Association of Molecular Markers With Perihematomal Edema and Clinical Outcome in Intracerebral Hemorrhage

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Background and Purpose—Perihematomal edema contributes to secondary brain injury in intracerebral hemorrhage (ICH). Increase of matrix metalloproteinases (MMPs) and growth factors is considerably involved in blood–brain barrier disruption and neuronal cell death in ICH models. We therefore hypothesized that increased levels of these molecular markers are associated with perihematomal edema and clinical outcome in ICH patients.

Methods—Fifty-nine patients with spontaneous ICH admitted within 24 hours of symptom onset were prospectively investigated. Noncontrast CT was performed on admission for diagnosis of ICH and quantification of initial hematoma volume. MRI was performed on day 3 to evaluate perihematomal edema. Concentrations of MMP-3, MMP-9, as well as vascular endothelial growth factor and angiopoietin-1 on admission were determined by enzyme-linked immunosorbent assays. Clinical outcome was assessed by modified Rankin Scale at 90 days.

Results—Increased MMP-3 levels were independently associated with perihematomal edema volume (P<0.05). Cytotoxic edema surrounding the hematoma was seen in 36 (61%) cases on 3-day MRI. Cytotoxic edema did not correlate with the level of any of the biomarkers studied. Levels of MMP-3 ≥12.4 ng/mL and MMP-9 ≥192.4 ng/mL but not vascular endothelial growth factor and angiopoietin-1 predicted poor clinical outcome at 90 days (modified Rankin Scale >3) independent of stroke severity and hematoma volume at baseline (odds ratio, 25.3, P=0.035; odds ratio, 68.9, P=0.023; respectively).

Conclusions—MMPs 3 and 9 seem to be significantly involved in secondary brain injury and outcome after primary ICH in humans, and thus should be further evaluated as targets for therapeutic strategies in this devastating disorder. (Stroke. 2013;44:XXX-XXX.)

Key Words: brain edema ■ diffusion-weighted MRI ■ ICH ■ inflammation ■ magnetic resonance imaging ■ matrix metalloproteinases ■ outcome

Intracerebral hemorrhage (ICH) accounts for ≈10% to 15% of strokes in Western countries and up to 20% to 30% in Asian countries.1 ICH is associated with higher mortality and worse clinical outcome than ischemic stroke, and no effective therapy is available.1,2 Subsequent to the initial physical trauma and mass effect of the bleeding, secondary brain injury, such as perihematomal edema (PHE) including vasogenic (extracellular) and cytotoxic (intracellular) edema, develops.3 The impact of PHE on clinical outcome is still under debate.4-7 Matrix metalloproteinase (MMP)-3 and MMP-9,8-10 as well as growth factors (GFs) such as vascular endothelial growth factor (VEGF) and Angiopoietin-1 (Ang-1),11 are expressed in abnormally high concentrations in brain and peripheral blood in ICH patients. In ICH animal models, elevated MMP-9 and MMP-3 contribute to blood–brain barrier (BBB) disruption,12,13 brain edema,14,15 and neuronal cell death.16,17 Other animal models of ICH and brain injury showed that alteration of VEGF and Ang-1 was related to increased BBB permeability and brain edema.18-20

Data on the implications of MMPs and GFs in secondary brain injury after ICH in humans are still scarce. A better understanding of these molecular pathophysiological mechanisms involved in secondary brain injury of ICH might help to develop new therapeutic options. Therefore, we aimed to investigate the relationship between the molecular markers MMP-3, MMP-9, VEGF, Ang-1, and PHE, as well as clinical outcome in patients with primary ICH.

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Methods

Study Population
All patients with spontaneous ICH admitted to the Neurological Department of Beijing Tiantan Hospital from January 2011 to December 2011 were screened for this study. Inclusion criteria were time from symptom onset to admission <24 hours, age ≥80 years, and absence of coma. Exclusion criteria were secondary ICH (hemorrhage resulting from aneurysm, vascular malformation, hemorrhagic infarction, tumor, or impaired coagulation), history of acute or chronic infection, malignant diseases and immunosuppressive treatment, contraindication for MRI, undergoing a surgical procedure, or refusal of participation. A total of 59 patients were prospectively included after informed consent from patients or their relatives. The study has been approved by the local ethics committee.

