Two Clinically Distinct Lacunar Infarct Entities?
A Hypothesis

Jelis Boiten, MD; Jan Lodder, MD; and Fons Kessels, MD

Background and Purpose: We investigated the hypothesis that patients with one or more asymptomatic lacunar infarcts and those with only one symptomatic lacunar infarct represent two clinically distinct lacunar infarct entities.

Methods: In a prospective series of 100 lacunar infarct patients, univariate and multivariate logistic regression analysis was performed on clinical features, vascular risk factors, and leukoaraiosis between patients with and without asymptomatic lacunar infarcts.

Results: Patients with asymptomatic lacunar infarcts had hypertension significantly more often (71% versus 43%; [crude] odds ratio, 3.31; 95% confidence intervals, 1.16–9.43; p<0.05) and had leukoaraiosis significantly more often (71% versus 19%; [crude] odds ratio, 10.67; 95% confidence intervals, 3.81–32.10; p<0.001) than those with only a symptomatic lacunar infarct. After multivariate logistic regression analysis, only leukoaraiosis was significantly associated with the presence of asymptomatic lacunar infarcts. The asymptomatic lacunar infarcts differed in location, involved vascular territory, and volume from the symptomatic infarcts.

Conclusions: Two distinct lacunar infarct entities might be broadly distinguished during life: lacunar infarct patients with a single, symptomatic lacunar infarct, and patients with multiple lacunar infarcts and a high frequency of hypertension and leukoaraiosis, in which the underlying small-vessel vasculopathy might be different. (Stroke 1993;24:652–656)

Key Words • lacunar infarction • leukoaraiosis • small-vessel disease
single perforating artery,\textsuperscript{14} i.e., a subcortical, small, sharply margined hypodense lesion with diameter smaller than 20 mm, or if no specific lesion was visible on CT. We distinguished four lacunar syndromes: pure motor stroke, sensorimotor stroke, pure sensory stroke, and ataxic hemiparesis including dysarthria–clumsy hand cases, as defined by Bamford \textit{et al}.\textsuperscript{14}

In asymptomatic lacunar infarction, the lacunar infarct was not considered compatible with the clinical signs and symptoms, i.e., either at least one lacunar infarct in the contralateral (clinical asymptomatic) hemisphere, or at least two ipsilateral lacunar infarcts, or both.

The following risk factors were recorded: hypertension (known hypertension treated with antihypertensive medication; two or more blood pressure recordings of higher than 160/90 mm Hg before stroke or taken later than 1 week after stroke), diabetes mellitus (known treated diabetes; fasting serum glucose higher than 6 mmol/L measured on at least two occasions), and history of ischemic heart disease (myocardial infarction, angina pectoris).

The lacunar infarcts were localized by means of an atlas comparing anatomic slices with standard CT slices.\textsuperscript{15} We distinguished the following locations: internal capsule (anterior limb, posterior limb), corona radiata, lentiform nucleus, thalamus, and caudate nucleus.

We distinguished four vascular territories using Damosio’s brain templates\textsuperscript{16}: medial striate arteries, lateral striate or lenticulostriate arteries, anterior choroidal artery, and thalamoperforant arteries.

Infarct volume was estimated according to Nelson \textit{et al}\textsuperscript{17}: the length and width of the infarct was measured at right angles. The product was multiplied by thickness and number of affected slices and divided by 2.

Leukoaraiosis was defined as focal or diffuse hypodensities in the periventricular or deep white matter, without involving the cortex, and with ill-defined margins, which distinguish it from infarction.\textsuperscript{9}

CT scans were reviewed independently by two of the authors. The presence of lacunar infarcts and of leukoaraiosis on CT was determined separately in two sessions. Interobserver agreement for the assessment of leukoaraiosis on CT was determined, and the results were analyzed using kappa statistics.\textsuperscript{18} The interobserver agreement was good with corresponding $\kappa$ of 0.84. In case of disagreement on the presence of an infarct or leukoaraiosis, CT was regarded as negative.

