Spontaneous Intracerebral Hemorrhage and Liver Dysfunction

Hiroshi Niizuma, MD, Jiro Suzuki, MD, Tsutomu Yonemitsu, MD, and Taisuke Otsuki, MD

We evaluated liver function and coagulation parameters in 117 patients with spontaneous intracerebral hemorrhage (68 men and 49 women) admitted to our clinic within 24 hours after onset. Liver dysfunction was more common among men than women due to differences in alcohol consumption. Number of thrombocytes and fibrinogen concentrations were lower, especially among men with elevated concentrations of glutamic oxaloacetic transaminase or glutamic pyruvic transaminase and/or elevated y-globulin fraction. Five of the 78 patients undergoing stereotactic hematoma aspiration and one of the 39 treated nonsurgically rebled. All six of the patients who rebled were men, heavy alcohol consumers with liver dysfunction. Fibrinogen concentration was abnormally low in four of the six and at the lower end of the normal range in one. Two showed thrombocytopenia and one case showed prolonged prothrombin time. These facts suggest that liver disorders produce a state in which hemorrhage occurs more readily and that this hemorrhagic tendency may be one of the causal factors of spontaneous intracerebral hemorrhage. (Stroke 1988;19:852–856)

Although hypertension is considered the cause of bleeding in the majority of spontaneous intracerebral hemorrhage cases, the existence of cases in which a hemorrhagic diathesis is the cause must be considered when deciding upon surgical therapy. Prior to November 1985, we performed computed tomography (CT)-guided stereotactic aspiration in 125 patients with intracerebral hematoma. Among those patients, eight rebled subsequent to the surgery. When those patients in whom the rebleeding due to problems in postoperative care or the technique used for aspiration of the hematoma were excluded, there remained three patients with a history of liver disease.

Those three patients drew our attention to the possible involvement of chronic liver disorders in spontaneous intracerebral hemorrhage and, specifically, to the possibility that patients might develop a tendency to bleed due to liver dysfunction. To clarify the degree to which such a tendency is involved in intracerebral hemorrhage, we studied alcohol consumption, liver function, and coagulation parameters in 117 patients admitted to our clinic with spontaneous intracerebral hemorrhage.

Subjects and Methods

Between December 1985 and February 1987, we evaluated 202 patients with spontaneous intracerebral hemorrhage in whom diagnoses of aneurysm, arteriovenous malformation, or moyamoya disease had been excluded by cerebral angiography. Of those patients, 85 had been admitted to our clinic >24 hours after onset or had received incomplete examinations on admission. Therefore, only 117 patients met the criteria for this study. There were 68 men and 49 women. The men ranged in age from 30 to 77 (mean ± SD 54.9 ±9.9) years and the women from 33 to 84 (mean ± SD 60.1 ±9.7) years. The sites of bleeding were the putamen in 66 patients, the thalamus in 38, the cerebellum in 6, the cerebral subcortex in 3, the caudate nucleus in 2, and the pons in 2.

The patients’ medical history and facts concerning alcohol consumption were recorded on admission. To determine which patients might have hemorrhagic tendencies, the number of thrombocytes, bleeding time (Duke’s method), prothrombin time, activated partial thromboplastin time, plasma fibrinogen concentration, and the amount of fibrin degradation products (FDP) were measured. For the determinations of prothrombin time, activated partial thromboplastin time, and plasma fibrinogen concentration, a Cobas Fibro apparatus (Tegimenta AG, Rotkreuz Schweiz, Switzerland) was used. As measures of liver function, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transamin-
TABLE 1. History of Hypertension and Liver Dysfunction in 117 Patients With Spontaneous Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Men (n = 68)</th>
<th>Women (n = 49)</th>
<th>Total (N = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>48</td>
<td>42</td>
<td>90</td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Unclear</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver dysfunction</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>High γ-GTP</td>
<td>29</td>
<td>3</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>High GOT, GPT, and/or γ-globulin</td>
<td>12</td>
<td>2</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>High GOT and/or GPT</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>High γ-globulin</td>
<td>5</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Total cases with liver dysfunction 31 4 35