Clinical data of patients were collected on admission. The variables included sex, age, body mass index, alcohol and tobacco use, a detailed history of vascular risk factors and concomitant medications, body temperature, systolic and diastolic blood pressure, and laboratory tests. Stroke severity was evaluated by Glasgow Coma Scale and National Institutes of Health Stroke Scale at admission. Poor clinical outcome was defined as modified Rankin Scale >3 assessed at 90-day follow-up.

Radiological Protocol
Noncontrast cerebral computed tomography (NCCT) scans were performed on admission, according to the protocol of the neuroradiological department with an image matrix of 512×512, 4.5-mm-wide slices for posterior fossa, and 9-mm-wide slices for medium and anterior fossae. Cerebral MRI was performed by 3.0 Tesla scanners (Trio-Tim, Siemens, Erlangen, Germany) on 3±1 days. MRI included conventional T1-weighted and T2-weighted (T2*), diffusion-weighted (DWI) images, gradient-recalled echo imaging (T2*), diffusion-weighted (DWI) images using 2 levels of diffusion sensitization (b=0 and 1000 s/mm²), and apparent diffusion coefficient (ADC) maps created from DWI images by the image analysis system. Additionally, in 50 patients, a follow-up NCCT was done at 24 hours as a clinical routine.

Investigators who analyzed the images were blinded to clinical and biomarker information. Hematoma location (supratentorial, infratentorial), and the presence of intraventricular hemorrhage (IVH) were recorded. Hematoma volume and total lesion area were calculated by the summation-of-area method on each slice multiplied by the interslice thickness on both NCCT and 3-day MRI. The levels of diffusion sensitization (b=0 and 1000 s/mm²) and apparent diffusion coefficient (ADC) maps created from DWI images were used to identify different patterns of edema on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) images. Relative PHE volume was defined as absolute PHE volume divided by hematoma volume, yielding a dimensionless ratio variable. Areas of increased DWI-b1000-signal and reduced ADC value by >10% compared with the mirror region of interest were interpreted as cytotoxic edema (CE) and manually outlined,7 confirmed by a 3D-multiplanar localization function of the image analysis software (Figure 1).

Imunoassay Methods
For the measurement of markers, blood samples were drawn using EDTA and serum tubes from each patient on admission. Plasma was immediately separated by centrifugation at 3000 rpm for 15 minutes and stored at −80°C. The levels of MMP-3, MMP-9, VEGF, and Ang-1 were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer instructions (R&D Systems). MMP-9 was measured in EDTA plasma.23,24 MMP-3, VEGF, and Ang-1 in serum.

Statistical Analysis
Statistical analysis was performed using the SPSS statistical package Version 11.5. Categorical variables are shown as numbers and percentages. Continuous variables are presented as mean±SD, or median values [interquartile range] as appropriate. Tests performed were the χ² or Fisher exact tests for categorical variables, and the Student t test or the Mann–Whitney U test for continuous variables as appropriate. Spearman correlation analysis was used to study correlations between continuous variables. Cut-off points of studied markers were determined using the receiver operating characteristic curve and Youden Index. Multivariable analysis using a multiple linear regression model was performed to assess the relationship between the molecular markers and the PHE volume at day 5. A stepwise logistic regression analysis was performed to determine factors that could be considered independent predictors of unfavorable clinical outcome at 3 months.

Results

Baseline Clinical, Neuroimaging, and Laboratory Findings
Baseline variables are shown in Table 1 (n=59). Median time from symptom onset to baseline NCCT was 3.5 (1.6–7.5) hours. Twenty-four-hour follow-up CT was performed in 50 patients. The median hematoma volume on baseline and 24-hour follow-up CT was 9.9 (5.4–21.3) ml and 10.9 (5.6–25.8) ml, respectively (n=50). Hematoma expansion was found in 3 patients who had follow-up CT and in none of the

Figure 1. Example of edema surrounding the hematoma on 3-day MRI. Black and white arrows indicate hematoma and perihematomal edema (PHE) on the T2-weighted image, respectively. Region of interest of cytotoxic edema (CE) is outlined on the apparent diffusion coefficient (ADC) image.
remaining 9 patients who only underwent follow-up MRI. MMP-3, MMP-9, VEGF, and Ang-1 levels did not correlate with hematoma volume at baseline. No correlation between these molecular markers and the absolute increase of hematoma volume was found ($P>0.05$).

