Leukoaraiosis Predicts Parenchymal Hematoma After Mechanical Thrombectomy in Acute Ischemic Stroke

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Background and Purpose—The purpose of this study was to determine whether leukoaraiosis (LA) predicts hemorrhagic transformation and poor outcome in patients with acute ischemic stroke treated by mechanical thrombectomy.

Methods—We retrospectively analyzed patients with anterior circulation stroke treated with Merci devices and identified LA in the deep white matter (DWM) and periventricular white matter on the preintervention MR images. We dichotomized patients into those with moderate or severe LA in the DWM versus those without. Hemorrhage rates and outcomes were evaluated between 2 groups. We analyzed the association of moderate or severe LA with hemorrhagic transformation and poor outcome.

Results—Twenty-six of 105 patients had moderate or severe LA in the DWM. Patients with moderate or severe LA in the DWM were older, had more severe neurological deficits and worse outcome, had higher rates of hemorrhagic transformation and parenchymal hematoma, but had equivalent rates of hemorrhagic infarct and subarachnoid hemorrhage when compared with those without. Patients with only periventricular LA did not have a higher rate of parenchymal hematoma. Moderate or severe LA in the DWM was an independent predictor of hemorrhagic transformation (OR, 3.4; \(P = 0.019\)) and parenchymal hematoma (OR, 6.3; \(P = 0.005\)). Patients with parenchymal hematoma were less often independent (modified Rankin Scale \(\leq 2\), 3.8% versus 32.5%; \(P = 0.003\)) and had greater in-hospital mortality (50% versus 10.4%; \(P < 0.001\)).

Conclusions—Moderate or severe LA in the DWM increases the risk of parenchymal hematoma after Merci thrombectomy for patients with acute stroke. These findings require validation in a larger prospective study. (Stroke. 2012;43:1806-1811.)

Key Words: acute stroke ■ intracerebral hemorrhage ■ leukoaraiosis ■ mechanical thrombectomy ■ outcomes

Patients with acute ischemic stroke (AIS) may benefit from endovascular mechanical revascularization therapy by removal of large-vessel intracranial occlusions. An increasing number of predictors of clinical outcome and favorable revascularization in patients with AIS treated by mechanical thrombectomy have been recently reported. However, predictors of hemorrhagic transformation (HT) associated with mechanical thrombectomy for AIS have not been well described.

The radiological finding of leukoaraiosis (LA) indicating ischemic white matter damage in the penetrating small-vessel territory is common in the elderly and is a risk factor for future stroke. Although the association is controversial, the existing literature suggests that LA increases the risk of symptomatic HT in patients with AIS receiving thrombolysis. However, the association of LA with HT and clinical outcome after mechanical thrombectomy is unclear.

The purpose of this study was to determine whether LA confirmed on MRI before mechanical thrombectomy may predict HT and subsequent poor outcome in patients with AIS with large-vessel intracranial occlusions.

Methods

Patient Selection
All consecutive patients with AIS treated by mechanical thrombectomy with Merci Retriever devices (Concentric Medical, Inc, Moun-
taining View, CA) from August 2002 through August 2008 were prospectively maintained in a database at the University of California at Los Angeles stroke center according to a protocol approved by the local Institutional Review Board. We performed a retrospective analysis to identify patients with anterior circulation stroke who had a preintervention fluid-attenuated inversion recovery (FLAIR) sequence MRI and treated with Merci Retriever within 8 hours of symptom onset.

**Thrombectomy Treatment**

Patients treated by thrombectomy were either ineligible for intravenous (IV) tissue-type plasminogen activator (tPA) or the occluded vessel failed to recanalize after receiving IV tPA (0.9 mg/kg) within 3 hours of stroke onset. Intra-arterial (IA) tPA was allowed as an adjunct to thrombectomy. Rescue intracranial angioplasty or stenting was also performed after failed thrombectomy. Carotid stenting was allowed in cases with proximal stenosis or dissection after thrombectomy.

Collateral flow before thrombectomy and final revascularization or reperfusion status after treatment were recorded from the angiograms as done in our previous studies.4–6,14 Successful revascularization was defined as achieving Thrombolysis In Myocardial Infarction II or III flow in all treatable vessels documented on final postthrombectomy angiogram.

**Image Analysis of LA**

All patients underwent MRI before thrombectomy unless contraindicated. All patients underwent noncontrast CT immediately postthrombectomy. Patients also typically underwent MR 3 to 12 hours postthrombectomy. CT was performed for neurological deterioration at any time. Patients receiving thrombolytic therapy had CT or MRI 24 to 36 hours after symptom onset. Patients also typically underwent imaging at 3 to 5 days or at discharge to assess tissue outcome. A standardized MR image protocol was used, including diffusion-weighted imaging, perfusion-weighted imaging, T2* gradient-recall echo, and FLAIR sequences.

