Lacunar versus non-lacunar infarcts: pathogenetic and prognostic differences

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Abstract

To characterise the pathogenetic and prognostic features of lacunar infarcts, 88 patients with these infarcts were compared with 103 patients with non-lacunar infarcts. Potential cardioembolic sources were significantly more frequent among patients with non-lacunar infarcts ($p = 0.0025$). Although the prevalence of hypertension was higher among lacunar infarcts, this difference was not statistically significant. However, the distribution of hypertensive patients in the two groups of lacunar and non-lacunar infarcts was influenced by the presence or absence of cardioembolic sources: hypertension was significantly associated with the presence of cardioembolic sources among non-lacunar infarcts, whereas among lacunar infarcts it was significantly more frequent in patients without a cardioembolic source. This indicates that cardioembolism may exert a confounding effect by suppressing the relation between hypertension and lacunar infarcts. In a mean follow up period of 28.1 months, lacunar infarcts had a significantly lower incidence of stroke recurrence and of myocardial infarction (age-adjusted survival analysis: $p = 0.0008$); mortality from all causes was also lower in patients with lacunar infarct (age-adjusted survival analysis: $0.04 < p < 0.05$). In a multivariate regression analysis, stroke subtype was an independent predictor of new major vascular events. These findings support the lacunar hypothesis and should be considered in the planning of epidemiological and therapeutic studies in patients with cerebral infarction.

CM Fisher's pathological studies related lacunar infarcts to small-vessel disease caused by hypertension.^{1,2} Lacunar infarcts were also limited to specific clinical syndromes,^{3,4} raising the possibility of distinguishing a subgroup of cerebral infarctions on the basis of their pathogenesis. As these patients have a low early case-fatality rate and consequently a low necropsy rate, later attempts to verify this lacunar hypothesis employed CT to recognise such cases during life,⁵⁻⁷ and compared lacunar infarcts with other groups of ischaemic strokes by analysing the distribution of vascular risk factors and of several clinical and instrumental variables. The results of these studies suggested that cardiac and arterial embolism may also

give rise to lacunar infarcts, and since hypertension was absent in a substantial proportion of cases, the lacunar hypothesis has recently been questioned.⁸ Although there is general agreement on the favourable short-term prognosis of lacunar infarcts,⁹ only a few studies have reported on their long-term outcome, with contradictory conclusions.^{10,11}

As lacunar infarcts represent almost 25% of all ischaemic strokes¹¹ and an even higher proportion of stroke survivors, further characterisation of their pathogenetic and prognostic features appears of more than academic interest and may contribute to the design of therapeutic studies after acute stroke. We therefore compared a group of patients with lacunar infarct to another group with non-lacunar ischaemic stroke.

Patients and methods

The detailed method of our study has been described.¹² In brief, we included prospectively 191 consecutive patients with first-ever ischaemic stroke visited at the emergency room of the Policlinico Hospital in Milan within 72 hours after the onset of symptoms and hospitalised at the local neurological department. All patients had a neurological and general physical examination on arrival at the emergency room; this was repeated daily during the first week and twice weekly until discharge, enabling us to subdivide them into two groups according to their neurological state at the time of maximum deficit.

Lacunar infarct (LI) ($n = 88$), was defined as one of the following syndromes: pure motor stroke (unilateral pure motor deficit involving at least two of three areas—face, arm and leg); pure sensory stroke (unilateral pure sensory deficit involving at least two of three areas—face, arm and leg); ataxic hemiparesis (ipsilateral corticospinal and cerebellar-like dysfunction without other features clearly localising to the posterior circulation); dysarthria—clumsy hand syndrome (severe dysarthria with slight weakness and clumsiness of the hand); and hemichorea/hemiballism (involuntary arrhythmic unilateral movements involving at least two of three areas—face, arm and leg). At the time of our study the inclusion of sensorimotor strokes among the lacunar syndromes was still debatable, and these patients were therefore not included in this report.¹²

Non-lacunar infarcts (NLI) ($n = 103$) included all patients whose clinical picture did not conform to the preceding clinical syn-

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Figure 1 Comparison of the prevalence of risk factors, clinical and instrumental findings in lacunar and non-lacunar infarcts, showing the odds ratios (OR, vertical bars) and the 95% CI (horizontal bars) on a logarithmic scale. An OR > 1.0 indicates higher prevalence among lacunar infarcts (LI), and an OR < 1.0 a higher prevalence among non-lacunar infarcts (NLI).

dromes, but we also excluded all patients ($n = 61$) with impairment of consciousness on admission because of their poor short-term prognosis.

