Role of Platelet Function in Symptomatic Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage

Hiroki Ohkuma, MD; Shigeharu Suzuki, MD; Masahide Kimura, MD; and Eiji Sobata, MD

To evaluate the role of platelet function in the pathogenesis of cerebral vasospasm, we compared sequential changes of platelet aggregability and \( \beta \)-thromboglobulin and thromboxane \( \text{B}_2 \) concentrations in blood samples from the internal jugular and peripheral veins of 13 patients with aneurysmal subarachnoid hemorrhage. Platelet function in blood from the internal jugular vein tended to be enhanced during days 0–1 but recovered to the normal range during days 2–4. After day 5, platelet function showed various patterns depending on the presence of symptomatic vasospasm. In patients without symptomatic vasospasm, sequential changes were relatively minor, with normal or slightly high values. Patients with symptomatic vasospasm already showed high platelet aggregability during the early stage of vasospasm. The concentration of \( \beta \)-thromboglobulin increased several days after the onset of vasospasm, reaching 80 ng/ml or more in patients with a poor prognosis. Two of the five patients with symptomatic vasospasm showed markedly high concentrations of thromboxane \( \text{B}_2 \) after day 8. These results suggest that vasospasm activates platelets and promotes aggregability and that the resulting increased tendency for thrombus formation may affect the patient’s prognosis during the advanced stage. (Stroke 1991;22:854–859)

The pathogenesis of symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage (SAH) has not yet been fully clarified, but, to date, arterial luminal narrowing has most often been considered to cause cerebral ischemia. However, since angiographic vasospasm does not always correlate with cerebral ischemic symptoms or cerebral blood flow,\(^1\)–\(^3\) other factors such as intravascular components may also affect cerebral ischemia.\(^4\)–\(^7\) Endothelial damage and adhesion of aggregated platelets to the luminal surface are often observed histopathologically in vessels showing vasospasm.\(^8\)–\(^11\) Therefore, the platelet system in particular is believed to play an important role in this pathological state by the formation of microthrombi in cerebral peripheral vessels\(^12\) and by the synthesis of thromboxane \( \text{A}_2 \) (\( \text{TXA}_2 \)).\(^14\)–\(^19\)

However, serial changes of platelet function following SAH\(^6\),\(^7\) and their correlation with ischemic symptoms in patients with symptomatic cerebral vasospasm have not yet been evaluated in detail. To investigate this role, we conducted clinical studies to look at the evaluation period, sites of blood sampling, and measurement items.

Subjects and Methods

Our subjects consisted of 13 patients with ruptured cerebral aneurysms who were admitted \( \leq \)48 hours after the onset of SAH and who showed a high-density area in the subarachnoid space (group 3 according to the classification of Fisher et al\(^20\) on the initial computed tomograms. The patients’ clinical grades according to the World Federation of Neurological Surgeons scale\(^21\) were II or III (Table 1). No patient was given antiplatelet drugs, and none received calcium antagonists just prior to SAH. When symptomatic cerebral vasospasm occurred, the patients were receiving intravascular volume expansion and, in postoperative patients (cases 9, 11, and 13), induced arterial hypertension.\(^22\) Patients were considered to have symptomatic vasospasm when ischemic neurological deficits such as disturbance of consciousness or motor and speech impairment occurred between days 4 and 9 after SAH (day 0 being the day of aneurysmal rupture). Other causes for neurological deficits such as rebleeding, hydrocephalus, metabolic disturbances, or surgical complications were excluded.\(^23\)

