On the Etiology of Incident Brain Lacunes
Longitudinal Observations From the LADIS Study

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Background and Purpose—We investigated regional differences in MRI characteristics and risk factor profiles of incident lacunes over a 3-year period.

Methods—Baseline and 3-year follow-up MRI were collected within the LADIS study (n=358). Incident lacunes were characterized with respect to brain region, their appearance within pre-existent white matter hyperintensities (WMH), surrounding WMH size, and risk factors.

Results—106 incident lacunes were observed in 62 patients (58 subcortical white matter [WM], 35 basal ganglia, and 13 infratentorial). Incident subcortical WM lacunes occurred more often within preexisting WMH (P=0.01) and were mostly accompanied by new and expanded WMH (P<0.001), compared to incident basal ganglia and infratentorial lacunes. Risk factors for incident subcortical WM lacunes were history of hypertension and stroke, whereas atrial fibrillation predicted incident basal ganglia/infratentorial lacunes.

Conclusion—Differences in relation to WMH and risk factor profiles may suggest that incident lacunes in the subcortical WM have a different pathogenesis than those in the basal ganglia and infratentorial region. (Stroke. 2008;39:3083-3085.)

Key Words: lacunes ■ white matter hyperintensities ■ MRI

Incident lacunes are often defined as subcortical ischemic infarcts, resulting from an occlusion of a small perforating artery and are regarded as an expression of cerebral small vessel disease on MRI. They may cause typical lacunar syndromes but may also be clinically “silent”. Furthermore, they have been associated with subtle cognitive dysfunction and a higher risk of future stroke. White matter hyperintensities (WMH) are another MRI expression of small vessel disease and develop due to several mechanisms including incomplete infarction as a consequence of diffuse hypoxia. The pathogenesis of lacunes has not been fully elucidated, and it has been proposed that distinct lacunar entities exist. In this longitudinal study, we compared incident MRI-defined lacunes between brain regions, with respect to their relationship with WMH and risk factor profile.

Methods
Data were collected within the multi-center Leukoaraiosis and Disability (LADIS) study in which 639 independently living elderly subjects, who were stratified for WMH severity, were followed for 3 years. Vascular risk factors were assessed at baseline. Baseline and 3-year follow-up MRI were available for 396 subjects. For this study concerning detailed characterization of incident lacunes, 358 subjects were available as subjects with 0.5Tesla MRI scans (n=37) and movement artifacts (n=1) were excluded.

Incident lacunes were defined on MRI as newly emerged cavities with a diameter of 3 to 10 mm with signal intensities similar to cerebrospinal fluid in all performed scan sequences (1.5Tesla: T1-weighted 3D-magnetization prepared rapid-acquisition gradient-echo, T2-weighted FSE, and fluid-attenuated inversion recovery images). Incident lacunes were characterized with respect to brain region (subcortical white matter [WM], basal ganglia, or infratentorial region), the emergence within preexisting WMH at baseline, suggesting the development of a cavity within the WMH (yes/no) and the (change in) WMH size surrounding the incident lacune. Differences between groups and brain regions were tested using t tests and χ² tests. Specific risk factors (age, presence of hypertension, diabetes mellitus, stroke, and smoking [packyears]) of incident lacunes in the different brain regions were assessed using logistic regression analyses with presence of incident subcortical WM lacunes and presence of incident basal ganglia/infratentorial lacunes as the dependent variables (each compared with subjects without new lacunes in that particular brain region, corrected for age, gender, and center).

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3083
Results

There were 62 subjects with 106 new lacunes (range 1 to 8). Subjects with new lacunes had more severe WMH and lacunes at baseline than subjects without new lacunes (severe WMH 29 [47%] versus 54 [18%]; presence of baseline lacunes 44 [72%] versus 123 [41%] for subjects with and without new lacunes [n=296]). Groups were comparable with respect to age, gender, and education.

There were 58 (55%) new lacunes in the subcortical white matter, 35 (33%) in the basal ganglia, and 13 (12%) in the infratentorial region (Table). 47% of the new lacunes in the subcortical WM appeared in preexisting WMH that were visible on the baseline scan (Figure 1), compared to only 17% in the basal ganglia and 23% in the infratentorial region (P=0.01).

