Prospective Study of Single and Multiple Lacunar Infarcts Using Magnetic Resonance Imaging

Risk Factors, Recurrence, and Outcome in 175 Consecutive Cases

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Background and Purpose—We investigated whether lacunar infarct (LI) patients with >1 lacune have different vascular risk factors, a different prognosis, and poorer functional outcome than those with a single lacune.

Methods—The study included 175 first-ever LI patients. The group was divided according to the presence of multiple (n=136) or single (n=39) LI. The association of single or multiple LI with the principal vascular risk factors, leukoaraiosis, outcome, and recurrence was investigated with logistic regression models that included age, sex, and cardiac disease.

Results—No significant differences were found between single and multiple LI with respect to age, hypertension, hyperlipidemia, smoking, and heavy alcohol drinking. Diabetes mellitus (odds ratio [OR], 2.43; 95% CI, 1.09 to 5.4), high levels of hematocrit (>0.47) (OR, 1.09; 95% CI, 1.04 to 1.21), and leukoaraiosis (OR, 3.58; 95% CI, 1.77 to 7.51) were significantly related to multiple but not to single LI. Stroke recurrence rate was 7.7% in patients with single LI and 24.3% in the multiple LI group (OR, 3.84; 95% CI, 1.1 to 13.3). During a median follow-up of 12 months (range, 6 to 156 months), 94% of the single LI patients and 77.2% of the multiple LI patients had favorable outcomes (Rankin Scale score 0 to 2) (OR, 5.4; 95% CI, 1.25 to 23.9).

Conclusions—Diabetes mellitus, leukoaraiosis, and high levels of hematocrit are important risk factors in patients with >1 LI. The presence of multiple LI may be an important prognostic indicator not only for functional recovery but also for a higher rate of recurrence. (***Stroke*****. 2003;34:2453-2458.)**

Key Words: diabetes mellitus ■ hypertension ■ lacunar infarction ■ leukoaraiosis

Lacunar infarcts (LI) account for 11% to 25% of all strokes.[1–3] They are traditionally associated with risk factors, natural history, and clinical management that are significantly different from those of other types of brain infarcts.[2–8] Recently, Boiten et al[9] proposed that 2 distinct LI entities can be distinguished: (1) patients with a single LI and the usual vascular risk factors and (2) patients with multiple LI and a high frequency of hypertension and leukoaraiosis, in which the underlying small-vessel vasculopathy may be different. Although speculative, distinguishing these 2 clinical LI entities may enable more appropriate therapy.

It is unknown whether patients with a single LI will have a better prognosis over time than those with concomitant silent lacunar lesions. In this prospective study we compared risk factors and concomitant vascular disorders among 175 cases with a first episode of clinical lacunar syndrome confirmed by MRI. In addition, we investigated whether multiple LI have different vascular risk factors and a different prognosis in terms of functional outcome and recurrence compared with single LI.

Subjects and Methods

In this prospective study, we analyzed the collected risk factors and concomitant vascular disorders of 175 patients with a first symptomatic LI consecutively admitted to our hospital between January 1990 and December 2000.

We included patients with a neurological deficit of abrupt or gradual onset with duration of >24 hours attributed to a LI visualized on MRI and with a location in agreement with clinical data. The clinical syndromes included were classified according to Fisher[4,5]: pure motor syndrome, ataxic hemiparesis, dysarthria–clumsy hand, pure sensory stroke, and sensorimotor stroke; other clinical manifestations were classified as miscellaneous. MRI was performed with 0.5-T equipment (Siemens). All patients had multislice spin-echo pulse sequences with contiguous T2-weighted images (repetition time 2000 ms, echo time 60 to 120 ms) on the axial view, from the medulla to the vertex, and T1-weighted images (inversion recovery; repetition time 2000 ms; echo time 40 ms). The sections were 6 or 9 mm thick. The MR images were evaluated simultaneously by at least 3 participating neurologists. A lacune was defined as a hyperintense signal shown in the first and second echo images with sharp margins, <2.5 cm in diameter, located in the deeper structures and irrigated by penetrating branches. A dilation of perivascular space

