Brush Sign on 3-T T2*-Weighted MRI as a Potential Predictor of Hemorrhagic Transformation After Tissue Plasminogen Activator Therapy

Yuka Terasawa, MD; Nobuaki Yamamoto, MD; Ryoma Morigaki, MD; Koji Fujita, MD; Yuishin Izumi, MD, PhD; Junichiro Satomi, MD, PhD; Masafumi Harada, MD, PhD; Shinji Nagahiro, MD, PhD; Ryuji Kaji, MD, PhD

Background and Purpose—The brush sign (BS) is the enlargement of medullary veins on 3-T T2*-weighted MRI seen in patients with ischemic stroke because of major cerebral artery occlusion. However, the clinical relevance of BS in patients with acute stroke remains unclear. We assessed the correlation between detecting BS with the development of hemorrhagic transformation after intravenous thrombolysis.

Methods—We enrolled consecutive patients with M1 or M2 occlusion treated with intravenous tissue plasminogen activator. We classified the patients into 2 groups: the group positive for BS (P-BS) and the group negative for BS (N-BS). We investigated the differences in MRI findings and the clinical outcome between the 2 groups.

Results—The subjects consisted of 36 patients (19 men; mean age, 74.7 years). Twenty-one patients (58%) had M1 occlusion, and 15 (42%) had M2 occlusion. Twenty-five patients (69%) were classified into the P-BS group and 11 (31%) into the N-BS group. Recanalization was observed in 15 (60%) and 10 (90%) patients in the P-BS and N-BS groups, respectively (P=0.116). Hemorrhagic transformation on MRI was observed more frequently in the P-BS group than in the N-BS group (64% versus 18%; P=0.027). A good outcome (mRS, 0–1) at discharge was found in 24% of patients in the P-BS group and in 45% of patients in the N-BS group (P=0.152). A multivariate logistic regression analysis revealed that the presence of BS (odds ratio, 9.08; 95% confidence interval, 1.4–59.8; P=0.022) was independently associated with hemorrhagic transformation.

Conclusions—BS may predict the development of hemorrhagic transformation in patients with acute stroke treated with intravenous tissue plasminogen activator. (Stroke. 2014;45:274-276.)

Key Words: brush sign ■ magnetic resonance imaging ■ T2* weighted image ■ tissue plasminogen activator

The brush sign (BS) is the hypointensity of medullary veins detected on 3-T T2*-weighted MRI. BS is reported to be seen in patients with acute ischemic stroke because of major cerebral artery occlusion and may predict ischemic penumbra.1 Morita et al1 reported that 96% of patients with major vessel occlusion who underwent 3-T MRI within 12 hours of stroke onset had BS. Previous reports suggest that BS may show ischemic penumbra and that patients who have BS are likely to become worse before discharge. In another report about patients in the chronic phase of Moyamoya disease, BS was reported to predict the severity of ischemia.2 However, in patients with hyperacute stroke, the proportion of patients with BS and the clinical relevance of BS in terms of the prognosis and treatment remain unclear. We consider 2 contradictory hypotheses about BS in patients with hyperacute ischemic stroke before performing revascularization procedures: the presence of BS is good and the presence of BS is a bad sign. If BS shows ischemic penumbra, it is likely to improve after recanalization. However, if BS reveals strong ischemia, it is not likely to improve.

In this study, we evaluated whether detection of BS in patients with hyperacute stroke before intravenous (IV) thrombolysis was correlated with the rate of complications or the prognosis.

Materials and Methods

Patients and Clinical Protocol

We prospectively studied consecutive patients with acute anterior circulation ischemic stroke treated with tissue plasminogen activator (t-PA) within 3 hours of stroke onset between October 2005 and December 2011 in our hospital. The inclusion and exclusion criteria for IV t-PA were used in accordance with the Japan Alteplase Clinical Trial.3 The clinical data were obtained for all patients (details are provided in the online-only Data Supplement).

Received June 26, 2013; accepted September 10, 2013.