We investigated our hypothesis by comparing the frequency of clinical features (age, sex), vascular risk factors (hypertension, diabetes mellitus, history of ischemic heart disease), and leukoaraiosis between two groups of lacunar infarct patients, namely those with or without asymptomatic lacunar infarcts. Furthermore, we determined whether location, involved vascular territory, and volume differed between the asymptomatic and symptomatic lacunar infarcts. In univariate analysis, dichotomous variables were analyzed by means of (crude) odds ratios [(c)OR] with 95\% confidence intervals (CI)\textsuperscript{19,20} and $\chi^2$ test with Yates’s correction,\textsuperscript{21} whereas the two-sample $t$ test was used for analysis of continuous variables. Multivariate logistic regression analysis was subsequently used to determine the relative contribution of age, sex, hypertension, diabetes mellitus, history of ischemic heart disease, and leukoaraiosis, with asymptomatic lacunar infarcts (present or absent) as the dependent variable. In particular, the independent contributions of hypertension and leukoaraiosis were determined separately, after stepwise controlling for the other variables. Statistical analysis was performed with (adjusted) odds ratio [(a)OR] with 95\% CI and $\chi^2$ test.

### Results

One-hundred-three patients with symptomatic lacunar infarction were registered. We excluded three patients because CT quality was insufficient. Twenty-one of these 100 patients (21\%; 95\% CI, 13–29\%) also had one or more asymptomatic lacunar infarcts on CT, whereas 79 patients had only symptomatic lacunar infarction. Mean age and male/female ratio did not differ between the patients with and without asymptomatic lacunar infarction (Table 1). Patients with asymptomatic lacunar infarction had leukoaraiosis and hypertension significantly more often [(c)OR, 10.67; 95\% CI, 3.81–32.10; $p<0.001$ and (c)OR, 3.31; 95\% CI, 1.16–9.43; $p<0.05$, respectively]. Prevalence of the remaining risk factors did not differ between both groups. Multivariate logistic regression analysis showed that leukoaraiosis was significantly associated with the presence of asymptomatic lacunar infaracts after controlling for the other variables [(a)OR, 11.90; 95\% CI, 3.32–42.80; $p<0.001$] (Table 1). Hypertension was still correlated with asymptomatic lacunar infarcts, but after

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Features, Vascular Risk Factors, and Leukoaraiosis in Lacunar Infarct Patients With and Without Asymptomatic Lacunar Infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical feature/risk factor</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>HID</td>
</tr>
<tr>
<td>Leukoaraiosis</td>
</tr>
</tbody>
</table>

An odds ratio (OR) $>1$ indicates that the risk factor is more frequent in the asymptomatic lacunar infarct (ALI) group. (c)OR, crude OR; CI, confidence interval; (a)OR, adjusted OR (after multivariate logistic regression analysis); HID, history of ischemic heart disease. *$p<0.05$, †$p<0.001$ by $\chi^2$ test.
controlling for leukoaraiosis this correlation was no longer statistically significant [(a)OR, 2.64; 95% CI, 0.79–8.90], indicating an association between hypertension and leukoaraiosis.

For further analysis of location, involved vascular territory, and volume of the symptomatic and asymptomatic lacunar infarcts, three patients who had two lacunar infarcts on the symptomatic side were excluded because it was not known which of the two infarcts was the symptomatic infarct. In the remaining 97 patients, CT showed one symptomatic lacunar infarct in 54 patients (43 had no symptomatic infarct visible on CT) and 24 asymptomatic lacunar infarcts in 18 patients. Locations of these 54 symptomatic lacunar infarcts differed from the 24 asymptomatic infarcts (Table 2): 19 (35%) of the symptomatic infarcts were located in the posterior limb of the internal capsule versus two (8%) of the asymptomatic infarcts; 11 (46%) of the asymptomatic infarcts were located in the anterior limb of the internal capsule and caudate nucleus versus five (9%) of the symptomatic infarcts. The frequency of the other involved locations did not differ between both groups. The frequency of the involved vascular territories in the symptomatic and asymptomatic lacunar infarcts also differed (Table 2): anterior choroidal artery territory was involved in almost 70% of the symptomatic infarcts, whereas the lateral and medial striate arteries were involved in 75% of the asymptomatic infarcts. Moreover, the symptomatic lacunar infaracts were significantly larger than the asymptomatic lacunar infarcts (Table 2).

