Role of local hyperfibrinolysis in the etiology of chronic subdural hematoma

HARUHIDE ITO, M.D., PH.D., SHINJIRO YAMAMOTO, M.D., PH.D., TOSHIO KOMAI, M.D., AND HIDETAKA MIZUKOSHI, M.D., PH.D.

Department of Neurosurgery, School of Medicine, University of Kanazawa, Kanazawa, Japan

The authors describe studies performed on material aspirated from chronic subdural hematomas. Patients were given $^{51}$Cr-labeled red cells prior to aspiration, and it was possible to demonstrate that the mean daily hemorrhage into the hematoma space amounted to 10.2% of its volume. Immunoelectrophoresis of the aspirated hematoma fluid by monospecific anti-human fibrinogen revealed the presence of fibrin and fibrinogen degradation products that, measured by hemagglutination-inhibition immunoassay techniques, varied between 5.0 and 10,500 μg/ml with an average of 2604 μg/ml in 18 cases. The tissue activator was demonstrated by Todd's histological localization in the outer membrane of the chronic subdural hematoma in 11 cases, but not in the inner membrane. These results indicate that if a clot in the subdural space causes the formation of neomembrane, and excessive fibrinolysis occurs, the subdural clot would not only liquefy, but also enlarge by continuous hemorrhage from the neomembrane. Therefore, local hyperfibrinolysis and continuous bleeding are important in the etiology of the chronic subdural hematoma.

KEY WORDS: chronic subdural hematoma, hemorrhage, fibrin and fibrinogen, degradation products, local hyperfibrinolysis, tissue activator

Virchow\textsuperscript{10} used the words "pachymenigitis hemorrhagica interna" to describe an encapsulated collection of fluid blood in the subdural space, because it resembled a well-established lamelated clot on the inner side of the dura. In 1914, Trotter\textsuperscript{9} reported a case of head trauma, in which a tear in a bridging vein resulted in hemorrhage into the subdural space. He proposed that this was responsible for the chronic subdural hematoma. Gardner,\textsuperscript{2} Zollinger and Gross,\textsuperscript{12} and Munro and Merritt\textsuperscript{5} proposed a theory explaining this process. Following encapsulation of the original hematoma and breakdown of its cellular constituents, a raised osmotic gradient causes the transport of cerebrospinal fluid into the subdural sac. This osmotic theory has recently been questioned. In 1953, O'Connell\textsuperscript{6} reported that tears of lateral lacunae by minor injuries gave rise to hemorrhage, and subvenous intracranial pressure was considered responsible for continued hemorrhage and the growth of the hematoma.

Many other mechanisms of pathogenesis of the chronic subdural hematoma have been described. These theories are so varied that a reconsideration of this problem is useful.
Hyperfibrinolysis in chronic subdural hematoma

**Material and Methods**

The study included 16 patients with chronic subdural hematoma, three of whom had bilateral hematomas. In addition, control studies were performed on the contents of five acute and two subacute subdural hematomas. Acute subdural hematomas are less than 1 week old; subacute are from 1 to 3 weeks old; and chronic subdural hematomas are more than 3 weeks old.

In cases with chronic subdural hematoma we made a burr hole or trephine craniotomy and aspirated the contents of the hematoma, avoiding any artifactual bleeding. The contents were then subjected to four different studies.

**Daily Hemorrhage into Chronic Subdural Hematoma**

This test was performed with five patients with chronic subdural hematoma. A mixture was prepared of 30 ml of each patient's blood and 10 ml of acid citrate dextrose (ACD) solution (citric acid, 80 mg; sodium citrate, 250 mg; dextrose, 132 mg) and 100 μCi of Na$_{51}$CrO$_4$. This fluid was mixed for 30 minutes, then washed with normal saline and centrifuged. The $^{51}$Cr-labeled red cells were transfused in each case about 24 hours before evacuation of the hematoma. During the operation, we collected blood simultaneously with the hematoma fluid aspiration. The $^{51}$Cr content of blood, serum, hematoma fluid, and its supernatant was then measured by scintillation counter. The amount of daily hemorrhage could be expressed in the following equation:

\[
W = \frac{(H-S')}{(B-S)} \frac{24}{T} \cdot V
\]

where \(W\) is the amount of daily hemorrhage; \(B, S, H, S'\), the $^{51}$Cr content of blood, serum, hematoma, and its supernatant, respectively; \(T\), hours between the administration of $^{51}$Cr-labeled red cells and collection of blood and hematoma; and \(V\), volume of hematoma. When the volume of the hematoma was not measured, the ratio of the amount of daily hemorrhage to the volume of the hematoma could be expressed as:

\[
\frac{W}{V} = \frac{(H-S')}{(B-S)} \frac{24}{T}
\]