When new lacunes appeared outside preexisting WMH, those located in the subcortical WM were often surrounded by development of new significant WMH (71%), whereas most of the incident basal ganglia (86%) and infratentorial lacunes (90%) only had a hyperintense rim or no surrounding (new) WMH at all (P<0.001; Figure 2). When new lacunes emerged within preexisting WMH, the surrounding WMH of 23 (64%) new lacunes increased in size, whereas in 10 new lacunes (28%) there was no difference and in 3 cases (8%) the surrounding WMH decreased in size (no regional difference).

Risk factors for incident subcortical WM lacunes were history of hypertension and stroke (OR [95% CI]=5.8 [1.7 to 19.8], P<0.01 and 4.5 [2.1 to 9.9], P<0.001), whereas age, diabetes, atrial fibrillation, and smoking were not predictive (OR [95% CI]=1.0 [0.9 to 1.0]; 1.8 [0.7 to 4.3]; 0.4 [0.0 to 3.2] and 1.0 [1.0 to 1.0]). Atrial fibrillation was the only risk factor for incident basal ganglia/infratentorial lacunes (OR [95% CI]=3.4 [1.1 to 10.7], P<0.05), whereas age, history of

Table. Characteristics of Incident Lacunes

<table>
<thead>
<tr>
<th></th>
<th>Subcortical WM, n=58 (55%)</th>
<th>Basal Ganglia, n=35 (33%)</th>
<th>Infratentorial, n=13 (12%)</th>
<th>( P ) Value (( \chi^2 ) tests)</th>
<th>Total, n=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance in preexistent WMH</td>
<td>27 (47%)</td>
<td>6 (17%)</td>
<td>3 (23%)</td>
<td>0.01</td>
<td>36 (34%)</td>
</tr>
<tr>
<td>Surrounding WMH size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outside preexistent WMH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant WMH</td>
<td>22 (71%)</td>
<td>4 (14%)</td>
<td>1 (10%)</td>
<td>&lt;0.001</td>
<td>27 (39%)</td>
</tr>
<tr>
<td>No or rim of WMH</td>
<td>9 (29%)</td>
<td>25 (86%)</td>
<td>9 (90%)</td>
<td></td>
<td>43 (61%)</td>
</tr>
<tr>
<td>In preexistent WMH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>19 (71%)</td>
<td>3 (50%)</td>
<td>1 (33%)</td>
<td>Not significant</td>
<td>23 (64%)</td>
</tr>
<tr>
<td>No difference</td>
<td>6 (22%)</td>
<td>2 (33%)</td>
<td>2 (67%)</td>
<td></td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Decrease</td>
<td>2 (7%)</td>
<td>1 (17%)</td>
<td>0 (0%)</td>
<td></td>
<td>3 (8%)</td>
</tr>
</tbody>
</table>

Values are numbers (%). WM(H) indicates white matter (hyperintensities).

Figure 1. FLAIR (A and B) and MPRAGE images (C and D) of a patient with an incident subcortical white matter lacune appearing within preexistent white matter hyperintensities (arrows).

Figure 2. An incident subcortical white matter lacune is surrounded by significant white matter hyperintensities (A1=baseline, A2=follow-up). An incident infratentorial lacune that is not surrounded by white matter hyperintensities is shown in B1 (baseline) and B2 (follow-up).
hypertension, diabetes, stroke, and smoking were not significant (OR [95% CI] = 1.0 [0.9 to 1.1]; 1.5 [0.6 to 3.5]; 1.5 [0.6 to 3.8]; 1.9 [0.9 to 4.1]; and 1.0 [1.0 to 1.0]).

