Early Recurrent Ischemic Lesions on Diffusion-Weighted Imaging in Symptomatic Intracranial Atherosclerosis

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Background: Prior observations have shown that early recurrent ischemic lesions (ERILs) on diffusion-weighted imaging occur frequently within the first week after an index stroke.

Objective: To investigate differential patterns of ERILs among stroke subtypes, particularly intracranial large-artery atherosclerosis (IC-LAA).

Design: Retrospective study.

Setting: Tertiary university hospital.

Patients: We included 133 patients who experienced an acute ischemic stroke and who underwent initial diffusion-weighted imaging within 24 hours and subsequent diffusion-weighted imaging within 7 days after onset, and whose stroke subtype was IC-LAA, extracranial LAA (EC-LAA), or cardioembolism (CE).

Main Outcome Measure: Early recurrent ischemic lesions were defined as new ischemic lesions on follow-up diffusion-weighted imaging, separate from the index stroke lesion.

Results: Early recurrent ischemic lesions were observed in the following proportions: 50.9% (28/55) in the IC-LAA group, 47.4% (9/19) in the EC-LAA group, and 44.1% (26/59) in the CE group. Early recurrent ischemic lesions in the IC-LAA group had the following characteristics: (1) they occurred mostly (27 [96.4%] of 28) in the pial area of the same vascular territory as the index stroke; (2) they were more frequently observed in a higher grade of stenosis than in milder stenosis (P < .001), whereas ERILs in the EC-LAA group were not related to the degree of stenosis; (3) they were not associated with subsequent recanalization, whereas ERILs in the CE group were mostly associated with subsequent recanalization (P < .001); and (4) they were more closely associated with clinical recurrence than in the EC-LAA or CE group (P = .02).

Conclusion: Early recurrent ischemic lesions in the IC-LAA group are relatively frequent and have different patterns than in the EC-LAA or CE group.

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CLINICALLY SILENT EARLY recurrent ischemic lesions (ERILs) on diffusion-weighted imaging (DWI) are much more frequent than the clinical recurrence within the first week and up to 1 to 3 months after the onset of index stroke.1-3

The risk of early recurrent stroke is likely related to the underlying causative stroke subtypes. Population-based studies4,5 have reported that patients with large-artery atherosclerosis (LAA) had the highest risk of early clinical recurrent stroke, and the DWI study1 showed that LAA was the most frequent stroke subtype associated with ERILs. These studies, however, were performed in Western countries, in which the prevalence of intracranial LAA (IC-LAA) is much lower than that of extracranial LAA (EC-LAA), and they did not distinguish between IC-LAA and EC-LAA. Although the classic Trial of Org 10172 in Acute Stroke Treatment classification has lumped IC-LAA and EC-LAA together,4 there is evidence that the 2 types of stroke differ in ethnicity, risk factors, natural history, mechanism of index stroke, and long-term recurrence.7,8 We, therefore, sought to determine the characteristic pattern and mechanism of ERILs in IC-LAA compared with other stroke subtypes, EC-LAA, and cardioembolism (CE).

METHODS

PATIENTS

This is a retrospective analysis of all consecutive stroke patients admitted to the Stroke Cen-
arterial stenosis of 50% or more or occlusion, if follow-up MRA showed symptomatic atherosclerotic intracranial arteries with residual stenosis of 50%; ie, grade 1 on follow-up MRA), or complete (grade 0 on follow-up MRA).

STROKE SUBTYPE CLASSIFICATION

The stroke subtypes were determined according to the Trial of Org 10172 in Acute Stroke Treatment classification, with the following modifications. Intracranial LAA was diagnosed if the initial MRA showed symptomatic atherosclerotic intracranial arterial stenosis of 50% or more or occlusion, if follow-up MRA showed persistent steno-occlusion, and if neither a cardiac nor an extracranial arterial embolic source could be identified. Extracranial LAA was diagnosed if there was symptomatic extracranial arterial stenosis of 50% or more or occlusion without evidence of IC-LAA or CE. Stroke subtype was diagnosed by the consensus of 3 stroke neurologists (D.-W.K., S.U.K., and J.S.K.) blinded to ERIL results.

