.4) | 16 (13.3) | 10 (10.5) |
| Hachinski Ischemic Score ≥45% | 29 (30.5) | 47 (39.2) | 30 (31.6) |
| Ischemic ST-T patterns‡ | 35 (36.8) | 29 (24.2)§ | 24 (25.3) |
| Atrial fibrillation‡ | 7 (7.4) | 1 (0.8)§ | 1 (1.1) |
| Degree of LA |         |         |         |
| Mild | 56 | ... | ... |
| Moderate | 28 | ... | ... |
| Severe | 11 | ... | ... |
| CT scan findings |         |         |         |
| Multiple lacunes | 25 (26.3) | 15 (12.5)§ | 15 (15.8) |

LA+, patients with leukoaraiosis (LA); LA−, patients without LA; mLAA, age- and sex-matched patients without LA; CT, computed tomographic.

*By history.
†Serum cholesterol ≥250 mg/dl.
‡In electrocardiograms. $p<0.001$, $p<0.01$, $p<0.05$, different from LA+ patients.

**Figure 1. Recurrent stroke rate curves of lacunar infarct patients with and without leukoaraiosis. LA+, patients with leukoaraiosis; LA−, patients without leukoaraiosis.**
bral infarctions, and two were cerebral hemorrhages. New episodes were lacunar infarctions in six and cerebral hemorrhage in one of the seven LA- patients. The 1-, 2-, and 3-year cumulative incidence of recurrent stroke was 13.5%, 21.4%, and 28.2%, respectively, in LA+ patients versus 3.5%, 6.0%, and 6.0%, respectively, in LA- patients (4.5%, 7.4%, and 7.4%, respectively, in mLA- patients). Generalized Wilcoxon analysis of the data showed that recurrent stroke throughout follow-up was significantly more frequent in LA+ patients than in either LA- patients ($z=2.883$, $p=0.004$) or mLA- patients ($z=2.302$, $p=0.021$).

The prevalence of dementia 1 month after the first stroke was 15.8% in LA+ patients and 1.7% in LA- patients (2.1% in mLA- patients) (Figure 2). By the end of follow-up, dementia in LA+ patients had increased to 22.1% compared with 2.5% in LA- patients (3.2% in mLA- patients). The new-onset dementias, in patients not demented 1 month after their index stroke, were considered to be due to recurrent stroke in all but one LA+ patient. Therefore, dementia was observed significantly more often in LA+ patients than in either LA- patients ($z=2.883$, $p=0.004$) or mLA- patients ($z=2.302$, $p=0.021$).

Self-care ability was noted in all patients throughout the study. One month after the index stroke, 30.5% of LA+ patients were partially or totally dependent in ADL, compared with only 8.3% of LA- patients (10.5% of mLA- patients) (Figure 3). At the end of follow-up, these figures increased to 38.9% in LA+ patients and 10.8% in LA- patients (13.7% in mLA- patients). Both 1 month after the index stroke and at the end of follow-up, the number of patients at least partially dependent in ADL was significantly higher in LA+ patients (LA+ versus LA-, both parameters, $p<0.001$; LA+ versus mLA-, $p<0.001$ and $p<0.001$, respectively). All patients diagnosed to be demented in this study scored 7 or higher on the Ischemic Score, so they were considered vascular dementia cases.

Leukoaraiosis has been reported to be frequent among stroke patients. Generalized cerebral arteriosclerosis is often noted in pathological studies of LA, and sclerosis of the medullary arteries reportedly correlated well with the degree of white matter lesions. Moreover, investigations of cerebral blood flow in patients with LA have shown diffuse hypoperfusion. Although these close relations between LA and cerebrovascular disorders have been emphasized, it failure), two due to bronchopneumonia possibly related to immobility, one due to recurrent stroke, one due to malignant neoplasm, and two due to other causes. One LA- patient died of bronchopneumonia and two of other causes. The 1-, 2-, and 3-year survival rates were 92.5%, 90.5%, and 87.2%, respectively, in LA+ patients versus 98.9%, 97.8%, and 97.8%, respectively, in LA- patients (98.7%, 97.3%, and 97.3%, respectively, in mLA- patients). Generalized Wilcoxon analysis showed a significantly lower survival rate in LA+ patients than in either LA- patients ($z=2.508$, $p=0.012$) or mLA- patients ($z=2.085$, $p=0.037$).
remains uncertain whether LA is related to prognosis in stroke patients. We investigated the relevance of LA in the long-term prognosis of patients with lacunar infarction, which is closely associated with LA.\textsuperscript{15,16}