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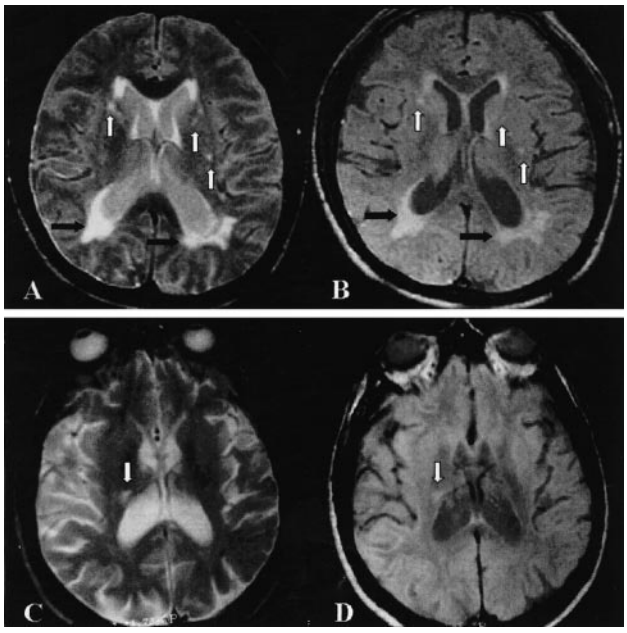

T2-weighted and proton density–weighted MRI sequences show multiple (A and B) and single (C and D) LI (white arrows). A and B also show leukoaraiosis in the posterior horns of the lateral ventricles (black arrows).

was defined as multiple, small, round, hyperintense signals, disseminated at the level immediately above the bifurcation of the internal carotid artery, isointense, with nonflowing cerebrovascular fluid.[4] Leukoaraiosis was defined as the presence of bilateral, symmetrical, and diffuse abnormalities located in the white matter surrounding the frontal horns or in the parieto-occipital region encircling the lateral ventricles or in hyperintense areas in the centrum semiovale. LI was classified as single or multiple (>1) according to the number of lacunes. The anatomic location of the lacunes was correlated with the clinical signs and symptoms. The interobserver variation of the number, location, or nature of the lesion was determined. The Figure shows MRI sequences with multiple and single LI and leukoaraiosis.

An ECG was registered at the time of assessment to document cardiac rhythm abnormalities, and in selected cases echocardiography, Doppler ultrasound, or angiography was performed to rule out emboligenic sources.

Clinical or ECG evidence of angina pectoris, coronary insufficiency, myocardial infarction, congestive heart failure, or cardiac dysrhythmia was collectively considered heart disease.

We registered age, sex, smoking habits (at least 5 cigarettes per day), history of transient ischemic attack (TIA), atrial fibrillation, or other cardiac arrhythmias in each case. According to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,[10] we considered hypertension to be present when systolic blood pressure was ≥140 mm Hg or when the patient had been consistently taking antihypertensive drugs. Hypertension was categorized as mild, moderate, or severe. The diagnosis of diabetes mellitus was established when a patient took oral hypoglycemic drugs on a regular basis or when the patient fulfilled the established WHO criteria. Hyperlipidemia was considered when a patient received treatment for hyperlipidemia or when the patient's postinfarct cholesterol levels were >2.4 g/L and triglyceride levels were >1.4 g/L. TIA was defined as a neurological episode of abrupt beginning, with complete patient recovery in <24 hours. A heavy alcohol drinker was defined as any subject consuming >60 g/d, according to the criteria of a recent science advisory for healthcare professionals from the Nutrition Committee, Council on Epidemiology and Prevention, and Council on Cardiovascular Nursing of the American Heart Association.[11] The Rankin Scale was used to assess general functional status 6 months after the onset of stroke.