DEFINITION OF CLINICAL RECURRENCE

Clinical stroke recurrence within 1 week was identified by another investigator (S.-H.Y.) blinded to the magnetic resonance imaging data as “any recurrent stroke occurring >24 hours after onset of the index stroke, irrespective of VT.” Systemic causes of clinical deterioration after an initial stroke (eg, infection) and worsening of initial symptoms because of the progression or hemorrhagic transformation of the initial stroke were not classified as clinical recurrences.

DATA ANALYSIS

Baseline demographics, time to magnetic resonance imaging, risk factors, intravenous thrombolysis, anticoagulant vs antiplatelet therapy during the first week, and the proportion of patients with initial multiple infaracts were compared between those with and those without ERILs. The previously mentioned variables together with ERILs and clinical recurrence were also compared among groups of patients with stroke subtypes. The association between ERILs and the degree of stenosis in the LAA group, the association between ERILs and recanalization of initially occluded vessels, and the association between lesion volume (of total lesions and ERILs) and clinical recurrence were also explored. The Pearson χ² test with exact method, an analysis of variance, or a nonparametric Kruskal-Wallis test was used where appropriate. All statistical analyses were performed using a commercially available software program (SPSS for Windows, version 12.0; SPSS Inc, Chicago, Ill).

RESULTS

During the study, we identified 133 patients (80 men and 53 women; mean ± SD age, 65.6 ± 11.9 years) who met the eligibility criteria. The median time from onset to the initial DWI scan was 5.85 hours (range, 0.3-23.9 hours); and to follow-up DWI, 4.0 days (range, 1.03-6.82 days). Intracranial LAA was diagnosed in 55 patients, EC-LAA in 19 patients, and CE in 59 patients. Early recurrent ischemic lesions were observed in 63 (47.4%) of the 133 patients. Baseline characteristics did not differ between patients with and without ERILs, except that the frequency of multiple infarcts on initial DWI was significantly higher in patients with ERILs (40 [63.5%] of 63 patients) than in patients without ERILs (24 [34.3%] of 70 patients) (P= .001). Antplatelet or anticoagulant treatments did not influence the occurrence of ERILs (P=.94).

Baseline characteristics among stroke subtypes were comparable, except that time to initial DWI from onset was shorter in patients with CE and history of diabetes mellitus was more frequent in patients with EC-LAA. Early recurrent ischemic lesions were observed in 50.9% of the IC-LAA group, 47.4% of the EC-LAA group, and 44.1% of the CE group (percentages are “off” for the EC-LAA and CE groups using values given in Figure 1 because of rounding). The distribution of ERILs differed across stroke subtypes. Relative to index stroke lesions, ERILs in the same VT were most frequent in the IC-LAA group,
whereas ERILs in different VTs or in different cerebral circulations were most frequently observed in the CE group (Table and Figure 1).

Of the 28 patients with IC-LAA who had ERILs, 18 had recurrent lesions in the pial territory, 5 in the pial territory and border zone, 3 in the pial and perforator territories, 1 in the pial and perforator territories and the cortical border zone, and 1 in the cortical border zone alone. Overall, 27 (96.4%) of these 28 patients developed recurrent lesions involving the pial territory.

Of the 55 patients with IC-LAA, 13 had moderate stenosis, 12 had severe stenosis, and 30 had occlusion on initial MRA; the frequency of ERILs was 0% (0/13), 75.0% (9/12), and 63.3% (19/30), respectively ($P_{<0.01}$). In contrast, of the 19 patients with EC-LAA, 6 each had moderate and severe stenosis and 7 had occlusion; the frequency of ERILs caused by index arterial lesions was not associated with the degree of stenosis ($P_{=0.33}$), being 66.7% (4/6), 33.3% (2/6), and 28.6% (2/7), respectively (Figure 2).

The association between recanalization and ERILs was compared in patients who showed intracranial steno-occlusive lesions on initial MRA and ERILs in the same VT (ie, in 28 patients with IC-LAA, 11 patients with CE, and 0 patients with EC-LAA). Early recurrent ischemic lesions were accompanied by no (21 [75.0%]) or partial (7 [25.0%]) recanalization in the IC-LAA group, but by complete (8 [72.7%]), significant (1 [9.1%]), partial (1 [9.1%]), and no (1 [9.1%]) recanalization in the CE group ($P_{<0.001}$) (Figure 3 and Figure 4).