γ-GTP, gamma-glutamyl transpeptidase; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

Hypertension was found in 41 men and two women, of <50 years old. Consumption of >50 g/day was found in 41 men and two women, of <50 years old. Interestingly, the incidence of hypertension was higher among the women although the difference was not significant (p<0.01). A definite history of hypertension was found in 32 patients (27.4%) among the men (11.1% of 29 men, 42.6% of 68 men). A history of liver dysfunction was found in six patients (four men, two women) and got in three (all men, two of whom also showed renal failure).

Alcohol consumption was significantly greater among the men (p<0.01). Consumption of >50 g/day was found in 41 men and two women, of <50 g/day in 18 men and five women, and of no alcohol in nine men and 42 women. There was no significant relation between a history of hypertension and alcohol consumption.

Platelet counts (normal: 13–32 × 10^9/mm^3) were significantly lower (p<0.05) among the men (mean ± SD 22.04 ± 5.82 × 10^9/mm^3) than the women (24.80 ± 8.22 × 10^9/mm^3). Fifty of the six patients with platelet counts of <13 × 10^9/mm^3 were also men.

Prothrombin times were significantly shorter (p<0.01) among the patients (11.1% of 29 men, 6.1% of 68 men) than among 100 normal controls (12.80 ± 0.61 seconds). Only two male patients had prothrombin times of >15 seconds. In contrast, all patients had activated partial thromboplastin times within the normal range.

With regard to the plasma fibrinogen concentration (normal: 180–380 mg/dl), the men (248.9 ± 63.1 mg/dl) had values significantly lower (p<0.01) than the women (288.2 ± 75.8 mg/dl). All six patients with fibrinogen levels of ≤179 mg/dl were men, and all six reached alcohol consumption of ≥50 g/day.

Twelve patients had FDP concentrations of between 10 and 40 mg/dl, but the remaining 105 had normal levels (p<0.01). There were no patients diagnosed as having disseminated intravascular coagulation. The bleeding time was measured in 96 patients, 71 of whom had normal values (2–5 minutes); five had prolonged values. In contrast, reduced bleeding times of 1.0–1.5 minutes were recorded in the remaining 20 patients.

Summarizing the above findings, 11 of the 117 patients (9.4%) showed thrombocytopenia, low fibrinogen concentrations, or prolonged prothrombin times. When the five patients with prolonged bleeding times are also included, a total of 16 patients (13.7%, 13 men and three women) showed abnormal hematologic results suggestive of a bleeding tendency.

Thirty-five patients (29.9%) showed some form of liver function abnormality (Table 1). γ-GTP concentrations above the normal range of ≤40 units were found in 32 patients (27.4%). Noteworthy is the fact that increased concentrations were found in a much larger percentage of the men (29 of 68, 42.6%) than the women (three of 49, 6.1%). Moreover, the correlation between alcohol consumption and γ-GTP concentration was significant for the men (p<0.01, Table 2).

Eleven men and one woman had high GOT and/or GPT concentrations. Ten of these 11 men were alcohol users, none of whom drank ≥50 g/day, and all 10 had increased γ-GTP concentrations. The remaining man had a γ-GTP concentration within the normal range, but he had a history of liver disorders and was thought to have chronic liver dysfunction in light of the high value (26.1%) of his γ-globulin fraction.