TABLE 1. Diagnostic Studies Performed

Study	n	%
Magnetic resonance imaging	175	100
CT scan	166	95
Doppler ultrasound	147	84
Transcranial Doppler	60	34.3
Echocardiography	47	27
Angiography	15	8.6

Data were evaluated according to arithmetic means, SD, median, ranges, and percentages. Statistical analysis was performed with the Statistical Package for Social Sciences 10 (SPSS) computer program. We calculated and compared baseline characteristics using bivariate analysis. Groups were compared according to risk factors. Bivariate analysis for the presence of LI was performed by *t* test for continuous variables and by χ^2 test or Fisher exact test for categorical variables. Difference in frequency of categorical variables was expressed in terms of an odds ratio (OR) with a 95% CI.

In the logistic regression analysis, the dependent dichotomous variable was the number of LI (single or multiple). A backward stepwise analysis with likelihood ratio criteria was performed in a logistic regression. The level of statistical significance was set at $P<0.05$. In addition, we added a test for interaction between age and leukoaraiosis.

Results

Interobserver agreement on number of lesions ($\kappa=0.78$), anatomic location of lesions ($\kappa=0.72$), and nature of abnormal signals ($\kappa=0.69$) was adequate. The group included 12% of all stroke patients at our hospital. The patients' mean age was 63.08±10.83 years (range, 35 to 89 years); 99 (56.6%) were men, and 76 (43.4%) were women. The majority of LI (102=58.3%) occurred in patients aged >65 years; 53 (30.2%) occurred in patients aged 66 to 75 years, and 20 (11.4%) occurred in patients aged >75 years.

Table 1 lists the diagnostic studies performed in all cases. In 39 cases (22%) we documented only 1 lesion on MRI. In 136 (78%) we found ≥2 lesions: 2 to 5 lesions in 98 cases (56%), 6 to 10 lesions in 25 cases (14.3%), and >10 lesions in 13 cases (7.4%). Leukoaraiosis was found in 109 cases (62%) by the same method.

Table 2 shows the bivariate analysis of risk factors associated with single and multiple LI. The most common risk factors were hypertension in 125 patients (71.4%), diabetes mellitus in 72 patients (41.1%), hyperlipidemia in 74 patients (42.3%), heart disease in 50 patients (28.5%), smoking in 82 patients (46.9%), and heavy alcohol drinking in 58 patients (33.1%). The median of follow-up duration for hypertension was 3.5 years in the single LI group versus 4 years in the multiple LI group ($P=0.437$). Hypertension and diabetes mellitus occurred concomitantly in 52 cases, hypertension and hyperlipidemia in 49 cases (28%), hypertension and smoking in 59 cases (33.7%), and diabetes mellitus and hyperlipidemia in 35 cases (20%). With regard to risk factors, no significant differences existed between single and multiple LI for age, hypertension, hyperlipidemia, smoking, and heavy alcohol

TABLE 2. Bivariate Analysis of Risk Factors Associated With Single and Multiple Lacunar Infarcts