Clinical recurrence within 1 week was observed in 8 (6.0%) of the 133 patients (7 with IC-LAA and 1 with EC-LAA). Early recurrent ischemic lesions in the IC-LAA group were more closely associated with clinical recurrence (7 [25.0%] of 28 patients) compared with ERILs in the EC-LAA group (1 [11.1%] of 9 patients) and CE group (0 patients). In patients with ERILs, the mean ± SD total infarct volume on initial (5.9 ± 4.9 vs 8.4 ± 12.0 mL; $P_{=0.79}$) and follow-up (14.7 ± 8.7 vs 17.0 ± 25.1 mL; $P_{=0.20}$) DWI and the mean ± SD volume of ERILs (5.0 ± 9.7 vs 1.8 ± 5.1 mL; $P_{=0.12}$) did not differ between patients with and without clinical recurrence. In addition, the volume of ERILs did not differ across stroke subtypes (Table).

### Table. Clinical and MRI Characteristics Among Stroke Subtypes*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IC-LAA (n = 55)</th>
<th>EC-LAA (n = 19)</th>
<th>CE (n = 59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>26 (47.3)</td>
<td>5 (26.3)</td>
<td>22 (37.3)</td>
<td>.25</td>
</tr>
<tr>
<td>Age, y†</td>
<td>64.7 ± 13.0</td>
<td>67.7 ± 8.0</td>
<td>65.8 ± 11.9</td>
<td>.63</td>
</tr>
<tr>
<td>Onset to initial DWI, h†</td>
<td>8.5 ± 6.5</td>
<td>6.4 ± 4.9</td>
<td>5.8 ± 4.7</td>
<td>.05</td>
</tr>
<tr>
<td>Onset to follow-up DWI, d†</td>
<td>3.9 ± 1.2</td>
<td>3.5 ± 1.5</td>
<td>4.0 ± 1.5</td>
<td>.44</td>
</tr>
<tr>
<td>Time between DWI scans, d†</td>
<td>3.6 ± 1.2</td>
<td>3.3 ± 1.4</td>
<td>3.7 ± 1.5</td>
<td>.41</td>
</tr>
<tr>
<td>Risk factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>43 (78.2)</td>
<td>11 (57.9)</td>
<td>47 (79.7)</td>
<td>.15</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (20.0)</td>
<td>10 (52.6)</td>
<td>13 (22.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>11 (20.0)</td>
<td>6 (31.6)</td>
<td>17 (28.8)</td>
<td>.47</td>
</tr>
<tr>
<td>Current smoking</td>
<td>25 (45.5)</td>
<td>10 (52.6)</td>
<td>23 (39.0)</td>
<td>.57</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>15 (27.3)</td>
<td>6 (31.6)</td>
<td>8 (13.6)</td>
<td>.12</td>
</tr>
<tr>
<td>Intravenous thrombolysis</td>
<td>3 (5.5)</td>
<td>1 (5.3)</td>
<td>8 (13.6)</td>
<td>.27</td>
</tr>
<tr>
<td>Multiple infarcts on initial DWI</td>
<td>28 (50.9)</td>
<td>12 (63.2)</td>
<td>24 (40.7)</td>
<td>.20</td>
</tr>
<tr>
<td>ERILs on 5-d DWI</td>
<td>28 (50.9)</td>
<td>9 (47.4)</td>
<td>26 (44.1)</td>
<td>.82</td>
</tr>
<tr>
<td>Within same VT</td>
<td>28 (50.9)</td>
<td>7 (36.8)</td>
<td>16 (27.1)</td>
<td>.04</td>
</tr>
<tr>
<td>Within different VT</td>
<td>0</td>
<td>2 (10.5)</td>
<td>10 (16.9)</td>
<td>.005</td>
</tr>
<tr>
<td>Within same circulation</td>
<td>28 (50.9)</td>
<td>8 (42.1)</td>
<td>19 (32.2)</td>
<td>.13</td>
</tr>
<tr>
<td>Within different circulation</td>
<td>0</td>
<td>1 (5.3)</td>
<td>7 (11.9)</td>
<td>.03</td>
</tr>
<tr>
<td>No. of ERILs, median (range)</td>
<td>3.5 (1-9)</td>
<td>1.0 (0-5)</td>
<td>2.5 (1-10)</td>
<td>.19</td>
</tr>
<tr>
<td>Volume, median (range), mL</td>
<td>0.3 (0.01-6.7)</td>
<td>0.7 (0.03-28.3)</td>
<td>0.7 (0.01-31.7)</td>
<td>.72</td>
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<tr>
<td>Clinical recurrence</td>
<td>7 (12.7)</td>
<td>1 (5.3)</td>
<td>0</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CE, cardioembolism; DWI, diffusion-weighted imaging; EC-LAA, extracranial large-artery atherosclerosis; ERIL, early recurrent ischemic lesion; IC-LAA, intracranial LAA; MRI, magnetic resonance imaging; VT, vascular territory.