**Table 2. Location, Involved Vascular Territory, and Volume of Asymptomatic and Symptomatic Lacunar Infarcts**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ALI (n=24)</th>
<th>SLI (n=54)</th>
<th>OR</th>
<th>95% CI*</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICPL</td>
<td>2 (8)</td>
<td>19 (35)</td>
<td>0.17</td>
<td>0.04–0.87</td>
<td>0.01</td>
</tr>
<tr>
<td>ICAL/CN</td>
<td>11 (46)</td>
<td>5 (9)</td>
<td>8.29</td>
<td>2.14–34.03</td>
<td>0.0005</td>
</tr>
<tr>
<td>LN</td>
<td>2 (8)</td>
<td>6 (11)</td>
<td>0.73</td>
<td>0.14–4.52</td>
<td>NS</td>
</tr>
<tr>
<td>CR</td>
<td>8 (33)</td>
<td>22 (41)</td>
<td>0.73</td>
<td>0.24–2.22</td>
<td>NS</td>
</tr>
<tr>
<td>Th</td>
<td>1 (4)</td>
<td>2 (4)</td>
<td>1.13</td>
<td>0.10–13.29</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular territory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSA</td>
<td>6 (25)</td>
<td>5 (9)</td>
<td>3.27</td>
<td>0.76–14.48</td>
<td>NS</td>
</tr>
<tr>
<td>LSA</td>
<td>12 (50)</td>
<td>11 (20)</td>
<td>3.91</td>
<td>1.23–12.66</td>
<td>0.01</td>
</tr>
<tr>
<td>ACA</td>
<td>5 (21)</td>
<td>36 (67)</td>
<td>0.13</td>
<td>0.04–0.46</td>
<td>0.0002</td>
</tr>
<tr>
<td>TPA</td>
<td>1 (4)</td>
<td>2 (4)</td>
<td>1.13</td>
<td>0.10–13.29</td>
<td>NS</td>
</tr>
<tr>
<td>Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mL)</td>
<td>0.20</td>
<td>1.12</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.12–0.28</td>
<td>0.87–1.37</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Range</td>
<td>0.02–0.81</td>
<td>0.07–3.69</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

An odds ratio (OR) >1 indicates higher frequency in the asymptomatic lacunar infarct (ALI) group. SLI, symptomatic lacunar infarct; CI, confidence interval; ICPL, internal capsule (posterior limb); ICAL, internal capsule (anterior limb); CN, caudate nucleus; LN, lentiform nucleus; CR, corona radiata; Th, thalamus; MSA, medial striate arteries; LSA, lateral striate or lenticulostriate arteries; ACA, anterior choroidal artery; TPA, thalamoperforant arteries.

*95% CI according to Cornfield's method or Miettinen's method (comparison of Th location and TPA vascular territory).†Two-sample t test (mean volume) or Fisher’s exact test.

Discussion

We found that most patients with asymptomatic lacunar infarcts had leukoaraiosis (71%) and hypertension (71%). Asymptomatic lacunar infarcts were independently highly associated with leukoaraiosis, whereas its association with hypertension was partially dependent on the presence of leukoaraiosis. The findings may support our hypothesis that two distinct lacunar infarct entities can be broadly distinguished during life: patients with a single, symptomatic lacunar infarct and the usual vascular risk factors; and patients with multiple lacunar infarcts and a high frequency of hypertension and leukoaraiosis. In neurologically normal persons, silent lacunar lesions were also associated with hypertension and periventricular white matter lesions.22 Autopsy studies in a limited number of patients showed that leukoaraiosis and small, multiple, and usually asymptomatic lacunar infarcts were related to arteriolosclerosis, whereas large, single, and usually symptomatic lacunar infarcts were caused by microatheromatous disease.2,3,5,10,11 Although speculative, our two distinct lacunar infarct entities likely reflect these two causes of local small-vessel obstruction: patients with multiple lacunar infarcts and leukoaraiosis may have arteriolosclerosis, and those with a single, symptomatic lacunar infarct without leukoaraiosis may have microatheromatous disease.

Our finding that the asymptomatic lacunar infarcts were significantly smaller and differed from the symptomatic infarcts in location and involved vascular territory may reflect that the smaller a lesion is and the more a lesion is located in a clinically nonstrategic area, the more likely it is that it does not produce symptoms. On the other hand, combined with the fact that these asymptomatic infarcts are associated with hypertension and leukoaraiosis, these findings may also reflect that arteriolosclerosis is the dominating cause of obstruction in the striate arteries. Subsequently, microatheromatosis might be the dominating vasculopathy of the anterior choroidal artery.