	Lacunar Infarction			
Risk Factor	Single (n=39), N (%)	Multiple (n=136), N (%)	OR (95% CI)	Significance
Female	19 (49)	57 (42)	0.759 (0.37–1.50)	0.450
Male	20 (51)	79 (58)		
Age, mean±SE	58.7±11.5	64.3±10.3		0.004
Hypertension				
No hypertension	7 (17.9)	25 (18.4)		0.218
High normal	2 (5.2)	16 (11.7)		
Grade I (mild)	10 (25.6)	39 (28.7)		
Grade II (moderate)	15 (38.5)	29 (21.3)		
Grade III (severe)	5 (12.8)	27 (19.9)		
Total hypertension	30 (76.9)	95 (69.9)		
Follow-up, y	3.5 (1–50)	4.0 (1–48)		0.437
Diabetes mellitus	10 (26)	62 (46)	2.430 (1.09–5.40)	0.026
Follow-up, y	4.5 (1–14)	3.0 (1–28)		0.706
Hyperlipidemia	16 (41)	58 (43)	1.069 (0.52–2.20)	0.857
Smoking	19 (49)	63 (46)	0.908 (0.45–1.85)	0.792
Heavy alcohol drinker	10 (26)	48 (35)	1.582 (0.59–3.52)	0.259
Leukoaraiosis	15 (39)	94 (69)	3.581 (1.77–7.51)	0.000
≥65 y+leukoaraiosis	7 (17.9%)	59 (43.4%)	3.50 (1.45–8.49)	0.004
Heart disease				
Cardiac arrhythmias	2 (5.1)	4 (2.9)	1.78 (0.31–10.12)	0.616
Ischemic cardiopathy	5 (12.8)	16 (11.8)	1.10 (0.38–3.23)	0.787
Hypertensive cardiopathy	6 (15.4)	17 (12.5)	1.27 (0.47–3.49)	0.638
Hematocrit	44.2±6.1	47.1±4.9	1.09 (1.04–1.21)	0.003

drinking. Nevertheless, diabetes mellitus was more frequent in multiple LI patients (46% versus 26%; $P=0.026$), as was leukoaraiosis (69% versus 39%; $P=0.000$). In addition, mean age was significantly higher in multiple LI patients (64.3±10.3) than in single LI patients (58.7±11.5; $P=0.004$). When the groups were analyzed by age, only 5 of the 39 patients with single LI were aged ≥70 years, while in the multiple LI group, 44 of 136 were aged ≥70 years ($P=0.016$). Of the 49 patients aged ≥70 years, 42 (86%) presented with leukoaraiosis compared with only 36.5% (46 of 126) of the patients aged <70 years ($P<0.001$). A hematocrit value >0.47 was also associated with multiple LI ($P=0.003$). Table 3 shows the multiple logistic regression analysis for risk factors associated with multiple LI.

The clinical syndromes observed were similar in both groups ($P=0.68$); the more frequent locations were the lenticulocapsular region and thalamus.

The median follow-up period was 12 months, ranging from 6 to 156 months. With regard to outcome, 95% of the patients with single LI (37 of 39) and 77% (105 of 136) of the patients of multiple LI had a Rankin Scale score ≤2 ($P=0.013$) (Table 4).

Global recurrence was 20.6% (36 of 175), with 7% recurrence in patients with single LI (3 of 39) and 24% recurrence (33 of 136) in patients with multiple LI ($P=0.0024$). We thus estimated the recurrence frequency per patient and per year for the entire group and for the single LI and multiple LI groups. We found that the probability of recurrence was 4% per patient per year in patients with single LI and 13% per patient per year in patients with multiple LI.

Discussion

In this hospital series we analyzed the clinical characteristics, risk factors, prognosis, and recurrence of consecutive LI in a group of 175 cases studied and followed for a 10-year period. However, this study cannot evaluate the incidence of LI in the general population because it is hospital based and has many potential recruitment biases. The overall frequency of LI in this Mexican population was 12%, similar to epidemiological reports comparing the prevalence of lacunar and nonlacunar infarcts.[12,13] Although the incidence of LI has been reported to be higher in Mexican Americans,[14] we found that the frequency was similar to that of other Hispanic populations.[15]

Different studies have shown that the risk factors, natural history, and clinical management associated with LI are different than those associated with other types of brain infarcts. Boiten et al[9] and Lodder et al[16] stated that advanced age, sex, hypertension, diabetes mellitus, ischemic cardiopathy, TIA, and smoking are risk factors for LI. In our study the prevalence of risk factors was similar to that found by other

TABLE 3. Multiple Logistic Regression for Risk Factors Associated With Multiple Lacunar Infarcts