From the Department of Clinical Neuroscience (Y.T., N.Y., K.F., Y.I., R.K.), Department of Neurosurgery (R.M., J.S., S.N.), and Department of Radiology (M.H.), The University of Tokushima, Tokushima, Japan.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.002640/-/DC1.

Correspondence to Yuka Terasawa, MD, Department of Clinical Neuroscience, Institute of Health Biosciences, Graduate School of Medicine, University of Tokushima, 3-18-15, Kuramoto-cho, Tokushima City 770-8503, Japan. E-mail tera@clin.med.tokushima-u.ac.jp

© 2013 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.113.002640

274
MRI Protocol
We included patients who underwent an MRI study on a 3-T imaging system (Signa 3T HDxt; GE Healthcare, Milwaukee, WI) before t-PA infusion. We performed follow-up MRI using 3-T MRI within 24 hours after t-PA therapy with the same protocol as the first MRI. Further details are provided in the online-only Data Supplement. On initial magnetic resonance angiography, we only included the middle cerebral artery (M1 and M2) occluded patients. We defined recanalization on follow-up magnetic resonance angiography as modified Mori grades 2 and 3 and no recanalization as modified Mori grades 0 and 1.4 On initial T2* imaging, we assessed patients for the presence of BS. BS was defined as follows according to a previous article1: an asymmetrical hypointense area along the course of the subependymal and medullary veins in the deep white matter (Figure 1A and 1B).

Hemorrhagic transformation (HT) was defined as the new appearance of low-intensity lesions on the follow-up T2*-weighted image compared with the initial T2* images.

We classified all patients into 2 groups according to the presence of BS: the patients with BS (P-BS) and the patients without BS (N-BS). First, we investigated the differences in the clinical characteristics and MRI findings (recanalization and HT) between the 2 groups. Next, we examined the risk factors for HT after IV t-PA.

Statistical Analysis
The significance of intergroup differences was assessed using the Fisher exact test for categorical variables and the Mann–Whitney U test for continuous variables. Further details are provided in the online-only Data Supplement.

Results
We performed IV t-PA for 100 patients. Nine patients had posterior circulation strokes. We did not perform MRI in 2 patients with pacemakers and performed 1.5-T MRI in 4 patients. Of the remaining 85 patients, 22 patients had no major vessel occlusion, and we could not accurately evaluate the lesion responsible for the occlusion in 8 patients with body motion artifacts. Also after excluding patients with internal carotid artery occlusion, 36 patients (19 men [53%]; mean age, 74.7±10.6 years) were enrolled in the present study. Of these 36 patients, 25 (69%) were classified into the P-BS group and 11 (31%) into the N-BS group. There were no significant differences between the P-BS and N-BS groups in terms of the baseline characteristics (online-only Data Supplement), including the National Institutes of Health Stroke Scale (NIHSS; median NIHSS on admission, 14.2 versus 13.5; P=0.685).

Twenty-one patients (58%) had M1 occlusions, and 15 (42%) had M2 occlusions. Recanalization was observed in 15 (60%) patients in the P-BS group and 10 (90%) patients in the N-BS group (P=0.116) at 24 hours after t-PA. HT occurred in 18 (50%) patients and was observed more frequently in the P-BS group than in the N-BS group (64% versus 18%; P=0.027; Figure 2). The proportion of patients with a good outcome (mRS, 0–1) at discharge tended to be lower in the P-BS group than in the N-BS group (24% versus 45%; P=0.152; Figure in the online-only Data Supplement).

The variables related to HT in the univariate analysis were the initial NIHSS, cardioembolic stroke, and positive BS (data not shown). The results of the multivariate logistic regression analysis are presented in the Table. A positive BS (odds ratio, 9.08; 95% confidence interval, 1.4–59.8; P=0.022) was found to be independently associated with HT in patients who received IV t-PA therapy (Table).