CT was performed on admission and repeated after five to eight days. All CT scans were reviewed "blindly" by a neuroradiologist (EB) who subdivided ischaemic lesions into lacunes (deep hypodense areas with a maximum diameter of 15 mm on no more than two adjacent 10 mm tissue sections) and non-lacunar infarcts (larger or cortical lesions). All the patients that were included were screened for the presence of cerebrovascular risk factors (hypertension, smoking, diabetes, plasma cholesterol and triglycerides, occurrence of previous transient ischaemic attacks (TIA)). Hypertension was diagnosed if blood pressure was repeatedly higher than 160/90 mm Hg and in those patients already taking antihypertensive medications. A cardiological examination with ECG and chest x rays were performed in all cases.

Depending on specific diagnostic needs, M-mode and B-mode echocardiograms were obtained in 31 NLI (30.1%) and in 20 LI (22.7%), and 24 hour ECG monitoring was obtained in seven patients with NLI (6.8%) and in four with LI (4.5%). Ischaemic heart disease was diagnosed if patients had a typical history of angina or acute myocardial infarction, or clear-cut ECG evidence of previous myocardial infarction. Emboligenic heart disease was diagnosed in the presence of atrial fibrillation, endocarditis, mitral valve disease, left ventricular aneurysm or thrombus. A continuous-wave doppler study of the extracranial vessels was performed¹³ in all patients except three (all with NLI), who died early after admission to hospital.

Sixty one patients considered for carotid-endarterectomy had cerebral angiography by transfemoral catheterisation. Their angiographic picture was correlated with the results of ultrasonic examination.

Deaths occurring as a consequence of stroke

Table 1 Age, sex and cerebrovascular risk factors according to stroke subtype

	Lacunar infarcts $n = 88$	Non-lacunar infarcts $n = 103$
Age*	63.5 (12.5)	66.1 (12.4)
Male sex	55 (62.5%)	63 (61.2%)
Hypertension	57 (64.8%)	54 (52.4%)
Diabetes	17 (19.3%)	17 (16.5%)
Smoking	36 (40.9%)	46 (44.7%)
Previous TIA	20 (22.7%)	16 (15.5%)
Cholesterol (mg/dl)*	227.7 (41.7)	223.0 (57.5)
Triglycerides (mg/dl)*	153.2 (96.6)	135.9 (60.0)

* Mean (SD)

were recorded, and residual disability in survivors was established at one month and classified as follows: Not disabled—dependent in self-care, with return to pre-stroke activities; Partially disabled—requiring help in activities of daily living, able to walk with or without assistance; Severely disabled—bed-ridden or confined to a wheel chair, requiring constant care.

All patients who survived their first-ever stroke were followed for at least 12 months or until death, and occurrence of new cerebrovascular events was reported. Stroke recurrence was classified as: mild if there was no or only slight persistent deterioration with respect to previous neurological deficit; severe if deterioration was significant; or fatal. Occurrence of myocardial infarction and of death from other causes were also recorded.

Statistical methods

The strength of association between the considered variables and the type of stroke (LI or NLI) was calculated by means of odds ratio (OR)¹⁴ and their statistical significance was evaluated by chi-square. Confidence intervals of OR were calculated as suggested by Cornfield.¹⁵ The significance of the difference between means was tested with two-tailed t tests for unpaired data. Survival analyses on the cumulative time dependent probability of major vascular events (stroke, myocardial infarction) and of death were carried out by the Kaplan-Meier method and the strength of the association of these probabilities with possible prognostic variables was evaluated by hazard ratio (HR).¹⁶ Cox's model was employed to carry out multivariate regression analysis.¹⁷

Table 2 CT results, cardiological findings and prevalence of thromboembolic sources

	Lacunar infarcts $n = 88$	Non-lacunar infarcts $n = 103$
Positive CT scan (congruous infarct)	37 (42.0%)	71 (68.9%)
Ischaemic heart disease	10 (11.4%)	19 (18.4%)
Emboligenic heart disease	11 (12.5%)	33 (32.0%)
Stenosis/occlusion of symptomatic vessel (doppler)	16 (18.2%)	27* (27.0%)
Total with ascertained thromboembolic source	27 (30.7%)	56† (54.4%)

