Coagulation-fibrinolysis Activity is not Accelerated in Patients with Diffuse Axonal Injury

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ABSTRACT

Background: The plasma level of D-dimer (DD) on admission is useful as a prognostic marker of head injury. Methods: Eighty patients with isolated blunt head trauma were grouped according to the type of brain parenchymal injury using MRI. The differences in the DD levels among the groups, and the correlation between the DD levels and the patients' outcome, were investigated. Results: All patients were categorized into the following groups: diffuse axonal injury (DAI, n=24), cerebral contusion (CON, n=47), and no intraparenchymal lesion (NIL, n=9). The DD level was significantly higher in the CON-group than in the other two groups. In the CON-group, the patients with an unfavorable outcome had significantly higher DD levels. In the DAI-group, however, the DD level remained generally low regardless of the outcome. Conclusions: The DD level was sensitive to the type of brain injury. In the DAI-group, however, the coagulation-fibrinolysis activity was not accelerated to as great an extent as it was in the CON-group, therefore even the DD level was not a good prognostic indicator.

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INTRODUCTION

Abnormal acceleration of the coagulation cascade during the early phase of head trauma is a well-known entity. This process subsequently initiates fibrinolysis, resulting in the formation of molecular markers, such as the thrombin-antithrombin III complex (TAT), the α2-plasmin inhibitor-plasmin complex (PIC), and the D-dimer (DD). Since these markers are nearly undetectable in normal plasma, elevated levels reliably indicate excessive coagulation-fibrinolysis activity, whether or not this process is manifested clinically. The DD, in particular, is the direct evidence of defibrination and is the ultimate product of the activated coagulation-fibrinolysis cascade; thus, the plasma DD level is considered to reflect the amount of damaged brain tissue in an isolated head injury. It is reported that an elevated plasma DD level at the time of admission has prognostic value in patients with head injuries. However, an association between the DD level and the type of brain injury has not yet been documented.

Some prior reports have suggested a relation between coagulation-fibrinolysis abnormality and the delayed hematoma in cerebral contusion. In contrast, in cases of diffuse axonal injury (DAI), which is another morphological feature of brain parenchymal injury and characterized by small and scattered hematomas in the white matter, delayed hematomas rarely develop during the course of injury. The aim of the present study is to clarify differences in coagulation-fibrinolysis aspects, particularly in relation to DD levels, between patients with DAI and those with contusions. The differences may contribute to the less-severe hemorrhagic nature of DAI.

MATERIAL AND METHODS

Patients and medical management

We enrolled 80 consecutive patients with isolated blunt head trauma who were admitted to the Osaka prefectural
Nakakawachi Medical Center of Acute Medicine between May 1998 and December 2001. All of the enrolled patients fulfilled the following criteria: no coexisting injury with an Abbreviated Injury Scale score of more than 4; between 16 and 69 years of age; transferred directly from the scene of the accident within an hour of sustaining their injuries; no preexisting liver diseases, coagulofibrinolytic disorders, or treatment with drugs influencing hemostasis; no apparent brain damage secondary to ischemia and/or hypoxia; and no critical intracranial hypertension on admission (since these patients were usually unable to undergo an early MRI examination).

An initial CT scan was performed as soon as possible to assess the presence and type of intracranial extraparenchymal hematoma and determine a therapeutic strategy. All patients were treated using standardized protocols in compliance with the “GUIDELINES FOR THE MANAGEMENT OF SEVERE HEAD INJURY” (1995, Brain Trauma Foundation)7, which emphasizes the immediate evacuation of large mass lesions and the prevention of secondary insults. The prevention of respiratory complications and excessive hyperthermia were also points of concern. Artificial ventilation, a tracheostomy, body-surface cooling using a water-circulating blanket, and the administration of non-steroidal anti-inflammatory agents were performed, if necessary. Although the minimum dose of midazolam or propofol necessary for management was utilized, the unnecessary continuous administration of sedatives was strictly avoided.

MRT

Combination MRI scans using fluid attenuated inversion recovery (FLAIR) and T2* weighted gradient echo (T2*) sequences were performed in all patients within two weeks following injury; both of these techniques can be used to detect traumatic lesions with a high degree of sensitivity8. All scans were obtained in the axial and sagittal planes at 1.0 T (Siemens Magnetom Impact Expert). The detailed sequence parameters have been described in a previous report6. The location and appearance of intraparenchymal lesions in each patient were assessed by an attending neuroradiologist and two neurosurgeons. The duration of unconsciousness (DOU) and the outcome were assessed for each patient by two consulting neurosurgeons. The duration of unconsciousness was determined one month after the injury using the Glasgow outcome scale (GOS)10. For statistical comparison, patients with a GOS of no, mild, or moderate disability were classified as having a favorable outcome; those whose outcome was death, a vegetative state, or severe disability were classified as having an unfavorable outcome.