It was demonstrated at autopsy that arteriolosclerosis is the primary factor in the pathogenesis of diffuse white matter lesions.3 However, a clinical study showed that
some patients with diffuse white matter lesions had large-artery strokes as well as small-artery strokes on follow-up. Apparently arteriolosclerosis of the small cerebral arteries does not exclude patients from suffering future large-artery strokes.

Our study has some limitations, and therefore the results must be interpreted with caution. Our registry is hospital-based and not population-based. However, our hospital is the only hospital in the Maastricht referral area, and furthermore, only approximately 16% of stroke patients in The Netherlands are not admitted to the hospital. These are probably primarily rapid lethal and rapid reversible strokes usually representing cerebral hemorrhage and transient ischemic attack, respectively, both of which are not included in our study. Therefore, we consider any significant referral bias unlikely. Furthermore, all our patients had symptomatic lacunar infarction. In future studies, the association of asymptomatic lacunar infarcts with leukoaraiosis and hypertension should also be investigated in neurologically asymptomatic patients. Finally, our hypothesis, which is based on clinical and radiological data, can only be definitely established in autopsy studies, but in view of the low early case fatality rate of lacunar infarct patients such studies will remain difficult to perform.

In some patients the two types of cerebral small-vessel obstruction may coexist. Fisher found both types of small-vessel obstruction at autopsy in one patient. Moreover, arteriolosclerosis and microatheromatosis could be related because they have morphological similarities at the microscopic level. The clinical separation of the two lacunar infarct entities may not have been absolute because some (asymptomatic) lacunar infarcts go undetected by CT. Although specificity of magnetic resonance imaging (MRI) is low, future MRI studies could possibly make the intended distinction between the two groups more accurately.

The role of hypertension as a major risk factor for lacunar infarction has been questioned frequently. In clinical studies many lacunar infarct patients were not hypertensive, whereas the frequency and degree of hypertension did not differ between lacunar infarct patients and those with infarction involving the cortex. This could be explained by the fact that hypertension is a risk factor for all types of stroke and by our finding that of all lacunar infarct patients, only a minority will suffer from presumed arteriolosclerosis. Therefore, the higher frequencies of hypertension in the arteriolosclerosis patients are lost in those of the lacunar infarct group as a whole. The varying frequencies of hypertension between different lacunar infarct studies could be due to a varying degree by which patients with either type of small-vessel disease were included.

Interestingly, Fisher suggested that the severity and duration of the hypertension might determine the type of small-vessel vasculopathy. More severe and longstanding hypertension tended to give rise to the arteriolosclerosis type of small-vessel vasculopathy. However, a problem is the characterization of the hypertension in a particular patient because one needs to know the duration of hypertension and, in assessing the severity of hypertension, one has to have at his disposal repeated blood pressure measurements over time. Such information may indirectly be derived from the degree of hypertensive end-organ damage, but this does not always reliably reflect the degree of longstanding hypertension. Only a prospective study of a very large series of newly diagnosed hypertensive patients could provide an answer to this interesting problem.

The asymptomatic lacunar infarcts in our study were predominantly located in the frontal parts of the deep regions. These findings concur with those of Ishii et al, who found diffuse softening of the white matter and multiple lacunes, both predominantly located in the frontal lobes, in 30 autopsy cases of vascular dementia with a lacunar state. The penetrating small arteries all exhibited arteriolosclerosis. This further supports the hypothesis that arteriolosclerosis in particular causes diffuse white matter softenings along with multiple lacunar infarcts, with eventual development of subcortical vascular dementia. Therefore, differentiating between the two lacunar infarct entities is important because this could provide the possibility of recognizing during life those patients who are probably at high risk to eventually develop subcortical vascular dementia. Hypertension seems to be the major important risk factor for arteriolosclerosis, diligent treatment of which may substantially reduce the risk of mental impairment and eventual subcortical vascular dementia.

Finally, it is important to realize that the issue of white matter lesions, hypertension, and arteriolosclerosis is still far from being solved and that more clinical and especially pathological studies are needed to solve this problem and to definitely establish the hypothesis that has been presented in this study.

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References

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