The controls consisted of 22 age-matched healthy individuals (mean \( \pm \)SD age 49 \( \pm \)12 years).
The evaluation period was approximately 2 weeks after SAH. Blood was drawn into a disposable polyethylene syringe with a 22-gauge needle from a peripheral vein and the internal jugular vein simultaneously at 3-day intervals after admission, and, if possible, from the superior sagittal sinus during surgery (cases 2, 9, 11, and 13). We collected blood from the internal jugular vein in addition to the peripheral vein because the former is closer to the intracranial lesion and might reflect the pathological status better. Evaluation items were platelet aggregability as a basis for platelet function; the concentration of \( \beta \)-thromboglobulin (\( \beta \)-TG), which is contained in the \( \alpha \) granules of platelets and released into the plasma with disintegration or strong aggregation of the platelets and is considered to reflect the pathological status better; and the concentration of thromboxane \( \beta_2 \) (TXB2), which is a stable metabolite of TXA2. To evaluate platelet aggregability, blood was mixed with sodium citrate and left for 1 hour at room temperature; the maximum aggregation for 10 minutes induced by 10 \( \mu \)M adenosine diphosphate (final concentration) was measured using a whole-blood aggregometer (impedance method) (ChronoLog Corp., Havertown, Pa.). For measurements of \( \beta \)-TG and TXB2 concentrations, blood was placed in test tubes containing theophylline for \( \beta \)-TG and indomethacin for TXB2, cooled, and centrifuged. The supernatant was stored frozen, and measurements were made using a radioimmunoassay kit (New England Nuclear, Boston, Mass.).

**Results**

Figure 1a shows platelet aggregability in blood from the jugular and peripheral veins. Internal jugular venous blood showed elevated platelet aggrega-
bility in seven of the 13 cases on admission, but aggregability recovered to the normal range by day 4 in five of the seven. After day 5, the patients were divided into two groups, those with elevated platelet aggregability and those with normal platelet aggregability. Peripheral venous blood also showed slightly high values in four of the 13 cases on admission and in six of the 13 cases after day 8, but changes were smaller than those in internal jugular venous blood. Changes of β-TG concentration in internal jugular venous blood were similar to those of platelet aggregability (Figure 1b). Concentrations were markedly high in two patients on admission and in three patients after day 5. In peripheral venous blood, however, β-TG concentrations were within the normal range or only slightly high. The concentration of TXB₂ showed changes similar to those for β-TG in both internal jugular venous blood and peripheral venous blood (Figure 1c).

We compared the differences between values in superior sagittal sinus blood and internal jugular venous blood with the differences between values in superior sagittal sinus blood and peripheral venous blood in four patients (cases 2, 9, 11, and 13) (Figure 2). The differences between the former were smaller than those between the latter.

In the patients who showed two or more consecutive high values (platelet aggregability: ≥ mean+2 SD; β-TG and TXB₂ concentrations: ≥ mean+6 SD), the values in internal jugular venous blood were serially compared with those in peripheral venous blood (Figure 3). While platelet function was enhanced, internal jugular venous blood showed higher values than peripheral venous blood for all three parameters.

We evaluated changes in these parameters during the clinical course using internal jugular venous blood (Figure 4). In the eight patients without symptomatic vasospasm, platelet aggregability was slightly high on admission and between days 8 and 11, but the values were almost within the normal range for the rest of the evaluation period. The five patients with symptomatic vasospasm showed increased platelet aggregability after day 5, from the early stage of vasospasm. However, there were no differences be-

### Table 1. Summary of Cases of Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Site of aneurysm</th>
<th>Symptomatic vasospasm</th>
<th>Clinical grade</th>
<th>Days to surgery</th>
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<td>M</td>
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<td>III</td>
<td>1</td>
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<tr>
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<td>F</td>
<td>ACoA</td>
<td>−</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
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<td>F</td>
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<td>II</td>
<td>3</td>
</tr>
<tr>
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<td>60</td>
<td>F</td>
<td>ACoA</td>
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<td>III</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>F</td>
<td>ACoA</td>
<td>−</td>
<td>II</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>M</td>
<td>ICA</td>
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<td>II</td>
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<td>45</td>
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<td>11</td>
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<tr>
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<td>ACoA</td>
<td>+</td>
<td>III</td>
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</tr>
</tbody>
</table>

Clinical grade according to World Federation of Neurological Surgeons scale.¹³ M, male; F, female; ACoA, anterior communicating artery; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; BA, basilar artery.