* available in 100 patients

† four patients had concomitance of emboligenic heart disease and pathological doppler findings

Table 3 Distribution of hypertension among lacunar and non-lacunar infarcts according to presence or absence of cardioembolic sources

	Absence of cardioembolic source		Presence of cardioembolic source	
	Hypertension +	Hypertension -	Hypertension +	Hypertension -
Lacunar infarcts	51	26	6	5
Non-lacunar infarcts	34	36	20	13
Presence of hypertension in patients with cardioembolic source	OR * (95% CI): 0.8 (0.2–3.0)			
Presence of hypertension in patients without cardioembolic source	OR * (95% CI): 2.1 (1.1–4.0)			
Presence of cardioembolic source in patients with hypertension	OR * (95% CI): 0.2 (0.1–0.5)			
Presence of cardioembolic source in patients without hypertension	OR * (95% CI): 0.5 (0.2–1.7)			

* Non-lacunar infarcts as reference category (an OR > 1.0 indicates higher prevalence among lacunar infarcts, and an OR < 1.0 a higher prevalence among non-lacunar infarcts)

Results

Out of our 88 patients with LI, 67 presented with a pure motor stroke, eight with ataxic hemiparesis, six with pure sensory stroke, five with dysarthria—clumsy hand syndrome, and two with hemichorea/hemiballism. Overall, their age- and sex-distribution was rather similar to those of NLI, as shown in table 1, which also reports the prevalence of cerebrovascular risk factors in the two groups. No significant difference was observed either for continuous variables (age: $t = 0.45$, $p = 0.65$; cholesterol: $t = 0.64$, $p = 0.52$; triglycerides: $t = 1.51$, $p = 0.13$) nor for dichotomous variables (figure 1), although the frequency of hypertension was higher among patients with LI ($p = 0.11$). Of the 57 patients with LI diagnosed as hypertensive, 46 (80.7%) had known hypertension, while pre-stroke blood pressure levels were reported as normal in eight (14.0%) and were unavailable in three (5.3%); for NLI, the corresponding figures were respectively, 43 (79.6%), seven (13.0%), and four (7.4%). A non-sudden onset of symptoms with a gradual, stepwise or stuttering course up to a maximum deficit was observed in 36 LI (40.9%) as opposed to only 18 NLI (17.5%) ($p = 0.006$; figure 1).

Results of cardiological and instrumental evaluations are reported in table 2. CT scan demonstrated a congruous infarct (that is, appropriate to the side of symptoms) in 42.0% of LI and in 68.9% of NLI ($p = 0.0003$; figure 1). All 37 patients with LI and a positive CT scan showed evidence of a lacunar lesion. In contrast, of the 71 patients with NLI who had a congruous infarct visualised at CT scan, 64 had evidence of a cortical or large subcortical

Figure 2 Interval to first recurrent stroke.

lesion, and only seven had evidence of a lacune. With the cardiological findings, no important difference was found in the prevalence of ischaemic heart disease, but atrial fibrillation and other emboligenic heart diseases were significantly more frequent among NLI ($p = 0.0025$; figure 1). Occlusion or stenosis of the symptomatic arterial district was demonstrated by angiography in 10 of 19 patients with NLI and in 10 of 42 LI. However, since angiography was performed only in a selected group of patients, we assessed the prevalence of vascular lesions by means of a Doppler ultrasound examination, which was available in 98.4% of our population, and whose sensitivity and specificity in diagnosing stenosis > 50% of the carotid and vertebral arteries was higher than 95% when compared with subsequent angiographic results. Although the higher frequency of obstructive lesions of the symptomatic arterial district among NLI compared with LI did not reach statistical significance ($p = 0.21$), overall 54.4% of NLI had pathological Doppler results, emboligenic heart disease or both. The prevalence of such potential thromboembolic sources was significantly lower among LI ($p = 0.002$) (figure 1).

As the prevalence of emboligenic heart disease was significantly higher among NLI, we examined the relation between this variable and hypertension in our two groups. As shown in table 3, the distribution of hypertensive patients in our two groups of LI and NLI was influenced by the presence or absence of emboligenic heart disease: among patients without emboligenic heart disease hypertension was significantly more frequent in LI ($0.04 < p < 0.05$), whereas no such relation was apparent among patients with emboligenic heart disease. Accordingly, among hypertensive patients, cardioembolic sources were more frequent in the group with NLI ($p = 0.002$), whereas no significant difference was observed in non-hypertensive patients.