**Association of PHE Volume With Hematoma Volume and Molecular Markers**

Median time to follow-up MRI was 76 (69–88) hours. PHE was present in all patients on 3-day T2-weighted images. A high correlation was found between absolute PHE and hematoma volume at baseline and day 3 ($r=0.922$ and $r=0.959$, respectively; both $P<0.001$; Figure 2). Absolute PHE volume was positively correlated with MMP-3 ($r=0.311$; $P=0.017$), but not with MMP-9, VEGF and Ang-1. Hematoma volume on day 3 was positively correlated with MMP-3 ($r=0.311$; $P=0.017$) and negatively correlated with Ang-1 ($r=-0.281$; $P=0.031$), but did not correlate with MMP-9 nor with VEGF. The linear stepwise regression model revealed that MMP-3 was independently associated with absolute PHE volume ($\beta=0.370$; $P=0.004$), irrespective of age and gender. MMP-3 ($\beta=0.138$; $P=0.043$) remained independently associated with absolute PHE volume when baseline hematoma volume ($\beta=0.868$; $P<0.001$) was also considered. However, only hematoma volume on day 3 ($\beta=0.942$; $P<0.001$) remained as an independent predictor of PHE volume when it was included in the multivariate model instead of hematoma volume on baseline.

**Table 1. Baseline Clinical, Radiological, and Laboratory Characteristics of All Patients and Patients Grouped by 90-Day Outcome**

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>All (n=59)</th>
<th>Favorable Outcome (n=50)</th>
<th>Unfavorable Outcome (n=9)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>41 (69.5)</td>
<td>35 (70.0)</td>
<td>6 (66.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age, y</td>
<td>56±11</td>
<td>56±11</td>
<td>60±14</td>
<td>0.338</td>
</tr>
<tr>
<td>BMI</td>
<td>25.3±3.5</td>
<td>25.4±3.5</td>
<td>24.7±3.8</td>
<td>0.601</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>52 (88.1)</td>
<td>44 (88.0)</td>
<td>8 (88.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>11 (18.6)</td>
<td>9 (18.0)</td>
<td>2 (22.2)</td>
<td>0.670</td>
</tr>
<tr>
<td>History of stroke</td>
<td>13 (22.0)</td>
<td>12 (24.0)</td>
<td>1 (11.1)</td>
<td>0.673</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>24 (40.7)</td>
<td>19 (38.0)</td>
<td>5 (55.6)</td>
<td>0.619</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>26 (44.1)</td>
<td>22 (44.0)</td>
<td>4 (44.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>26 (44.1)</td>
<td>21 (42.0)</td>
<td>5 (55.6)</td>
<td>0.697</td>
</tr>
<tr>
<td>Antiplatelet medication</td>
<td>8 (13.6)</td>
<td>6 (12.0)</td>
<td>2 (22.2)</td>
<td>0.494</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>168±29</td>
<td>165±24</td>
<td>180±25</td>
<td>0.108</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>97±15</td>
<td>98±15</td>
<td>91±15</td>
<td>0.163</td>
</tr>
</tbody>
</table>

**Imaging data on initial CT**

| Hematoma volume | 10.0 [5.2–23.9] | 9.5 [4.1–20.1] | 25.2 [16.5–38.1] | 0.003* |
| PHE volume      | 6.5 [3.0–11.9]  | 5.7 [2.5–11.7]  | 10.0 [6.7–22.1]  | 0.062  |
| Deep location   | 49 (83.1)       | 40 (80.0)       | 9 (100)          | 0.322  |
| Intraventricular hemorrhage extension | 13 (22.0) | 12 (24.0) | 1 (11.1) | 0.673 |

**Laboratory data**

| Leukocyte, 10E9/L | 9.0±2.7 | 8.9±2.7 | 9.9±3.1 | 0.313 |
| Platelet, 10E9/L  | 220.7±47.3 | 218.5±49.1 | 232.9±34.9 | 0.406 |
| Glucose, mmol/L   | 7.0±2.1 | 7.2±2.2 | 6.0±0.8 | 0.144 |
| Creatinine, μmol/L | 64.4±18.4 | 64.2±19.6 | 65.6±10.2 | 0.844 |
| INR              | 0.99±0.06 | 0.99±0.06 | 0.99±0.06 | 0.928 |
| Fibrinogen, g/L   | 2.6±0.9 | 2.5±0.8 | 3.0±0.8 | 0.118 |
| MMP-3, ng/mL      | 10.7 [7.5–21.0] | 9.9 [6.9–18.7] | 17.0 [10.3–28.1] | 0.124 |
| MMP-9, ng/mL      | 140.2 [102.4–217.0] | 135.2 [100.4–192.2] | 232.7 [97.7–306.8] | 0.124 |
| VEGF, pg/mL       | 324.9 [186.7–516.2] | 331.7 [197.2–523.2] | 270.6 [164.6–404.9] | 0.411 |

*P≥0.05 was considered significant. Data are expressed as n (%), mean±SD, or median [IQR] as appropriate. Chi-square test was used for dichotomizing variables; the Student t test or Mann–Whitney U test was used for continuous variables.