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Figure 1. Bar graphs comparing platelet (Pit) aggregability (a), β-thromboglobulin concentration (β-TG) (b), and thromboxane B₂ concentration (TX-B₂) (c) in blood samples taken from superior sagittal sinus (SSS), internal jugular vein (JV), and peripheral vein (PV) of four patients. [SSS-JV], absolute value of difference between SSS and JV blood; [SSS-PV], absolute value of difference between SSS and PV blood; *p<0.05 different from [SSS-PV] value by Student's t test.
between the degree of enhancement of aggregability in the two patients with symptomatic vasospasm followed by improvement and that of the three patients with symptomatic vasospasm followed by deterioration. In the patients without symptomatic vasospasm, β-TG concentrations were normal or slightly high, while in the patients with symptomatic vasospasm values became high beginning several days after the onset of vasospasm. In this group, β-TG concentrations fluctuated within the range <60 ng/ml in the patients whose ischemic symptoms of vasospasm improved, but values increased to >80 ng/ml in the patients whose ischemic symptoms did not improve.

In the patients without symptomatic vasospasm, TXB₂ concentrations were high on admission but fell to almost within the normal range after day 5. Two of the five patients with symptomatic vasospasm showed markedly high TXB₂ values after day 8. One was a patient whose ischemic symptoms improved, and the other was a patient whose symptoms did not improve.

**Discussion**

We studied platelet function in SAH patients to evaluate its association with cerebral vasospasm. The values in internal jugular venous blood were similar to those in superior sagittal sinus blood. In addition,
in patients with enhanced platelet function, the degree of enhancement was more marked in internal jugular venous blood than in peripheral venous blood. These results suggest that internal jugular venous blood reflects intracranial conditions more sensitively.24

We also studied the association between platelet function, clinical course, and the values in internal jugular venous blood. All three items were enhanced during the early stage of SAH and recovered to the normal range in a few days but showed various patterns after day 5. Enhancement seen during the early stage of SAH may be attributable to activation of platelets for hemostasis following aneurysmal rupture and to systemic factors such as increases in catecholamine concentrations during the acute stage.26

Platelet function was also affected by cerebral vasospasm itself since changes of platelet function after day 5 were minimal in patients without symptomatic vasospasm but tended to be enhanced in those with symptomatic vasospasm. The fact that platelet aggregability increased at the onset of symptomatic vasospasm indicates that platelets may be activated during the early stage of cerebral vasospasm. This observation is consistent with the report of platelet attachment to the arterial luminal surface during the early stage of cerebral vasospasm.11 On the other hand, the β-TG values increasing several days after the onset of symptomatic vasospasm suggest that the activated state of platelets, which was observed as promoted aggregability, might progress to microthrombus formation.12-13 The markedly high concentrations of β-TG obtained in patients with unimproved ischemic symptoms suggest that thrombus formation affects the severity of ischemic symptoms and the prognosis after vasospasm. Recently, antiplatelet agents, such as a thromboxane synthetase inhibitor29 or ticlopidine,27 have been reported to be useful for cerebral ischemic symptoms accompanied by cerebral vasospasm. These reports and the results of our study indicate that the platelet system is an important factor in the cause of ischemic symptoms after vasospasm.

We obtained markedly high concentrations of TXB2 in two patients with symptomatic vasospasm, but the association with the severity of ischemic symptoms or prognosis after vasospasm was obscure. Moreover, there are both affirmative28 and negative29 reports regarding possible correlations of the plasma TXB2 level with vasospasm or ischemic symptoms. Further studies are needed to clarify measurement techniques28 and the balance between TXA2 and prostaglandin I2 concentrations.

References

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