Discussion
In this article, we first demonstrated that patients who had BS before t-PA therapy tended to have HT. Intracranial hemorrhage is the most common and critical complication after t-PA therapy.5–7 Recently, there were several reports that asymptomatic hemorrhage was not truly asymptomatic.8,9 Therefore, it is important to predict HT. Cardioembolic stroke,5 recanalization,5 ischemic lesion volume,1 baseline systolic blood pressure, and hyperglycemia were previously reported to be the risk factors for HT after IV t-PA therapy. As previously reported, cardioembolic stroke and recanalization were related to HT,
but ischemic lesion volume, a well-established predictor of HT, was not related in our cohort. The reason is that we included only M1 or M2 (excluded internal carotid artery) occluded patients, and all patients have ≥6 DWI ASPECTS (Alberta Stroke Program Early CT Score on diffusion-weighted imaging). The multivariate analysis showed that BS is the most significantly related factor.

BS is considered to be caused by the same mechanism as the blood oxygen level–dependent phenomenon as a result of a relative increase in IV deoxyhemoglobin.1310 The previous report revealed that BS showed ischemic penumbra and provided the information about reversible regions of ischemia.1 Therefore, we expected that patients with BS would have a good outcome after recanalization because they have penumbra. However, the prognosis of P-BS patients seemed to be worse than that of N-BS patients, contrary to our expectations. One reason for these findings was that the patients in the P-BS group was likely to have M1 occlusion more frequently than those in the N-BS group (68% versus 36%; P=0.141, not significant), and the recanalization rate was lower in the P-BS group than in the N-BS group (60% versus 90%; P=0.116, not significant). Another reason was that patients in the P-BS group experience HT more frequently than those in the N-BS group. Our study included only patients with hyperacute ischemic stroke within 3 hours of onset. We speculate that patients who had BS even in the hyperacute phase were likely to have more severe ischemia and more fragile tissue than patients without BS, and more active oxygen may exist in the area with BS. Therefore, HT was more frequently seen in patients with BS, who had more damage from ischemia, than in patients without BS.

Recently, the indication for t-PA therapy was expanded to 4.5 hours after stroke onset.10 Our study included only patients treated within 3 hours. It is unclear whether the patients who are treated from 3 to 4.5 hours after onset and have BS on their MRI before t-PA therapy are more likely to have HT. Future studies will be needed to assess these patients.

The present study has several limitations. This is a single-center and small cohort study. To confirm our results, further studies including larger cohorts will be needed. Second, we excluded patients with internal carotid artery occlusion because we performed endovascular therapy if they had no recanalization after t-PA therapy. Therefore, another study about patients with internal carotid artery occlusion and endovascular therapy should also be performed.

In conclusion, 69% of patients have BS on 3-T T2*-weighted MRI examined within 3 hours after stroke onset, and the presence of BS predicts the development of HT after IV t-PA therapy.

Table. Multivariate Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brush sign</td>
<td>9.08</td>
<td>1.380–59.772</td>
<td>0.022</td>
</tr>
<tr>
<td>Cardioembolic stroke</td>
<td>3.50</td>
<td>0.529–23.115</td>
<td>0.194</td>
</tr>
<tr>
<td>Recanalization</td>
<td>1.04</td>
<td>0.179–5.999</td>
<td>0.969</td>
</tr>
<tr>
<td>DWI ASPECTS &lt;7</td>
<td>0.83</td>
<td>0.133–5.169</td>
<td>0.840</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>0.63</td>
<td>0.110–3.588</td>
<td>0.629</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; DWI ASPECTS, Alberta Stroke Program Early CT Score on diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

Disclosures

None.