Short-term prognosis was significantly better for LI than for NLI both in terms of mortality as a direct consequence of stroke,

Table 4 Short- and long-term outcome according to stroke subtype

	Lacunar infarcts <i>n</i> = 88	Non-lacunar infarcts <i>n</i> = 103
<i>At 1 month</i>		
Absent disability	51 (58.0; 47.0–68.4)	31 (30.1; 22.1–41.0)
Partial disability	33 (37.5; 27.4–48.5)	43 (41.7; 33.1–53.3)
Complete disability	4 (4.5; 1.3–11.2)	14 (13.6; 7.9–22.4)
Dead	0 (0.0; 0.0–4.1)	15 (14.6; 8.7–23.5)
<i>Follow up results</i>		
Mean duration (months)	31.1	25.1
TIA	7 (8.0; 3.3–15.7)	3 (3.4; 0.7–9.6)
Stroke	12 (13.6; 7.3–22.6)	20 (22.7; 14.5–32.9)
mild	4	4
severe	3	5
fatal	5	11
Myocardial infarct	0 (0.0; 0.0–4.1)	4 (4.5; 1.3–11.2)
fatal	—	2
Non-vascular death	3 (3.4; 0.7–9.6)	8 (9.1; 4.0–17.1)

χ^2 for trend = 24.73; $p < 0.0001$.

Numbers in brackets are the proportions and their 95% CI.

Figure 3 Cumulative probability of survival free from stroke and myocardial infarction according to stroke subtype. Follow up times of patients who died from causes other than stroke and myocardial infarction were censored at the time of death. Numbers are those of patients at risk at the beginning of each time interval.

and in terms of residual disability at one month (table 4). Among survivors, the cumulative one year probability of stroke recurrence was 7.9% for LI and 11.4% for NLI (OR = 0.67; $p = 0.06$). The timing of these recurrences is shown in figure 2. Overall, in a mean period of 28.1 months, new vascular events occurred in 30.7% of NLI and in 21.6% of LI (table 4). This difference was even more remarkable if end-points were limited only to major vascular events (stroke, myocardial infarction), as their incidence among NLI (27.3%) was more than twice with respect to LI (13.6%). Survival analysis for major vascular events confirmed the strikingly better long-term outcome of LI (HR = 2.7, 95% CI 1.4–5.2; $p = 0.004$) (figure 3), which became even more evident when adjusting for age (HR = 3.0, 95% CI 1.6–5.6; $p = 0.0008$).

When only stroke recurrence is considered, HR was 2.2 (95% CI 1.1–6.6; $p = 0.027$) and age-adjusted HR was 2.4 (95% CI 1.2–4.8; $p = 0.01$). Results of a multivariate regression analysis including all tested variables demonstrated that the stroke subtype (that is, LI or NLI) represented—together with age, occurrence of previous TIA, and residual disability at one month—an independent prognostic factor for the subsequent occurrence of major vascular events (table 5).

Table 5 Variables associated with major vascular events (stroke, myocardial infarction) in multivariate regression analysis

	Hazard ratio	95% CI	p-value
Age*	1.03	1.00–1.07	0.05
Previous TIA			
No#	1.0	—	—
Yes	2.19	1.07–4.46	0.03
Type of stroke			
LI#	1.0	—	—
NLI	2.26	1.05–4.83	0.04
Residual disability**			
absent#	1.0	—	—
partial	2.41	0.98–5.92	0.06
complete	3.65	1.25–10.68	0.02

* Continuous variable.

reference category.