We reviewed the prethrombectomy FLAIR MR images. The presence of LA was defined as regions of hyperintensity in the white matter starting at the lateral ventricular border and extending up to the corticalmedullary junction on FLAIR MR images.8,9 The boundaries of LA were differentiated from the acute ischemic lesion by visually coregistering FLAIR images with the diffusion-weighted imaging. Chronic ischemic lesions appear clearly in a vascular territory with well-defined borders, whereas chronic lacunar infarctions appear as cavitated lesions with cerebrospinal fluid intensity on FLAIR. The extent of LA was determined for the deep white matter (DWM) and the periventricular white matter using the visual rating (FLAIR) sequence MRI and treated with Merci Retriever within 8 hours of symptom onset.

We reviewed the postthrombectomy CT and gradient-recall echo MR images to assess HT and subarachnoid hemorrhage (SAH). In patients who only underwent postprocedural CT examinations, hyperdensity seen on the immediate postprocedural CT examination but clearing within 24 hours was considered contrast enhancement, whereas hyperdensity persistently present 24 hours after therapy was considered hemorrhage. HT was classified into hemorrhagic infarct and parenchymal hematoma (PH) using the European Cooperative Acute Stroke Study definition.1,2 SAH was classified into isolated SAH and SAH coexisting HT.14

**Statistical Analysis**

We recorded the clinical variables of age, sex, risk factors, premorbid medications, laboratory findings on admission, admission National Institutes of Health Stroke Scale score, time interval from symptom onset to arterial puncture, procedural duration, site of arterial occlusion, number of thrombectomy attempts, and pretreatment collateral flow. Clinical outcome at discharge was assessed using the modified Rankin Scale. Good outcome was defined as modified Rankin Scale ≤2.

Patients were dichotomized into 2 groups: those with moderate or severe LA in the DWM versus those without. Clinical variables, revascularization rates, hemorrhage rates, in-hospital mortality, and outcomes were evaluated between 2 groups. We also determined whether moderate or severe LA in the DWM predicted any HT or PH and whether PH predicted poor clinical outcome.

Categorical data were analyzed by the Fisher exact and χ2 tests. Continuous data were assessed for normality by the Kolmogorov-Smirnov test; normally distributed continuous data were analyzed by Student t test and unevenly distributed continuous data by the Mann-Whitney U test. All variables with P<0.1 in the univariate analysis were entered into a binary forward stepwise multivariate logistic regression model. SPSS software (Version 13; SPSS Inc, Chicago, IL) was used to perform the analysis.

**Results**

**Demographics**

There were 1843 consecutive patients with AIS evaluated by the stroke team during the study time. We identified a total of 136 patients with AIS treated by Merci thrombectomy alone or with adjunctive therapy, whereas 26 patients were treated with IA thrombolysis. In the 136 patients with Merci thrombectomy therapy, MR scan was contraindicated in 21 patients and interpretable FLAIR MR images were not achieved in 2 patients. In 113 patients with FLAIR MR images, 8 patients had vertebrobasilar occlusions. A total of 105 patients with anterior circulation stroke met inclusion criteria. Fifty-nine (56.2%) patients were treated by thrombectomy alone with Merci devices. Thirty-two (30.5%) patients were administered adjuvant IV or IA tPA thrombolytics, including IV tPA in 24 patients, IA tPA in 6 patients, and IV combined with IA tPA in 2 patients. Rescue endovascular modalities after unsuccessful thrombectomy were used in the remaining 14 patients, including intracranial angioplasty in 5 patients, carotid artery or internal carotid artery stenting in 6 patients, and microscrew retrieval in 3 patients.

Twenty-six (24.8%) patients presented with moderate or severe LA in the DWM (Fazekas scores 2–3). Forty-three (41.0%) patients presented with moderate or severe periventricular LA with or without LA in the DWM. Moderate or severe periventricular LA alone was present in 18 patients (17.1%), whereas 25 patients presented with moderate or severe LA in both periventricular and deep white matter. Patients with moderate or severe LA in the DWM were older than those without, had more severe neurological deficits, more often had a history of hypertension and atrial fibrillation, and more often had a cardioembolic stroke source (Table 1). There were no differences in other baseline characteristics for the study cohort.