Measurement of the DD level and other coagulation-fibrinolysis variables

Blood samples were collected within one hour following injury via a femoral artery puncture, mixed with 3.8% sodium citrate solution, and immediately centrifuged (4,000 rpm for 3 min at 4 °C) to determine the DD plasma level on admission. In addition, the following coagulation-fibrinolysis variables were measured using the same samples: the prothrombin time (PT) and the activated partial thromboplastin time (APTT), representing the global coagulation function; fibrinogen, antithrombin 3 (AT3), plasminogen, and α2-plasmin inhibitor (α2-PI) levels, representing physiologic coagulation-fibrinolysis factors. All variables were measured with standard techniques using an automated measuring apparatus (MDA180, Hitachi High-Technology Corporation, Tokyo, Japan). The measuring method, the reagent, and the normal range in each variable were as follows: the DD, latex particle immunoassay, MDA IATROACE D-Dimer, normal range = < 1.0 μg/ml; the PT, clot time method, MDA Simplastin L, normal range = 80-120%; the APTT, clot time method, MDA Platelin LS, normal range = < 40 sec; the fibrinogen, Clauss method, MDA Fibriquik, normal range = 150-350 mg/dl; the AT3, Chromogenic assay, MDA Antithrombin 3, normal range = 80-120%; the plasminogen, Chromogenic assay, MDA Plasminogen, normal range = 80-120%; and the α2-PI, Chromogenic assay, MDA alpha-2-Antiplasmin, normal range = 80-120%. All reagents were provided by bioMerieux Japan Ltd., Tokyo, Japan.

Clinical assessment

The duration of unconsciousness (DOU) and the outcome were assessed for each patient by two consulting neurosurgeons. The duration of unconsciousness was defined as the time lapse until simple orders, such as “open your mouth and stick out your tongue” or “clench and loosen your hand”, were obeyed with the eyes opening spontaneously. Unconsciousness was defined as coma plus a vegetative state, according to the guidelines of the Multi-Society Task Force on PVS9. The outcome was determined one month after the injury using the Glasgow outcome scale (GOS)10. For statistical comparison, patients with a GOS of no, mild, or moderate disability were classified as having a favorable outcome; those whose outcome was death, a vegetative state, or severe disability were classified as having an unfavorable outcome.
Table 1. Clinical profiles for each patient group.

<table>
<thead>
<tr>
<th>Feature</th>
<th>DAI (n=24)</th>
<th>CON (n=47)</th>
<th>NIL (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age*</td>
<td>31 ± 15</td>
<td>41 ± 18</td>
<td>38 ± 18</td>
</tr>
<tr>
<td>GCS score*</td>
<td>7.2 ± 3.1</td>
<td>8.5 ± 4.1</td>
<td>10.8 ± 4.0</td>
</tr>
<tr>
<td>DOU (days)*</td>
<td>15 ± 14</td>
<td>7 ± 8*</td>
<td>3 ± 3**</td>
</tr>
<tr>
<td>outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>favorable</td>
<td>10</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>unfavorable</td>
<td>14</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

* Values are expressed as the means ± SD. †, ‡ Statistical significant difference from the DAI-group (p=0.04, *p=0.01).
DAI, diffuse axonal injury; CON, cerebral contusion; NIL, no intraparenchymal lesion; GCS, Glasgow coma scale; DOU, duration of unconsciousness

Statistical analysis

All values were expressed as the mean ± standard deviation (SD). Statistical analyses were performed using Stat View (Abacus Concepts Inc), and a probability (p) value of less than 0.05 was considered to be significant. The frequency of each outcome was analyzed using the χ² test. Differences in age, the GCS score, DOU, and coagulation-fibrinolysis variables between the three groups were analyzed using the post hoc Scheffe’s test for multiple comparison. The correlation between the DD level and the outcome in each group was analyzed using a Mann-Whitney U test.

RESULTS

Patient characteristics

The clinical profiles of the patients grouped according to MRI finding are summarized in Table 1. All 80 patients were categorized into one of the three groups; the DAI-, CON-, and NIL-groups consisted of 24, 47, and 9 patients, respectively. No significant difference in age or admission GCS score was observed between the three groups. The DOU was calculated for patients who recovered from unconsciousness within one month; patients who recovered from unconsciousness in the DAI-, CON-, and NIL-groups were 19, 36, and 9 respectively. The DOU in the DAI-group was significantly longer than those in the CON- and NIL-groups (p=0.04 and p=0.01, respectively). The outcome in the DAI-group was also significantly poorer than those in the other two groups (p<0.01). None of the patients in the study population died within a month of their injury.