**Immunelectrophoresis of Fibrinogen**

This was performed in 12 cases of chronic subdural hematoma using the techniques of Marder and Shulman. Two wells were prepared in the thin agar layer of a glass slide and one was filled with 2 μl of supernatant of the hematoma fluid and the other with 2 μl of plasma. Electrophoresis was performed for 90 minutes with a constant current of 4 mA/cm. After the reaction of anti-human fibrinogen reagent, which was placed in a long trough between the two wells, the precipitate was stained with Ponceau 3 R.

**Determination of Fibrin and Fibrinogen Degradation Products**

We used fibrinogen degradation product (FDP) kits, to add specific anti-fibrinogen reagents and fibrinogen-sensitized sheep red cells to serial dilutions of samples after absorption of nonspecific agglutinins. In this hemagglutination-inhibition system the end points were read as the last dilution showing a clear button-pattern of cells with no trace of agglutination. The concentration of FDP in samples was calculated in comparison with standard fibrinogen.

**Tissue Activator, Plasmin, and Plasminogen**

Histological localization of the fibrinolytic activator was performed on the hematoma membrane in 11 cases with chronic subdural hematoma using the technique of Todd. Frozen sections of the hematoma membrane were placed on glass slides covered with a thin layer of fibrin, then incubated at 37° C in a moist chamber for 30 to 90 minutes, fixed with formalin, and stained with hematoxylin and eosin.

*Anti-human fibrinogen reagent was made by Boehringer-Mannheim GmbH, Verkauf Biochemica, Postfach 51, 6800 Mannheim 31, West Germany.

†Kits obtained from Wellcome Reagents Ltd., Beckenham, Kent, England.
### TABLE 1

**Daily hemorrhage into chronic subdural hematoma in five cases**

<table>
<thead>
<tr>
<th>Age, Sex</th>
<th>Laterality</th>
<th>Hematoma Content</th>
<th>Amount of Hemorrhage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>57 M</td>
<td>R</td>
<td>mixed</td>
<td>11.0</td>
</tr>
<tr>
<td>51 M</td>
<td>L</td>
<td>fluid</td>
<td>2.0</td>
</tr>
<tr>
<td>28 M</td>
<td>R</td>
<td>fluid</td>
<td>3.9</td>
</tr>
<tr>
<td>27 M</td>
<td>L</td>
<td>fluid</td>
<td>13.2</td>
</tr>
<tr>
<td>60 M</td>
<td>R</td>
<td>fluid</td>
<td>5.8</td>
</tr>
<tr>
<td>L</td>
<td>solid</td>
<td></td>
<td>12.8</td>
</tr>
</tbody>
</table>

* Percentage of daily hemorrhage of the volume of the hematoma.

Using Enzo-diffusion fibrin plates,‡ we determined available plasmin, active plasmin, and total plasminogen in the content of the chronic subdural hematoma in five cases and serum of the patients from whom the sections were taken.

### Results

#### Daily Hemorrhage into Chronic Subdural Hematoma

Smears made from content of chronic subdural hematoma revealed many fresh red cells with few deformities. This suggests that new hemorrhage occurs in chronic subdural hematoma. Using Equation 3, we estimated that daily hemorrhage ranged from 2.0% to 27.2% of the hematoma content, with an average of 10.2% (Table 1). The patients who had shown serious clinical deterioration for a few days had hematomas consisting of clot and the most new bleeding. From these findings it appears obvious that continuous or intermittent hemorrhage occurs in chronic subdural hematoma.

#### Immunelectrophoresis of Fibrinogen

No fibrinogen was detected by the usual clotting method in the chronic subdural hematomas. However, immunelectrophoresis, performed with specific anti-human fibrinogen reagent for analysis of fibrinogen and its derivatives, revealed the presence of FDP in the hematoma content (Fig. 1). The shifted reaction patterns were the result of cross-immunoreaction between fibrinogen and FDP. These corresponded to a form which was produced after the reaction of plasmin to fibrinogen. The absence of fibrinogen and the presence of FDP might explain the loss of clotting power of chronic subdural hematoma, because FDP acts as an anticoagulant.