References

Brush Sign on 3-T T2*-Weighted MRI as a Potential Predictor of Hemorrhagic Transformation After Tissue Plasminogen Activator Therapy
Yuka Terasawa, Nobuaki Yamamoto, Ryoma Morigaki, Koji Fujita, Yuishin Izumi, Junichiro Satomi, Masafumi Harada, Shinji Nagahiro and Ryuji Kaji

Stroke. 2014;45:274-276; originally published online October 30, 2013;
doi: 10.1161/STROKEAHA.113.002640
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
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:
http://stroke.ahajournals.org/content/45/1/274

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/10/29/STROKEAHA.113.002640.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
SUPPLEMENTAL MATERIAL

The Brush Sign on 3-Tesla T2*-Weighted MRI as a Potential Predictor of Hemorrhagic Transformation After t-PA Therapy

Yuka Terasawa¹ MD, Nobuaki Yamamoto¹ MD, Ryoma Morigaki² MD, Koji Fujita¹ MD, Yuishin Izumi¹ MD, PhD, Junichiro Satomi² MD, PhD, Masafumi Harada³ MD, PhD, Shinji Nagahiro² MD, PhD, Ryuji Kaji¹ MD, PhD.

Materials and methods
1. Patients and clinical protocol
The clinical data obtained for all patients; 1) age and gender, 2) arterial blood pressure before IV t-PA, 3) NIHSS score before and 1 and 24 hr and 7 days after IV t-PA, 4) presence of arterial occlusion on MRA before IV t-PA, 5) presence or absence of recanalization of occluded arteries within 24 h after IV t-PA, 6) vascular risk factors, including hypertension (HT), diabetes mellitus (DM) and hyperlipidemia (HL), 7) presence of potential cardiac sources of emboli, 8) presence of significant arterial stenosis, 9) presence of right-to-left shunt as a cause of paradoxical embolism as detected using transcranial Doppler (TCD), 10) stroke subtype according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria¹, 11) laboratory parameters before IV t-PA, 12) administration of antiplatelet agents or anticoagulation before onset and 13) modified Rankin scale (mRS) 90 days after IV t-PA.

2. Magnetic resonance imaging protocol
We performed the initial magnetic resonance imaging (MRI) studies of all patients before t-PA infusion. Most of the patients underwent a MRI study on a 3-Tesla imaging system (Signa 3T HDxt; GE Healthcare, Milwaukee, WI, USA). In this study, we excluded the patients we couldn’t examined initial MRI or were examined with a 1.5-Tesla MRI. The neuroimaging protocol for acute stroke in our hospital included DWI, MRA and T2*WI. We performed follow-up MRI using 3.0-Tesla MRI within 24 hours after t-PA therapy with the same protocol as first MRI. The imaging sequence and parameters were: T2*WI gradient echo sequence (T2*WI): TR/TE 400/28 ms, flip angle 25°, slice thickness/gap (mm) 6/1.5; diffusion-weighted echo-planar spin-echo images (DWI): TR/TE 10000/71.5 ms, b value 1000 s/mm², slice thickness/gap (mm) 5/1 and MRA: TR/TE 30/3.9 ms, flip angle 15°, slice thickness 12.4 mm, overlap 4 mm.
On initial MRA, we assessed the presence of major arterial occlusion. Occlusion was searched for in the internal carotid artery (ICA) and middle cerebral artery (M1 and M2). We excluded the patients who had no occluded vessels on MRA or in whom we were unable to assess the lesion of occlusion because of the presence of an artifact. We defined recanalization on MRA as Modified Mori Grades 2 and 3, and no recanalization as Modified Mori Grade 0 and 1.2.

On initial T2* imaging, we assessed the patients for the presence of the brush sign (BS). The BS was defined as follows according to a previous paper 3: an asymmetrical hypointense area along the course of the subependymal and medullary vein in the deep white matter (Figure 1A, B). Two physicians, a neurologist and a neurosurgeon, independently assessed the images for the presence of the BS. The intra-observer concordance rate was 0.95. Hemorrhagic transformation was defined as the new appearance of low intensity lesions on the follow-up T2*-WI compared to the initial T2* images.

3. Statistical analysis

The significance of inter-group differences was assessed using Fisher’s exact test for categorical variables and the Mann-Whitney U test for continuous variables. The statistical analysis was performed using the SPSS ver. 2 software program (Statistical Package for the Social Sciences, Inc. Chicago, IL). A multivariate logistic regression analysis was performed to identify the independent factors associated with hemorrhagic transformation. Variables with a value of p<0.2 in the univariate analysis were included in the multivariate model.