Intracranial extraparenchymal hematomas were identified as a result of the admission CT scan in 33 patients: 4, 26, and 3 patients in the DAI-, CON-, and NIL-groups, respectively. Delayed development or enlargement of an intraparenchymal hematoma was observed in 4 patients, all of whom were in the CON-group.

DD level

The DD level in the CON-group was significantly higher than in the other two groups, as shown in Fig. 1. The mean values ± SD of DD levels in the DAI-, CON-, and NIL-groups were 3.3 ± 2.9, 8.7 ± 10.2, and 1.0 ± 1.1, respectively. The correlation between the DD level and the outcome in the DAI- and CON-groups is shown in Fig. 2. In the DAI-group, no statistical difference in DD levels was observed between the patients with a favorable outcome and those with an unfavorable outcome (3.0 ± 2.4 and 3.5 ± 3.2, respectively). In the CON-group, D-dimer level in patients with a favorable outcome was significantly lower than that in patients with an unfavorable outcome (5.4 ± 5.1 and 13.0 ± 13.6, respectively). In addition, there was also a significant difference between the DD level in patients with a favorable outcome and those with an unfavorable outcome in the whole study population (4.0 ± 4.5 and 9.1 ± 11.5, respectively, p < 0.01).

Other coagulation-fibrinolysis variables

No statistical differences among the coagulation-fibrin-
The correlation between the DD level and the outcome in the DAI- and CON-groups.

In the DAI-group, no statistical difference in DD levels was observed between the patients with a favorable outcome and those with an unfavorable outcome. In the CON-group, D-dimer level in patients with a favorable outcome was significantly lower than that in patients with an unfavorable outcome.

DAI, diffuse axonal injury; CON, cerebral contusion; favorable, the patients with a favorable outcome; unfavorable, the patients with an unfavorable outcome. *Statistically significant difference.

Table 2. Coagulation-fibrinolysis variables for each patient group.

<table>
<thead>
<tr>
<th>Feature (normal range)</th>
<th>DAI (n=24)</th>
<th>CON (n=47)</th>
<th>NIL (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer (&lt; 1.0 μg/ml)</td>
<td>3.3 ± 2.9 *</td>
<td>8.7 ± 10.2</td>
<td>1.0 ± 1.1**</td>
</tr>
<tr>
<td>PT (80-120%)</td>
<td>79.0 ± 19.1</td>
<td>80.3 ± 22.7</td>
<td>78.2 ± 24.1</td>
</tr>
<tr>
<td>APTT (20-40 sec)</td>
<td>26.6 ± 4.3</td>
<td>33.5 ± 27.6</td>
<td>27.9 ± 3.4</td>
</tr>
<tr>
<td>fibrinogen (150-350mg/dl)</td>
<td>208.9 ± 52.2</td>
<td>223.7 ± 76.7</td>
<td>196.5 ± 44.1</td>
</tr>
<tr>
<td>AT3 (80-120%)</td>
<td>97.4 ± 16.2</td>
<td>97.1 ± 14.6</td>
<td>93.0 ± 9.2</td>
</tr>
<tr>
<td>plasminogen (80-120%)</td>
<td>110.2 ± 21.6</td>
<td>113.4 ± 21.7</td>
<td>107.9 ± 27.2</td>
</tr>
<tr>
<td>α2-PI (80-120%)</td>
<td>101.1 ± 114.4</td>
<td>100.9 ± 15.7</td>
<td>103.3 ± 9.1</td>
</tr>
</tbody>
</table>

All values are expressed as the means ± SD. *, ** Statistical significant difference from the CON-group (*p=0.03, **p=0.04). PT, prothrombin time; APTT, activated partial thromboplastin time; AT3, antithrombin 3; α2-PI, α2-plasmin inhibitor

DISCUSSION

The present study shows a difference in plasma DD concentration soon after injury in the DAI- and CON-groups. The DD concentration in the DAI-group was significantly lower than that in the CON-group but was not statistically different from that in the NIL-group. Moreover, the DD level in DAI patients with an unfavorable outcome was almost equal to that in DAI patients with a favorable outcome. These results suggest that coagulation-fibrinolysis activity is not as accelerated in DAI patients as it is in patients with contusions and that DD levels cannot predict either severity or outcome in DAI patients. On the contrary, a correlation between elevated DD levels and an unfavorable outcome was clearly observed in the CON-group. In addition, the larger number of patients in the CON-group, compared with the other two groups, pro-
duced the same correlation overall; these results were compatible with those of prior reports. The global coagulation variables (PT and APTT) and the level of physiologic coagulation-fibrinolysis factors (ATIII, fibrinogen, plasminogen, and α2-PI) remained within the normal ranges in each group. Furthermore, none of the participants developed systemic coagulopathy. These findings support the opinion that the activation of the coagulation-fibrinolysis cascade following head trauma is usually so brief that physiological inhibition functions are sufficient to prevent systemic coagulopathy. Only the DD level was sensitive to the presence of this pathology. Alternatively, some investigators have reported that a disruption in the coagulation-fibrinolysis system, as demonstrated by a prolonged APTT or a reduction in α2-PI activity, can occur in patients with severe head injury and that these values can predict a patient’s outcome; however, we failed to confirm these findings. This discrepancy may have arisen from a bias in our study population, described below.