Several groups have investigated the long-term prognosis for patients with lacunar infarction,\textsuperscript{20-29} but there have been no studies on the prognosis for lacunar infarct patients with LA. Gandolfo et al\textsuperscript{20} reported a higher recurrent stroke rate in lacunar infarct patients with hypertension or over 65 years of age. The mean age and the incidence of hypertension were not significantly different in LA+ and mLA− patients. We did, however, find a significantly higher recurrent stroke rate in LA+ patients. Thus, we supposed that diffuse arteriosclerosis and impaired cerebral circulation frequently associated with LA may play a role in the higher recurrent stroke rate. Our results suggest that LA may be a predictor of recurrent stroke in lacunar infarct patients.

Tatemichi et al\textsuperscript{30} reported dementias diagnosed by DSM-III criteria in 7.5% of the patients with first-ever lacunar infarction. In this study the overall prevalence of dementia was 11.2% at the end of the follow-up. Although DSM-III criteria are very subjective, these values are relatively close.

Leukoaraiosis has been reported to be associated with intellectual deterioration in patients with stroke or cerebrovascular risk factors.\textsuperscript{31-33} We found that dementia occurring within 1 month after the index stroke was more frequent in LA+ patients than in age-matched patients without LA. Moreover, LA+ patients without dementia 1 month after their first stroke developed more new-onset dementia during the study than LA− patients, which might relate to the higher recurrent stroke rate in these patients. Our results suggest that in LA+ patients, various forms of cerebrovascular diseases (including LA), each of which alone does not suffice to cause detectable dementia, can, in combination, produce clinically overt dementia. Thus, LA may represent a risk factor for later intellectual deterioration.

Bamford et al\textsuperscript{37} demonstrated that one third of patients with lacunar infarction are not capable of independent living 1 month after stroke onset. In another report, moderate to severe disabilities persisted in 20% of the lacunar infarct patients after the acute phase.\textsuperscript{34} In the present study, one third of the LA+ patients were dependent in ADL 1 month after stroke onset, which was three times the number of the dependent patients among LA− patients. LA itself is often associated with some neurological deficits.\textsuperscript{35-37} Therefore, one possible reason for the less favorable functional recovery in LA+ patients is that they had been subclinically affected before the index stroke by LA. However, in addition to this, the increase in ADL dependence after the first stroke in LA+ patients may be related to their higher rate of recurrent stroke. These data suggest that functional recovery from lacunar infarction is less favorable in LA+ patients.

The prognosis was significantly less favorable in LA+ patients than in LA− patients. Although few, if any, patients die as a direct neurological consequence of lacunar infarction, those with lacunar infarction are as vulnerable to the complications of cardiac disease and immobility as patients with other types of stroke.\textsuperscript{27} Cardiovascular disorders or systemic arteriosclerosis is often associated with subcortical arteriosclerotic encephalopathy,\textsuperscript{2,38} which is characterized by white matter lesions associated with arteriosclerosis. During our follow-up period, four of 10 deaths among LA+ patients were due to heart disease, whereas no LA− patients died of cardiac disease. Thus, cardiac disease was the major cause of death in LA+ patients. Also, heart failure and ischemic ST-T patterns and atrial fibrillation in electrocardiograms were more frequently observed in LA+ patients. We presume that lacunar infarct patients with LA generally have more advanced systemic arteriosclerosis and their risk of cardiac disease is greater, so mortality would be greater after lacunar infarction.

On the other hand, a higher degree of disability was previously found to relate to a poor prognosis in lacunar patients.\textsuperscript{26} This is compatible with our results that LA+ patients experienced a marked decline in daily activities. Thus, LA may be associated with less favorable prognosis for survival because cardiac disease and diseases related to immobility are likely involved.

Millikan and Futrell\textsuperscript{39} noted that lacunar infarct disease is not always a benign process. We agree with this view and believe the poor prognosis for patients with lacunar infarction may be partially related to LA. In summary, our results suggest that lacunar infarct patients with LA are prone to recurrent stroke, causing a significantly higher prevalence of dementia and more dependence in ADL. The prognosis for survival is less favorable in these patients mostly because of cardiac complications and diseases related to immobility. In conclusion, the presence or absence of LA may be an important prognostic indicator for both functional ability and survival.

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