Ang indicates angiopoietin; BMI, body mass index; GCS, Glasgow Coma Scale; INR, international normalized ratio; MMP, matrix metalloproteinase; NIHSS, National Institutes of Health Stroke Scale; PHE, perihematomal edema; and VEGF, vascular endothelial growth factor.
Larger PHE volume on day 3 (P<0.001) but not on admission (P=0.062) was observed in those patients with unfavorable clinical outcome compared with those with favorable outcome. No association was found between outcome and presence or absence of CE. Receiver operating characteristic analysis was performed for concentrations of MMP-3, MMP-9, VEGF, and Ang-1. A possible cut-off point for the discrimination of dichotomized clinical outcome was calculated for MMP-3 as 12.4 pg/mL, MMP-9 as 192.4 pg/mL, VEGF as 317.6 pg/mL, and Ang-1 as 27.3 pg/mL. Using these cut-off points, univariate analysis found that MMP-3 ≥12.4 pg/mL and MMP-9≥192.4 pg/mL predicted unfavorable 90-day outcome (P=0.029 and P=0.018, respectively), whereas VEGF and Ang-1 did not (P=0.277 and P=0.252, respectively). Initial hematoma volume, Glasgow Coma Scale, and National Institutes of Health Stroke Scale score on admission were determined to be predictors of outcome as well. In addition to all the significant variables in univariate analysis, age, sex, and hematoma expansion were included in a multivariate logistic analysis to determine independent predictors for unfavorable outcome. As a result, MMP-3 ≥12.4 pg/mL (OR, 25.3; P=0.035), MMP-9 ≥192.4 pg/mL (OR, 68.9; P=0.023), and National Institutes of Health Stroke Scale score at baseline (OR, 1.7; P=0.005) were identified as independent predictors of unfavorable 90-day outcome.

**Discussion**

The main findings of the present study in acute patients with spontaneous ICH are: (1) the circulating levels of MMP-3 are correlated with absolute PHE volume; (2) increased levels of MMP-3 and MMP-9 at admission are independent predictors of poor clinical outcome; and (3) no association of the investigated markers (MMP-3, MMP-9, VEGF, and Ang-1) with clinical outcome compared with those with favorable outcome. As a result, MMP-3 ≥12.4 pg/mL (OR, 25.3; P=0.035), MMP-9 ≥192.4 pg/mL (OR, 68.9; P=0.023), and National Institutes of Health Stroke Scale score at baseline (OR, 1.7; P=0.005) were identified as independent predictors of unfavorable 90-day outcome.
Table 2. Radiological Characteristics and Marker Levels Grouped by Presence of Cytotoxic Edema

<table>
<thead>
<tr>
<th>Radiological Data</th>
<th>Patients Without Cytotoxic Edema (n=23)</th>
<th>Patients With Cytotoxic Edema (n=36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep location of hematoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraventricular hemorrhage extension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline hematoma volume, ml</td>
<td>6.9 [2.8–12.5]</td>
<td>14.7 [7.7–25.1]</td>
<td>0.011*</td>
</tr>
<tr>
<td>Baseline PHE volume, ml</td>
<td>4.7 [0.1–9.3]</td>
<td>8.0 [4.7–16.3]</td>
<td>0.010*</td>
</tr>
<tr>
<td>Time to follow-up MRI, h</td>
<td>78.6±13.1</td>
<td>76.6±11.0</td>
<td>0.237</td>
</tr>
<tr>
<td>Hematoma volume on day 3, ml</td>
<td>7.6 [2.9–17.5]</td>
<td>21.1 [10.0–41.3]</td>
<td>0.001*</td>
</tr>
<tr>
<td>PHE volume on day 3, ml</td>
<td>20.3 [6.9–40.9]</td>
<td>52.1 [28.7–98.6]</td>
<td>0.001*</td>
</tr>
<tr>
<td>Relative PHE on day 3</td>
<td>3.0 [2.4–3.9]</td>
<td>2.7 [2.0–3.5]</td>
<td>0.359</td>
</tr>
<tr>
<td>MMP-3, ng/mL</td>
<td>9.5 [6.0–21.0]</td>
<td>11.1 [8.0–20.8]</td>
<td>0.484</td>
</tr>
<tr>
<td>MMP-9, ng/mL</td>
<td>140.2</td>
<td>139.6</td>
<td>0.938</td>
</tr>
<tr>
<td>VEGF, pg/mL</td>
<td>341.8</td>
<td>302.5</td>
<td>0.446</td>
</tr>
<tr>
<td>Ang-1, ng/mL</td>
<td>28.3 [22.5–34.8]</td>
<td>25.7 [20.5–35.0]</td>
<td>0.524</td>
</tr>
</tbody>
</table>