Risk Factor	Multiple Lacunar Infarction, OR (95% CI)	Significance
Sex, F/M	1.03 (0.44–2.92)	0.758
Age	1.03 (0.99–1.07)	0.152
Hypertension		
No hypertension		0.302
High normal	2.26 (0.36–14.19)	0.385
Grade I (mild)	1.24 (0.37–4.17)	0.726
Grade II (moderate)	0.57 (0.17–1.89)	0.361
Grade III (severe)	1.86 (0.45–7.58)	0.390
Hyperlipidemia	1.27 (0.55–2.96)	0.580
Smoking	0.99 (0.37–2.65)	0.978
Heavy alcohol drinker	1.56 (0.63–3.89)	0.340
Heart disease		
Heart arrhythmia	0.60 (0.08–4.24)	0.606
Ischemic cardiopathy	1.25 (0.32–4.90)	0.747
Hypertensive cardiopathy	1.05 (0.31–3.53)	0.935
Diabetes mellitus	2.95 (1.25–6.97)	0.031*
Leukoaraiosis	3.74 (1.71–8.18)	0.001*
≥65 y+LA (interaction)	1.47 (0.36–5.95)	0.593
Hematocrit	1.12 (1.04–1.21)	0.003*

Note: The Backward method was used for multivariable analysis.

authors.[16–20] Although hypertension was the most prevalent factor in patients with single and multiple LI, diabetes mellitus was significantly associated with multiple LI ($P=0.02$). This suggests that diabetes mellitus plays an important role in the etiology of disseminated cerebral small-vessel disease. A synergistic effect between hypertension and diabetes mellitus was not found. A previous study analyzing the presence of diabetes mellitus and hypertension in patients with lacunar and nonlacunar infarcts[21] revealed no association and no synergistic effect for either of these diseases. In our series hypertension and diabetes mellitus concurred in 51 of 136 cases (37.5%). At autopsy, Fisher[4] distinguished 2 types of local small-vessel obstructions: lipohyalinosis, mainly found in hypertensive patients with small, multiple, and usually asymptomatic lacunes; and microatheromatous disease, mainly occurring in cases with larger and usually single symptomatic lacunes. These 2 types of penetrating brain vessel obstruction may be present in patients with other risk factors in addition to hypertension, particularly diabetes mellitus.[21] Clinical or morphological evidence of hypertension was found in 97% of the cases in the same study of Fisher and in >70% in other series.[17,18,22] Despite these findings, the role of hypertension in LI has been questioned, mainly because other causal factors for LI such as embolus of cardiac or carotid origin have been found recently.[3,4,6,7,9,16,23,24] Kappelle and van Gijn[7] revised 14 LI studies and found that 43% to 83% of the patients were hypertensive. In a study of isolated systolic hypertension, Davis et al[25] found that diabetes mellitus and smoking are particularly associated with LI. Similar results were obtained by You et al,[26] who reported an OR of 8.9 for LI in the presence of hypertension and of 2.3 in the presence of diabetes mellitus.

TABLE 4. Prediction and Recurrence on Singular and Multiple Lacunar Infarcts

	Singular (n=39), N (%)	Multiple (n=136), N (%)	OR (95% CI)	*P*
Rankin Scale				
0 to 2	37 (94.9)	105 (77.2)	5.462 (1.25–23.95)	0.013
3 to 5	2 (5.1)	31 (22.8)		
Recurrences	3 (7.7)	33 (24.3)	3.845 (1.11–13.30)	0.024

Note: Results expressed by χ^2 with 95% CI.

According to the lacunar hypothesis, hypertensive small-vessel disease is the most important cause of lacunar strokes. In addition, diabetes mellitus may cause microatheroma in small vessels, which may be present in LI. Other publications[26–28] have reported associations between diabetes mellitus and multiple LI in accordance with our findings. In our series, 62 of 136 multiple LI patients were diabetic ($P=0.026$). Without a doubt, hypertension is the most important risk factor for all types of strokes[6,7]; however, according to our results, diabetes mellitus also plays an important role in the development of small-vessel disease, especially in the presence of multiple LI.

