Leukoaraiosis Is a Risk Factor for Symptomatic Intracerebral Hemorrhage After Thrombolysis for Acute Stroke

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Background and Purpose—The aim of the study was to evaluate whether leukoaraiosis (LA) is a risk factor for symptomatic intracerebral hemorrhage (sICH) in patients treated with thrombolysis for acute stroke.

Methods—In this retrospective, multicenter analysis, we evaluated data from acute anterior circulation stroke patients (n=449; <6 hours after symptom onset) treated with thrombolysis. All patients had received standard magnetic resonance imaging evaluation before thrombolysis, including a high-quality T2-weighted sequence. For the analysis, LA in the deep white matter was dichotomized into absent or mild versus moderate or severe (corresponding to Fazekas scores of 0 to 1 versus 2 to 3).

Results—The rate of sICH was significantly more frequent in patients with moderate to severe LA of the deep white matter (n=12 of 114; 10.5%) than in patients without relevant LA (n=13 of 335; 3.8%), corresponding to an odds ratio of 2.9 (95% CI, 1.29 to 6.59; P=0.015). In a logistic-regression analysis (including age, National Institutes of Health Stroke Scale score at presentation, and type of thrombolytic treatment), LA remained a significant independent risk factor (odds ratio, 2.9; P=0.03).

Conclusions—LA of the deep white matter is an independent risk factor for sICH after thrombolytic treatment for acute stroke. (Stroke. 2006;37:2463-2466.)

Key Words: intracerebral hemorrhage • leukoaraiosis • stroke, acute • thrombolysis

Symptomatic intracerebral hemorrhage (sICH) is the main complication of treatment of acute stroke patients with tissue plasminogen activator (tPA). The identification and possible exclusion of patients at high risk for sICH would be of major importance in reducing the overall complication rate. In addition to improving thrombolysis during the first 3 hours after symptom onset, it could open the opportunity to extend the time window for treatment more safely beyond 3 hours.

In the past, several clinical markers have been established as indicators of an increased risk for sICH, including advanced age, increasing stroke severity, and a history of diabetes and cardiac disease, as well as an elevated pretreatment mean blood pressure. One imaging parameter consistently associated with an increased risk for sICH is the presence of extensive, early infarct signs on CT, particularly when they exceed one third of the middle cerebral artery territory. However, reevaluations of the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tPA Stroke Study indicated that exclusion of stroke patients on the basis of the presence of early infarct signs is not supported by the data, at least not when considering treatment within the first 3 hours after symptom onset.

Only a few human MRI studies have investigated possible markers of an increased risk for sICH after thrombolysis, all showing that severe ischemia, as indicated by a low apparent diffusion coefficient or a severe perfusion deficit, is associated with a higher risk of sICH. One recent study systematically investigated the relevance of microbleeds in patients receiving intravenous thrombolysis and could not confirm previous suggestions of an increased risk. From animal studies, pretreatment blood-brain barrier damage was found to indicate an increased hemorrhage risk, but this has not been systematically investigated in humans.

The aim of the present MRI study therefore was to evaluate the clinical importance of leukoaraiosis (LA) as a possible marker of an increased risk of sICH after thrombolysis.
a radiological marker indicating chronic ischemic damage of the cerebral microcirculation, which could enhance the negative effects of both acute ischemia and tPA at the blood-brain barrier. We hypothesized that LA, being a marker of pretreatment cerebral microcirculatory damage, might be associated with an increased risk of sICH.

Patients and Methods

Patients
This retrospective, multicenter analysis was performed on data provided by 6 well-established, academic stroke centers (Frankfurt, Hamburg, Jena, Los Angeles, Mannheim, and Paris). The study was conducted as an initiative of the MR Stroke group, which is an international group of stroke physicians who meet regularly with the aim of coordinating and standardizing MRI research in acute stroke. Each of the centers participating in the current study uses standardized MRI protocols for acute stroke patients, approved by all local ethics committees.