**Discussion**

WMH develop because of stenosis of multiple vessels and vary from subtle diffuse ischemia/hypoxia to incomplete infarction. On the other end of the spectrum of small vessel disease, lacunes are caused by occlusion of a single deep thalamoperforant, lenticulostriate, or pontine paramedian arteriole. However, a subtype of lacunes has been described that is not cavitated yet and may represent an intermediate stage between WMH and a fully cavitated lacune. We found that incident subcortical WM lacunes often developed within preexistent WMH and were surrounded by significant new WMH. In the light of previous studies, we postulate that subcortical WM lacunes often develop slowly in an area with already compromised perfusion, ie, preexistent WMH, attributable to increasing hypoxia/ischemia, leading to frank infarction. As the subcortical WM is a watershed area, it is more vulnerable to ischemia. On the other hand, our finding that new lacunes in the basal ganglia and infratentorial region often appeared with only few surrounding WMH and in locations that appeared normal at baseline, suggests a more acute development. The direct origin from large arteries might make these arterioles more prone to acute occlusion. The hypothesis that distinct lacunar entities exist with differences in etiology and prognosis has also been proposed by clinical studies. Alternatively, tissue characteristics may influence the survival as the neurons in the deep gray matter may react differently to ischemia than glial cells in the subcortical WM. The difference in risk factor profile support our MRI findings and suggest that incident lacunes in the subcortical WM may have a different pathogenesis than lacunes in the basal ganglia and infratentorial region.

**Appendix**

**List of Participating Centers and Personnel**

Helsinki, Finland (Memory Research Unit, Department of Clinical Neurosciences, Helsinki University): Timo Erkinjuntti, MD, PhD, Tarja Pohjasvaara, MD, PhD, Pia Pihlanen, MD, Raija Ylikoski, MD, Hanna Jokinen, MD, Meija-Marjut Someroski, MD, PSych, Riitta Mäntylä, MD, PhD, Oili Salonen, MD, PhD; Graz, Austria (Department of Neurology and Department of Radiology, Division of Neuroradiology, Medical University Graz): Franz Fazekas, MD, Reinhold Schmidt, MD, Stefan Ropele, PhD, Brigitte Rous, MD, Katja Petrovic, MagPsychol, Ulrike Garmehi, Alexandra Seewann, MD; Lisbon, Portugal (Servicio de Neurologia, Centro de Estudos Egas Moniz, Hospital de Santa Maria): José M. Ferro, MD, PhD, Ana Verdelho, MD, Sofia Madureira, PsyD, Carla Moleiro, PhD; Mannheim, Germany (Department of Neurology, University of Heidelberg, Klinikum Mannheim): Michael Hennerici, MD, Christian Blahak, MD, Hansjorg Baezner, MD, Martin Wiarda, PsyD, Susanne Seip, RN; Copenhagen, Denmark (Memory Disorders Research Group, Department of Neurology, Rigshospitalet, and the Danish Research Center for Magnetic Resonance, Hvidovre Hospital, Copenhagen University Hospitals): Gunhild Waldemar, MD, DSMc, Egill Rostrup, MD, MSc; Charlotte Ryberg, MSc, Tim Dybyr MSc, Olaf B. Paulson, MD, DSMc; Newcastle-on-Tyne, UK (Institute for Ageing and Health, University of Newcastle): John O’Brien, DM, Sanjeet Pakrasi, MRCPsych, Mani Krishnan MRCPsych, Andrew Teodorczuk, MRCPsych, Michael Firbank, PhD, Philip English, DCR, Thais Minett, MD, PhD.

The Coordinating center is in Florence, Italy (Department of Neurological and Psychiatric Sciences, University of Florence): Domenico Inzitari, MD (Study Coordinator); Luciano Bartoloni, PhD, Anna Maria Basile, MD, PhD, Eliana Magmani, MD, Monica Martinis, MD, Mario Mascalchi, MD, PhD, Marco Moretti, MD, Leonardo Pantoni, MD, PhD, Anna Poggesi, MD, Giovanni Pracucci, MD, Emilia Salvadori, PhD, Michela Simoneni, MD.

The LADIS Steering Committee is formed by Domenico Inzitari, MD (study coordinator), Timo Erkinjuntti, MD, PhD, Philip Scheltens, MD, PhD, Marieke Visser, MD, PhD, and Peter Langhorne, MD, BSC, PhD, FRCP who replaced in this role Kjell Asplund, MD, PhD beginning with 2005.

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**Disclosures**

None.

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