The serum γ-globulin fraction was ≥20% in six patients (five men, one woman) and GOT and/or

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>≤40</th>
<th>41–99</th>
<th>100+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 g/day</td>
<td>14</td>
<td>14</td>
<td>13</td>
<td>41</td>
</tr>
<tr>
<td>&lt;50 g/day</td>
<td>16</td>
<td>2</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>None</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

Total 39 16 13 68

γ-GTP, gamma-glutamyl transpeptidase.
Fibronogen (mg/dl)

FIGURE 1. Fibronogen concentration and thrombocyte count in relation to liver function in 49 women with spontaneous intracerebral hemorrhage. A, normal liver function (n=45); ●, high gamma-glutamyl transpeptidase (γ-GTP) concentration (n=2); ○, high glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and/or γ-globulin concentrations (n=1); △, high values for both γ-GTP and other liver functions (n=1).

GPT concentration and/or the γ-globulin fraction were high in a total of 14 patients (12 men, two women; 12.0%).

The correlation between liver function, number of thrombocytes, and fibrinogen concentration was studied separately for the men and women. Normal or relatively high levels of thrombocytes and fibrinogen were found among the women with the exception of one with a history of cholelithiasis, a low thrombocyte count (10.0 x 10^4/mm^3), and a low fibrinogen concentration for a woman (189 mg/dl) (Figure 1).

In contrast, the number of thrombocytes and fibrinogen concentration were low in men (Figure 2). The tendency was notable in those with abnormal GOT or GPT concentrations or γ-globulin values. Among the 68 men, the mean ± SD thrombocyte count in the 12 with abnormally high GOT, GPT, and/or γ-globulin values was 17.67 ± 7.99 x 10^4/mm^3, whereas the thrombocyte count was significantly higher (p<0.01) in the 56 men without GOT, GPT, or γ-globulin abnormalities (22.98 ± 4.84 x 10^4/mm^3). Similar findings were obtained with regard to fibrinogen concentration. The 12 men with high GOT, GPT, and/or γ-globulin levels had fibrinogen concentrations of 202.6 ± 45.0 mg/dl, whereas those without such abnormalities had fibrinogen concentrations of 258.9 ± 62.3 mg/dl, a significant difference (p<0.01).

Rebleeding was found in five of the 78 patients (6.4%) undergoing stereotactic hematoma aspiration (52 men, 26 women) (Table 3). We divided these five patients into two groups, those suffering a major rebleeding, in whom the hematoma was as large as or larger than the preoperative hematoma, and those suffering minor rebleeding, in whom the postoperative hematoma was smaller. Minor rebleed-

TABLE 3. Patients With Spontaneous Intracerebral Hemorrhage Who Rebled

<table>
<thead>
<tr>
<th>Case/age</th>
<th>Hypertension</th>
<th>Thrombocytes (× 10^4/mm^3)</th>
<th>Fibrinogen (mg/dl)</th>
<th>FDP (mg/dl)</th>
<th>Bleeding time (min)</th>
<th>PT (sec)</th>
<th>APTT (sec)</th>
<th>Total protein (g/dl)</th>
<th>A:G ratio</th>
<th>γ-globulin (%)</th>
<th>GOT (IU)</th>
<th>GPT (IU)</th>
<th>γ-GTP (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative rebleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/37</td>
<td>No</td>
<td>23</td>
<td>195</td>
<td>&lt;10</td>
<td>12.0</td>
<td>33.0</td>
<td>7.1</td>
<td>1.12</td>
<td>22.0</td>
<td>59</td>
<td>45</td>
<td>248</td>
<td></td>
</tr>
<tr>
<td>2/51</td>
<td>Yes</td>
<td>8</td>
<td>146</td>
<td>&lt;10</td>
<td>3.0</td>
<td>14.0</td>
<td>38.2</td>
<td>8.1</td>
<td>1.38</td>
<td>23.2</td>
<td>51</td>
<td>31</td>
<td>149</td>
</tr>
<tr>
<td>3/52</td>
<td>Yes</td>
<td>26</td>
<td>162</td>
<td>&lt;10</td>
<td>4.5</td>
<td>9.8</td>
<td>30.9</td>
<td>6.6</td>
<td>2.28</td>
<td>11.1</td>
<td>13</td>
<td>17</td>
<td>147</td>
</tr>
<tr>
<td>4/50</td>
<td>No</td>
<td>20</td>
<td>121</td>
<td>&lt;10</td>
<td>2.0</td>
<td>11.8</td>
<td>33.6</td>
<td>7.7</td>
<td>2.03</td>
<td>11.0</td>
<td>57</td>
<td>49</td>
<td>224</td>
</tr>
<tr>
<td>5/44</td>
<td>Yes</td>
<td>27</td>
<td>274</td>
<td>10–40</td>
<td>8.0</td>
<td>10.9</td>
<td>36.5</td>
<td>6.9</td>
<td>1.84</td>
<td>16.2</td>
<td>25</td>
<td>24</td>
<td>85</td>
</tr>
<tr>
<td>Nonoperated case</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/65</td>
<td>No</td>
<td>5</td>
<td>160</td>
<td>&lt;10</td>
<td>3.0</td>
<td>16.1</td>
<td>39.7</td>
<td>6.6</td>
<td>1.24</td>
<td>24.9</td>
<td>82</td>
<td>19</td>
<td>325</td>
</tr>
</tbody>
</table>