Patients were included in the current analysis if (1) they presented with an anterior circulation stroke within 6 hours of symptom onset; (2) thrombolytic therapy was administered; (3) an MRI, including a high-quality T2-weighted sequence, was performed before or shortly after the initiation of treatment; and (4) it was known whether or not the patient had developed an sICH after treatment.

General patient variables (not related to treatment or MRI), which were recorded owing to their influence on sICH after thrombolysis, included age, National Institutes of Health Stroke Scale (NIHSS) score on admission, blood glucose level, and platelet count. In addition, the time between symptom onset and both MRI and thrombolytic treatment was recorded.

Treatment
Thrombolytic treatment regimens included (1) intravenous tPA treatment (n=363; treatment within 3 hours, 69%) and (2) intravenous or combined intravenous/intra-arterial treatment with either tPA or urokinase (n=86; treatment within 3 hours, 30%). sICH was defined, as in the NINDS trial, as a CT- (or MRI-) documented parenchymal hemorrhage that occurred within 36 hours from treatment onset and was temporally related to deterioration in the patient’s clinical condition in the judgment of the clinician. The hemorrhage volume on CT or MRI images was measured in all patients with sICH.

MRIs were performed with the use of 1.5-T scanners, all equipped with echoplanar imaging data acquisition capabilities. In >90% of patients, MRI was performed before thrombolysis, and in the remaining patients, during or shortly after treatment (after CT had been performed to rule out hemorrhage). Stroke protocols were not entirely uniform in the 6 participating centers, but all included a high-resolution T2-weighted sequence, which, for the assessment of LA, had to be either a standard, nonechoplanar imaging, T2-weighted sequence or a fluid-attenuated inversion recovery sequence. There were no predefined MRI patterns (such as diffusion-weighted/perfusion-weighted mismatch) required for inclusion in the study.

The severity of LA was rated in a decentralized manner at the participating centers by single, blinded reviewers using the visual rating scale proposed by Fazekas and Schmidt,15 with scores ranging from 0 to 3. The extent of LA was determined on the fluid-attenuated inversion recovery sequence images or on the high-resolution, T2-weighted sequence for the deep white matter (DWM) and the periventricular white matter (PVWM). Examples of different degrees of LA are shown in the Figure. For the DWM, scores correspond to the following characteristics: 0, no lesion; 1, punctuate foci; 2, beginning confluent foci; and 3, confluent changes. For the PVWM, scores correspond to the following characteristics: 0, no changes; 1, caps or a pencil-thin lining; 2, smooth halo; and 3, irregular changes extending into the DWM. For statistical analysis, the results for both the DWM and PVWM were dichotomized into 0 to 1 and 2 to 3. To obtain an estimate of potential differences in ratings between centers, data from 1 center (contributing n=103 patients) were rated by an investigator from a different center (T.N.H.) in addition to the local investigators. The dichotomized data, there was excellent agreement (n=95 of 103) for DWM, corresponding to a k value of 0.78, and good agreement (n=90 of 103) for PVWM, corresponding to a k value of 0.72.

Statistics
All statistical tests were done with the SPSS 10.0 software package. In the statistical analysis, we tested the (prospectively defined) hypothesis that moderate to severe LA (score of 2 or 3) in the DWM region is a risk factor for sICH by Fisher exact test. Using logistic regression (method included in SPSS), we analyzed whether moderate to severe LA is an independent risk factor for sICH. Results were considered statistically significant at the 5% level.

Results
Data from n=449 patients meeting the inclusion criteria were analyzed. Demographic and clinical variables are listed in the

Grade 0/1

Grade 2

Grade 3

Three examples illustrating different degrees of LA in DWM (arrow) and periventricular areas (with identical scores for deep and periventricular changes).
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**Table.** Thrombolysis was administered within 3 hours in 65% of the total patient population (intravenous thrombolysis in 82%) and after 3 hours in 35% (intravenous thrombolysis in 67%). Moderate to severe LA (scores of 2 to 3 for DWM) was present in 114 (25.4%) patients. The only baseline variable significantly associated with LA was age (75 versus 61 years; \( P < 0.01 \)), whereas the NIHSS score on admission, blood glucose level, platelet count, and time between symptom onset and thrombolysis were not significantly different between patients with and without LA (see the Table).

