Early Disruption of the Blood–Brain Barrier After Thrombolytic Therapy Predicts Hemorrhage in Patients With Acute Stroke

Andreas Kastrup, MD; Klaus Gröschel, MD; Thomas M. Ringer, MD; Christoph Redecker, MD; Robert Cordesmeyer, MD; Otto W. Witte, MD; Christoph Terborg, MD

Background and Purpose—Leaks of the blood–brain barrier can be detected on postcontrast-enhanced T1-weighted MRIs. Although early disruptions of the blood–brain barrier appear to be an important risk factor for tissue plasminogen activator-related hemorrhages in rodents, little is known about their incidence and consequences in human stroke.

Methods—This is a retrospective analysis of a prospectively collected stroke database over the past 6 years. In 52 patients, multimodal MRI (including diffusion-weighted, perfusion-weighted, and postcontrast-enhanced T1-weighted MRI to detect blood–brain barrier changes) had been performed immediately before systemic thrombolysis and in 48 patients within a median of 30 minutes (interquartile range: 30 to 60 minutes) after recombinant tissue plasminogen activator treatment. The incidence of symptomatic hemorrhage (SICH), defined as any parenchymal hemorrhage leading to deterioration in the patient’s clinical condition, was related to several clinical and imaging variables, including early blood–brain barrier changes.

Results—Overall, SICH was detected in 9 (9%) patients and among these, 2 died. Although no blood–brain barrier changes were detectable before thrombolysis, 3 of 48 patients (6.25%) had a parenchymal gadolinium enhancement in the areas of initial infarction after tissue plasminogen activator treatment. All 3 patients developed SICHs at sites corresponding to the areas of enhancement. The presence of a parenchymal enhancement was significantly associated with SICH (P<0.01), whereas other clinical and imaging variables did not predict SICH in this series.

Conclusion—Early parenchymal enhancement after intravenous tissue plasminogen activator is significantly associated with subsequent SICH and could therefore become a useful imaging sign for the rapid initiation of preventive strategies in the future. (Stroke. 2008;39:2385-2387.)

Key Words: thrombolytic therapy ■ hemorrhage ■ magnetic resonance imaging

Intravenous thrombolysis with tissue plasminogen activator (tPA) is currently the only proven therapy for acute ischemic stroke when given within the first few hours after symptom onset. However, the efficacy of this therapy is counteracted by an increased risk of symptomatic intracerebral hemorrhage (SICH). Aside from various clinical and radiological factors, including advanced age, the severity of the perfusion deficit, or the extent of hypoattenuation on CT, among other factors,1,2 animal models of stroke have indicated that an early disruption of the blood–brain barrier (BBB), as demonstrated on postcontrast-enhanced T1-weighted images, may be another important risk factor for recombinant tPA-related hemorrhages.3,4 Although early parenchymal contrast enhancement on T1-weighted imaging has also recently been demonstrated in individual human stroke subjects after thrombolysis,5,6 the predictive value of this imaging parameter for SICH after intravenous thrombolysis in humans is unknown.

Therefore, using contrast-enhanced T1-weighted imaging, the aim of this study was to investigate if early changes of the BBB are predictive of subsequent SICH in human stroke.

Methods

Study Population

Patients presenting with acute ischemic stroke were selected retrospectively over the past 6 years from a prospectively collected stroke database. As part of our imaging protocol, all patients with acute stroke primarily receive a multimodal MRI if this can be performed without time delay; otherwise, a computerized cranial tomography scan is obtained before thrombolysis. Patients were included if the following criteria were fulfilled: (1) treatment with intravenous tPA (0.9 mg/kg alteplase, maximum 90 mg) within 6 hours of symptom onset; (2) multimodal MRI either performed before or within 3 hours after tPA administration; and (3) computerized cranial tomography scan or MRI 1 to 2 days after treatment to assess for intracerebral hemorrhage. Informed consent was obtained in all cases, and the protocol had been approved by our local ethics committee.
MRI Protocol

The stroke imaging protocol (1.5 T Sonata; Siemens) included diffusion-weighted imaging (section thickness = 5 mm; TR/TE 4500/107; field of view = 230, b values 1000 s/mm² and 0 s/mm²), perfusion-weighted imaging (12 slices, slice thickness = 5 mm; TR/TE 1440/47; field of view = 230, 0.2 mmol/kg gadolinium-DTPA), time-of-flight, and in some instances, gadolinium-enhanced MR angiography of the intracranial vessels, T1-weighted imaging (TR/TE 500/16) before and 10 minutes after gadolinium administration.

Image and Data Analysis

MRI analysis was performed jointly by two investigators (AK, RC), who were both blinded to the clinical data. The diffusion-weighted lesions were determined by using the images with the highest b value (b = 1000). TTP maps were generated using a time delay of 6 seconds relative to the unaffected contralateral hemisphere. On T1-weighted contrast-enhanced MRIs, the presence of a parenchymal enhancement within the infarcted brain areas was determined.

Noncontrast CT scans or MRIs performed 1 to 2 days after thrombolysis were used to detect SICH. SICH was defined, like in the National Institute of Neurological Diseases and Stroke trial, as a 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.

Statistical Analysis

Categorical data were analyzed with two-tailed χ² statistics with Yates correction or the univariate Fisher exact test and continuous variables were analyzed with an unpaired Student t test or, in case of abnormally distributed data, with a Mann Whitney U test. A value of P < 0.05 was considered a statistically significant difference.