Site of hematoma was putamen in all patients; alcohol consumption was ≥50 g/day in all patients; all patients were men. FDP, fibrin degradation products; PT, prothrombin time; APTT, activated partial thromboplastin time; A:G ratio, albumin:globulin ratio; GOT, glutamic oxaloacetic transaminase; IU, international units; GPT, glutamic pyruvic transaminase; γ-GTP, gamma-glutamyl transpeptidase.
The liver is the site for the synthesis and metabolism of thrombocytes. Disturbances of these functions naturally result in a tendency to hemorrhage, but before 1973 spontaneous intracerebral hemorrhage caused by such a tendency was considered to be a rare and exceptional condition.

In 1973, McCormick and Rosenfield reported that four men (2.8%) of their 144 cases of massive brain hemorrhage leading to death had a bleeding tendency resulting from alcoholic cirrhosis. In 1980, Boudouresques et al reported a pathological study of 282 cases of spontaneous intracerebral hemorrhage that were compared with a control group of 100 cases. In the control group, liver cirrhosis was found in 7%. In the intracerebral hemorrhage group, on the other hand, liver cirrhosis was noted in 15.6%. Therefore, Boudouresques et al concluded that such a condition is a major risk factor for spontaneous intracerebral hemorrhage. Cahill and Ducker also described spontaneous intracerebral hemorrhage due to liver cirrhosis, and the importance of the state of the liver for intracerebral hemorrhage has gradually been brought to attention.

In our study, there was a considerable number of spontaneous intracerebral hemorrhage patients with abnormalities of liver function, and such patients were particularly frequent among the heavy alcohol users. Among such patients, those with increased GOT or GPT concentrations and/or γ-globulin fraction showed a tendency to have decreased fibrinogen and thrombocyte levels. Previously, it has been held that a thrombocyte count of <5 × 10^9/mm^3 or a fibrinogen concentration of <60–100 mg/dl constitute high bleeding risk parameters, but our findings of postoperative rebleeding and rebleeding during conservative treatment suggest that a significantly increased risk already exists in cases of spontaneous intracerebral hemorrhage, especially when the thrombocyte count is ≤13 × 10^9/mm^3 and the fibrinogen concentration is ≤180 mg/dl.