In total, sICH occurred in \( n = 25 \) of \( 449 \) (5.6%) patients. The median hemorrhage volume in sICH was \( 40 \) cm³ (range, 3 to 189 cm³). There was no significant difference in the NIHSS rate between patients receiving thrombolysis within 3 hours after symptom onset (5.6%) and those receiving thrombolysis after 3 hours (5.7%). However, sICH was significantly more frequent in patients with moderate to severe LA \( (n = 12 \) of \( 114; 10.5\%) \) than in patients without relevant LA \( (n = 13 \) of \( 335; 3.8\%) \), corresponding to an odds ratio (OR) of 2.9 (95% CI, 1.29 to 6.59; \( P = 0.015 \)).

Logistic-regression analysis was performed to determine whether LA was an independent risk factor for sICH. In addition to age, which was significantly different between patients with and without LA, the NIHSS score on admission and the type of thrombolytic treatment (intravenous versus intra-arterial/intravenous–intra-arterial) were included in the analysis. Blood glucose level and platelet count were not included owing to incomplete data sets. LA remained a significant independent risk factor (OR, 2.9; \( P = 0.03 \)), whereas age was not (\( P = 0.82 \)). As expected, the NIHSS score was also independently associated with sICH \( (P = 0.019) \).

In addition, the relevance of LA to sICH was tested for the large subgroup of patients treated with intravenous thrombolysis \( (n = 363) \). Again, the rate of sICH was significantly greater in the group with LA \( (n = 8 \) of \( 89; 9.0\%) \) than in the group without LA \( (n = 6 \) of \( 274; 2.2\%) \), corresponding to an OR of 4.4 (95% CI, 1.49 to 13.01; \( P = 0.008 \)). Periventricular LA alone (as opposed to deep LA with or without periventricular LA) was present in 27 patients. None of these patients experienced an sICH, indicating that LA of the DWM is the important aspect conferring an increased risk for sICH.

**Demographic and Clinical Variables**

<table>
<thead>
<tr>
<th></th>
<th>Without, ( n = 335 )</th>
<th>With, ( n = 114 )</th>
<th>All, ( n = 449 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>61±14</td>
<td>75±9</td>
<td>65±14</td>
<td>0.001</td>
</tr>
<tr>
<td>NIHSS score at presentation, mean±SD</td>
<td>12.7±5.9</td>
<td>13.7±5.9</td>
<td>13.2±6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Blood glucose, mean±SD</td>
<td>131±42</td>
<td>128±41</td>
<td>132±44</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet count, mean±SD</td>
<td>245±95</td>
<td>239±90</td>
<td>244±95</td>
<td>NS</td>
</tr>
<tr>
<td>Time to thrombolysis, mean±SD, min</td>
<td>189±59</td>
<td>187±65</td>
<td>188±64</td>
<td>NS</td>
</tr>
</tbody>
</table>

LA refers to a DWM change corresponding to a Fazekas score of 2 or 3. Student \( t \) test was used for the comparisons of age, NIHSS score at presentation, blood glucose, platelet count, and time to thrombolysis.

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**Discussion**

This multicenter study shows that moderate to severe LA is an independent risk factor for sICH after thrombolytic treatment for acute stroke. LA, a term initially coined by Hachinski and coworkers to describe an abnormal CT appearance of the subcortical brain white matter in elderly or demented individuals, is most easily identified on T2-weighted MRI images. Pathophysiologically, chronic cerebral ischemia and hypoperfusion are thought to be the main etiologies for LA, often attributable to cerebral microangiopathy. LA is a known risk factor for dementia and does seem to be associated with increased morbidity and mortality, partly attributable to an enhanced risk of ischemic stroke.