*Data are given as number (percentage) of each group unless otherwise indicated.
†Data are given as mean ± SD.
Figure 2. Frequency of early recurrent ischemic lesions (ERILs) according to degree of stenosis in the intracranial large-artery atherosclerosis (IC-LAA) and extracranial (EC) LAA groups.

Figure 3. Early recurrent ischemic lesions (ERILs) and recanalization in the intracranial large-artery atherosclerosis (IC-LAA) and cardioembolism (CE) groups.

Figure 4. Pattern of early recurrent ischemic lesions (ERILs) related to recanalization in a patient with intracranial large-artery atherosclerosis (IC-LAA) (A and B) and in a patient with cardioembolism (CE) (C and D). The follow-up diffusion-weighted imaging in both patients (B and D) showed multiple ERILs in the pial and/or border zone areas (thin arrows). Follow-up magnetic resonance angiography showed persistent middle cerebral artery stenosis in a patient with IC-LAA (thick arrow) (B), whereas the artery showed recanalization in the patient with CE (thick arrow) (D).
We have shown herein that the patterns of ERILs in patients with IC-LAA had characteristics differentiating them from the patterns of ERILs in patients with EC-LAA or CE. Early recurrent ischemic lesions in those with IC-LAA occurred predominantly in the pial area of the same VT as the index stroke, whereas the pattern of recurrence was unpredictable in patients with EC-LAA. Our data are consistent with these findings and provide further evidence that silent recurrent ischemic lesions occur earlier and more frequently than clinically recurrent stroke.

Early recurrent ischemic lesions occurred more frequently in patients with IC-LAA who had a higher grade of stenosis, whereas the degree of stenosis was not related to ERILs in patients with EC-LAA. This finding suggests that different pathogenic mechanisms may be associated with the genesis of ischemic stroke. In those with IC-LAA, the progression of stenosis may be associated with an increased risk of recurrent ischemic stroke, such that patients with high-grade stenosis are at greater risk of artery-to-artery embolization or hemodynamic failure than those with milder stenosis. In contrast, in those with EC-LAA, plaque heterogeneity rather than the degree of stenosis may be more important in pathogenesis. However, our results are limited by a lack of Doppler data regarding microemboli detection and plaque characteristics to support this hypothesis.

We also found a striking difference between the IC-LAA and CE groups in the development of ERILs within the same VT as the index stroke. In the IC-LAA group, ERILs occurred without subsequent recanalization, whereas in the CE group, ERILs were associated with significant recanalization. These results suggest that in patients with IC-LAA, ERILs may be caused by recurrent ischemic events, whereas in patients with CE, ERILs may result from fragmentation of the initial embolus. A previous study also found that ERILs occurring within the initial perfusion defect (“local lesion recurrence”) were associated with subsequent reperfusion. In this group, ERILs may represent the natural evolution of the initial ischemic event. In the IC-LAA group, however, recurrent artery-to-artery embolism or hemodynamic failure may be a plausible mechanism for ERILs. Additional studies using serial DWI or MRA and microembolic signal monitoring are needed to determine the precise mechanism of ERILs in these patients.

In this study, ERILs in those with IC-LAA were more closely associated with clinical recurrence within the first week compared with other stroke subtypes. Patients with stroke resulting from IC-LAA are at high risk of recurrent stroke (>20% over 2 years), indicating a need for more effective therapies. Our results suggest that ERILs in those with IC-LAA may be a marker of increased risk of clinical recurrence, but additional studies are required to determine whether ERILs in those with IC-LAA are associated with a higher risk of subsequent clinical events.

This study has several limitations, including its retrospective design, the relatively small size of the EC-LAA group, and the lack of long-term magnetic resonance imaging and clinical follow-up data. Although we performed repeated MRA for the diagnosis of IC-LAA, some embolic occlusion might be misclassified as atherosclerotic occlusion.

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