Data are expressed as n (%), mean±SD, or median [IQR] as appropriate. Noncontrast CT scan was performed on baseline and MRI on day 3. Studied molecules were measured from blood withdrawals at baseline.

Ang indicates angiopoietin; MMP, matrix metalloproteinase; PHE, perihematomal edema; and VEGF, vascular endothelial growth factor.

*P<0.05 was considered significant.

Previous studies showed increased MMP-9 levels in patients who developed hematoma expansion and neurological deterioration after ICH. Increased MMP-9 levels on admission were reported to be associated with mortality in ICH patients, both MMP-3 and MMP-9, with the residual scar volume at 3 months.27 Our study confirmed a significant role of the MMPs in the pathology after ICH because both MMP-3 and MMP-9 were associated with unfavorable 90-day outcome independent of hematoma volume and stroke severity at baseline. Therefore, targeting MMPs for preventing unfavorable clinical outcome might be a potential strategy in ICH treatment.

CE is defined as a premorbid cellular process, which can either be reversed or develop into necrotic cell death. However, the existence of CE in ICH is controversially discussed. Some previous DWI studies showed that ADC values increased globally in the perihematomal region. Other studies observed a decrease of ADC in the perihematomal area in part of the patients in the hyper-acute stage (<6 hours) until day 6 postictus, and therefore suggested the presence of CE in ICH. CE surrounding the hematoma was detected in the ultraearly stage after ICH in 2 MRI studies. Kidwell et al visualized a rim of perihematomal decreased ADC values within 6 hours in 3 among 12 patients with ICH. Schellinger et al detected CE in 7 among 32 patients within 6 hours after ICH onset. Patients with CE tended to develop poor clinical outcome. Carhuapoma et al found 1 among 9 patients with a decreased ADC on day 6. Recently, Olivot et al examined 23 ICH patients within 3 days after symptom onset. They found that two-thirds of the patients exhibited patchy regions with increased diffusivity mixed with reduced diffusion in the perihematomal region. This is in line with our data. We detected CE in a similar proportion of patients (61%) on day 3. Instead of an association of CE with the MMP and GF levels, we found that CE was highly correlated with the hematoma volume. We therefore hypothesize that this secondary brain cell injury is likely a consequence of the primary mass effect, or caused by cytotoxic molecules, which are released from the clot or the destroyed brain parenchyma.

VEGF and Ang-1 levels were found to be related to BBB disruption and brain edema in animal models of ICH and brain injury. In a clinical ICH study, high levels of VEGF and Ang-1 at 72 hours after symptom onset were associated with good functional outcome and reduced lesion volume. In our study, neither VEGF nor Ang-1 were associated with PHE or clinical outcome. This could be a result of the different time points of GFs assessment.

Our study has some limitations. Overall, the sample size is small. However, considering the fact that MRI was used, and thus the best available method to quantify PHE, this study includes a relatively high number of cases. Second, our findings cannot be generalized to patients with coma on admission and to those noneligible for MRI. Particularly in patients with large hematomas who were not eligible for this study according to the exclusion criteria, pronounced CE and larger PHE volume can be expected. Third, we only investigated molecular marker levels on baseline, although after ICH significant changes over time were reported.

In conclusion, our data show that MMP-3 levels are associated with perihematomal edema in acute spontaneous ICH patients. Increased levels of MMP-3 and MMP-9 are independently associated with poor clinical outcome. Further investigations are needed to explain the mechanisms behind them, which might lead to treatment options for the prevention of secondary brain damage and unfavorable outcome.

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Disclosures
None.

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