** Trend analysis: HR = 1.88/95% CI: 1.13–3.12/ $p = 0.02$.

Discussion

To test the lacunar hypothesis we compared a group of patients with LI to another group with NLI. Unlike several previous studies,^{9,18,19} we did not try to subdivide the latter strokes according to their pathogenesis into cardioembolic and atherothrombotic, since this distinction is often difficult or even impossible, and despite extensive investigations up to 40% of cerebral infarcts may remain of undetermined cause.²⁰ We did not exclude patients with vertebrobasilar strokes because LI may also be located in the brainstem, and because there is no firm evidence that posterior circulation infarcts have a different pathogenesis and prognosis than carotid territory infarcts. Several authors have employed rigid criteria for the diagnosis of LI, requiring absence of haemodynamic or embolic sources²¹ or even normal angiographic findings;¹⁸ however, these conditions may be difficult to fulfil, particularly on a large-scale basis, since they would require performance of extensive and often unnecessary instrumental investigations. In our study we relied on clinical examination for the diagnosis of LI, a simple method which can be easily applied in all settings. However, we included only patients with first-ever stroke, since residual signs of a previous insult may prevent correct diagnosis of a lacunar syndrome. Moreover, since our study was hospital-based, we were able to include patients with acute stroke (91% of them were visited within 24 hours of onset) and to diagnose a lacunar syndrome when they had reached their maximum neurological deficit, as determined by repeated examinations, thus avoiding misdiagnosis in patients whose lacunar syndrome may just represent the outcome of a previously more extended clinical deficit.

Adherence to these criteria may explain why none of our patients with a lacunar syndrome had a non-lacunar lesion visualised at CT scan. Conversely, 6.8% of those with NLI had an appropriate lacunar lesion; although in a recent necropsy study 20% of symptomatic lacunes had presented with aphasia in addition to right hemiparesis,²² such lesions may well represent casual findings, since we observed lacunes also in the asymptomatic hemisphere of 11 (10.7%) patients with NLI.

The 12.5% prevalence of potential cardiac sources of embolism among our LI agrees with previous reports;^{23,24} it was significantly lower than among NLI, which again agrees with other series.^{25,26} Indirect support to the conclusion that embolism occurred more often among NLI is provided by the significantly higher frequency of an abrupt onset of stroke in this group, as this feature has been positively associated with cardiogenic brain embolism.^{27,28}

Although lacunar strokes are commonly attributed to hypertensive arteriolopathy, the prevalence of hypertension among LI was not significantly higher in our study as in previous studies,^{18,24,29} even if different diagnostic criteria for hypertension were considered.²⁵ These studies concluded that “hypertension is no more important in the development of LI

than it is in the development of other types of stroke", and a recent review drew the same conclusions.⁸ However, previous studies did not take into account potential confounding variables; this effect should be considered if such variables are dishomogeneously distributed between the groups. Of our LI, without cardioembolic sources, 66.2% were hypertensive as opposed to only 48.6% of NLI; this statistically significant difference was not observed in patients with cardioembolic sources. This, combined with the significant association between hypertension and cardioembolic sources among NLI, leads to the conclusion that cardioembolism may exert a confounding effect by suppressing the actual relationship between hypertension and LI.

The long-term prognosis of LI has received little attention. One study¹⁰ concluded that their average recurrence rate was "much lower than that in survivors from cerebral infarction". Another study¹¹ found a one year recurrence rate of 11.9% (95% CI, 5.5%–18.0%), "similar to that reported in other groups of patients with stroke". Both these contradictory conclusions were based on a comparison with historical controls. By directly comparing our patients with LI with a group of NLI, we found that the occurrence of new major vascular events was significantly lower in LI than in NLI. This agrees with the results of a recent study³⁰ reporting a lower one year stroke recurrence rate among LI than for other types of cerebral infarction. The authors further interpreted the distinct low even recurrence rate among LI as compatible with the hypothesis that for a further stroke to develop another perforating artery needs to become symptomatic. Although the recurrence pattern among our patients with LI was similar to that study, we did not observe a similarly high recurrence rate among our cases with NLI, whose survival curve maintained a fairly constant slope even after the first year. The worse long-term prognosis of NLI in our study was reflected also by their higher overall mortality (age-adjusted survival analysis: HR = 2.0, 95% CI 1.0–4.0; 0.04 < p < 0.05).

Moreover, in multivariate regression analysis, stroke subtype was a predictor of new major vascular events, independent from other prognostic variables including degree of disability after the first stroke. This indicates that the probability of new major vascular events is related not only to severity of the first stroke, but also to its pathogenetic mechanisms. Despite the fact that in a clinical setting adequate investigation is appropriate to recognise the minority of patients in whom LI is caused by thromboembolism, the pathogenetic and prognostic peculiarities of this subgroup of ischaemic strokes should be considered in the

planning of epidemiological and therapeutic studies after cerebral infarction.

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