To our knowledge, no previous study investigated whether LA is a risk factor for sICH after thrombolytic treatment. One retrospective study found that LA may be a risk factor for ICH in patients who received anticoagulation for cerebral ischemia of presumed arterial origin (hazard ratio, 2.7). This finding of an association between LA and warfarin-related hemorrhage was confirmed in an independent case-control study investigating poststroke patients who received anticoagulation in the commonly used international normalized ratio range of 2.0 to 3.0. Thus, LA is possibly a marker of an increased susceptibility to hemorrhagic treatment complications, rather than a condition indicating a specific risk of thrombolytic treatment.

Preexisting chronic damage of the cerebral microcirculation (functionally including endothelial dysfunction) appears to increase the risk of vessel rupture and subsequent major hemorrhage. In stroke, acute ischemic damage to endothelial cells and astrocytes is an additional mechanism weakening the blood-brain-barrier. With thrombolytic treatment, further damage to the blood-brain barrier attributable to either tPA itself or thrombolysis reaction products is of further importance.

Old age was previously found to be a risk factor for sICH. In our study, although patients with moderate to severe LA were older than those without, LA remained a significant risk factor for sICH after adjustment for age. Indeed, the variable age itself no longer showed a trend toward significance when both LA and age were added to the logistic-regression analysis. Thus, based on our data, age itself could be merely a "biological" marker of a statistically age-related degenerative process (probably cerebral microangiopathy). This would be in line with 2 recent reports showing that the risk of sICH after thrombolysis is not necessarily increased in the very old. Based on our data, it appears possible that the parameter "LA" indicating biological age will prove to be a better marker of sICH risk than chronological age.

The main limitation of our analysis is the retrospective nature of the study, which is susceptible to bias. However, we would like to point out that our primary hypothesis was predefined. In addition, we are confident that the patient population is largely representative of patients being treated with thrombolysis at larger stroke centers, as the rate of sICH was very similar to that in randomized trials and large thrombolysis surveys. At all contributing centers, MRI has been used routinely for the evaluation of acute stroke patients for several years, and relevant bias attributable to MRI being
a requirement for inclusion is unlikely. Follow-up MRI, however, was not a requirement for inclusion to prevent dropout attributable to poor clinical status. Finally, we would like to point out that our study does not answer the question whether or not thrombolyis should be withheld in patients with LA; this can only be answered in a randomized trial of patients with LA wherein outcomes in treated versus untreated patients are compared.

Worldwide, CT is still used in the majority of patients being evaluated as potential candidates for thrombolyis. Assessment of LA, however, is easier with MRI than with CT. Nevertheless, moderate to severe LA can also be seen on CT images and is, in our opinion, easier to identify than early infarct signs. Thus, it should be possible to translate our findings to CT-based evaluations in acute stroke patients.

In conclusion, this large MRI-based analysis shows that LA is a relevant risk factor for sICH after thrombolysis in acute stroke patients. Implementation of our findings into clinical practice requires confirmation in larger prospective trials. However, because these trials are unlikely to be performed in the near future, the presence or absence of moderate to severe LA in the DWM may be included cautiously in the decision-making process for or against thrombolysis as 1 of several factors to be considered (eg, age, time from symptom onset, NIHSS score, and history of diabetes), particularly in elderly patients.

Acknowledgments

The authors acknowledge the contribution of the following UCLA thrombolysis investigators: Jeffrey R. Alger, Latisa K. Ali, Brian H. Buck, Gary R. Duckwiler, Reza Jahan, Doojin Kim, Bruce Ovbiagele, Noriko Salamon, Nerses Sanossian, Sidney Starkman, Paul M. Vespa, J. Pablo Villablanca, Fernando Vinuela.

Disclosures

None.

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Stroke. 2006;37:2463-2466; originally published online August 24, 2006;
doi: 10.1161/01.STR.0000239321.53203.ea

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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