**Revascularization Rates and Outcome**

Patients with moderate or severe LA in the DWM tended to have a shorter time to intervention than those without (5.0 versus 5.8 hours; P=0.06). The final revascularization rates were similar between groups (80.8% versus 72.2%) with...
comparable distribution of thrombolytic use. Patients with moderate or severe LA in the DWM had worse modified Rankin Scale at discharge (5.0 versus 4.0; \( P < 0.02 \)) and higher rates of in-hospital mortality (48% versus 11.5%; \( P < 0.001 \)) when compared with those without (Table 2).

### Predictors of Hemorrhage

HT occurred in 50 patients (47.6%) including hemorrhagic infarct in 24 patients (22.9%) and PH in 26 patients (24.8%). SAH occurred in 19 patients. Isolated SAH occurred in 8 patients, whereas coexisting HT was found in the remaining 11. Patients with moderate or severe LA in the DWM had higher rates of any HT when compared with those without (65.4% [17 of 26 patients] versus 41.8% [33 of 79 patients]; \( P = 0.04 \)) but had similar rates of SAH (Table 2). Although there was no significant difference in the rates of hemorrhagic infarct, the rate of PH was twice as high in patients with moderate or severe LA in the DWM than in those without (42.3% [11 of 26 patients] versus 19% [15 of 79 patients]; \( P = 0.03 \)). Patients with moderate or severe LA in the DWM also had higher rates of PH-2 compared with those without (23.1% [6 of 26 patients] versus 5.1% [4 of 79 patients]; \( P = 0.02 \)). Patients with moderate or severe periventricular LA had similar rates of HT when compared with those without (44.2% [19 of 43 patients] versus 50.0% [31 of 62 patients]) or PH (30.2% [13 of 43 patients] versus 21.0% [13 of 62 patients]). The 18 patients with moderate or severe LA in the periventricular white matter alone did not have higher rates of HT when compared with the remaining 87 patients (16.7% [3 of 18 patients] versus 54.0% [47 of 87 patients]) or PH (16.7% [3 of 18 patients] versus 26.4% [23 of 87 patients]).

In the thrombectomy alone subgroup, there was no difference in the rates of PH between patients with moderate or severe LA in the DWM and those without (23.1% [3 of 13 patients] versus 15.2% [7 of 46 patients]; \( P = 0.68 \)). In the thrombectomy and adjuvant thrombolysis subgroup, there was also no difference in PH rates between 2 groups (60% [6 of 10 patients] versus 27.3% [6 of 22 patients]; \( P = 0.12 \)). Within the 26 patients with moderate

### Table 1. Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Without Moderate or Severe LA (n=79)</th>
<th>With Moderate or Severe LA (n=26)</th>
<th>Total (n=105)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.6±19.1</td>
<td>79.0±10.1</td>
<td>65.9±18.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≥80 y</td>
<td>20.3% (16/79)</td>
<td>57.7% (15/26)</td>
<td>29.5% (31/105)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardioembolic stroke source</td>
<td>60.8% (48/79)</td>
<td>88.5% (23/26)</td>
<td>67.6% (71/105)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57.0% (45/79)</td>
<td>92.3% (24/26)</td>
<td>65.7% (69/105)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>29.1% (23/79)</td>
<td>53.8% (14/26)</td>
<td>35.2% (37/105)</td>
<td>0.03</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>32.9% (26/79)</td>
<td>69.2% (18/26)</td>
<td>41.9% (44/105)</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>17.5±6.0</td>
<td>19.8±6.4</td>
<td>18.1±6.1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

LA indicates leukoaraiosis; NIHSS, National Institutes of Health Stroke Scale.