When interpreting our results, it should be noted that patients with immediate or impending brain death as a result of massive brain destruction, brain herniation, or progressive disorders such as talk and deteriorate, were excluded from the study, since these patients were unable to undergo an early MRI examination. Consequently, our study population lacked patients who should have been graded as having the most serious contusions. This bias may explain why none of the coagulation-fibrinolysis variables, other than DD levels, were disturbed. The biased study population may also explain why both the outcome and the DOU were significantly poorer in the DAI-group than in the CON-group.

MRI can apparently show the extent of contusional lesions as high-intensity areas on FLAIR images but tends to overlook the small and scattered lesions that are characteristic of DAI. Hence, the extent of DAI brain damage cannot be compared with that produced by contusions using existing imaging modalities; however, we believe that relatively low DD level in patients with DAI originated not from a low amount of damaged brain tissue, but from the pathological characteristics of this injury. Even in the patients with severe DAI conditions, who had extensive white matter injury apparent on their MRI, elevation in DD levels was not so significant as was in the patients with severe contusions (Fig. 3).

The accelerated coagulation process in head injuries might be ascribed to the release of tissue factor (TF), an initiator of the extrinsic coagulation pathway, from traumatized brain tissue into the circulatory system. Although its detailed distribution is still debated, the cellular component of the cerebral cortex has been confirmed to be a prominent site of constitutive TF expression, while the white matter is not. Based on the anatomical location of injuries, this finding is compatible with our result that the coagulation-fibrinolysis cascade is more strongly activated in cerebral contusions than in DAI. On the other hand, an immunochemical study has shown that TF is induced in peripheral blood monocytes and vascular endothelial cells in response to various stimuli. Since the induction of TF via various stimuli requires at least a few hours, however, this mechanism is unlikely to be related to the immediate activation of the coagulation-fibrinolysis cascade after head injury.

Patients with head injury often sustain multiple trauma. We are apt to avoid early surgical treatment for associated non-lethal injuries such as limb fractures, being concerned about delayed cerebral hemorrhage sometimes encountered in cerebral contusions. Although further investigations are needed, the present study may imply the lower risk of delayed hemorrhage particularly in DAI patients.

CONCLUSIONS

In this study, the DD level was sensitive to the features of brain parenchymal injury while other coagulation-fi-
brinolysis variables were not. The accelerated coagulation-
fibrinolysis activity, represented as the elevated DD level,
was not observed in the patients with DAI to as great an
extent as it was in the patients with cerebral cortical con-
tusion.

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原著論文

びまん性軸索損傷では、脳挫傷にみられる顕著な凝固線溶亢進状態が認められない

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岸本 正文 尾中 敦彦 矢嶋 祐一

要旨 【背景】頭部外傷患者では受傷早期に一過性の血液凝固線溶亢進がみられる。凝固線溶系検査のうち、血漿D-dimer濃度（DD）は脳損傷の重症度を反映し、予後の指標として有用であることが報告されている。しかし、脳実質損傷の形態とDDの関連は明らかにされていない。【方法】単独頭部外傷患者に対するルーチン検査として、受傷後1時間以内の採血により、DD、その他の凝固線溶パラメーターを測定した。このうち、受傷後2週間以内にMRIを施行し得た80名の患者を対象として、MRI所見に基づいた脳実質損傷の分布を分布、DD、その他の凝固線溶パラメーターについて、群間の差異、および1か月転帰との相関を検討した。【結果】80名の患者は、MRI所見により、びまん性軸索損傷（DAI群、24名）、脳挫傷（CON群、47名）、明らかな脳実質損傷なし（NIL群、9名）のいずれかに分類された。対象患者に死亡者はなく、1か月転帰はDAI群で不良であった。凝固線溶パラメーターのうち、DDのみ群間に有意差を認め、CON群で高値を呈した。また、CON群において転帰不良例のDDは有意に高値であった。一方、DAI群では、DDは転帰に関わらず概ね低値を示した。【結論と考察】DDは脳実質損傷の形態を反映した。DAI群ではDDは低値であり、CON群ほど凝固線溶が亢進しないことが示唆された。加えて、DAI群ではDDと転帰に関連を認めなかった。

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キーワード：びまん性軸索損傷、脳挫傷、D-dimer

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