References
2. Mori E, Minematsu K, Nakagawara J, Yamaguchi T, Sasaki M, Hirano T. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan alteplase clinical trial ii (j-act ii). Stroke.41:461-465
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>P-BS</th>
<th>N-BS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=36</td>
<td>n=25</td>
<td>n=11</td>
<td>p</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>19 (53)</td>
<td>13 (52)</td>
<td>6 (55)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>74.7±10.6</td>
<td>75.2±10.8</td>
<td>73.5±10.5</td>
<td>1.000</td>
</tr>
<tr>
<td>Time from onset to treatment, min</td>
<td>142.0±30.6</td>
<td>141.3±30.2</td>
<td>143.6±33.0</td>
<td>0.919</td>
</tr>
<tr>
<td>Past history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (AF), n (%)</td>
<td>23 (64)</td>
<td>16 (64)</td>
<td>7 (64)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>22 (61)</td>
<td>16 (64)</td>
<td>6 (54)</td>
<td>0.716</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>5 (14)</td>
<td>3 (12)</td>
<td>2 (18)</td>
<td>0.631</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>11 (31)</td>
<td>7 (28)</td>
<td>4 (36)</td>
<td>0.703</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>2 (6)</td>
<td>1 (4)</td>
<td>1 (9)</td>
<td>0.524</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>12 (33)</td>
<td>9 (36)</td>
<td>4 (36)</td>
<td>0.715</td>
</tr>
<tr>
<td>Alcohol, n (%)</td>
<td>11 (30)</td>
<td>7 (28)</td>
<td>4 (36)</td>
<td>0.703</td>
</tr>
<tr>
<td>Initial NIHSS score</td>
<td>14±5</td>
<td>14.2±5.4</td>
<td>13.5±5</td>
<td>0.685</td>
</tr>
<tr>
<td>DWI-ASPECTS</td>
<td>8±2</td>
<td>8±2</td>
<td>9±1.5</td>
<td>0.261</td>
</tr>
<tr>
<td>Occluded artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>21 (58)</td>
<td>17 (68)</td>
<td>4 (36)</td>
<td>0.141</td>
</tr>
<tr>
<td>M2</td>
<td>15 (42)</td>
<td>8 (32)</td>
<td>7 (64)</td>
<td>0.141</td>
</tr>
<tr>
<td>Recanalization, n (%)</td>
<td>25 (69)</td>
<td>15 (60)</td>
<td>10 (90)</td>
<td>0.116</td>
</tr>
<tr>
<td>Stroke Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic stroke, n (%)</td>
<td>25 (69)</td>
<td>18 (72)</td>
<td>7 (64)</td>
<td>0.703</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>24.1±3.7</td>
<td>24.3±3.5</td>
<td>23.7±4.4</td>
<td>0.233</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>157.3±22.1</td>
<td>157.9±23.6</td>
<td>155.0±19.1</td>
<td>0.946</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb A1c, %</td>
<td>5.7±0.6</td>
<td>5.6±0.5</td>
<td>5.7±0.8</td>
<td>0.917</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>137.7±52.2</td>
<td>139.9±61.1</td>
<td>132.3±20.2</td>
<td>0.642</td>
</tr>
<tr>
<td>Platelets</td>
<td>23.2±7.6</td>
<td>22.8±5.3</td>
<td>26.9±10.6</td>
<td>0.396</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>118.6±19.5</td>
<td>118.9±19.9</td>
<td>118.2±20.1</td>
<td>1.000</td>
</tr>
<tr>
<td>Ddimer</td>
<td>4.4±10.2</td>
<td>5.1±11.6</td>
<td>1.8±1.8</td>
<td>0.889</td>
</tr>
</tbody>
</table>
Fig. The proportion of patients with a good outcome at discharge

Patients in the N-BS group were more likely to have a better outcome than those in the P-BS group (mRS0-1; 45% in N-BS vs 24% in P-BS; p=0.152).