### Table 2. Revascularization and Clinical Outcome by Leukoaraiosis

<table>
<thead>
<tr>
<th></th>
<th>Without Moderate or Severe LA (n=79)</th>
<th>With Moderate or Severe LA (n=26)</th>
<th>Total (n=105)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure thrombectomy</td>
<td>58.2% (46/79)</td>
<td>50.0% (13/26)</td>
<td>56.2% (59/105)</td>
<td>0.50</td>
</tr>
<tr>
<td>IV or IA lytic use</td>
<td>27.8% (22/79)</td>
<td>38.5% (10/26)</td>
<td>30.5% (32/105)</td>
<td>0.33</td>
</tr>
<tr>
<td>Symptom onset to groin puncture, h</td>
<td>5.8±2.2</td>
<td>5.0±1.4</td>
<td>5.6±2.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Final TIMI II/III flow</td>
<td>72.2% (57/79)</td>
<td>80.8% (21/26)</td>
<td>74.3% (78/105)</td>
<td>0.45</td>
</tr>
<tr>
<td>Procedure-related vessel perforation</td>
<td>5.1% (4/79)</td>
<td>15.4% (4/26)</td>
<td>7.6% (8/105)</td>
<td>0.20</td>
</tr>
<tr>
<td>All HT</td>
<td>41.8% (33/79)</td>
<td>65.4% (17/26)</td>
<td>47.6% (50/105)</td>
<td>0.04</td>
</tr>
<tr>
<td>PH</td>
<td>19.0% (15/79)</td>
<td>42.3% (11/26)</td>
<td>24.8% (26/105)</td>
<td>0.03</td>
</tr>
<tr>
<td>PH-2</td>
<td>5.1% (4/79)</td>
<td>23.1% (6/26)</td>
<td>9.5% (10/105)</td>
<td>0.02</td>
</tr>
<tr>
<td>HI</td>
<td>22.8% (18/79)</td>
<td>23.1% (6/26)</td>
<td>22.9% (24/105)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>All SAH</td>
<td>17.7% (14/79)</td>
<td>19.2% (5/26)</td>
<td>18.1% (19/105)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Isolated SAH</td>
<td>10.1% (8/79)</td>
<td>0% (0/26)</td>
<td>7.6% (8/105)</td>
<td>0.21</td>
</tr>
<tr>
<td>SAH coexisting HT</td>
<td>7.6% (6/79)</td>
<td>19.2% (5/26)</td>
<td>10.5% (11/105)</td>
<td>0.19</td>
</tr>
<tr>
<td>mRS at discharge</td>
<td>4.0 (0–6)</td>
<td>5.0 (1–6)</td>
<td>4.0 (0–6)</td>
<td>0.02</td>
</tr>
<tr>
<td>mRS ≤2 at discharge</td>
<td>25.6% (20/78)</td>
<td>24.0% (6/25)</td>
<td>25.2% (26/103)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>mRS 3 to 5 at discharge</td>
<td>62.8% (49/78)</td>
<td>28.0% (7/25)</td>
<td>54.4% (56/103)</td>
<td>0.003</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>11.5% (9/78)</td>
<td>48.0% (12/25)</td>
<td>20.4% (21/103)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LA indicates leukoaraiosis; IV, intravenous; IA, intra-arterial; TIMI, Thrombolysis In Myocardial Infarction; HT, hemorrhagic transformation; PH, parenchymal hematoma; HI, hemorrhagic infarct; SAH, subarachnoid hemorrhage; mRS, modified Rankin Scale.
or severe LA in the DWM, there was no difference in the PH rate with regard to thrombolytic use (60% [6 of 10 patients with thrombolysis] versus 31.3% [5 of 16 patients without thrombolysis]; P = 0.23).

Univariate analysis of potential factors associated with any HT and PH is shown in Table 3. The potential factors associated with HT and PH were entered into the multivariate analysis and listed in Table 4. Moderate or severe LA in the DWM was the only independent predictor of HT on the multivariate logistic analysis (OR, 3.43; 95% CI, 1.23–9.57; P = 0.019). On multivariate analysis, independent predictors of PH were moderate or severe LA in the DWM (OR, 6.26; 95% CI, 1.74–22.45; P = 0.005), premorbid use of warfarin (OR, 11.21; 95% CI, 1.78–70.74; P = 0.01), IA thrombolytic use (OR, 8.40; 95% CI, 1.20–58.81; P = 0.032), and female sex (OR, 0.22; 95% CI, 0.07–0.71; P = 0.012).

### Outcome by PH

Patients with PH had worse discharge modified Rankin Scale (5.5 versus 3.0; P < 0.001), were less often independent at discharge (modified Rankin Scale ≤2, 3.8% versus 32.5%; P = 0.003), and had greater in-hospital mortality (50% versus 10.4%; P < 0.001).

In the 26 patients with moderate or severe LA in the DWM, 21 patients achieved successful final revascularization including 9 patients with PH. All 6 patients with good outcome achieved successful revascularization without experiencing PH. None of the remaining 14 patients with either PH or unsuccessful revascularization had good outcome at discharge, and 9 of them died postthrombectomy.
Discussion

Although predictors of HT after IV or IA thrombolysis for AIS are known, few predictors associated with mechanical thrombectomy have been reported. Our findings suggest that moderate or severe LA in the DWM may be associated with HT after mechanical thrombectomy. Moderate or severe LA in the DWM may be also an independent predictor of PH and subsequently worse functional outcome in our cohort.