Results

A total of 100 patients (47 male and 53 female; mean age 67 ± 14 years) fulfilled the inclusion criteria. The median (interquartile range) initial National Institutes of Health Stroke Scale of these patients was 11 (7.5 to 15.5). Eighty-six patients were treated with intravenous tPA within 3 hours, whereas 14 patients were treated from 3 to 6 hours after stroke onset. In 52 patients, MRI was performed immediately before thrombolysis and in 48 patients within a median of 30 minutes (interquartile range: 30 to 60 minutes) after tPA treatment, respectively. Although no parenchymal enhancement was detectable before thrombolysis, 3 of 48 patients (6.25%) had a parenchymal enhancement in the areas of initial infarction after tPA treatment. In one of these patients, MR angiography still demonstrated a persistent middle cerebral artery occlusion, whereas a reperfusion had occurred in both other patients in whom middle cerebral artery occlusions had been documented with ultrasound before tPA treatment.

With respect to the entire group of patients scanned after tPA treatment, 33 of 48 patients (69%) had a persistent occlusion of a major cerebral artery. Overall, SICH was detected in 9 (9%) patients (5 parenchymal hemorrhage type 1, 4 parenchymal hemorrhage type 2 according to Larrue et al1). Two of these patients died and in the remaining patients, the National Institutes of Health Stroke Scale dropped by a mean of 3.6 ± 1.9 points. In 6 patients with SICH, MRI had been performed before thrombolysis and in 3 after tPA treatment, respectively. Thus, all 3 patients with a parenchymal enhancement developed SICHs, of which the sites corresponded to the areas of enhancement (Figure). The presence of a parenchymal enhancement was significantly associated with SICH (P < 0.01), whereas other clinical and imaging variables did not predict SICH (Table).

Discussion

The present study demonstrates a clear association between an early disruption of the BBB after intravenous...
Table. Comparison of Clinical and Imaging Parameters Between Patients With and Without SICH

<table>
<thead>
<tr>
<th>Imaging variables</th>
<th>Without SICH</th>
<th>With SICH</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=91)</td>
<td>(n=9)</td>
<td></td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD), years</td>
<td>67±14</td>
<td>65±7</td>
<td>0.4</td>
</tr>
<tr>
<td>Male, %</td>
<td>47</td>
<td>44</td>
<td>1.0</td>
</tr>
<tr>
<td>Median (IQR) National Institutes of Health Stroke Scale on admission</td>
<td>11 (7–15)</td>
<td>15 (9.5–17.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>66</td>
<td>67</td>
<td>1.0</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>32</td>
<td>22</td>
<td>0.7</td>
</tr>
<tr>
<td>Current tobacco use, %</td>
<td>10</td>
<td>11</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>20</td>
<td>22</td>
<td>1.0</td>
</tr>
<tr>
<td>Median time to treatment, minutes</td>
<td>150</td>
<td>160</td>
<td>0.8</td>
</tr>
<tr>
<td>Imaging variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) initial DWI lesion volume, mL</td>
<td>15 (6–41)</td>
<td>17 (7–84)</td>
<td>0.9</td>
</tr>
<tr>
<td>Median (IQR) initial PWI lesion volume, mL (TTP 6)</td>
<td>40 (16–72)</td>
<td>69 (26–98)</td>
<td>0.2</td>
</tr>
<tr>
<td>PWI/DWI mismatch,* %</td>
<td>34</td>
<td>56</td>
<td>0.3</td>
</tr>
<tr>
<td>Parenchymal enhancement</td>
<td>0/91</td>
<td>3/9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Defined as PWI lesion volume ≥120% DWI lesion volume with a minimum of 10-mL mismatch.
IQR indicates interquartile range; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging.

Disclosures
AK has received speaker honoraria from Boehringer Ingelheim.

References

Thrombolysis, as evidenced by parenchymal enhancement on contrast-enhanced T1-weighted images, and subsequent development of SICH. This finding corroborates previous animal studies as well as a small human case series and supports the notion that an early loss of the integrity of the BBB is highly predictive for SICH after tPA treatment. In contrast, BBB changes before tPA application appear to be extremely rare and therefore do not significantly contribute to SICH after treatment.

The early BBB changes observed in this study are distinct from the enhancement of cerebrospinal fluid, which has recently been observed on fluid-attenuated inversion recovery images in patients with acute stroke and termed hyperintense acute reperfusion marker. Although this sign also reflects disruption of the BBB, it only becomes apparent on delayed MRI and therefore does not appear to be a suitable early marker of SICH risk.

Similar to a previous study, we were unable to detect any significant influence of other baseline MRI variables on the risk of SICH. Moreover, previously identified clinical variables, including age and diabetes among others, were not associated with SICH, which is likely attributable to the rather small number of patients with SICH in this series.

In addition, we did not incorporate measures of reperfusion into our analyses, which have recently been shown to be important independent determinants of SICH after thrombolytic therapy. Although there were no obvious differences in time to treatment or other key variables between patients scanned before thrombolysis compared with those imaged after thrombolysis the effects of tPA on the BBB can eventually only be determined by studying a control group treated without tPA within the same time range.

Despite these limitations, our data clearly show that early parenchymal enhancement after intravenous tPA is significantly associated with subsequent SICH and could therefore become a useful imaging sign for the rapid initiation of preventive strategies in the future.
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