Effect of Insular Injury on Autonomic Functions in Patients With Ruptured Middle Cerebral Artery Aneurysms

Joji Inamasu, MD; Keiko Sugimoto, PhD; Eiichi Watanabe, MD; Yoko Kato, MD; Yuichi Hirose, MD

Background and Purpose—Insular injuries are known to cause autonomic derangements. Patients with ruptured middle cerebral artery aneurysms frequently develop temporal hematomas (THs) in addition to subarachnoid hemorrhages, and those with TH may sustain autonomic derangements more frequently than those without TH. Hemispheric lateralization in autonomic derangements has been reported in patients with insular ischemic stroke, and this study was conducted to clarify whether such lateralization was also observed in patients with TH resulting from middle cerebral artery aneurysm rupture.

Methods—A retrospective analysis on the medical records of 79 patients with ruptured middle cerebral artery aneurysms was performed on the basis of lateralization and presence of TH. They were quadrichotomized as left TH+ (LTH+; n=17), right TH+ (n=25), left TH− (n=15), and right TH− (n=22). Comparisons, mainly between LTH+ and right TH+, were made on demographic variables, autonomic/cardiac parameters, plasma catecholamines and glucose levels, and outcomes.

Results—There were no significant differences in demographic or cardiac parameters between the 2 groups. Systolic blood pressures were lower in LTH+ (139±34 versus 174±47 mmHg; P=0.05). The LTH+ group also tended to be more bradycardiac (80±19 versus 101±22 bpm; P=0.13). The LTH+ group exhibited significantly lower plasma norepinephrine (1008±975 versus 2549±2133 pg/mL; P=0.03) and glucose levels (9.3±1.8 versus 12.2±4.5 mmol/L; P=0.04). However, in-hospital mortality did not differ significantly (41% versus 44%; P=1.00).

Conclusions—Lateralization of autonomic derangements observed might not have had a significant effect on the outcomes. Nevertheless, autonomic derangements associated with insular injury should be considered in the management of subarachnoid hemorrhage patients with TH. (Stroke. 2013;44:3550-3552.)

Key Words: autonomic derangement ■ catecholamine ■ intracranial aneurysm ■ insula

Association between insular injury and autonomic derangements has been studied extensively in patients with ischemic stroke, and there seems to be hemispheric laterality in the autonomic derangements.1,2 On the other hand, such studies have rarely been conducted in patients with aneurysmal subarachnoid hemorrhage (SAH). The middle cerebral artery (MCA) bifurcation aneurysms are anatomically unique because they are located adjacent to the insula. Ruptured MCA aneurysms frequently cause temporal hematomas (THs), and resultant insular injury may cause autonomic derangements. This study was conducted with an aim to clarify whether lateralization of autonomic derangements was observed in SAH patients with TH and whether the lateralization influenced the outcomes. Stroke-induced autonomic derangements have been attributed to systemic release of catecholamines.3 The second aim of this study was to investigate whether hemispheric lateralization in plasma catecholamines was observed in SAH patients with TH.

Methods

Patients

Between January 2009 and December 2012, 86 patients with ruptured MCA aneurysms were admitted. They underwent surgical obliteration of aneurysms unless they were considered unfit for surgery. For patients surviving to discharge, activities of daily living were evaluated 90 days after onset using the modified Rankin Scale score. Medical records of the 79 patients admitted within 24 hours of onset were reviewed. They were quadrichotomized on the basis of lateralization and presence of TH: left MCA aneurysm with/without TH (LTH+; n=17), right MCA aneurysm with/without TH (RTH+; n=25/RTH−, n=22). Hematoma volumes were calculated using the ABC/2 method.4 The χ²/Fisher exact tests were used for comparison of categorical variables. Unpaired t test was used for comparison of continuous variables, and 1-way ANOVA with Bonferroni correction was used for 4-group comparison. JMP software (SAS Institute; Cary, NC) was used for statistical analysis. Data are indicated by mean±SD, and P<0.05 was considered statistically significant. The study protocol was approved by institutional internal review board, and informed consent was obtained from patients’ surrogates.

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levels in LTH+ were significantly lower than those in RTH+ (100±875 versus 254±2133 pg/mL; \( P = 0.03 \); Figure 2A). The plasma epinephrine levels in LTH+ tended to be lower than those in RTH+ (150±180 versus 352±327 pg/mL; \( P = 0.12 \); Figure 2B). The blood glucose levels in LTH+ were significantly lower than those in RTH+ (9.3±1.8 versus 12.2±4.5 mmol/L; \( P = 0.04 \); Figure 2C). No significant intergroup differences in any cardiac parameters were observed (Table). The in-hospital mortality rates did not differ significantly (41% in LTH+ versus 44% in RTH+; \( P = 1.00 \)). Similarly, the frequency of patients with a 90-day modified Rankin Scale score ≤3 did not differ significantly (29% in LTH+ versus 23% in RTH+; \( P = 0.71 \)).