The association of LA with HT after thrombectomy in our cohort is consistent with recent studies of thrombolysis for AIS. In a series of 820 patients from the Canadian multicenter study, the rate of severe white matter damage was 8.6%, and 8.4% of patients with extensive LA developed symptomatic HT after IV tPA.11 In another series of 400 patients treated with IV tPA within 4.5 hours of stroke onset, the rate of severe LA was 24%, and 11% of patients with LA developed symptomatic HT after thrombolysis. Patients with LA tended toward a higher rate of symptomatic HT and an associated poor outcome after tPA treatment when compared with patients without LA.12

The sensitivity of CT and MR to LA may differ and be 1 explanation of the debatable relationship between LA and post-tPA HT. The preponderance of CT-based evidence comes from the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tPA trial, which showed that the rate of symptomatic HT was 7.9% in patients with severe LA but did not establish LA on baseline CT as an independent predictor of symptomatic HT or poor outcome after thrombolysis.13 We used the same FLAIR-based MR criteria of LA assessment as a recent study of 449 patients treated by IA or IV thrombolysis.10 The reported 25.4% rate of moderate or severe LA in the DWM was similar to our cohort’s rate of 24.8%. Results from this multicenter study also confirmed that moderate or severe LA in the DWM was a predictor for symptomatic HT after thrombolysis.

Regional blood–brain barrier disruption with increased permeability in the white matter may increase the likelihood of endothelial dysfunction and the development of LA.16–18 In patients with AIS with severe white matter lesions, ischemic damage may further induce the failure of endothelial function and blood–brain barrier disruption with resultant blood extravasation and subsequent parenchymal injury. In the NINDS recombinant tPA trial, there was a 2.9% rate of symptomatic HT in 34 patients with AIS with severe LA who received placebo treatment.13

Although LA may increase the rate of HT after both thrombolysis and mechanical thrombectomy, the mechanisms of injury may differ between 2 therapies. The deep white matter in particular may be more susceptible to blood–brain barrier failure than periventricular white matter after treatment. Either tPA itself or the breakdown products of thrombolysis are contributors for further blood–brain barrier disruption and subsequent hemorrhage after thrombolysis in patients with LA. HT is also attributable to reperfusion injury after successful reopening of the occluded vessel in both thrombolysis and thrombectomy. In our cohort, PH rates were higher than that in studies of IV thrombolysis. This may be related to the concomitant effects of reperfusion injury and thrombolysis-related damage to white matter, because nearly one third of our patients were treated with both modalities. HT may be mainly related to reperfusion injury when pure thrombectomy was used for patients with AIS with LA.

In our small cohort, patients with moderate or severe LA in the DWM were older and had higher National Institutes of Health Stroke Scale scores, implying worse natural history. Although >60% of the 14 patients with moderate or severe LA with either PH or unsuccessful revascularization died after thrombectomy, their outcome with thrombectomy may still be better than their inherent natural history. Whether patients with AIS with moderate or severe LA truly benefit from mechanical thrombectomy is not known.

The main limitation of our study is a retrospective analysis with a small cohort size. In the present study, procedure-related vessel perforation and higher baseline National Institutes of Health Stroke Scale were more common in patients with moderate or severe LA in the DWM. They are both associated with an increased risk of PH after thrombectomy. When the patients with 8-vessel perforation were eliminated from the series, post hoc analysis showed that there was a trend toward more frequent PH in patients with moderate or severe LA in the DWM than in those without, but this difference did not reach statistical significance (31.8% [7 of 22 patients] versus 18.7% [14 of 75 patients]; P=0.23). Vessel perforation may be more frequent in patients with LA because the same changes in parenchymal microvasculature that cause the LA may similarly affect the compliance in the walls of the medium-sized arteries within which the thrombectomy and associated perforation occurs.

Our study has several other limitations. We did not perform volumetric analysis of LA burden. We also did not compare LA severity with symptomatic HT. In our cohort, HT was mostly defined on gradient-recall echo, and half of all patients
with PH on gradient-recall echo were asymptomatic. We did not assess 3-month clinical outcome. We do not know whether the influence of LA on HT is restricted to reperfusion by Merci thrombectomy or is similarly present with other endovascular modalities such as the Penumbra system or newer “stentriever.”

In conclusion, moderate or severe LA in the DWM may be associated with HT in patients with AIS after Merci thrombectomy and is associated with an increased risk of PH but not hemorrhagic infarct, which bodes worse clinical outcome. Our data need to be interpreted cautiously due to the retrospective design and small cohort size. However, these findings may be useful for clinicians to better anticipate the potential risks of thrombectomy in patients with LA. A larger randomized study of thrombectomy selected by MRI is needed to confirm these results.

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Disclosure
Dr Duckwiler is a Scientific Advisor and shareholder in Concentric Medical. Dr Liebeskind is a consultant for Concentric Medical. Dr Saver is a scientific consultant for CoAxia, Concentric Medical, and Talecris.

References
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