#### Fibrin and Fibrinogen Degradation Products

The FDP concentration in the fluid of chronic subdural hematoma was measured by hemagglutination-inhibition immunoassay techniques. The results showed extremely high levels of FDP, varying between 8.0 and 10,500 μg/ml with an average of 2604 μg/ml in 18 cases. The amount of daily hemorrhage and the value of FDP were simultaneously determined in the three patients with bilateral subdural hematoma. The side on which the FDP level was higher showed a greater...
amount of hemorrhage than the other side. However, we could not establish whether clinical or laboratory correlation is present between high and low FDP content in chronic subdural hematoma. The amount of FDP in five cases with acute subdural hematoma was less than 5.6 μg/ml, whereas in two cases of subacute subdural hematoma there was a moderate increase of FDP, with values of 5.0 and 79 μg/ml.

The FDP levels in blood, cerebrospinal fluid, and urine in patients with chronic subdural hematoma remained nearly normal (Fig. 2); the mean values were 5.4, 1.8, and 1.3 μg/ml, respectively. In one patient FDP was hardly detectable in the CSF, because the FDP method used was insufficiently sensitive to detect FDP at the level of 10⁻⁴ μg/ml. The FDP levels in chronic subdural hematoma content were locally extremely high.

**Tissue Activator, Plasmin, and Plasminogen**

The outer membrane of chronic subdural hematoma contained many clear areas related to blood vessels (Fig. 3). These indicate remarkable tissue fibrinolysis by tissue activator in the outer membrane and moderate fibrinolysis in dura mater but not in the inner membrane.

On Enzo-diffusion fibrin plate tests, active plasmin in the hematoma fluid was less than that in serum of the same patient. Available plasmin and total plasminogen of the hematoma fluid was not detected in all five cases tested. It is assumed that plasminogen would be consumed in the chronic subdural hematoma by diffusion of a tissue activator from the outer membrane. More exploration will be needed to explain the low active plasmin level in hematoma fluid.

**Discussion**

The subdural space is a closed space. Its outer wall is dura mater that consists of a dense fibrous membrane with poor vascularization, and its inner wall is the vascularized arachnoid with no capillary bed. Lymphatics have never been found in the dura mater nor in the arachnoid. All surfaces of all serous cavities normally absorb any foreign material with which they come in contact; however, when hemorrhage is limited in the subdural space without arachnoid tear, the arachnoid does not participate in the process of absorption. Granulation tissue from the dura mater is usually first noticed only during the second week or later. The inner surface of the clot later develops its own pseudomembrane, separating the clot from the arachnoid. At the same time, the subdural clot becomes liquefied and does not clot immediately after removal nor even after standing for many days or weeks. Dandy suggested that subdural hematoma fluid lost clotting power because the fibrinogen had been used to build up the neomembrane. However, it seems reasonable that fibrinogen degrades in FDP due to local hyper-fibrinolysis, so subdural hematoma fluid does not usually clot. This is revealed by our observation of fibrinogen with immunoelectrophoretically different features, by the raised FDP levels in the content of chronic subdural hematoma, and by the histological evidence.
Gradual increase of FDP levels from acute to chronic subdural hematoma suggests that fibrinolysis takes place in subdural hematoma. Some degree of fibrinolysis is required to absorb the clot in the subdural space, while abnormal excessive activation of fibrinolysis may well give rise to hemorrhage from the cavity-lining membrane. Dandy¹ has already shown that the hematoma increases in size because of secondary bleeding from the organizing outer membrane adjacent to the dura mater. Putnam and Cushing⁷ explained that recurrent hemorrhage caused progressive enlargement of the hematoma. On calculation, using ⁶⁷Cr-labeled red cells, we have demonstrated that a continued or intermittent hemorrhage occurs, amounting to 10.2% of the volume of the subdural hematoma.¹¹ Such continuous or intermittent hemorrhage is the most important factor to keep or enlarge chronic subdural hematoma, and is caused by local hyperfibrinolysis. Therefore, excessive local activation of fibrinolysis plays an important role in the etiology of chronic subdural hematoma.

References

Hyperfibrinolysis in chronic subdural hematoma


5. Munro D, Merritt HH: Surgical pathology of subdural hematoma based on a study of one hundred and five cases. Arch Neurol Psychiatry 35:64–78, 1936


Address reprint requests to: Haruhide Ito, Ph.D., Marine Biomedical Institute, 200 University Boulevard, Galveston, Texas 77550.