Intracerebral hemorrhage is more common in men than in women, but an understanding of this difference has not been achieved. In our series of patients, we found the frequency of hypertension to be slightly higher among women, indicating that the higher frequency of spontaneous intracerebral hemorrhage in men cannot be explained solely on the basis of the frequency of hypertension. If, however, the frequency of liver disorders due to alcohol consumption is considered, the high frequency of hemorrhage among the men might be partially explained. That is, in nine of the 68 men with intracerebral hemorrhage (13.2%), notable decreases in thrombocyte and/or fibrinogen levels were found. Most of these patients (eight of nine) had liver dysfunction. Moreover, even in patients in whom liver disorders had not progressed to such a stage, the men were generally heavier alcohol consumers and, as a consequence, showed signs of liver dysfunction. There were also significant decreases in thrombocyte and fibrinogen concentrations (in three patients). Noteworthy is the fact that excessive aspiration was not done, rebleeding occurred either during the operation or on the following day. All four of these patients had significant liver abnormalities, in the form of 1) high γ-GTP concentrations, 2) abnormally low or low-normal fibrinogen concentrations, and 3) high GOT and GPT concentrations (in three patients). Noteworthy is the fact that six of the 117 patients had fibrinogen concentrations of ≤179 mg/dl. Of these six, five underwent stereotactic aspiration, and three of the five showed subsequent rebleeding.

The remaining patient with postoperative rebleeding (Case 5) had renal gout and was given a blood transfusion on admission due to anemia (an erythrocyte count of 255 × 10^6/mm^3, hemoglobin concentration of 9.1 g/dl) and a bleeding time of 8 minutes. This patient was also a heavy alcohol consumer and had a high γ-GTP concentration. The stereotactic operation was performed on the fifth day after onset, after improvement in hematologic parameters was documented. No further complications were evident during surgery or immediately thereafter, and the drainage tube was removed. CT scans showed only small residual hematoma in the putamen. At the time of follow-up CT scan on the eleventh postoperative day, minor rebleeding was identified and hematologic tests showed a return to the abnormally long bleeding time of >8 minutes.

Among the 39 patients treated conservatively, one (Case 6, Table 3) with liver function abnormalities, a low thrombocyte count, a low fibrinogen concentration, and a prolonged prothrombin time rebled on the fourth day following onset and died 3 days later.

**Discussion**

It is estimated that more than one half of all cases of spontaneous intracerebral hemorrhage are due to hypertension, but a bleeding diathesis can also be a causative factor. Such bleeding tendency is seen in liver disease, leukemia, hemophilia, aplastic anemia, and disseminated intravascular coagulation. The liver is the site for the synthesis and metabolism of fibrinolytic factors and various blood-clotting factors, including fibrinogen. Moreover, together with the spleen, the liver plays a major role in determining the systemic distribution and metabolism of thrombocytes. Disturbances of these functions naturally result in a tendency to hemorrhage, but before 1973 spontaneous intracerebral hemorrhage caused by such a tendency was considered to be a rare and exceptional condition.
fibrinogen levels among the men. These facts suggest that liver disorders produce a state in which hemorrhage occurs more readily, and this hemorrhagic tendency is one of the causes for the higher frequency of spontaneous intracerebral hemorrhage in men than in women.

The most important factor to check when considering stereotactic hematoma aspiration is whether the patient has a tendency to bleed. Thrombocyte count and fibrinogen concentration were good indexes of the tendency to hemorrhage. Consequently, when making therapeutic decisions about patients with spontaneous intracerebral hemorrhage, it is important to pay close attention not only to drastic decreases in the thrombocyte count (to $5 \times 10^4$ mm$^3$) or fibrinogen concentration (to 60 mg/dl), but also to decreases to the lower end of the normal range, that is, to a thrombocyte count of $13 \times 10^4$ mm$^3$ or a fibrinogen concentration of 180 mg/dl. In such cases, great care is needed in performing an operation, and it may be better to delay surgery until >24 hours after onset to avoid rebleeding.

References


**KEY WORDS** • cerebral hemorrhage • liver diseases
Spontaneous intracerebral hemorrhage and liver dysfunction.
H Niizuma, J Suzuki, T Yonemitsu and T Otsuki

Stroke. 1988;19:852-856
doi: 10.1161/01.STR.19.7.852

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 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/19/7/852

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/