Patients were evaluated at their first clinical presentation. Thus, in the multiple lacune population prior infarcts were asymptomatic and may reflect poor control over the principal risk factors, particularly hypertension and diabetes mellitus.

Interestingly, another factor significantly associated with multiple LI in our series was hematocrit >0.47. Although elucidation of the mechanism responsible for the high hematocrit level will require further examination in a properly designed study, it is probably related to Mexico City's altitude of 2240 m above sea level. This geographic factor may confer a specific stroke risk profile due to increased blood viscosity and impaired oxygen consumption, similar to the reports in patients with polycythemia with elevated packed cell volume.[29] Whether high blood viscosity is a cause of ischemic events in stroke or simply reflects the presence of secondary acute-phase reactants remains controversial. However, our results are supported by other observations and suggest that blood hyperviscosity is a risk factor for the development of multiple LI. Kario et al[30] revealed that silent multiple LI is closely associated with hypercoagulability. Coull et al[31] found severe blood hyperviscosity in patients with acute brain infarct and in patients with known vascular risk factors, suggesting that blood hyperviscosity may precede cerebrovascular disease symptoms.

Many authors emphasized the significant correlation between leukoaraiosis and age, as well as that between hypertension and general arteriosclerosis.[32–35] Another consideration is the association of leukoaraiosis with LI, which is well established but was observed to be variable.[36] Nevertheless, some observations support the view that small-vessel disease is the common underlying abnormality behind LI and leuko-

araiosis.[36,37] In our study mean age of 64.3±10.3 years was associated with multiple LI, and we also observed that leukoaraiosis was associated with multiple LI even in patients aged <65 years. No interaction between age, leukoaraiosis, and multiple LI was found. Therefore, our results suggest that leukoaraiosis predisposes to multiple LI and provides further evidence of the concept that leukoaraiosis is related primarily to small-vessel disease.

Leukoaraiosis may be an important prognostic indicator of both functional ability and survival. In this study leukoaraiosis was present in 39% of the patients with single LI and 69% of the patients with multiple LI ($P<0.001$). Several groups have investigated the prognosis for LI patients with leukoaraiosis. Miyao et al[38] found a significantly higher recurrent stroke rate in patients with leukoaraiosis, leading to a significantly higher prevalence of dementia, a higher degree of dependence, and a less favorable survival prognosis. Although we did not assess dementia in the present study, our results suggest that multiple LI and leukoaraiosis are associated with a less favorable functional prognosis and higher recurrence. Recently, De Jong et al[39] found that prognosis for mortality, recurrent stroke, and overall functional outcome in LI patients with ≥1 silent lacunar lesion was less favorable than that in patients with no lesions.

In our study functional outcome at 12 months was significantly better (Rankin Scale score ≤2) in patients with single lesions (5% versus 23%; $P=0.013$). The overall percentage of patients with a Rankin score of 0 to 2 at 6 months was 81%, similar to the frequency of patients with independent life at 6 months reported by Samuelsson et al[40] (73% and 87%, respectively). We found a recurrence rate of 21%, in accordance with other series.[41–43] Furthermore, the time to recurrence reported here differs from that found in other series. The recurrence rate was 4% per patient per year in single LI patients and 13% in multiple LI patients. This annual recurrence is slightly higher than that reported by other authors.[41–43] This difference may be explained by the different methods used to calculate the recurrence frequencies with respect to time, our reliance on a high percentage of patients with multiple, monosymptomatic LI, and the fact that the mean age of stroke occurrence is lower in Mexico than in developed countries.

Because of the study design, it was difficult to determine other factors associated with recurrence. Nevertheless, similar to other studies that have reported data similar to ours,[27,28] we supposed that risk factors found in multiple LI patients may be associated with higher recurrence.

In conclusion, the main risk factors associated with multiple LI in the present series were diabetes mellitus, leukoaraiosis, and high hematocrit levels. The presence of multiple LI may be an important prognostic indicator not only for functional recovery but for a higher rate of recurrence as well.

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