**Discussion**

This is probably the first clinical study to evaluate association among TH, autonomic/cardiac parameters, and plasma catecholamine levels in patients with SAH. Elevated systolic blood pressure and tachycardia in RTH+ group (Figure 1) might be attributable to the increased catecholamine levels (Figure 2). Although the etiopathogenesis of the catecholamine increase remains unclear, anatomic asymmetry of the subcortical catecholaminergic pathways may be involved.2 There were no significant intergroup differences in left ventricular ejection fraction or ECG finding, and the elevated systolic blood pressure might be because of increased cardiac output after tachycardia and by norepinephrine-induced increase in peripheral vascular resistance.

Another important finding was that blood glucose levels were significantly elevated in RTH+ (Figure 2C). Insular injury was independently associated with hyperglycemia in 31 patients with ischemic stroke.4 Christensen6 reported that blood glucose levels were nonsignificantly higher in ischemic stroke patients with right-sided insular injury. Patients with SAH develop hyperglycemia more frequently than patients with ischemic stroke,6 probably because of higher plasma catecholamine levels in the former. The number of patients with diabetes mellitus did not differ significantly, and higher epinephrine levels in the latter might be responsible for the hyperglycemia.

There are several limitations to this study. First, despite the autonomic lateralization, the outcomes (in-hospital mortality/frequency of patients with a 90-day modified Rankin Scale score ≤3) did not differ significantly between LTH+ and RTH+.

**Clinical/Laboratory Parameters**

Systolic/diastolic blood pressures and heart rates were analyzed only before implementation of antihypertensive therapy because most patients underwent intensive blood pressure reduction to prevent aneurysmal rebleeding. Plasma norepinephrine and epinephrine levels were measured using high-performance liquid chromatography. ECGs were evaluated for the presence of cardiac arrhythmia and any ECG changes. Transthoracic echocardiography was obtained using a General Electric Vivid 7 (GE Healthcare; Tokyo, Japan). Systolic function was evaluated using the left ventricular ejection fraction.

**Table. Demographics and Cardiac Parameters**

<table>
<thead>
<tr>
<th></th>
<th>LTH+ (n=17)</th>
<th>RTH+ (n=25)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.9±10.3</td>
<td>68.0±10.6</td>
<td>0.37</td>
</tr>
<tr>
<td>Male:female</td>
<td>6:11</td>
<td>8:17</td>
<td>1.00</td>
</tr>
<tr>
<td>WFNS grade IV/V, %</td>
<td>82</td>
<td>84</td>
<td>1.00</td>
</tr>
<tr>
<td>Hematoma volume, mL</td>
<td>Range: 17–99</td>
<td>Range: 16–102</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Mean: 38±22</td>
<td>Mean: 42±23</td>
<td></td>
</tr>
<tr>
<td>History of heart diseases, %</td>
<td>0</td>
<td>4</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>6</td>
<td>8</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiac arrhythmias, %</td>
<td>24</td>
<td>32</td>
<td>0.73</td>
</tr>
<tr>
<td>ECG abnormalities, %</td>
<td>71</td>
<td>76</td>
<td>0.97</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>66±12</td>
<td>62±14</td>
<td>0.34</td>
</tr>
</tbody>
</table>

LTH+ indicates left middle cerebral artery aneurysm with temporal hematoma; LVEF, left ventricular ejection fraction; LVWMA, left ventricular wall motion abnormality; RTH+, right middle cerebral artery aneurysm with temporal hematoma; and WFNS, World Federation of Neurosurgical Societies.

**Results**

Of the 79 patients admitted, 29 were men and 50 were women (mean, 63.3±11.9 years of age). There were no significant differences in the demographics, including age, sex, frequency of World Federation of Neurosurgical Societies grade IV/V SAH, or mean hematoma volumes, between LTH+ and RTH+ groups (Table). Systolic blood pressures in LTH+ were lower compared with those in RTH+ with marginal significance (139±34 versus 174±47 mm Hg; \( P = 0.05 \); Figure 1A). By contrast, there was no significant difference in diastolic blood pressures between LTH+ and RTH groups (Figure 1B). Heart rates in LTH+ were lower than those in RTH+, although the difference was not significant (80±19 versus 101±22; \( P = 0.13 \)). The plasma norepinephrine

![Figure 1.](image-url)
groups. Many patients with TH succumbed to SAH-induced brain damage, and vigorous medical intervention to correct hyperglycemia might not have improved their outcomes. Second, autonomic derangements may differ depending on which portion of the insula is injured. The insula is not a uniform structure, and injury to the anterior versus posterior portion of the insula results in different deficits. The size of TH was large in many patients, and the derangements may have reflected injury to the entire insula. Finally, not all studies support the hypothesis of autonomic hemispheric lateralization. We acknowledge that further studies are necessary to verify our findings based on a retrospective observational study. We intentionally avoided direct comparisons between TH+ and TH− groups; instead, we focused on clarifying hemispheric differences. The SAH severity and hematoma volumes were similar between LTH+ and RTH+, and comparisons between the 2 groups should be valid.

In conclusion, autonomic derangements in ruptured MCA aneurysm patients with TH were influenced by hemispheric lateralization, in which right-sided hematomas had greater effect. Moreover, right TH was associated with hyperglycemia more frequently. The autonomic derangements observed may be attributable to increased plasma catecholamine levels associated with right insular injury. Autonomic derangements associated with insular injury should be considered in the management of SAH patients with TH.

Disclosures

None.

References

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